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Dermatology Reports
Edizione Italiana

Dermatology Reports è una rivista scientifica in lingua inglese, on-line open-access, indicizzata sui principali motori di ricerca, dal 2019 di proprietà di ADOI e organo ufficiale di ADOI, IMI e SIDCO.

L'edizione italiana pubblica aggiornamenti scientifici, rubriche e informazioni relative a quanto di rilevante accade all'interno di ADOI e della dermatologia italiana, nonché pagine dedicate a quegli aspetti umanistici, spesso trascurati, che sono alla base delle sue origini.

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Dermatology Reports

Edizione Italiana

2021; volume 2, n. 2

Indice

pagepress

EDITORIALE

Dalle stalle…

Telefonata ricevuta appena qualche giorno fa. Testuale.

Voce femminile: Pronto! Dott. Cusano?
Io: Sì…?!
Voce femminile: Sono la figlia della signora Carmela C., sua paziente; la signora con la psoriasi, che assume il farmaco O.; ricorda? È un po' che non ci si vede, a causa del COVID…
Io: Ah, sì, certo… come sta la signora?
Voce femminile: Bene, grazie. Ho verificato con il mio medico di famiglia che effettivamente il suo piano terapeutico è stato prorogato automaticamente, come mi aveva anticipato lei al telefono. Il medico di famiglia mi ha detto che sarebbe comunque meglio rinnovarlo.
Io: Certo signora, come vuole.
Voce femminile: Ah, bene! Allora è possibile raggiungerla in ospedale?
Io: Certo.
Voce femminile: Quando pensa sia possibile?
Io: Non ci sono grandi problemi in questi giorni, potrebbe venire anche il prossimo lunedì mattina.
Voce femminile: Occorre la richiesta del medico di famiglia?
Io: Certo, signora, come al solito.
Voce femminile: Cosa occorre che riporti la prescrizione?
Io: Visita dermatologica di controllo per psoriasi.
Voce femminile: E occorre telefonare al CUP per l'appuntamento?
Io: Bisognerebbe, sì. Ma se viene lunedì la possiamo inserire in sovrannumero comunque, non si preoccupi. Basta che passi direttamente al CUP a registrare la richiesta e pagare il ticket prima di salire in ambulatorio.
Voce femminile: Allora riepilogo: mi reco dal medico di famiglia, gli dico di prescrivere una visita dermatologica di controllo per psoriasi, quindi telefono al CUP dell'ospedale sperando mi diano un appuntamento in tempi brevi, in caso contrario il lunedì comunque registro la visita agli sportelli del CUP e poi salgo su da lei.
Io: Perfetto, signora. Ci vediamo lunedì.
Voce femminile: Bene, dottore. Però ho da chiederle un piacere personale, non mi dica di no.
Io: Se posso, signora, volentieri. Cosa le occorre?
Voce femminile: Potrebbe anche visitarla, mia madre, che ho l'impressione non stia andando benissimo con questo farmaco?

Dedicata ai nostri decisori e a tutti gli altri strani personaggi che affollano l'ambiente sanitario e da anni tentano di trasformare la nostra professione in una mera attività burocratica (spesso purtroppo riuscendoci).

Alle stelle…

Alcuni mesi fa il Blue Journal ha pubblicato un breve articolo, che è probabilmente sfuggito a molti di noi, dal titolo: *Top Authors in Dermatology by h-index: A Bibliometric Analysis of 1980-2020* (J Am Acad Dermatol 2020, Nov 17; S0190-9622(20)32911-X). In esso, l'autrice, Mindy Szeto, dell'Università del Colorado, si è divertita a stilare una graduatoria dei dermatologi più citati in letteratura. Sorprendentemente (ma non troppo) fra tanti nordamericani, inglesi e tedeschi figura anche il nome di un italiano; sorpresa delle sorprese, però, il nome che leggiamo e che occupa addirittura il settimo posto assoluto in questa particolare *hit parade* non è quello di uno dei nostri pur validissimi cattedratici, bensì quello di un collega che da sempre ha svolto la sua attività soltanto in ambito ospedaliero, prima a Bergamo, ora a Vicenza. Ed è da qualche anno attivo componente del Consiglio Direttivo ADOI nonché Editor-in-Chief di *Dermatology Reports.*
Senza voler caricare questa notizia di troppa enfasi, pure il percorso professionale di Luigi Naldi (è di lui che si tratta, ovviamente) resta un esempio per le future generazioni di dermatologi ospedalieri che vogliano aspirare a condire di cultura e ricerca applicata le attività assistenziali quotidiane a sostegno dei pazienti.

Ad maiora!

Francesco Cusano
Presidente ADOI

EDITORIALE

È con grande piacere che con questo breve editoriale comunico al lettore che, da questo numero, *Dermatology Reports* diviene rivista scientifica ufficiale della *Società Italiana di Dermatologia Chirurgica, Correttiva ed Estetica* (SIDCO).

Questo importante conseguimento a beneficio anche degli iscritti alla SIDCO, rappresenta uno degli effetti tangibili di una lungamente coltivata convergenza di intenti fra SIDCO e ADOI, capofila e promotrice di questa pregevole ed originale iniziativa editoriale, al cui Presidente, Francesco Cusano, al Consiglio Direttivo, ed al cui Editor-in-Chief, Luigi Naldi ed al Comitato Editoriale, va il nostro plauso e ringraziamento per l'opportunità offerta alla nostra società scientifica di apportarvi il proprio contributo. Anche gli iscritti alla SIDCO, infatti, oltre ad usufruire liberamente alla versione *Open Access* della rivista, riceveranno la rivista cartacea dell'edizione nazionale, nonché potranno accedere a titolo gratuito alla pubblicazione dei propri lavori scientifici, una volta selezionati dal comitato di redazione.

La compartecipazione anche di IMI e GISED all'editing della rivista, conferisce indubbiamente immagine e valore aggiunto alla sostanza di *Dermatology Reports*, la quale configura una inedita piattaforma di convergenza fra istanze e contenuti di società scientifiche di riferimento nella dermatologia italiana, con storia, struttura, valori ed orientamenti alquanto diversi. Si tratta di un segnale credo tangibile che i tempi sono decisamente maturi per un cambiamento di passo: insieme, nel rispetto delle proprie prerogative, si valorizzano posizioni differenti, insieme si acquisisce maggiore incisività e rappresentatività. *Dermatology Reports*, con la sua natura *Open Access*, la sua visibilità internazionale, con il suo taglio editoriale costituzionalmente aperto all'interattività e all'innovazione, rappresenta una inedita opportunità per la valorizzazione dell'intera comunità scientifica della Dermatologia italiana.

Auspichiamo che questa opportunità sia effettivamente colta, specialmente dai Dermatologi più giovani, operosi e capaci, a cui aspiriamo di affidare la Dermatologia italiana del futuro, a beneficio sia della ricchezza di contenuti scientifici e della qualità delle pubblicazioni quanto, in ultima analisi, della autorevolezza del servizio offerto ai nostri Pazienti.

Marco Dal Canton
Presidente SIDCO

IN MEMORIA

In Memoria del Prof. Raffaele Gianotti

Il Prof. Raffaele Gianotti ("Raf" per gli amici) nacque a Milano il 7 luglio del 1959. Suo padre, il Prof. Ferdinando Gianotti (1920-1984), fu stimato e riconosciuto dermatologo pediatrico che identificò la "papular acrodermatitis of childhood", ancora oggi riconosciuta col suo nome (Gianotti-Crosti Syndrome).[1]

Raffaele si laureò *cum laude* in Medicina e Chirurgia nel 1985 all' Università di Milano. Nel 1988 conseguì la prima specializzazione in Dermatologia a cui seguì nel 1992 la seconda in Anatomia Patologica. Nel 1993 fu fellow di Bernie Ackerman a New York; tornato a Milano iniziò la sua vita da dermatopatologo come Ricercatore Confermato all' Istituto di Scienze Dermatologiche Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena. Negli anni 2000-2005 collaboró con H. Kutzner a Friedricshafen (Germania) sul progetto Lampyris101, un software automatizzato per la diagnosi delle malattie infiammatorie cutanee. Nel 2005 conseguì anche l'International Board Certification in Dermatopathology.

Come accademico, pubblicò oltre 135 articoli scientifici su vari argomenti di malattie cutanee infiammatorie e neoplastiche raggiungendo un H-index di 27 (sorgente: Scopus, ultimo accesso 5 Aprile 2021). Particolarmente, fu molto attivo nel descrivere i quadri istopatologici delle lesioni cutanee indotte dall'infezione da COVID-19, diventando molto popolare per avere descritto il primo caso italiano accertato infettato da COVID-19 [2-3]

Raf fu anche autore di Dermosprint (https://www.dermosprint.com/), una collezione gratuita di dermatopatologia con il contributo di numerosi dermatopatologi di livello internazionale.

Raf é spirato lo scorso 27 Marzo 2021, all'etá di 61 anni.

In sua memoria, abbiamo deciso di pubblicare postumo in Dermatology Reports un editoriale che Raf scrisse per Dermosprint.

Ciao Raf!

Riposa in pace.

Cesare Massone,[1] Antonio Perasole[2]

[1]SC Dermatologia, EO Galliera, Genova, Italia
[2]Consulente Anatomo Patologo presso Lifebrain s.r.l. Limena, Padova, Italia

Il Prof. Raffaele Gianotti con i suoi due "eterni amori": dermatopatologia & motorbike.

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IN MEMORIA

Ma… chi è il migliore di tutti i tempi nella diagnosi delle lesioni melanocitarie?

Raffaele Gianotti

Clinica Dermatologica, Università degli Studi di Milano, Italy

Pubblicato postumo

Scrivendo il testo su Ackerman e raccontandovi i pensieri di giganti come LeBoit, Kutzner e Weedon mi sono chiesto: "Ma… chi è stato e chi è oggi il miglior dermatopatologo nel campo delle lesioni melanocitarie di tutti i tempi?" Non sto parlando di carisma del personaggio, del numero di pubblicazioni indexate, dei premi ricevuti o delle letture magistrali che ha tenuto ai quattro angoli del globo. Intendo quello che, seduto al microscopio, non sbaglia mai, o se preferisci, sbaglia di meno.

Quante volte i cronisti sportivi si sono chiesti: "Chi è stato il miglior tennista di tutti tempi? E…il calciatore? E… il pilota? Se Alessandro Manzoni scrivesse oggi un romanzo ambientato nel 1600 scritto con un lessico del 1800 non lo trovereste sugli scaffali della Esselunga. Impossibile dare una risposta se paragoniamo personaggi di epoche diverse.

Caro lettore ammettilo, anche tu, almeno una volta, hai pensato di essere più bravo nella diagnostica del tuo collega che lavora in un laboratorio o dipartimento distante centinaia di chilometri dal tuo posto di lavoro e che incontri ai congressi o alle riunioni interregionali.

È anche impossibile stabilire chi oggi sia il più talentuoso mentre esamina un preparato istologico in bilico tra un nevo di Spitz ed un melanoma spitzoide. Se ti dicessi che il mio amico e collega Giuseppe che lavora in anatomia patologica in un ospedale periferico di Gubbio ha uno score elevatissimo nelle patologie melanocitarie ci crederesti? Potrebbe essere, ma non è dimostrabile! Nel nostro lavoro non si "fanno punti", non c'è un cronometro che corre, non c'è un campionato che alla fine premia l'atleta dell'anno sulla base di risultati oggettivi.

In un lavoro australiano di pochi anni fa sono stati esaminati più di 26736 melanomi. Si è stabilito che solo il 4% dei pazienti con un Breslow sopra 0.75 mm non sopravvive ai 20 anni di malattia. Mi sono sempre chiesto: "Quanti dei quattro pazienti, prima di passare a miglior vita, riescono a contattare il patologo che magari, dieci anni prima, aveva diagnosticato la lesione come Spitz?" In base a questo studio potreste decidere di diagnosticare sempre come nevi melanocitari tutte le lesioni pigmentate che mettete sul piatto del microscopio, anche se fossero melanomi, a patto che non superino il fatidico 0.75 mm. Probabilmente nessuno si farebbe vivo o forse uno nell'arco della carriera di un dermatopatologo. E… vogliamo citare i pazienti a cui è stato diagnosticato erroneamente un melanoma. Non ne avrai più notizie. Hanno la sola seccatura di sognare spesso la "spada di Damocle" a foggia di melanoma che si stacca dal soffitto per colpirli al centro della fronte.

Come possiamo imparare dai nostri errori nella diagnostica delle lesioni melanocitarie? Quasi impossibile! Dato che si può essere certi di aver mancato la diagnosi di melanoma solo se il paziente muore per diffusione metastatica e questo fortunatamente avviene molto di rado. Ben diverso è il campo dei linfomi cutanei e delle forme infiammatorie. I pazienti non spariscono, tornano. E' un processo diagnostico lento. E' possibile imparare dai nostri errori diagnostici, rivedere il vetrino precedente e riformulare una diagnosi più consona all'andamento clinico con un secondo esame istologico. Possiamo conoscere le performances di un chirurgo perché il risultato si verifica poco tempo dopo l'intervento. Con le lesioni melanocitarie non si può. "Un colpo secco", diagnosi di Spitz e… poi il paziente sparisce. I lavori sull'argomento melanoma vs nevo riguardano generalmente forme molto rare, complesse e più profonde dello 0.75 mm. Presentano follow-up relativamente brevi, superano raramente la cinquantina di casi ed i vetrini li hanno visti solo quelli che hanno scritto il report. Gli altri possono solo prenderne atto, ma non possono interiorizzare profondamente una personale diagnosi, giusta o sbagliata che sia. Quindi non si può sapere chi tra il Dott. Riccardo di Roma, la Dott.ssa Erica di Pasadena, il Dott. Federico di Genova o la Dott.ssa Arianne di Hannover abbia sottodiagnosticato il maggior numero di melanomi oppure sovradiagnosticato dei nevi melanocitari.

Esiste un teorema statistico chiamato "Single shoot theory" elaborato da matematici russi per allenare gli atleti olimpici di tiro con la carabina, disciplina in cui i nostri amici dell'est sono sempre stati maestri. Le gare olimpiche si svolgono su sessanta tiri ed il teorema fa leva sugli atleti per convincerli ad essere costantemente super-concentrati, perché non si tratta di una unica competizione di sessanta colpi, bensì sessanta gare da un colpo. Cosa significa tutto ciò? Semplice: un tiratore medio al quindicesimo colpo potrebbe fare un po' meglio come punteggio di un atleta olimpico che si è deconcentrato. Però, alla fine della competizione, il campione sarebbe comunque avanti con un distacco "siderale". In una ipotetica competizione con Bernie Ackerman, sul singolo caso complesso potrei avere ragione io, se avessimo pareri contrastanti. Purtroppo alla fine dell'anno solare, dopo aver esaminato migliaia di casi difficoltosi, il mio distacco da lui sarebbe imbarazzante.

Pensateci quando mandate un caso complesso in consulenza ad un collega più esperto che non vi ha convinto, potrebbe essere il vostro quindicesimo colpo, ma ricordatevi di imparare dagli errori dei più esperti. "*A mistake is an error, but an error is not always a consequence of carelessness or indifference. On the contrary, mistakes can be made when great care has been exercised...*" Bernie Ackerman.

DERMATOPATOLOGIA

Quindici anni di riunioni melanomatose. Parte I

Antonio Perasole

Consulente Anatomo Patologo, Lifebrain s.r.l. Limena, Padova, Italia

Quando Raffaele Gianotti mi propose l'altro anno di spostare la sede dei nostri incontri in Clinica a Milano, pensai che avremmo finalmente trovato la soluzione al problema della limitata capienza e dell'accessibilità dell'aula di Vicenza. Purtroppo il COVID spense sul nascere l'entusiasmo del primo incontro milanese 2020 e dovemmo spostare in tutta fretta in videoconferenza gli incontri che avevamo già programmato, senza immaginare quanto avrebbe impattato tutto questo sulla riuscita del corso. Poiché la casistica era distribuita in formato digitale prima dell'incontro e lo spostamento al luogo del convegno era stato azzerato, nel volgere di un paio di mesi notammo che avevano cominciato a partecipare gli incontri virtuali molti altri colleghi da sedi geografiche anche molto distanti. A questo punto Cesare Massone, terzo mentore del nostro corso, con grande intuito e tempismo perfetto propone a Francesco Cusano e Luigi Naldi di offrirci uno spazio e tutta l'assistenza informatica necessaria per trasferire i contenuti e l'organizzazione degli incontri sul sito web ADOI allargando la platea dei potenziali partecipanti anche ai dermatologi afferenti all'associazione.

La scomparsa improvvisa di Raffaele, avvenuta sabato 27 marzo, ha privato tutti di uno dei più convinti sostenitori del progetto ed un brillante conduttore d'aula. Insieme a Cesare era un formidabile strumento di sintesi tra la valutazione clinica e l'esame al microscopio. Ha lasciato in chi lo ha conosciuto e ci ha lavorato assieme, un vuoto enorme ed a tutti noi un insegnamento di grande apertura mentale e voglia di ragionare fuori dagli schemi. Oggi il corso sulle lesioni melanocitarie è giunto a questo traguardo grazie alla sua volontà di sostenerlo ed ai suoi preziosi suggerimenti.[1]

C'era una volta …

Nel 2005, quando per mera contingenza fui nominato RAQ del sistema Qualità dell'Anatomia Patologica di Vicenza. Mi piovvero addosso una quantità di incombenze e adempimenti assurdi, tra questi quello di dover implementare una procedura di controllo di qualità delle diagnosi. Decisi di cominciare dal settore diagnostico di mia competenza: la dermatopatologia.

Iniziai a lavorare sulle diagnosi di melanoma. Organizzai subito una checklist partendo dai protocolli diagnostici del CAP del Royal College of Pathologists inglese, australiano e canadese e la misi in routine.[2-5] Visto che i paesi anglofoni si erano mossi come una falange romana e con una lungimiranza senza pari, partii senza indugi prendendo spunto ed organizzando tutto secondo quanto era scritto nei loro protocolli.

Il problema da risolvere fu di condividerla con i colleghi del reparto e rivedere tutte le prime diagnosi di melanoma che secondo il CAP avremmo dovuto fare alla pari. Ma… se io rivedevo tutte le diagnosi di melanoma fatte a Vicenza con chi avrei dovuto fare questo controllo incrociato se non con le stesse persone che verificavo? Non c'era via di uscita dovevo cercare fuori casa un aiuto.

Non ero a conoscenza di altre anatomie patologiche che avessero intrapreso questo percorso e decisi senza indugio di proporlo a due amici noti dermatofili. Angelo Cassisa che lavorava a Mantova e Marina Zannoni a Verona. Concordammo di incontrarci mensilmente a Vicenza per rivedere tutte le diagnosi di melanoma fatte il mese precedente presso i tre ospedali. Cominciammo un lavoro mai intrapreso in modo così sistematico in altri ospedali. Dopo pochi mesi mi stavo stufando perché il livello di concordanza delle diagnosi era indecentemente alto. Eravamo solo bravi? oppure ci piaceva giocare facile visto che le lesioni riviste erano quasi sempre dei melanomi clamorosi?

Era venuto il momento di alzare l'asticella e di estendere la revisione anche alla diagnosi delle lesioni incerte e complesse. Insomma bisognava pensare in grande e fare un lavoro al di fuori del protocollo. Però il numero dei casi da rivedere era notevole ed in caso di disaccordo mancavano arbitri e non sapevamo quanto fosse il K atteso per certe diagnosi. Eravamo scoraggiati, nessuno di noi era (o si riteneva) un super esperto rispetto agli altri due e non avevamo idea di come valutare gli scostamenti.

Quello che emerse da questi incontri fu però una scoperta per tutti; eravamo troppo spesso in disaccordo su casi che ci sembravano dovessero essere semplici e chiari.

Esistevano pochi studi sulla concordanza diagnostica e solo per alcuni tipi di lesioni melanocitarie. Erano studi organizzati da grossi centri di riferimento dove i "players" erano quasi sempre dei grossi nomi della dermatopatologia mondiale. Spesso erano studi deprimenti per il livello di disaccordo esistente anche tra gli assi della cute. Nessun benchmark era stato tentato per definire quale fosse lo scarto atteso, il Delta in un contesto operativo da general surgical pathology che legge un vetrino dermatopatologico.

E il resto del mondo?

Ero stato colpito dalle modalità con cui il CAP statunitense aveva elaborato i benchmark e come erano stati effettuati i rilievi tra le centinaia di laboratori accreditati per garantire una uniformità organizzativa ed operativa delle strutture sanitarie nell'ambito del paese.[6]

I range attesi sul tempo massimo di esecuzione di un esame intraoperatorio o la percentuale di campioni bioptici smarriti nel corso del ciclo di lavorazione preanalitico non erano più un tabù su cui tacere, erano stati indagati e determinati. I laboratori dovevano stare al di sotto delle soglie indicate.

L'industria automobilistica e quelle ad elevato contenuto tecnologico avevano adottato da moltissimo tempo un approccio rigoroso nella valutazione delle criticità della gestione della pro-

pria organizzazione. L'obiettivo era di raggiungere in modo ossessivo l'eccellenza nei processi produttivi.

Le case automobilistiche e motociclistiche nipponiche avevano conquistato i mercati mondiali perché erano organizzate con il Lean Six Sigma.[6] Per Toyota era la garanzia che i componenti delle proprie auto fossero prodotti e montati con sei deviazioni standard di precisione. Significava una precisione del 99,99966% pari a non più di 3-4 difetti per milione di elementi prodotti.

Mi chiesi se fosse pensabile accostare la qualità di un componente automobilistico o del propulsore di un razzo all'allestimento di un preparato istologico. Forse, ma non la diagnosi istologica.

Decisi allora di mettere a confronto i pareri e le diagnosi di un gruppo ben più numeroso ed eterogeneo di general pathologists dermato-amanti per valutare il livello dello scostamento diagnostico. Non un Lean Six Sigma, ma lo studio della distribuzione modale delle diagnosi per ogni dato caso.

Avviammo così questa serie di incontri a Vicenza. Il gruppo crebbe rapidamente di numero e naturalmente l'organizzazione si complicò. Si aprì alla condivisione anche di casi per una "second opinion" durante i meeting, ma era impossibile chiedere 20-30 pareri personali prima dell'incontro. La "second opininon" fu limitata alla sola osservazione in aula al microscopio multiteste in occasione della riunione.

Tutto cambiò quando nel 2014 ci dotammo di uno scanner di vetrini con il quale fu possibile superare questo limite. Chi voleva condividere un caso per una "second opinion", mi inviava una sezione che scannerizzavo e condividevo via Dropbox in forma anonima con i partecipanti al corso. Il parere era poi inviato da ciascuno via mail al richiedente. Il vetrino originale sarebbe stato rivisto collegialmente, per controllo, in aula al microscopio multiteste.

Un primo esame studiato su immagini digitali a casa ed uno successivo di controllo al microscopio: dunque, due diagnosi raccolte in luoghi ed ambienti di osservazione diversi e complementari.

In questo modo cominciammo a raccogliere e condividere una casistica sempre più numerosa con notevoli sfumature e diversi gradi di complessità interpretativa. Nei quindici anni trascorsi da allora abbiamo raccolto, visto e discusso circa 3000 lesioni melanocitarie.

Full throttle

Eravamo davvero disposti a metterci in gioco? Saremmo riusciti a farlo senza pudore e senza temere di fare figuracce portando in aula diagnosi più o meno complesse o magari sbagliate? Noi, primi tre esploratori, avevano stabilito un patto di gentlemen's agreement, mai tradito e più cambiato.

Sono trascorsi quindici anni ed il gruppetto dei "tre temerari" è cresciuto al punto che oggi abbiamo una mailing list che conta un centinaio di patologi e dermatopatologi di diversa estrazione professionale con i quali condividiamo casi digitalizzati che poi studiamo anche al microscopio in aula.

Una sfida senza speranza?

Negli anni abbiamo capito che erano conflittuali e molto complesse una vasta tipologia di lesioni come ad esempio i MELTUMP. Ricordate l'incubo del tutorial di Lorenzo Cerroni del 2008 a Graz?[7] I dieci migliori dermatopatologi del mondo avevano mostrato una riproducibilità diagnostica ed un agreement bassissimo quando si cimentavano con casi molto complessi. Per noi la riproducibilità era un maledetto problema anche per lesioni superficiali, in regressione e sclerosanti o per le lesioni prive di diffusione pagetoide. L'universo melanocitario!

Era giunto il momento di elogiare l'incertezza e la incapacità di diagnosticarla senza temere l'impopolarità. La mia incertezza spesso non era quella degli altri e vice versa. Non c'era l'abitudine al confronto ed alla condivisione dei casi. Il percorso mentale ed il valore attribuito ai parametri microscopici, a parità di osservazione, spesso era diverso da patologo a patologo.

Allora ho avuto una visione: cosa rende le lesioni melanocitarie, e l'esame al microscopio un atto mentale così speciale e variabile, talvolta banale a volte complesso e potenzialmente pieno di insidie?

Ho cominciato a chiedermi perché alcuni colleghi hanno un talento fuori dall'ordinario al microscopio mentre altri, nonostante abbiano dedicato tantissimo tempo allo studio ed alla osservazione al microscopio, restano nel limbo di una bravura di media levatura? Perché alcuni sono eccellenti diagnosti in particolari ambiti della patologia e modesti in campo melanocitario?

Il mondo "di sotto"

Esiste un mondo che io chiamo "di sotto" che risiede nella nostra mente di morfologi che gestisce una abilità speciale. Questa è determinante sin dalle prime fasi della nostra crescita professionale al punto che se mamma e papà ci avessero fornito di questa rete neurale speciale saremmo diventati finissimi diagnosti in breve tempo, altrimenti avremmo dovuto cercare di diventarlo usando vie alternative con training specifici.

Non si tratta, dunque di una abilità cosciente ma è presente, seduta vicino a noi al microscopio. È capace sia di guidarci correttamente lungo il processo di elaborazione della diagnosi quanto di farci imprevedibilmente mancare una diagnosi banale.

È una forma di intelligenza conoscitiva che è stata codificata dalle teorie della *gestalt psychology*[8,9] e che si alimenta di contenuti condivisi (swarm intelligence).[10,11] Probabilmente in un futuro poco lontano questi teoremi saranno il substrato per elaborare tecniche per allenare dei professionisti alla visione e diagnosi al microscopio.

La seconda parte dell'articolo sarà pubblicata nel prossimo numero.

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FOTOPROTEZIONE

Tumori cutanei non melanocitari e fotoprotezione sistemica: Aggiornamenti dalla letteratura e reale efficacia dei farmaci e integratori utilizzati

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Introduzione

I tumori cutanei non melanocitari (TCnM) rappresentano circa il 20% di tutte le neoplasie e la loro incidenza è in costante aumento.[1,2] Tali tumori sono costituiti dal carcinoma basocellulare (BCC), dal carcinoma squamocellulare (SCC) e dalla cheratosi attinica (CA). Sebbene l'incidenza riportata dei TCnM sia più elevata del melanoma, i dati epidemiologici tendono a sottostimarla in quanto spesso non vengono annotati nei registri nazionali. In Italia l'incidenza dei TCnM è pari a circa 100 casi ogni 100.000 abitanti.[3-5] Il BCC è il più frequente carcinoma dell'uomo nella razza caucasica ed il rapporto stimato BCC:SCC è circa 2.5:1 nella popolazione generale.[6] Tale rapporto si inverte nei pazienti trapiantati d'organo a causa della maggiore incidenza del SCC.[3]

Ad oggi esiste un dibattito sulla reale definizione della CA in quanto da molti è considerata una precancerosi mentre da altri un iniziale SCC *in situ*. Generalmente la CA compare nelle aree fotoesposte quali, in particolare, il viso e il cuoio capelluto, e può presentarsi all'interno di un campo di cancerizzazione, ossia l'area di cute in cui sono presenti multiple lesioni subcliniche. La CA potrebbe progredire nel tempo, se non adeguatamente trattata o se tralasciata a lungo, in un SCC infiltrante.

Il BCC è un tumore localmente invasivo: raramente metastatizza e presenta una mortalità estremamente bassa ma, nelle forme avanzate, può causare erosione di strutture anatomiche locali come nel caso dell'ulcus rodens, con sanguinamento e dolore.

L'SCC può metastatizzare nel 5-8% dei casi e tale carcinoma presenta una maggiore mortalità rispetto al BCC.[2,7]

Il principale fattore di rischio correlato all'insorgenza dei TCnM è l'esposizione cronica alle radiazioni ultraviolette (UV) del sole o delle lampade UV. Infatti, solitamente i TCnM insorgono su aree cutanee cronicamente esposte come la regione testa/collo, il dorso delle mani ed il tronco, in particolare in pazienti che svolgono attività lavorative o hobby all'aperto (*i.e.,* agricoltori, marinai etc…). Tale rischio è decisamente più elevato per le persone con fototipo chiaro.[2,7]

A causa della loro elevata incidenza, i TCnM rappresentano un onere significativo per il sistema sanitario nazionale. Considerando che tali tumori hanno un elevato tasso di guarigione se riscontrati e trattati precocemente, è indispensabile effettuare una adeguata prevenzione delle suddette neoplasie.[2,7]

La strategia di prima linea nella prevenzione dei TCnM è la fotoprotezione che può essere topica o sistemica.[8-10] La fotoprotezione topica è essenziale e consiste nell'uso di creme solari con un fattore di protezione solare (SPF) di 30 o superiore. D'altro canto, i filtri solari topici presentano una breve emivita, tale da comportare la necessità di applicazioni frequenti, mancano di un'efficacia sistemica, e possono provocare, seppur raramente, eventuali dermatiti da contatto.[8]

Di supporto alla fotoprotezione topica vi è la fotoprotezione sistemica che consiste nell'assunzione per via orale di specifici fotoprotettori quali vitamine, minerali, polifenoli, carotenoidi dotati di proprietà fotoprotettive e anti-fotocancerogene. Queste sostanze potenziano la protezione naturale contro gli effetti dannosi delle radiazioni UV e prevengono la carcinogenesi e l'invecchiamento foto-indotto.[8-10] I meccanismi protettivi attivati dai fotoprotettori sistemici sono molteplici e includono effetti antiossidanti, antinfiammatori e immunomodulatori.[8,9,11] La radiazione UV, infatti, oltre a indurre danni al DNA, determina un aumento dello stress ossidativo, innesca fenomeni infiammatori e induce immunosoppressione a livello cutaneo.[11-13]

Lo scopo di questa review è di riassumere lo stato attuale sulle conoscenze inerenti la fotoprotezione sistemica.

Vitamina D

La vitamina D viene principalmente sintetizzata dal nostro organismo attraverso l'assorbimento dei raggi solari da parte della cute. Questa vitamina è un regolatore del metabolismo del calcio e contribuisce a mantenere nella norma i livelli di calcio e di fosforo nel sangue.

Alcuni studi *in vitro* hanno dimostrato che la forma attiva della vitamina D (1,25-diidrossivitamina D3) protegge i cheratinociti dall'apoptosi indotta da radiazioni UV e dalla formazione di dimeri di pirimidina ciclobutano (CPD).[14,15] Per quanto concerne i TCnM, gli studi clinici osservazionali che hanno valutato la corre-

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lazione fra i livelli di vitamina D ed il rischio tumorale hanno riportato risultati contrastanti.[16-19] Nel caso del melanoma, gli studi osservazionali suggeriscono che livelli di vitamina D più bassi siano correlati con una prognosi infausta di melanoma.[20-23]

Uno studio controllato randomizzato che ha coinvolto 36.282 partecipanti ha valutato l'impatto del calcio giornaliero (1000 mg) e della vitamina D3 (400 UI) sull'incidenza dei TCnM e del melanoma in un arco temporale di 7 anni. I risultati dello studio hanno dimostrato che l'assunzione di calcio e vitamina D non ha effetto sull'incidenza dei melanomi e dei TCnM.

Inoltre, una meta-analisi non ha riscontrato alcuna associazione tra i livelli ematici di 25(OH)D e il rischio di melanoma o di TCnM. Infatti, non è stata rilevata alcuna associazione significativa tra l'assunzione di vitamina D (attraverso alimenti e/o integratori) e il melanoma o i TCnM.[24] Inoltre, la correlazione tra livelli elevati di vitamina D e rischio di TCnM suggerisce che l'esposizione al sole rappresenti una variabile confondente in molti degli studi esistenti.

Sebbene rara, può verificarsi tossicità a seguito dell'assunzione di vitamina D. I sintomi sono correlati all'ipercalcemia e si osservano dopo l'assunzione di dosi eccessivamente elevate di vitamina D (50.000-2.604.000 UI/giorno).[25] Negli studi descritti non sono stati riportati effetti collaterali in quanto l'assunzione della vitamina D è stata effettuata entro i limiti raccomandati.

La Tabella 1 riassume le raccomandazioni riguardo la Vitamina D per ciascuna indicazione (TCnM e melanoma) e il livello di evidenza disponibile.

Nicotinamide

La nicotinamide è una delle forme di vitamina B3, vitamina idrosolubile caratterizzata da acido nicotinico (o niacina, NA) e nicotinamide (o niacinamide, NAM). Il NA e il NAM rappresentano i due principali precursori del nicotinamide adenin dinucleotide (NAD+), cofattore enzimatico chiave per il metabolismo energetico della cellula.[26] Tuttavia, le due molecole hanno vie metaboliche e attività farmacologiche ben distinte (Figura 1).

Il NAD+ intracellulare agisce in due modi distinti: come cofattore, regola l'attività ossido/riduttiva di circa 500 enzimi coinvolti nel metabolismo cellulare. Inoltre, il NAD media il trasferimento di elettroni oscillando tra il suo stato ossidato (NAD+) e quello ridotto (NADH).[27] Virtualmente in questo caso non si ha consumo della molecola. Tuttavia, il NAD+ agisce anche da substrato per diversi enzimi tra cui l'enzima Poli ADP-ribosio polimerasi (PARP). E' importante notare che PARP è un enzima nucleare che viene attivato in risposta ai danni del DNA per promuoverne e coordinarne i processi di riparazione.[28]

Un importante contributo riguardo le proprietà fotoprotettive sull'uomo del NAM è stato senza dubbio fornito dagli studi condotti dal gruppo della dermatologa austrialiana Diona Damian. Due studi randomizzati hanno valutato gli effetti fotoprotettivi dell'assunzione di NAM orale dopo l'esposizione ai raggi UV e dopo terapia fotodinamica (PDT). Sebbene il NAM non abbia mostrato alcun effetto sulla dose minima di eritema rispetto al placebo, in entrambi gli studi è stata riscontrata una riduzione significativa dell'immunosoppressione indotta dall'irradiamento. Il NAM è in grado di ridurre l'immunosoppressione indotta dagli UV anche quando somministrata per via topica.[29,30] Uno studio randomizzato controllato a doppio cieco di fase 2 ha dimostrato come il NAM fosse in grado di ridurre significativamente in soggetti a rischio la ricorrenza delle CA. Dopo 4 mesi di trattamento, la riduzione del numero di CA è risultata maggiore nei pazienti trattati con NAM 500 mg due volte al giorno (35%) rispetto ai pazienti trattati con 500 mg/giorno (29%).[31] I risultati di due studi condotti su un piccolo numero di pazienti trapiantati suggeriscono che l'assunzione di NAM possa contribuire ad una sostanziale diminuzione delle dimensioni e del numero di CA rispetto al placebo.[32,33] Uno studio randomizzato controllato di fase 3 ha valutato gli effetti dell'assunzione orale di NAM a 1g/die per 12 mesi in pazienti ad alto rischio di TCnM. I risultati dello studio hanno riportato una riduzione pari al 23% del tasso di insorgenza di nuovi TCnM nei pazienti che avevano assunto NAM rispetto al placebo, tuttavia tale beneficio veniva vanificato nei 6 mesi di follow-up dopo l'interruzione della nicotinamide.[34] Quindi, le evidenze cliniche disponibili in lettera-

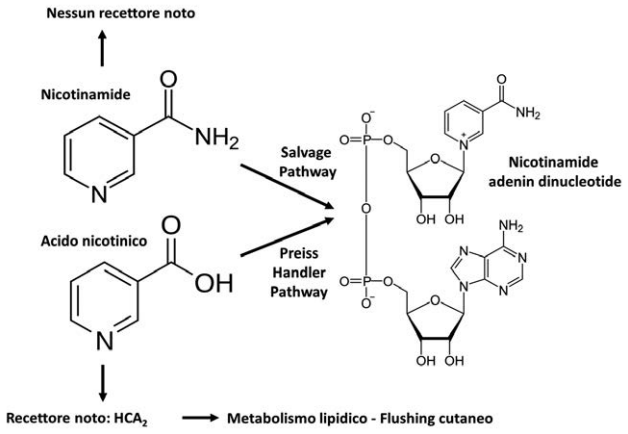

Figura 1. Differenza tra Nicotinamide e Acido Nicotinico. La nicotinamide è l'ammide dell'acido nicotinico ed è considerata la forma attiva della Vit B3 in quanto è la forma trasportata in tutte le cellule del corpo prima di essere convertita in NAD+. La nicotinamide, come l'acido nicotinico, agisce da precursori del NAD+ e del NADP, tuttavia le vie metaboliche di tale conversione sono diverse nelle due molecole. La nicotinamide è «riciclata» in NAD+ attraverso il salvage pathway guidato dall'enzima nicotinamide fosforibosil transferasi (NAMPT), mentre l'acido nicotinico è convertito in NAD attraverso la via metabolica di Preiss-Handler. L'acido nicotinico, a differenza della nicotinamide, interagisce con un recettore specifico (HCA2) implicato nella regolazione del metabolismo lipidico e nell'induzione del flushing cutaneo.

Tabella I. Vitamina D.

Uso	Dose	Risultati	Effetti collaterali	Livello di evidenza*
Prevenzione TCnM	Altamente variabile	Dati insufficienti per considerazioni conclusive	NR	IB

TCnM, tumori cutanei non melanocitari; NR, non riportato. *I livelli di evidenza si basano sulle linee guida del Journal of the American Academy of Dermatology: livello IA indica che le evidenze derivano da meta-analisi di studi randomizzati controllati; livello IB indica che le evidenze derivano da almeno uno studio controllato randomizzato; livello IIA indica che le evidenze derivano da almeno uno studio non randomizzato; livello IIB indica che le evidenze derivano da almeno un altro tipo di studio sperimentale; i dati di livello III comprendono evidenze provenienti da studi descrittivi non sperimentali, come studi comparativi, studi di correlazione e studi caso/controllo; livello IV indica che le evidenze derivano da relazioni o pareri di esperti, o esperienza clinica di autorità rispettate, o entrambe.

tura, hanno portato ad includere il trattamento con nicotinamide orale nelle linee guida nazionali e internazionali per la prevenzione dei TCnM. A partire dal 2018 inoltre la nicotinamide è entrata nella lista 648/96 per il trattamento preventivo di pazienti ad alto rischio di TCnM, ossia pazienti sottoposti a pregressa asportazione chirurgica di almeno due TCnM.[35-40]

La tossicità della nicotinamide è stata segnalata a dosi superiori a 3,5 g/die.[41] In Europa il limite superiore raccomandato di nicotinamide è di 900 mg/die, mentre per la niacina è di 54 mg/die.[42] I risultati qui descritti sono riassunti nella Tabella 2.

Polypodium

Il polypodium leucotomos (PLE), è una felce tropicale originaria dell'America Centrale. E' stato impiegato per la prima volta in Honduras come agente terapeutico per la psoriasi.[43] Il PLE è stato studiato *in vitro* per i suoi effetti antiossidanti e fotoprotettivi diretti.[44-47] Studi sull'estratto del PLE somministrato prima dell'irradiazione UV in individui sani hanno mostrato una significativa riduzione dell'eritema indotto dai raggi UV rispetto al gruppo di controllo.[48,49] Il più rilevante studio randomizzato controllato disponibile in letteratura ha valutato la sicurezza e l'efficacia del PLE in 20 partecipanti rispetto al placebo per 60 giorni. Gli individui pretrattati con PLE hanno mostrato un aumento della MED (minima dose eritematosa), una diminuzione dell'intensità dell'eritema indotta dai raggi UV e una diminuzione del rischio di ustioni solari al termine del trattamento rispetto al placebo.[50]

Ulteriori studi hanno valutato il ruolo del PLE in specifiche dermatosi e/o patologie cutanee. Due studi hanno mostrato un miglioramento soggettivo di fotodermatosi idiopatiche dopo due settimane di trattamento con PLE,[51,52] mentre l'uso di PLE nel melasma ha mostrato risultati contrastanti.[53,54] Entrambi gli studi non hanno mostrato differenze significative nell'indice di melanina (*i.e.,* differenza tra la cute normale pigmentata e quella adiacente valutata mediante la spettrofotometria di riflettanza a banda stretta) tra pazienti trattati con PLE vs placebo. Tuttavia, "l'indice di melanina" è stato maggiore nei soggetti trattati con PLE rispetto al placebo.[54] Un ulteriore studio controllato ha valutato l'assunzione di PLE nei pazienti affetti da CA sottoposti a terapia fotodinamica (PDT). A partire da una settimana dopo il trattamento, il PLE orale ha migliorato significativamente il tasso di clearance delle CA del cuoio capelluto rispetto alla sola PDT.[55] Sebbene i possibili meccanismi antiossidanti e fotoprotettivi del PLE non siano ancora stati pienamente chiariti, questi studi preliminari indicano che il PLE può rivelarsi un utile complemento ai trattamenti di specifiche fotodermatosi, del melasma e nei danni attinici. La Tabella 3 riassume i risultati degli studi e i livelli di evidenza relativi al PLE.

Retinolo e Retinoidi

Il retinolo è un composto della famiglia della vitamina A e regola una serie di attività biologiche tra le quali la proliferazione e il differenziamento cellulare. Ha anche un effetto sulla sorveglianza immunitaria, sostenendo sia le difese innate, quale l'integrità della cute e delle mucose, che quelle adattative cellulari, guidando il processo differenziativo linfocitario.[8]

Il retinolo orale e i retinoidi sintetici (*i.e.*, acitretina, isotretinoina, etretinato) sono stati valutati in studi prospettici in pazienti ad alto rischio di CA multiple o SCC, includendo anche i pazienti trapiantati d'organo,[56-61] pazienti affetti da xeroderma pigmentoso,[62] o affetti da psoriasi trattati con PUVA terapia (psoralen plus UV-A). I risultati di questi studi indicano che l'assunzione di retinolo e/o di retinoidi orali sia in grado di ridurre significativamente l'incidenza di nuovi SCC rispetto al placebo o rispetto ai normali tassi di incidenza durante i periodi in assenza di trattamento in pazienti ad alto rischio di lesioni neoplastiche multiple.[57-63] Al di

Tabella 2. Nicotinamide.

Uso	Dose	Risultati	Effetti collaterali	Livello di evidenza*
Fotoprotezione	500 mg/die-1,5 g/die	Riduzione dell'immunosoppressione indotta dall'esposizione solare, senza modifica della MED	NR	IB
Prevenzione delle CA	500 mg/die -1 g/die	Riduzione del numero di CA durante il trattamento	Nausea in un paziente che assumeva aspirina	IB
Prevenzione di TCnM e CA	1 g/die	Riduzione della frequenza di TCnM, incluse le CA. L'effetto è perso dopo sospensione della terapia	NR	IB

TCnM, tumori cutanei non melanocitari, CA, Cheratosi attinica; NR, non riportato. *I livelli di evidenza si basano sulle linee guida del Journal of the American Academy of Dermatology: livello IA indica che le evidenze derivano da meta-analisi di studi randomizzati controllati; livello IB indica che le evidenze derivano da almeno uno studio controllato randomizzato; livello IIA indica che le evidenze derivano da almeno uno studio non randomizzato; livello IIB indica che le evidenze derivano da almeno un altro tipo di studio sperimentale; i dati di livello III comprendono evidenze provenienti da studi descrittivi non sperimentali, come studi comparativi, studi di correlazione e studi caso/controllo; livello IV indica che le evidenze derivano da relazioni o pareri di esperti, o esperienza clinica di autorità rispettate, o entrambe.

Tabella 3. Polypodium.

Uso	Dose	Risultati	Effetti collaterali	Livello di evidenza*
Fotoprotezione	580 mg/die	Riduce la frequenza e l'intensità delle scottature solari	NR	IB
Fotodermatosi idiopatica	580 mg/die	Migliora i sintomi soggettivi	NR	IIB
Melasma	580 mg/die -720 mg/die	Dati contrastanti sull'efficacia nel melasma	NR	IB
Cheratosi attinica	580 mg/die -720 mg/die	Migliora l'efficacia della PDT nel trattamento delle CA del cuoio capelluto	NR	IIA

CA, cheratosi attinica; PDT: terapia fotodinamica; NR, non riportato. *I livelli di evidenza si basano sulle linee guida del Journal of the American Academy of Dermatology: livello IA indica che le evidenze derivano da meta-analisi di studi randomizzati controllati; livello IB indica che le evidenze derivano da almeno uno studio controllato randomizzato; livello IIA indica che le evidenze derivano da almeno uno studio non randomizzato; livello IIB indica che le evidenze derivano da almeno un altro tipo di studio sperimentale; i dati di livello III comprendono evidenze provenienti da studi descrittivi non sperimentali, come studi comparativi, studi di correlazione e studi caso/controllo; livello IV indica che le evidenze derivano da relazioni o pareri di esperti, o esperienza clinica di autorità rispettate, o entrambe.

fuori di questi gruppi ad alto rischio, l'efficacia della terapia del retinolo/retinoidi orali è meno chiara. Diversi studi randomizzati prospettici hanno valutato l'impatto del retinolo/retinoidi orali sullo sviluppo di CA o di BCC/SCC in pazienti non ad alto rischio. Uno studio randomizzato controllato è stato condotto in pazienti con 10 o più pregresse CA (almeno una CA nell'ultimo anno) ma non più di due precedenti SCC/BCC. I risultati hanno mostrato una riduzione del rischio dello sviluppo di ulteriori SCC ma non dei BCC nei pazienti che avevano assunto il retinolo orale rispetto al placebo.[64] Uno studio randomizzato controllato ha confrontato l'effetto dell'assunzione di retinolo orale e dell'isotretinoina rispetto al placebo, in pazienti con almeno 4 pregressi BCC e/o SCC.[65] I risultati dello studio hanno mostrato un numero simile di nuovi BCC e/o SCC nei tre bracci di trattamento e nessuna differenza significativa nel tempo di comparsa della prima nuova neoplasia. In un altro studio randomizzato controllato, pazienti immunocompetenti con almeno due pregressi BCC/SCC hanno assunto acitretina orale o placebo per due anni.[66] I risultati hanno mostrato che sebbene vi fosse un minor numero di TCnM nei pazienti in terapia con acitretina non è stata riscontrata una differenza statisticamente significativa fra i due bracci di trattamento.

Gli effetti collaterali associati ai retinoidi orali possono essere significativi. La maggior parte degli eventi avversi riportati in letteratura sono cheliti, ipersensibilità cutanea e alterazioni dei capelli.[56] Tuttavia, altri effetti collaterali meno frequenti comprendono le alterazioni epatiche e lipidiche, osteoporosi, calcificazione dei legamenti, disturbi neurologici e altri.[57,62,65,67] Allo scopo di cercare di limitare tali effetti avversi, uno studio ha valutato la somministrazione topica di treinoina 0,1% rispetto al veicolo di controllo in pazienti a rischio di sviluppare TCnM. Non c'è stata, tuttavia, alcuna differenza significativa tra i bracci di trattamento per lo sviluppo di nuovi SCC invasivi o *in situ*, BCC o CA.[68] Infine, i retinoidi vengono menzionati nelle linee guida nazionali e internazionali per la prevenzione dei TCnM in pazienti ad alto rischio di sviluppare TCnM (AIOM, 2019; NCCN, 2020).

Conclusioni

Le evidenze disponibili in letteratura scientifica relative ai fotoprotettori sistemici impiegati nella prevenzione dei tumori cutanei confermano come, allo stato attuale, l'unico farmaco che ha dimostrato la riduzione dei TCnM nelle diverse popolazioni esaminate è stata la terapia orale con nicotinamide. Tale farmaco viene riportato nelle linee guida nazionali e internazionali per la prevenzione dei TCnM e può essere prescritto con piano terapeutico mediante legge 648/96 per il trattamento preventivo in pazienti sottoposti ad asportazione di almeno due TCnM.

L'assunzione di retinolo/retinoidi orali ha dimostrato un ruolo nella prevenzione dei SCC in pazienti ad alto rischio di sviluppare TCnM (*i.e.,* trapiantati d'organo, pazienti affetti da xeroderma pigmentoso o da psoriasi trattati con PUVA terapia) ma non in altre popolazioni di studio. I retinoidi vengono riportati nelle linee guida nazionali e internazionali per la prevenzione dei TCnM in pazienti ad alto rischio di sviluppare TCnM ma gli effetti collaterali possono essere significativi.

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pagepress

PORT-WINE STAINS

Malformazioni capillari: L'importanza di una accurata caratterizzazione per pianificarne il trattamento

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Le malformazioni capillari, più comunemente definite Port-Wine Stains (PWS), sono classificate tra le malformazioni vascolari congenite a basso flusso. Generalmente insorgono in maniera sporadica, non hanno una predilezione di sesso e mostrano una prevalenza dello 0,3% nella popolazione generale. Si manifestano come macule eritematose omogenee, già presenti alla nascita, costituite istologicamente da capillari del plesso papillare e subpapillare dilatati ed aumentati in numero. Circa il 50% dei PWS si localizza al volto, lungo la distribuzione delle branche del nervo trigemino (V1, V2 e V3) od in sede centrofacciale, coinvolgendo cute e talvolta anche le mucose. La maggior parte dei PWS è costituita da malformazioni isolate unilaterali, raramente mediane o bilaterali, ma talvolta possono associarsi quadri sindromici, di gestione multidisciplinare, come la sindrome di Sturge-Weber in cui vi è associazione di malformazioni capillari della branca oftalmica del trigemino e malformazioni capillaro-venose leptomeningee e coroidali omolaterali, oppure la sindrome di Klippel-Trenaunay-Weber dove PWS localizzati ad un arto si associano a fistole-arterovenose che determinano ipertrofia e gigantismo dell'arto stesso.

A differenza degli emangiomi o di altre malformazioni vascolari, i PWS persistono per tutta la vita e nel tempo si ipertrofizzano manifestandosi con lesioni più scure, fino ad un colore violaceo, spesso complicate da aree nodulari, talvolta associate ad un "overgrowth" dei tessuti sottostanti.

Sebbene in passato siano state proposte numerose tecnologie laser e metodi fisici per il trattamento dei PWS, la laserterapia selettiva mediante FLPP (FlashLamp-Pumped Pulsed) Dye laser ne rappresenta oggi il gold standard. Idealmente, il trattamento dei PWS sarebbe da intraprendere precocemente, quando le lesioni sono ancora piane e prive di aree ispessite e ipertrofiche. Tuttavia, spesso il paziente non giunge in centri specializzati in laserterapia nelle fasi più precoci della vita ed accede al trattamento in età adulta, quando le lesioni sono complicate, oppure dopo numerosi trattamenti inefficaci. Inoltre, sebbene vengano utilizzate tecnologie adeguate, spesso i PWS risultano poco responsivi o recidivanti dopo le terapie.

Svariati fattori sono correlati di uno scarso risultato terapeutico, in particolare età avanzata, alcune localizzazioni del volto, ipertensione arteriosa e presenza di lesioni ipertrofiche. Inoltre, alcuni fattori emodinamici, che si esprimono da un punto di vista clinico con un pattern capillaroscopico/dermoscopico predominante, possono predire la risposta alla terapia.

Si distinguono pertanto PWS di Tipo I, caratterizzati da dilatazioni capillari balloniformi, considerato espressione di una malformazione più superficiale con coinvolgimento dei vasi papillari, e PWS di tipo II, che alla dermoscopia mostrano angectasie ad anello ed archi, senza dilatazioni balloniformi, e riflettono lesioni di pertinenza del plesso orizzontale subpapillare, più profonde e difficili da trattare. Recentemente abbiamo descritto un terzo pattern dermoscopico, il tipo III, caratterizzato da strutture balloniformi e glomerulari direttamente connesse ad archi ed anelli dilatati, definito come 'simil-aneurismatico', dovuto ad un progressivo sfiancamento del plesso orizzontale, correlato ad angiomi di vecchia data e all'ipertensione ed associato ad una peggior risposta al trattamento.

Sebbene siano noti i fattori associati ad una scarsa risposta terapeutica, i precedenti lavori presenti in letteratura non analizzano da un punto di vista emodinamico morfologico e microscopico i PWS refrattari alla laserterapia; per questo motivo, abbiamo deciso di caratterizzare più precisamente i PWS non responsivi alle terapie, documentandoli dermoscopicamente e mediante microscopia laser confocale. Infatti questa metodica rappresenta una tecnologia in grado di fornire informazioni in vivo e ad alta risoluzione, dinamiche sulle strutture vascolari, flusso e velocità. Lo studio è stato condotto presso l'Istituto di Chirurgia e Laserchirurgia in Dermatologia (I.C.L.I.D.) di Milano. Sono stati inclusi consecutivamente 65 pazienti portatori di PWS refrattari alle precedenti terapie. I pazienti giungevano alla nostra osservazione dopo trattamenti eseguiti presso altri centri, con scarso o nessun risultato oppure con recidiva delle lesioni. Le lesioni erano localizzate prevalentemente al volto (V1 4,7%, V1-V2 4,7%, V2 44.6%, V2-V3 13,8%, V3 9,2%, V3-collo 12,3%, tronco 1,5%, arti superiori 6,1%, arti inferiori 3,1%). L'età media al primo trattamento era di 24 anni (range 1-69 anni). Tutti i pazienti presentavano lesioni piane (non ipertrofiche), classificate alla capillaroscopia eseguita prima del trattamento iniziale come segue: Tipo I 3%, Tipo II 95,5%, Tipo III 1,5%. Le lesioni erano state trattate con le seguenti metodiche: FLPP dye laser (lunghezza d'onda 595 nm), Nd:YAG KTP laser (lunghezza d'onda 532 nm), argon laser (lunghezza d'onda 458-514 nm) e crioterapia, con un numero medio di trattamenti eseguiti di 9 (range 3-40 sedute) per una durata media di 2 anni (range 1-2%). Per quanto riguarda l'outcome clinico, il 20% dei pazienti riportava nessuna o minima risposta, il 36,9% scarso miglioramento, il 26,1% buona risposta ed il 17% eccellente; il tempo medio di ricorrenza dopo l'ultimo tratta-

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mento (nel caso delle lesioni con buona ed eccellente risposta) era di 6 anni.

Alla nostra valutazione i pazienti non presentavano aree ipertrofiche; alla capillaroscopia si evidenziava un pattern di Tipo II nel 18,4% dei casi e un Tipo III nell'81,6%. È stata evidenziata una relazione statisticamente significativa tra il pattern di Tipo II ed una risposta migliore ai precedenti trattamenti (p=0,001) ed un pattern capillaroscopico inziale inferiore (Tipo I o Tipo II, p=0,01), mentre il Tipo III era associato ad un pattern iniziale più elevato (Tipo II o Tipo III) e ad un tempo maggiore di recidiva (p=0.03). Non si è evidenziata correlazione tra l'evoluzione capillaroscopica e la sede dei PWS.

All'indagine in microscopia confocale, i PWS con pattern capillaroscopico di Tipo III hanno mostrato vasi più profondi ($p < 0.001$) e con un maggior diametro (p=0.042) rispetto al Tipo II. Mediante la valutazione dinamica in vivo con microscopia confocale, sono state individuate tre categorie: il Gruppo A, riscontrato nei PWS con pattern di Tipo II, caratterizzato da vasi lineari, con

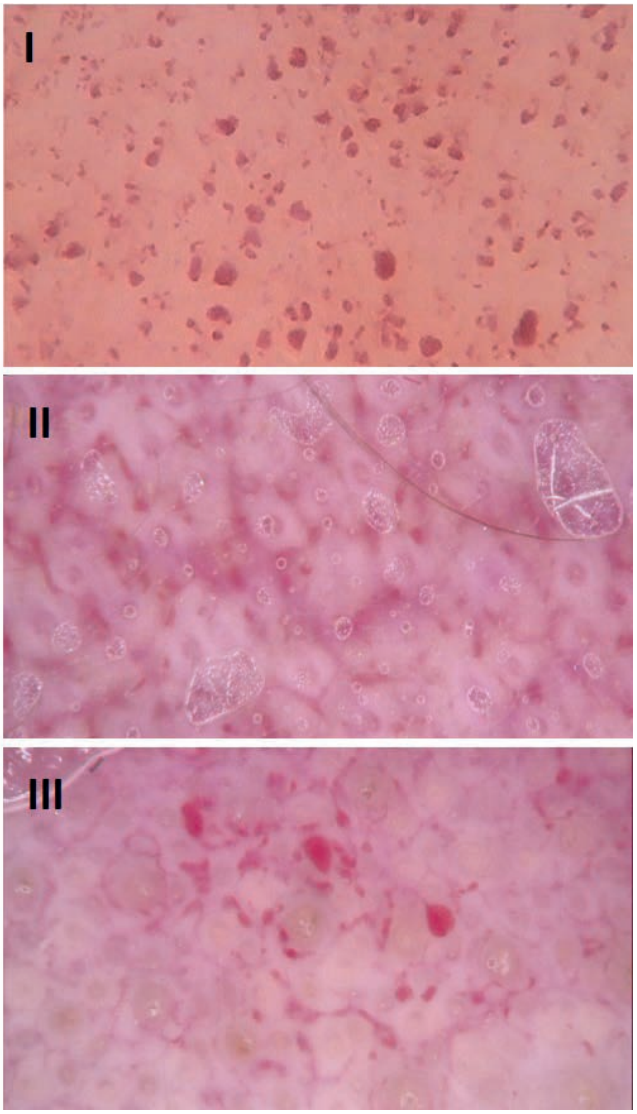

Figura 1. Pattern dermoscopici.

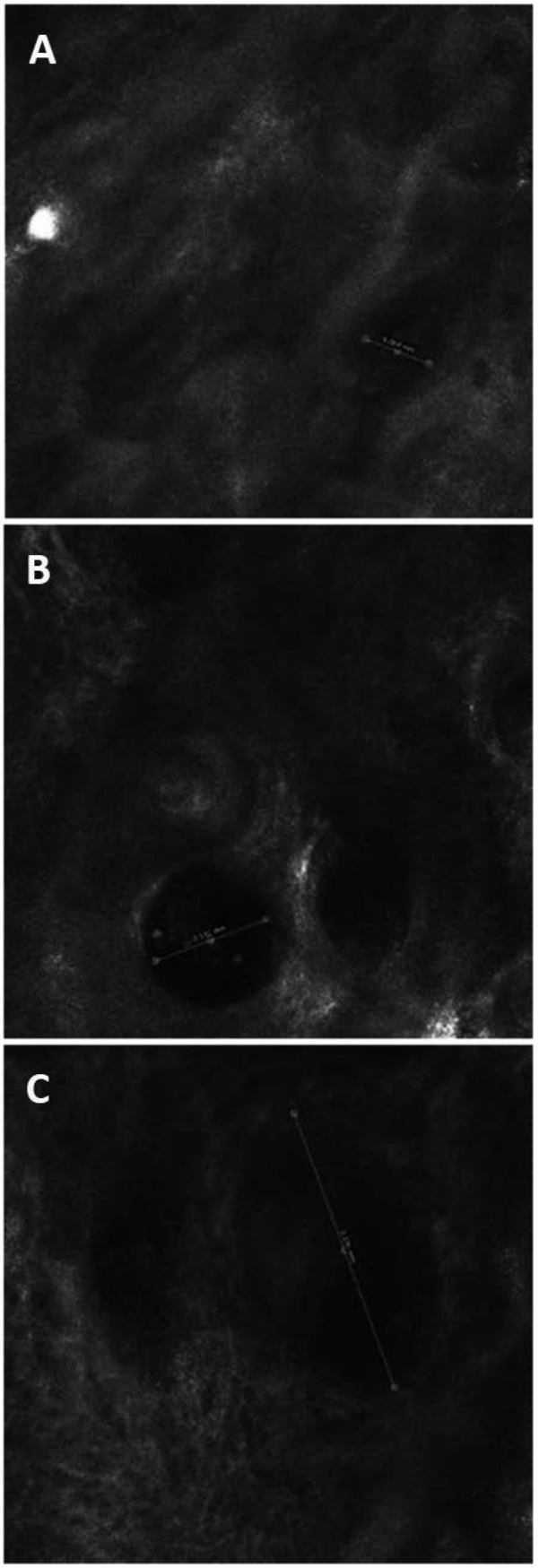

Figura 2. Gruppi alla microscopia confocale.

diametro contenuto e flusso più elevato rispetto agli altri sottotipi, corrispondente alle immagini dermoscopiche ad arco ed anello; il Gruppo B, anche questo riscontrato nel Tipo II, caratterizzato da vasi dilatati con flusso turbolento, che corrisponde alle ectasie del plesso subpapillare; il Gruppo C, riscontrato nel Tipo III capillaroscopico, formato da grandi dilatazioni aneurismatiche connesse a vasi di calibro inferiore rispetto al Gruppo A e B.

La metodica maggiormente utilizzata per il trattamento dei PWS è la fotocoagulazione dei vasi dilatati mediante fototermolisi selettiva. Clinicamente, la coagulazione completa dei vasi determina una buona risposta delle lesioni. Al contrario, i PWS non responsivi o recidivanti dopo terapia sono caratterizzati da una rivascolarizzazione o da incompleta coagulazione. Nel nostro studio, la maggior parte dei pazienti presentava alla valutazione precedente ai trattamenti un pattern capillaroscopico di Tipo II, confermando che queste lesioni sono più difficili da trattare, a causa della maggiore profondità dei vasi, mentre quelle con un pattern di Tipo I difficilmente ricorrono. Alla valutazione dopo recidiva, invece, la maggior parte dei pazienti presentava un Tipo III. Questo dato suggerisce il fatto che i PWS di Tipo II che rispondono scarsamente alle terapie o recidivano, evolvono in un pattern capillaroscopico di Tipo III. Inoltre, abbiamo individuato due distinte tipologie di PWS recidivanti. La prima è caratterizzata da lesioni che almeno in parte rispondono ai trattamenti ma con un minor tempo alla recidiva, caratterizzate da vasi più piccoli e superficiali, con flusso rapido. Si può ipotizzare che queste lesioni vadano incontro a fotocoagulazione completa durante i trattamenti, determinando il parziale miglioramento clinico. Dopo un certo lasso di tempo, verosimilmente si verificano rimodellamento dermico e neoangiogenesi, causando la recidiva clinica, con lo stesso pattern vascolare (Tipo II); morfologicamente si evidenziano due Gruppi confocali in queste lesioni con vasi lineari ad alto flusso e con vasi dilatati a flusso più lento (rispettivamente A e B).

La seconda tipologia invece è caratterizzata da scarsa o nessuna risposta ai trattamenti; queste lesioni rimangono stabili e poi peggiorano dopo un periodo di tempo più lungo. Alla valutazione capillaroscopica si evidenzia un pattern più elevato (prevalentemente di Tipo III), come precedentemente descritto nelle lesioni complicate, a cui corrisponde un Gruppo confocale C (profonde dilatazioni aneurismatiche a flusso turbolento connesse a vasi lineari più piccoli). Pertanto, si può ipotizzare che queste lesioni, formate da vasi più profondi e grandi, vadano incontro a coagulazione parziale durante le terapie; la chiusura incompleta del lume vascolare nel tempo determina un rimodellamento della parete vasale, che si ispessisce e induce una dilatazione aneurismatica a monte. Questi eventi probabilmente sono secondari a trattamenti inefficaci, eseguiti con energie o tecnologie non adeguate al trattamento di questa variante. Pertanto, gli aspetti morfologici descritti possono essere presi in considerazione nella progettazione del trattamento e nella scelta di durate di impulso laser più lunghe o lunghezze d'onda più penetranti per queste varianti.

Commento dell'articolo

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MEDICINA RIGENERATIVA

Medicina rigenerativa e chirurgia per la riparazione tissutale: Trattamento combinato con innesto cutaneo e cellule mononucleate da sangue periferico in plasma ricco di piastrine

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Esistono vari approcci per la riparazione tissutale quando il Dermatologo si trova ad affrontare una perdita di sostanza. Quando poi i trattamenti convenzionali di prima linea non hanno prodotto risultati, si può ricorrere a tecniche combinate associando la chirurgia tradizionale alla medicina rigenerativa. Abbiamo presentato le nostre osservazioni preliminari di un approccio combinato per ulcere cutanee resistenti di lichen erosivo plantare ed in un caso di lesioni di Malattia di Darier, in cui è stato confezionato un innesto cutaneo associato all'iniezione in sede di innesto di una miscela di cellule staminali ovvero cellule mononucleate da sangue periferico (PBMNCs) e di plasma ricco di piastrine (PRP).[1]

Tecnicamente, le PBMNCs sono state isolate dal sangue periferico intero dei pazienti utilizzando il sistema di filtrazione a gravità Pall Celeris TM (Figura 1a). Il PRP veniva prodotto mediante un sistema di centrifugazione. Poi si procedeva a miscelare la soluzione con PBMNCs e PRP autologo in un rapporto 2:1 (Figura 1b) al fine di stimolare l'attività proliferativa cellulare attraverso i fattori di crescita rilasciati dai granuli alfa piastrinici. Tale prodotto veniva infiltrato ripetutamente con la tecnica del micropomfo (0,1 ml) lungo i margini e all'interno del letto della ferita (Figura 1c).

Con questo protocollo è stata trattata una donna di 81 anni, che presentava da circa 2 anni erosioni recidivanti di grandi dimensioni, dolorose, essudanti, localizzate alla regione plantare sinistra e due piccole aree ulcerate in sede plantare destra, con esiti cicatriziali sinechianti alle dita dei piedi e spazi interdigitali (Figura 2). Nei precedenti 13 anni si erano sviluppati altri episodi ricorrenti di ulcerazioni dolorose plantari, diagnosticate istologicamente come lichen planus erosivo, trattate senza risultati soddisfacenti con prodotti topici e sistemici (compresi steroidi sistemici e topici in occlusione e ossigenoterapia iperbarica). Pertanto abbiamo proposto un autoinnesto cutaneo a rete 2x associato ad infiltrazioni intralesionali di PBMNCs in un substrato di PRP autologo (Figura 1c).

È stato quindi osservato un rapido miglioramento clinico con una guarigione completa entro 1 mese (Figura 3a,b). Nel postoperatorio è stato somministrato un breve ciclo di leggera analgesia, registrando il rapido effetto del PRP anche nella riduzione del dolore.[2,3] Ad un follow up di 4 anni, le aree trattate si mantenevano libere da recidive di malattia.

Abbiamo descritto inoltre il caso di una donna di 63 anni affetta da malattia di Darier confermata istologicamente, che si è presentata al nostro centro con multiple papule ipercheratosiche di colore rosso-giallastro, isolate o confluenti a formare placche verrucose, parzialmente disepitelizzate ed essudanti o coperte da spesse croste, dolenti e pruriginose, che coinvolgevano gli arti inferiori, il tronco, la regione genitale e i glutei (Figura 4a). La paziente aveva già assunto retinoidi per via sistemica per 35 anni e a seguire trattamenti con laser CO2, ossigenoterapia iperbarica e steroidi sistemici, oltre a topici, con scarsi risultati. Pertanto abbiamo eseguito un'ampia escissione delle aree patologiche delle cosce e copertura con un auto-innesto cutaneo retinato 2x a spessore parziale, associato ad infiltrazioni di PBMNCs in PRP autologo (Figura 4b).

Circa 3 settimane più tardi le aree trattate apparivano riepitelizzate senza alcuna complicanza (Figura 4c). Ad un anno di follow-up, gli innesti si presentavano ancora liberi da malattia.

Nei decenni successivi all'isolamento delle cellule staminali, sono state ritrovate diverse popolazioni di cellule progenitrici multipotenti nella frazione di PBMCs, che possiedono il potenziale per differenziarsi in cellule ematiche, endoteliali, epatociti, cardiomiociti, cellule muscolari lisce, osteoblasti, osteoclasti, cellule neurali, miofibroblasti, cellule epiteliali, suggerendo quindi che le PBMCs possono avere il potenziale per differenziarsi in una moltitudine di tipi cellulari funzionalmente maturi in microambienti specifici.[4] Le PBMNCs, in particolare la linea dei monociti, possono essere coinvolte nella riepitelizzazione, granulazione e neoagiogenesi attraverso la produzione di diverse citochine,[5] il differenziamento cellulare verso un profilo epiteliale,[6] e attraverso i cambiamenti dinamici dei macrofagi durante i vari momenti nel processo di guarigione delle ferite.[7] E' stato osservato che in un modello di ferita cutanea cronica a tutto spessore in topi diabetici le CD34+ PBMCs hanno accelerato la neovascolarizzazione (sia in termini di aumento dimensionale sia in termini del numero dei vasi) e la guarigione epidermica.[8]

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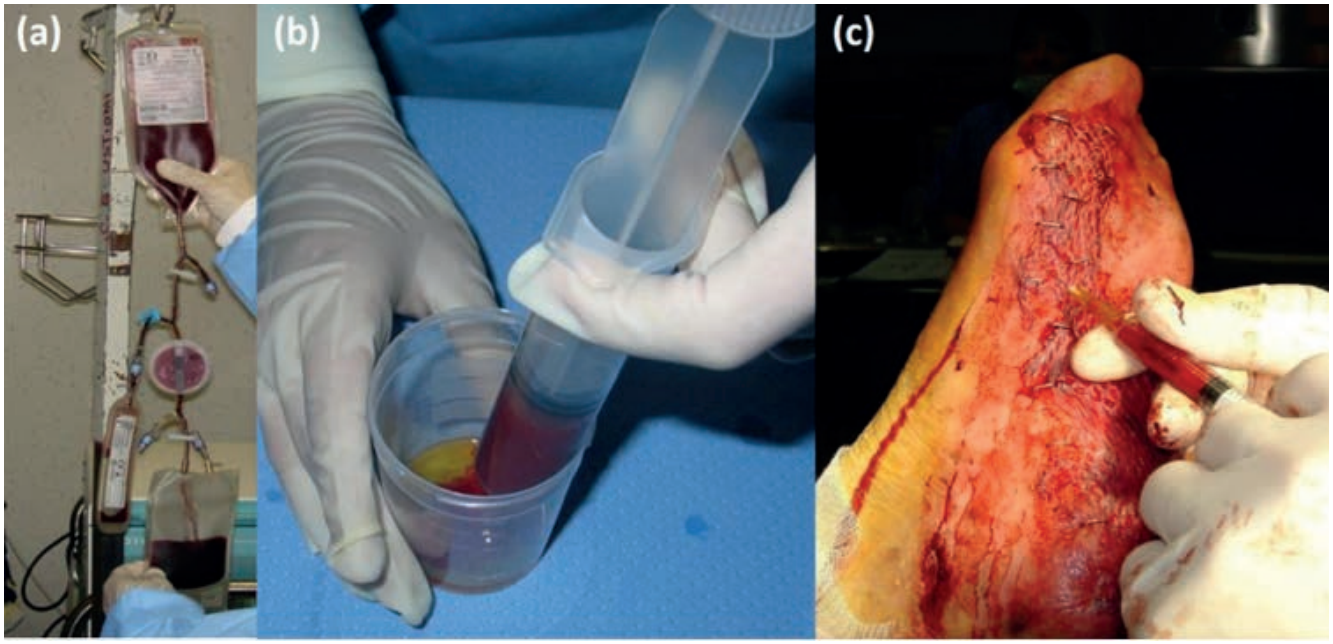

Figura 1. a) Raccolta delle cellule (PB-MNCs) con sistema a filtrazione selettiva; b) rapporto di miscelazione 1 (PRP): 2 (PBMNCs); c) autoinnesto cutaneo a rete con infiltrazione intralesionale di BPMNCs in PRP.

I fattori di crescita piastrinici ed i mediatori antinfiammatori nel PRP sono peptidi biologicamente attivi che intervengono in vari momenti della riparazione tissutale e cooperano nel reclutamento di cellule staminali, proliferazione e differenziazione cellulare.[9-11] Sono state descritte varie applicazioni cliniche del PRP autologo, per ferite croniche e acute, nella chirurgia implantare dentale, oculare, cardiaca, ortopedica, per lesioni muscolari e tendinee, per la rigenerazione ossea,[11,12] oltre alle notevoli applicazioni in dermatologia e medicina estetica in particolare nei settori delle alopecie per la ricrescita dei capelli, del ringiovanimento cutaneo, del trattamento delle cicatrici acneiche, delle strie distensae e dell'aumento del derma.[13]

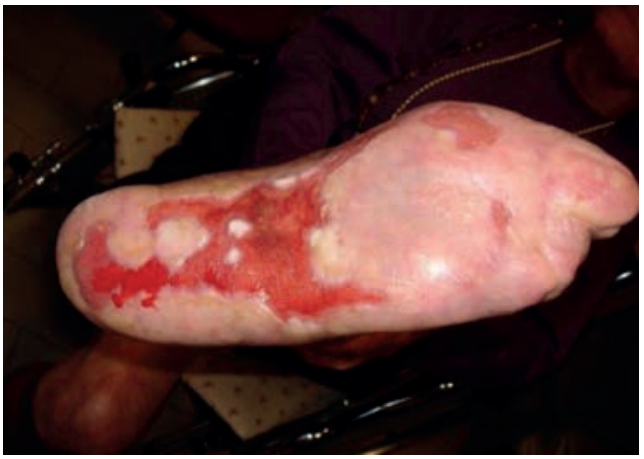

Figura 2. Paziente affetta da lichen erosivo plantare: alla prima osservazione si apprezzavano erosioni ampie, essudanti della regione plantare, con cicatrici sinechianti delle dita dei piedi e degli spazi interdigitali.

Il PRP è stato combinato anche con terapie cellulari come cellule staminali derivate da tessuto adiposo.[9] La co-cultura di PBMNCs con gel piastrinico suggerisce la capacità di influenzare l'intero processo di rigenerazione dei tessuti.[14,15]

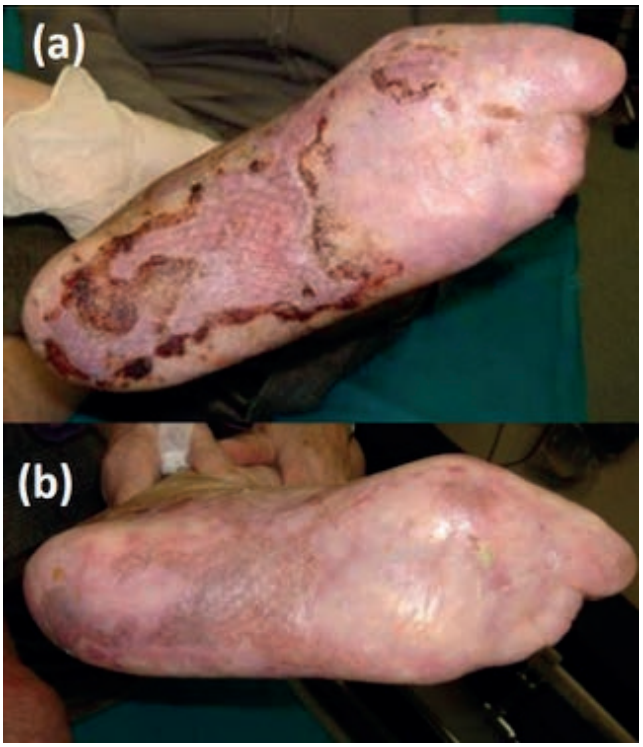

Figura 3. a) Guarigione completa ad un follow-up di un mese e (b) di circa due mesi, senza alcun segno di infezione o ricaduta.

Sulla base di queste esperienze, è stato ideato il nostro protocollo terapeutico. Inoltre, dopo aver realizzato un innesto cutaneo autologo, anche nella nostra pratica clinica, le complicanze postoperatorie principali sono rappresentate da infezioni o necrosi dell'innesto.[16] Pertanto, nell'approccio a situazioni difficili come un lichen erosivo plantare e una malattia di Darier refrattaria alle terapie, abbiamo proposto di associare alla chirurgia gli effetti positivi del PRP e delle cellule nucleate, per correre un minor rischio di infezione del sito chirurgico, avere una ridotta essudazione e sanguinamenti postoperatori, un adeguato controllo del dolore, un aumento della velocità e delle possibilità di completa guarigione della ferita, con un migliore trofismo cutaneo e degli esiti cicatriziali.[12,17]

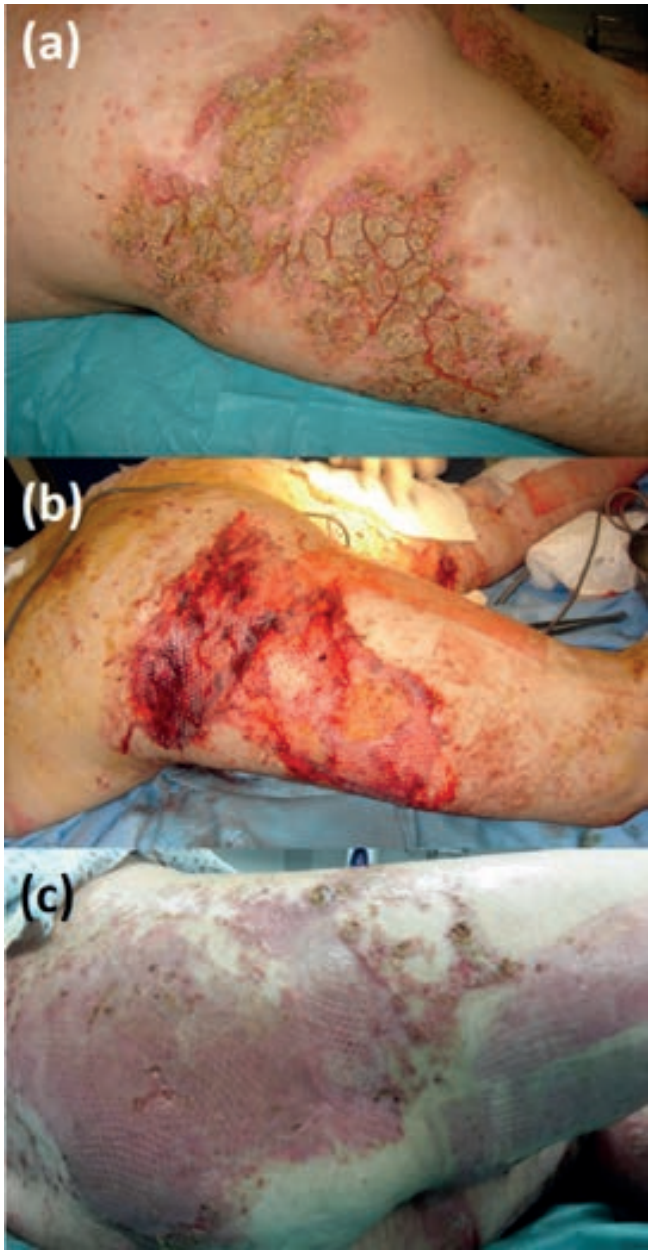

Figura 4. a) Paziente affetta da malattia di Darier: papule ipercheratosiche giallo-rossastre, confluenti a formare placche verrucose, parzialmente disepitelizzate ed essudanti ed in parte coperte da spesse croste. b) Autoinnesto cutaneo a rete con iniezione di BPMNCs in PRP durante la copertura del sito chirurgico.c) Ad un follow-up di 3 settimane, le aree trattate risultavano riepitelizzate, senza recidiva di malattia, anche se le lesioni erano ancora presente in altre parti del corpo.

Riteniamo che la nostra strategia combinata offra un approccio biotecnologico perioperatorio innovativo. Rappresenta infatti una strategia avanzata di terapia biologica di derivazione ematica, i cui componenti sono interamente autologhi e prodotti da un protocollo indipendente dall'operatore. Questa opzione di trattamento si colloca nel vasto scenario della medicina rigenerativa per la stimolazione della guarigione delle ferite e potrebbe essere considerata in condizioni patologiche particolarmente complesse, infatti abbiamo applicato questa procedura non solo in un'ulcera cutanea refrattaria ma anche per il trattamento chirurgico di una dermatosi estesa come il caso di malattia di Darier presentato. Poiché si prevede che questa procedura possa rafforzare l'innesto cutaneo con gli effetti positivi di PRP e PBMNCs,[12,17-19] si potrebbe valutare questa tecnica in casi selezionati in cui viene identificato un rischio consistente di fallimento del solo trattamento chirurgico, a causa della malattia primitiva, della sede e delle dimensioni del sito operatorio, considerando anche il dolore ed eventuali complicanze postoperatorie.

Si auspica comunque che verranno condotte ulteriori esperienze con questa procedura, al fine di validarne gli effettivi benefici.

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SIDCO

Società Italiana di Dermatologia Chirurgica, Oncologica, Correttiva ed Estetica

XXXIV Congresso Nazionale
Viareggio, 1-3 Ottobre 2021

Centro Congressi "Il Principino"

"Verso un nuovo mondo"

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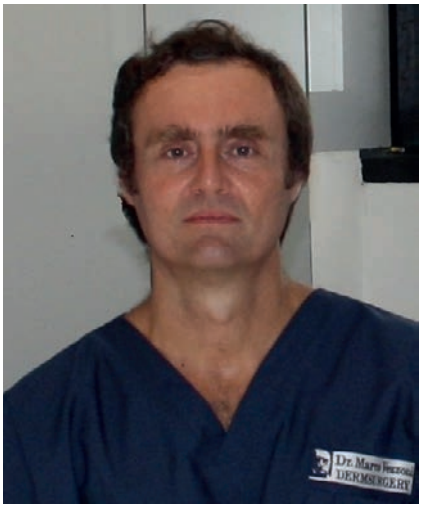
CONGRESSO SIDCO

Saluto del Presidente del XXXIV Congresso Sidco, Gian Marco Vezzoni

Gian Marco Vezzoni

È con grandissimo piacere che presento il XXXIV Congresso Nazionale SIDCO di Viareggio su **Dermatology Reports**, fresca rivista ufficiale anche della nostra Società Scientifica.
Quando nel 2017 ricevetti con entusiasmo l'incarico di organizzare il Congresso Nazionale, mai avrei immaginato in quali virulenti pelaghi tempestosi avremmo dovuto navigare noi del comitato, Marco Dal Canton, Cristina Ricci ed io.
Nell'aprile 2020, finalmente, l'idea del nuovo format congressuale che avevamo concepito avrebbe avuto realizzazione e la Società sarebbe tornata a riunirsi in casa propria dopo due anni congressuali particolari. Avevamo fatto i conti senza il Corona!
Il prossimo ottobre il nostro Congresso tornerà dunque ad essere quel momento di ritrovo tra amici e di crescita della Società che è sempre stato. La voglia di incontrarsi e di tornare a vivere un vero congresso è veramente forte!
Il programma scientifico, con le sue novità, nasce dall'ambizione di realizzare un "Congresso dei desideri", quello a cui avremmo voluto partecipare ma che non abbiamo mai avuto occasione di seguire.
Ci auguriamo che possa incontrare anche i desideri, la curiosità e la voglia di partecipare di tutti i dermatologi operativi e di coloro che lo vogliono diventare.
Il concetto informatore del programma è che l'aggiornamento scientifico e lo scambio di esperienze, "core" del momento congressuale, avvenga attraverso il contatto più stretto possibile tra relatore e partecipante.
Per raggiungere questo obiettivo, abbiamo affiancato ad una sessione in sala plenaria di letture magistrali e di Live Surgery interattiva, un format tutto nuovo.
Assoluta novità saranno gli otto FOCUS MEETINGS in contemporanea: incontri di un ora in cui l'esperto presenta e confronta con piccoli gruppi di colleghi il proprio lavoro, su focus di dermochirurgia e di dermochirurgia estetica.
Abbiamo voluto i CORSI come parte integrante del programma, a cui sarà possibile partecipare liberamente, compresi i quattro Corsi pratici di dermochirurgia che si svolgeranno "Hands on" su modelli di teste artificiali e su Pad anatomici. I Corsi, con la struttura di un vero corso didattico, si svolgeranno durante tutti i tre giorni congressuali e comprenderanno varie aree tematiche.
Partendo poi dalla constatazione che spesso le comunicazioni libere sono estremamente interessanti ma non hanno lo spazio e la discussione che meriterebbero, le abbiamo trasformate in LETTURE LIBERE INTERATTIVE: 15 minuti di presentazione e discussione di casi ed esperienze tecniche.
Un vero "must" è la SALA OPERATORIA DEL FUTURO, dove potremo fare esperienza pratica di hardware e software chirurgico "Hands Free" e di realtà aumentata.
Ultima ma non ultima, la novità del contributo scientifico aziendale: le Aziende proporranno contenuti scientifici di alto livello in Workshop, Focus, Letture e Live chirurgici, che, sebbene non ECM, costituiranno un aggiornamento professionale di valore. Abbiamo dedicato ad esse tre ore, con sospensione del programma ECM.
I curiosi potranno vedere sul sito web e su Fb le anteprime video del programma congressuale e delle proposte di attività sociali a Viareggio e in Versilia.
Vi invito con gioia a Viareggio, dove, oltre a vivere una nuova esperienza scientifica, potremo partecipare al Carnevale, famoso nel mondo per i suoi enormi carri allegorici, che quest' anno si svolge eccezionalmente in notturna all' inizio di ottobre.



A presto!

Gian Marco Vezzoni

pagepress

DERMATOLOGIA E ARTE

Cura delle verruche: Tra riti e magia

Massimo Papi

Responsabile Nazionale ADOI Gruppo di studio Ulcere cutanee e dermatologia vascolare

Le verruche sono una patologia molto diffusa e soggetta a trattamenti topici popolari. Nella tradizione contadina italiana si usavano soprattutto il latte di fico e l'aglio sottoforma d'impiastro locale ma, a seconda delle zone, numerosi altri rimedi venivano in passato consigliati prima di essere visitati dal medico di famiglia o da un dermatologo.

A causa della tendenza alle recidive ed al rischio di contagiosità sottoponiamo le verruche a terapie fisiche, a volte dolorose. Spesso, tuttavia, soprattutto e ancora nelle zone rurali, prima del trattamento con crioterapia, elettrobisturi o laser e a numerose cure con prodotti locali commerciali spesso efficaci, preferiamo dar retta al consiglio dell'amico guaritore o provare ad eliminarle pronunciando quella *formuletta magica che recitava la nonna, magari nelle sere di luna piena* (Figura 1). Se proprio non funziona, allora andrò da un dermatologo. Non solo in Italia, ma nella maggior parte dei paesi del mondo, seppure con modalità, aspetti ed elementi culturali diversi, questo è stato per molto tempo l'approccio più seguito nelle aree meno "cittadine", riassunto in modo semplice. Il "*gold standard*" di fronte ad una verruca che non vuole andare via spontaneamente o con sistemi terapeutici molto basilari è stato per decenni il ricorso al rito e all'incantesimo.

Nel film "*La notte di San Lorenzo*", dei fratelli Taviani, ricorre una filastrocca che nelle ultime immagini una madre recita per intero alla sua bambina che dorme davanti alla finestra aperta sul cielo stellato di agosto:

Merdocchia merdocchiati San Giobbe aveva i bachi
Medicina medicina un po' di cacca di gallina
Un po' di cane un po' di gatto domattina è tutto fatto
Pioggia pioggia corri corri fammi andare via i porri

Il film citato è ambientato in Toscana dove una delle "usanze tradizionali" per curare le verruche era quella della *segnatura.* Questa modalità di cura rituale era specifica per il tipo di affezione o di disturbo, si adattava alle singole persone e prevedeva simboli diversi a seconda delle zone dove era praticata. I *segnatori* erano noti e, di solito, tramandavano le conoscenze nell'ambito della famiglia. Tra i più frequenti riti adottati per le verruche, vi era quello del taglio della mela in quattro spicchi. Si usavano per eseguire il segno della croce sulle zone malate. La mela veniva in seguito ricomposta, spesso si legava con un filo rosso e alla fine del rito la mela si nascondeva o seppelliva a distanza del luogo abitato dalla persona. Trascorso un tempo variabile nell'attesa che il frutto marcisse, le verruche sarebbero progressivamente scomparse. La segnatura era molto praticata nell'Italia centrale e in alcune zone del sud.[1]

L'atto di segnatura si arricchiva con la recitazione di alcune formule specifiche, a cui si univa una gestualità simbolica che rimandava alla tradizione cristiana, seppur con importanti correlazioni con un passato di matrice pagana.[2]

La finalità molto simile e comune alla maggior parte dei riti popolari era quella di ottenere una completa adesione della persona all'incantesimo. La prima fase consisteva nel mettere in rapporto di analogia la verruca con un elemento usato (es. mela) e si concludeva con l'eliminazione dell'oggetto simbolo che veniva nascosto, fatto marcire o distrutto.[3] Un altro esempio, narrato alcuni anni fa da pazienti, descrive un rito diffuso in Abruzzo, per cui si metteva a contatto con le verruche una lumaca (nera e senza guscio) per 3 sere consecutive di luna calante. La lumaca veniva poi appesa ad un albero e si aspettava finché non fosse seccata perché scomparissero le verruche. Tutte queste "usanze" fondate su elementi magici (spesso conditi di sfumature esorcistiche) si fondavano sull'immaginario popolare che interpretava le verruche come segno della "contaminazione maligna" (Figura 2).

Nella tradizione italiana, altri elementi naturali sono stati privilegiati. Ad essi sono state attribuite proprietà sanificatrici e valori simbolici e terapeutici. In Sicilia, terra di saline, si applicava sale grosso sul volto al tramonto per 3 giorni consecutivi, per eliminare le verruche piane, tenendolo per pochi minuti e pronunciando parole rituali. Sappiamo che il sale applicato sulla cute può causare una esfoliazione anche marcata. Forse l'efficacia nei confronti delle verruche poteva essere attribuita al *peeling* indotto piuttosto che all'azione propiziatoria. Ma resta tutto da dimostrare…

L'effetto placebo e lo stimolo delle risposte immunitarie sono i meccanismi chiamati più spesso in causa per spiegare alcuni risultati sorprendenti ottenuti adottando modalità di tipo rituale o magico in pazienti che avevano eseguito (in modo corretto) terapia medica o fisica per sanare le verruche. Peraltro, l'influenza della psiche sulla capacità dell'organismo di debellare formazioni di origine virale come le verruche è ben nota nella comunità scientifica ed è stata oggetto di numerosi studi. Risultati brillanti in alcuni casi sono stati riportati in questo campo con l'ipnosi.

L'elevata tecnologia strumentale e farmacologica di cui si avvale oggi la dermatologia, sembrano stridere con le procedure magiche descritte. Esistono però testimonianze molto note dell'adesione a pratiche di cura rituali e simboliche in situazioni più complesse,[4] alle quali aderiamo nel momento in cui la medicina

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Figura 1. Vincent van Gogh Notte stellata. 1889.

Figura 2. Claudia Zuriati. Inquietudini saline 2010 resine poliplastiche e sale marino.

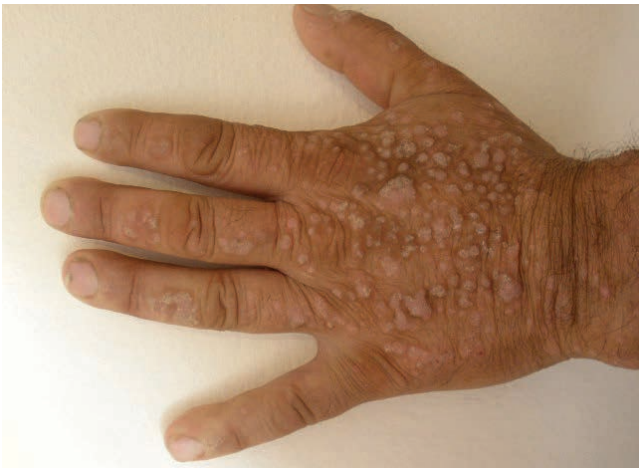

Figura 3. Verruche multiple recidivanti.

ufficiale non riesce a risolvere una malattia che ci affligge. La relazione di fiducia con il medico può essere taumaturgica ma, a volte, tutti possiamo essere tentati dal rito e dall'incantesimo, anche di fronte a verruche che non guariscono o recidivanti (Figura 3).

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DERMATOLOGIA E ARTE

La mia faccia è una carta geografica

Jackie Kay

Sono nata con una mappa dell'Australia sulla faccia;
era stupenda, mi ha detto mia madre,
nessuno al mondo era come me,
in grado di tracciare i confini del continente australe
sulle ispessite, trasposte vie dei canti della sua faccia.

Ero legata alle genti che vivono a testa in giù,
a quelli che ammirano il *bush* e i canguri.
Non potevo assolutamente ridere, piangere, aggrottare la fronte
per non far cadere dalla mia faccia la mappa straordinaria.
La mia faccia era ben stirata così che nessuno ci si perdesse.

Tenevo la testa salda e tenevo la testa alta.
Quando la gente spalancava la bocca, gli occhi, sghignazzava,
pensavo che stessero cercando di trovare Alice Springs,
di capire dove volevano andare, dove erano stati.
E quando qualcuno mi fissava a lungo, molto a lungo,

io chiedevo soltanto se c'erano stati davvero laggiù:
il più duro di cuore si scioglie quando vede un koala.
Le mie parole erano più lente di quelle degli altri bambini,
perché la mia mappa era cucita sulla bocca:
ogni volta che riuscivo a dire una frase intera

mi immaginavo una barchetta che salpava dal porto di Sidney.
Ieri si è parlato di scollarmi via quella mappa,
per cambiarmi la faccia in modo che assomigli alle altre;
mamma ha detto che dovrei pensarci bene,
che forse la mia vita sarebbe più facile …

Adesso ci penso, guardo duro nello specchio.
Seguo i duri confini del mondo sulla mia faccia.
Conosco gli sguardi duri di certe persone.
Senza la mia carta geografica, sarò la stessa persona?
Saprò dove sono, dove sono stata?

Traduzione di Damiano Abeni.

Jackie Kay è nata a Edinburgo nel 1961, da madre scozzese e padre nigeriano. Adottata da piccola dai coniugi Kay, una coppia impegnata in politica sociale, la sua poesia è sempre stata legata a temi concreti. Vincitrice di molti prestigiosi premi, è stata dal 2016 al 2021 Scots Makar, Poetessa Laureata di Scozia.
Della poesia "My Face is a Map" ha detto: "La Royal Society of Medicine mi aveva chiesto di scegliere un tema medico sul quale scrivere una poesia, e io ho scelto le cosiddette deformazioni facciali, che mi hanno sempre interessato moltissimo – in particolare quelle dei bambini. La RSM mi ha messo in contatto con lo scienziato Ian Hutchison di Saving Faces [una fondazione per la ricerca in chirurgia facciale] che mi ha fornito una ricchissima bibliografia. Ho letto montagne di articoli scientifici, ma più leggevo e meno mi sentivo in grado di scrivere. Poi un giorno mi sono svegliata con in mente la vivida immagine di una bambina che era nata con la mappa dell'Australia sulla faccia, e una volta fatta mia quell'immagine ho sentito che ne sarebbe uscita una buona poesia".

Damiano Abeni. Specializzatosi in epidemiologia e sanità pubblica alla Johns Hopkins University (Baltimora, USA), ha lavorato presso l'Istituto Superiore di Sanità, l'Osservatorio Epidemiologico e l'Agenzia di Sanità Pubblica della Regione Lazio. Dal 1998 all'IDI-IRCCS, conduce studi osservazionali e sperimentali sulle malattie croniche della pelle e sui tumori cutanei, con particolare attenzione alla ricerca traslazionale, all'outcome research (qualità della vita, benessere psicosociale dei pazienti), e all'interazione tra virus e tumori.
Dal 1973 traduce poesia anglosassone per i maggiori editori italiani.

QUIZ CLINICI

Quiz Clinico 1 - Lesioni eritemato-vescicolari agli arti inferiori

Riccardo Sirna

Soggetto di circa 60 anni che si presenta alla nostra osservazione nella seconda metà del mese di Giugno per la comparsa, alcuni giorni prima, di lesioni eritematose, vescicolose, associate a sensazione di bruciore che si erano successivamente ricoperte di manifestazioni squamo-crostose, pruriginose localizzate in modo particolare a carico del ginocchio sinistro (Figura 1). Le lesioni erano molto più accentuate nella zona del ginocchio vero e proprio mentre sfumavano sia verso l'alto che verso il basso ed erano quasi assenti nel cavo popliteo.
Alla anamnesi non si rilevavano patologie sistemiche degne di nota, ma emergeva che il paziente da tempo soffriva di un fastidioso dolore a carico del ginocchio stesso e che era solito periodicamente applicare un gel antidolorifico per attenuare la sintomatologia come raccomandato da pubblicità televisiva. Nei momenti di riacutizzazione era solito applicare il gel alla sera, fasciando il tutto durante la notte con un indumento di lana per "scaldare" la parte, come tradizione popolare vuole. Allo stesso fine la domenica precedente alla comparsa della reazione cutanea si era recato al mare alternando esposizione al sole con sabbiature calde della parte dolorante.

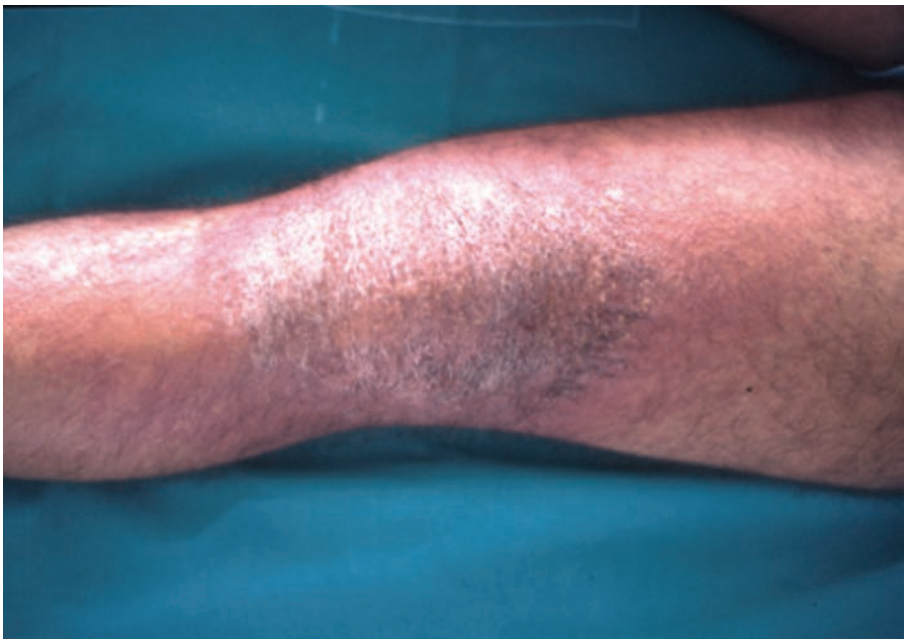


Figura 1. Quadro clinico della lesione.

QUIZ CLINICI

Quiz Clinico 2 - Edema gigante del labbro inferiore

Riccardo Sirna

Soggetto di circa 35 anni che, nel pomeriggio di una domenica primaverile, si presenta in urgenza alla nostra osservazione per la comparsa, poche ore prima, di edema imponente del labbro inferiore associato a sensazione in parte di bruciore, in parte di parestesia (Figura 1). Non si rilevavano adenopatie satelliti e, all'anamnesi, il paziente si definiva in "ottima forma" tanto che aveva trascorso tutta la mattinata in sella alla sua moto da cross a girovagare per la campagna maremmana insieme ad altri amici accomunati dalla stessa passione.
Negava diatesi allergica e negava parimenti l'assunzione di bevande fredde o gelati precisando che alla sua partenza da casa non presentava lesioni di nessun tipo a carico del labbro inferiore.

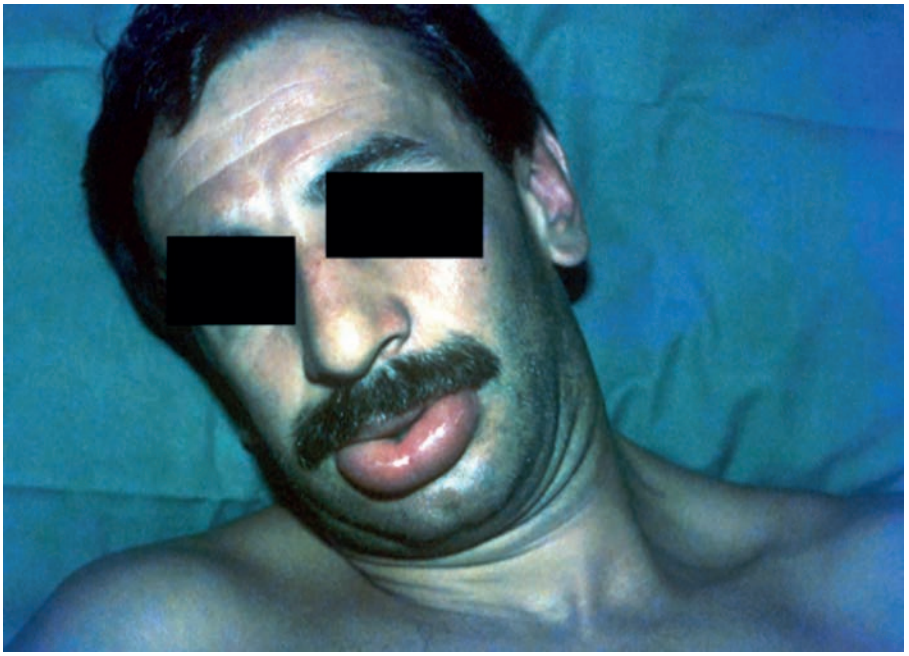
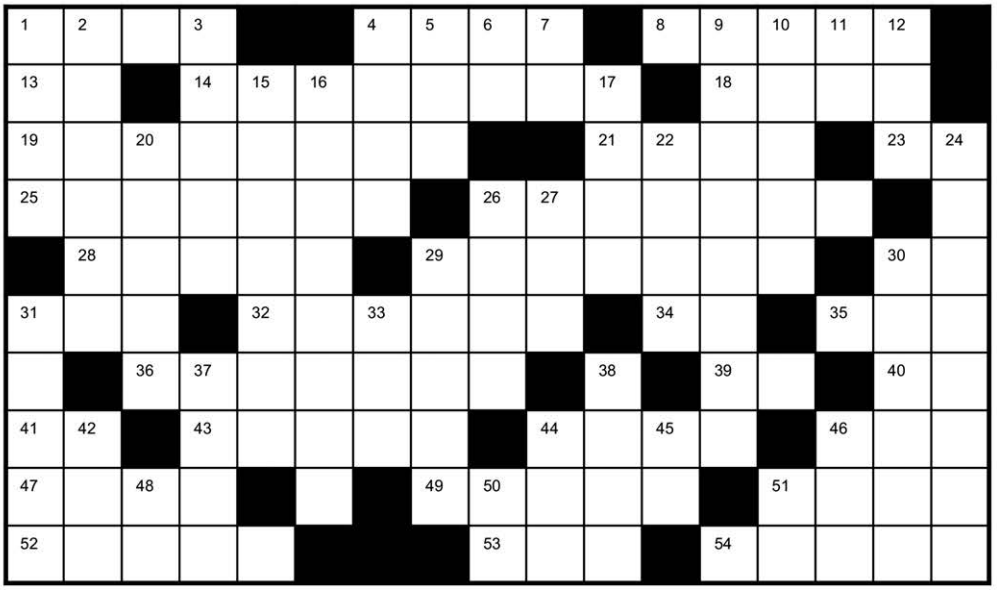


Figura 1. Quadro clinico della lesione.

GIOCHI

CruciDerma

Ferdinando Amerighi



ORIZZONTALI

1) Squadra calcistica di Ferrara
4) Una delle tante card
8) Cantilena. litania
13) Il musicista Avitabile
14) Ancora, ancora e poi ancora
18) Imbarcazioni
19) C'è quello Armeno
21) Insieme a Ric
23) L'attore Lupo
25) Un Marco imperatore a Roma
26) Gli etruschi si facevano chiamare così
28) Fiume etrusco
29) All'inizio delle "Cinque Terre"
30) In mezzo al bricco
31) Può essere per capelli
32) Isoletta del Golfo di Napoli
34) La città del collega Norat
35) Prinz, mitica auto tedesca del passato
36) Commediografo del "teatro dell'assurdo"
39) Fabi cantante famoso per i capelli
40) In mezzo all'orma
41) 'ncredibbile…allenatore dell'Inter
43) Uccelli che… orlano le torri
44) Recipiente di pelle
46) Organizzazione Onu per l'alimentazione
47) Dietro la testa
49) Associazione Nazionale Pubbliche Assistenze
51) Paradiso terrestre
52) Quartiere parigino
53) Isola del Mar d'Irlanda
54) Lago prosciugato tra Grosseto e Castiglione della Pescaia

VERTICALI

1) Attrezzo del falegname
2) Oggetti da arredo, abbigliamento, ornamento, accomunati dallo stesso disegno o stile
3) Una legge per Orazio
4) Città etrusca del Lazio
5) Andato
6) Forse
7) La città etrusca della Chimera
9) Per il cancro della prostata con metastasi
10) Nomignolo dell'autore del crucidermo
11) Ilaria Volpi
12) Cortile di campagna
15) C'erano quelle di Ercole
16) L'orgoglio del leone
17) Agenzia Gestione Salute Ambientali
20) I barbari di Odoacre
22) Talvolta è ridens
24) Re Etrusco
26) Giovane nato da vacche o cavalle
27) Gardner… come lava!!!
29) Terra di provenienza degli Etruschi
30) Confina con Syria and Egypt
31) C'era anche quello bifronte
33) Sistema Sanitario Locale
37) Il nome del "Cabeson" di Juve e Napoli
38) Con Oliver (Ollio)
42) Vi si prenota una visita
44) Offerta Pubblica d'Acquisto
45) In mezzo all'Arno
46) Lo guida la Meloni
48) Caserta
50) Vice Presidente ADOI
51) Articolo romanesco

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SOLUZIONI - QUIZ CLINICI

Soluzione Quiz Clinico 1

DIAGNOSI: Fotodermatite da uso di FANS topici

Il paziente riferiva che il sabato sera, dato il riacutizzarsi del dolore a carico del ginocchio sinistro, si era applicato una robusta dose di Fans gel soprattutto nella zona anteriore, sfumando sia verso l'alto che il basso ed il cavo popliteo. Essendo però nel mese di giugno non aveva applicato la consueta copertura con la lana e la domenica si era recato in spiaggia esponendo la parte all'azione dei raggi solari. Ad un ulteriore esame clinico degli arti inferiori si notava che una reazione eritematosa era presente anche alla parte mediale del ginocchio di destra (Figura 2). Alla richiesta del modo di dormire il paziente ci confermava che la sua posizione tipica era la postura sul fianco destro: questo spiegava il trasporto passivo di una parte del medicinale anche su tale arto, anche se la reazione era, ovviamente, minore rispetto alla zona di prima applicazione.
Come è noto, alcune sostanze, ingerite o applicate topicamente, predispongono, dopo l'esposizione al sole, a reazioni che vengono classificate in fototossiche e fotoallergiche.
Nelle reazioni di tipo fototossiche, le sostanze che assorbono la luce generano radicali liberi e mediatori infiammatori provocando un danno tissutale caratterizzato da eritema, edema ed anche vescicolazione associato a dolore e/o bruciore. Le reazioni fototossiche non coinvolgono la cute non-fotoesposta e non richiedono una precedente esposizione solare e possono apparire con gravità variabile soprattutto dopo applicazione sulla cute di svariate sostanze come profumi, piante (fito-foto-dermatiti) e Fans, in modo particolare il Ketoprofene.
A proposito di quest'ultimo l'AIFA, in accordo con EMA, ha prodotto in data 06/06/2014 un comunicato diretto agli operatori sanitari circa il profilo rischio/beneficio dei farmaci topici a base di Ketoprofene.
Il profilo rischio/beneficio di tale farmaco rimane favorevole, ma viene evidenziato che esistono casi di fotosensibilità da Ketoprofene per uso topico dovuti alla fotodegradazione di tale sostanza da parte della luce solare e che tale fenomeno si verifica anche in caso di cielo coperto da nuvole.
Nel nostro caso il trattamento delle lesioni si è basato sull'utilizzo di corticosteroidi topici e nella sospensione del gel, specialmente in prospettiva della stagione estiva.

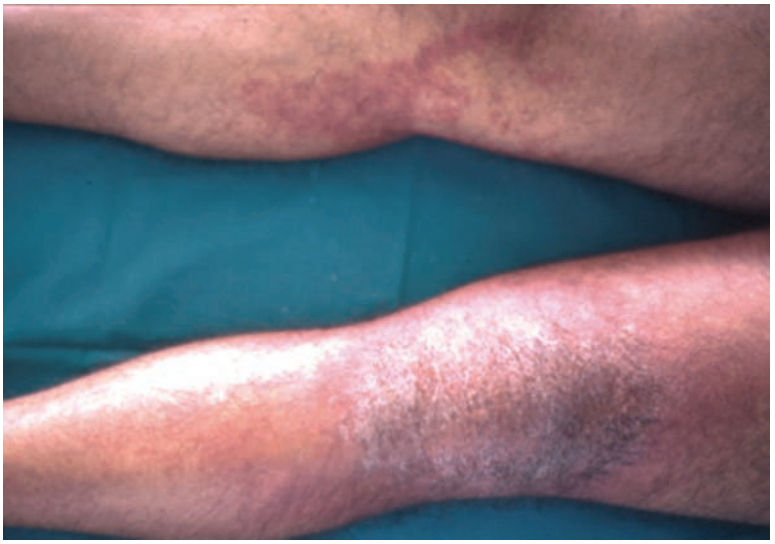

Figura 2. Reazione eritematosa presente alla parte mediale del ginocchio destro dovute al contatto e trasporto di modeste quantità di medicamento durante la notte.

SOLUZIONI - QUIZ CLINICI

Soluzione Quiz Clinico 2

DIAGNOSI: Reazione a puntura di vespa

Ad un più attento esame della bocca si evidenziava, proprio nella porzione centrale del labbro inferiore, anche se minimizzata dall'edema imponente, una piccola emorragia puntiforme che ci faceva sospettare potesse trattarsi del punto di infissione del palpo o del pungiglione di un insetto.
Indagando sull'abbigliamento utilizzato dal nostro paziente si evidenziava che non utilizzava, durante le sue gite in motocicletta, un casco integrale, bensì un classico casco aperto anteriormente associato ad occhialoni a contatto cutaneo per evitare possibili schizzi di acqua o di fango. Pertanto sia il naso che la bocca restavano non coperti da mezzi di protezione per cui era accettabile l'ipotesi di una puntura di insetto che, data la velocità, l'ambiente attraversato ricco di rami di alberi ed arbusti urtati frequentemente e l'entusiasmo della competizione con gli altri motociclisti, gli avevano impedito di avvertire.

Ma da quale insetto poteva essere stato punto?
Abbiamo subito scartato l'ipotesi di un ematofago. I "tafani" sono insetti di discrete dimensioni dotati di un robusto apparato pungente necessario a suggere il sangue non soltanto dalla cute umana, ma addirittura attraversando la robusta pelle di animali di grossa taglia come bovini o cavalli. Tuttavia un tafano difficilmente avrebbe scelto come suo bersaglio un centauro su una moto rombate ed in movimento anche perché avrebbe dovuto sostare del tempo sulla mucosa per suggere il sangue.

Ci siamo pertanto concentrati su insetti che casualmente potevano entrare in contatto con il volto del nostro paziente e che potevano aver punto il labbro come meccanismo di difesa. Il sospetto quindi si è concentrato su insetti non ematofagi come api, vespe e calabroni. Questi ultimi sono quelli di dimensione più grande e l'urto contro il labbro sarebbe stato sicuramente tale da non passare inosservato. Le api hanno un pungiglione particolare che, una volta trafitta la cute, difficilmente si estrae e quindi rimane infisso e visibile, spesso con piccola porzione dell'intestino dell'insetto e sua conseguente morte. Si sa infatti che ogni ape solitamente può pungere una sola volta.

Pertanto ci è sembrato plausibile che si sia trattato della puntura di una vespa. Questo insetto ha un pungiglione retraibile, può pungere quindi più volte, non è particolarmente grosso, può provocare reazioni anche particolarmente gravi, specie in soggetti predisposti ed è di comune incontro nelle campagne della Maremma.

SOLUZIONI - GIOCHI

Soluzione CruciDerma

dermatology reports

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Dermatology Reports

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Official Journal of the Italian Association of Hospital Dermatologists (ADOI - Associazione Dermatologi-Venereologi Ospedalieri Italiani e della sanità pubblica), of the Italian Melanoma Intergroup (IMI) and of the SIDCO (Società Italiana Dermatologia Chirurgica Oncologica, Correttiva ed Estetica).

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Lewis J, Ossowski S, Hicks J, Errami M, and Garner HR. **Text similarity: an alternative way to search MEDLINE**. Bioinformatics 2006; 22:2298-2304.

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A lobulated mass on the upper back with prominent vasculature: A giant basal cell carcinoma

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Abstract

Basal cell carcinoma (BCC) is characterized by slow but locally invasive growth. Although there is low metastatic potential, if not treated early, these skin cancers can lead to significant morbidity and mortality. In this case report, we present a man with a neglected BCC that developed into what is termed a giant BCC or one that is greater than 5 cm. This tumor was discovered only upon workup of orthostatic lightheadedness and iron deficiency anemia. Although rare, basal cell carcinoma must be included on the differential of a large cutaneous lesion and may be a source of significant blood loss.

Introduction

Basal cell carcinoma (BCC) is characterized by slow but locally invasive growth, a low metastatic potential, and a pearly pink appearance on physical exam.[1] Giant basal cell carcinoma is the term used to describe a BCC greater than 5 cm.[1-3] Most basal cell carcinomas are small lesions with only 0.5% meeting the size criteria for a giant lesion.[4] Giant basal cell carcinomas are most common in elderly males and show a predilection for the head, neck, and upper back.[1,3,5] We present a man with symptomatic iron deficiency anemia caused by a giant BCC.

Case Report

A 60-year-old Caucasian male with no personal history of skin cancer, immunosuppression, or radiation exposure presented to the emergency department for assessment of a three-day history of fatigue and orthostatic lightheadedness. The patient had a history of essential hypertension treated with metoprolol but no other known chronic medical conditions. His initial labs were notable for a hemoglobin of 7.2 (reference 13.2-16.9 g/dl), mean corpuscular volume of 73.6 (reference 76.2-98.6 femtoliters), ferritin of 6 (reference 30-400 ng/ml), and unsaturated iron binding capacity of 371 (112-346 mcg/dl), consistent with iron deficiency anemia. On exam, he was found to have a 15×10×4 cm firm, fungating, lobulated, violaceous-pink tumor with areas of ulceration leaking serosanguinous fluid on his upper back (Figure 1). Along the surface of the tumor and extending inferolaterally into the peritumoral skin were radiating dilated violaceous vessels. Extending beyond the dominant growth was a rim of violaceous-pink patches. The total area of skin involvement (combining both the excrescence and rim of involved tissue) was 20×18 cm. Upon further questioning, the patient stated that the mass had been present and slowly enlarging for 18 years. On computerized tomography, the mass was found to be heterogeneously enhancing involving the skin and subcutaneous fat overlying the trapezius muscle with no bony or visceral involvement. The patient's lesion was excised primarily by surgical oncology leaving exposed left scapula, trapezius, spinous processes, and occipital fascia (Figure 2). Excisional margins were noted as less than 2 mm from the deep margin and greater than 2 cm from all other margins. Microscopic examination of the tumor specimen demonstrated dermal nodules of pleomorphic, hyperchromatic purple cuboidal and columnar cells with scattered keratin pearls in a background of loose fibrous stroma and a moderate lymphocytic infiltrate, consistent with a diagnosis of BCC (Figure 3). Two weeks later, plastic surgery performed a rotational skin flap from suboccipital region and split thickness skin grafting from lower back to upper back wound. This patient had no additional treatments.

Discussion

Prior to this case, approximately 14 cases of basal cell carcinomas greater than or equal to 20 cm have been reported in the literature.[4,6-10] When they exceed 20 cm, they are termed super giant BCCs.[7] The primary cause of a giant BCC is attributable in the majority of cases to either tumor neglect or local recurrence of a previously treated lesion.[4,6-10] Relative to smaller tumors, giant BCCs are more likely to be of a histologically aggressive subtype (morpheaform, micronodular, metatypical) and are more likely to recur following simple excision.[1,3] In contrast to the very low metastatic incidence of BCCs overall (0.03%), the rate has been reported to be as high as 45% in tumors greater than 10 cm and 100% in tumors greater than 25 cm.[11] The most common sites of metastasis are the lymph nodes and lungs, with a mean survival after metastatic spread of only 8-14 months.[11,12] Although minor bleeding has been associated with BCCs secondary to tissue friability common to these neoplasms, only 10 cases of acute or chronic anemia subsequent to giant BCC have been reported.[6]

Wide and deep surgical excision is the mainstay curative treatment of giant BCC.[13] The ideal margin size for large BCC is unknown given the rarity of the tumor, but

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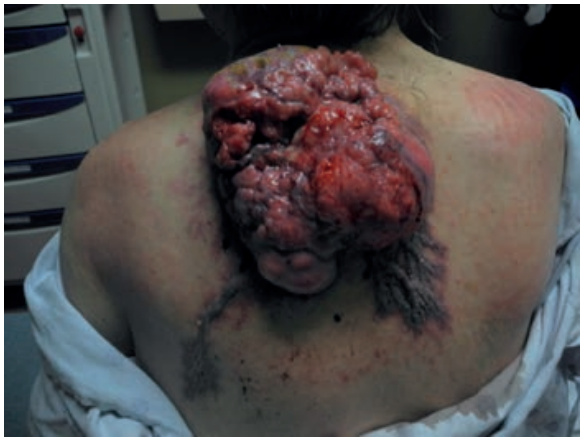

Figure 1. Clinical photograph. Gross view of mass on upper back demonstrating the pink-violaceous, lobulated, shiny surface with prominent vasculature extending from the inferolateral surfaces.

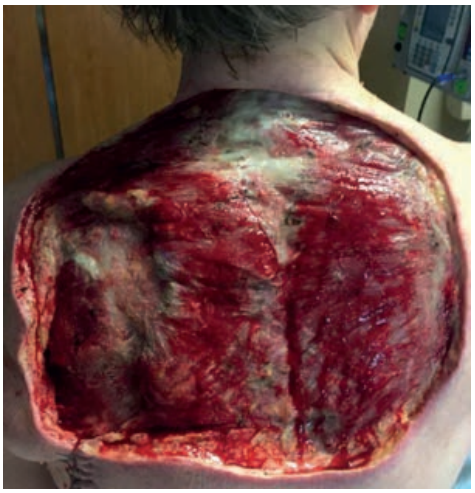

Figure 2. Clinical photograph. Gross view of upper back after surgical excision of mass demonstrating a large defect with exposed musculature.

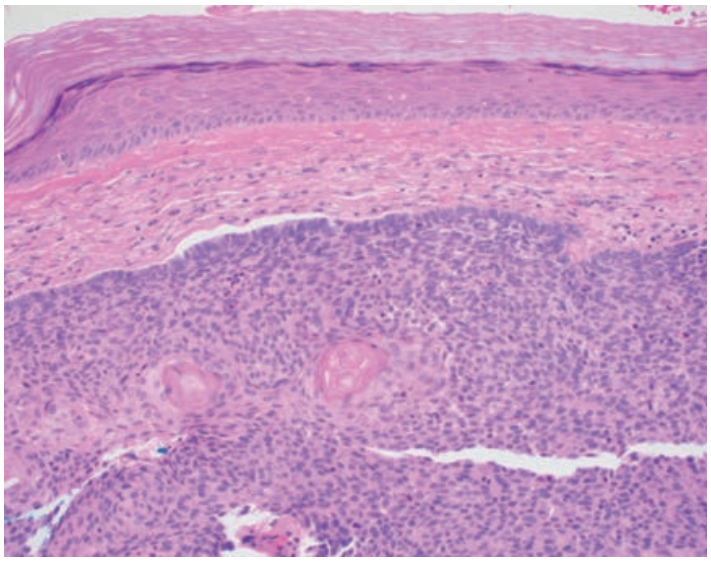

Figure 3. Skin histopathology. Hematoxylin & Eosin stain of a shave biopsy specimen at 100× magnification demonstrating a basaloid nodule in the dermis, with peripheral palisading of nuclei and retraction between tumor and stroma.

recommendations vary from 5 mm to 1 cm.[2,4-5,13] Mohs micrographic surgery offers the advantage of assessing for residual tumor at the time of operation and has been recommended as the treatment of choice for lesions in cosmetically sensitive regions.[2,14] Additional treatments can be considered including oral treatment with hedgehog pathway inhibitors, vismodegib and sonidegib, approved in 2012 for those with locally advanced, metastatic, or inoperable BCC.[15] Vismodegib has been shown to have an overall response rate of 43% in locally advanced diseases and has been reported to be effective in giant basal cell carcinomas.[4,16] Treatment can be therapeutic or neoadjuvant, with a successful case demonstrating a giant BCC treated with vismodegib as a debulking agent prior to surgery.[17] However, another study documented that although there may be reduction in the cutaneous lesion of the giant BCC, there was no reduction in the deeper tumor plane, and the patient still required adequate deep margins.[18] Furthermore, usage of this drug may be challenging secondary to tumor resistance, the side effect profile, and recurrence after cessation of the drug.[18-20] Other considerations must be taken into account when prescribing hedgehog inhibitors, including patient compliance. Monitoring a patient's response to treatment is essential in the case of a giant BCC.[18] A patient who is at risk for non-compliance, such as those with giant BCCs, may not be ideal candidates for this intervention. The patient in this case had difficulty obtaining insurance and was lost to follow-up after surgical intervention; therefore, no additional treatments were performed.

Conclusions

This report presents a case of a very large neglected giant basal cell carcinoma, which was discovered upon workup of orthostatic lightheadedness and iron deficiency anemia. Although rare, basal cell carcinoma must be included on the differential of a large cutaneous lesion and may be a source of significant blood loss.

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Diffuse cutaneous mastocytosis masquerading as linear IgA bullous dermatosis of childhood

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Abstract

Diffuse cutaneous mastocytosis is a rare form of cutaneous mastocytosis that can appear in heterogeneous clinical presentations, including eruption of papules, erythematous plaques, blisters, and erythroderma. We report a 1.5-year-old boy who presented with itchy wheals and blisters spreading on his body. The patient was initially managed as a linear IgA bullous dermatosis of childhood (LABD) because of the similarity of clinical symptoms and the presenting of linear IgA deposits at the basement membrane. Due to the development of urticarial plaque after the resolution of the blisters, the diagnosis of diffuse cutaneous mastocytosis was made based on clinical, histopathological (hematoxylin-eosin, Giemsa, and toluidine blue staining), and direct immunofluorescent examinations (IgA, IgG, IgM, C3). The symptoms were improved following antihistamines and oral corticosteroid treatment.

Introduction

Mastocytosis is a group of diseases with clinical symptoms caused by massive infiltration of mast cells in various tissues, including skin, blood, gastrointestinal, cardiovascular, and musculoskeletal systems.[1] Nettleship first described the disease entity in 1889 as a rare form of urticaria.[2] Mastocytosis has a prevalence of 1 in 10,000 population, and the incidence ranges from 5 to 10 cases per million individuals per year in the United States.[3]

Cutaneous mastocytosis is the most common form of mastocytosis in children and has several forms, including urticaria pigmentosa, diffuse cutaneous mastocytosis (DCM), mastocytoma, and teleangiectacia macularis eruptive perstans.[4,5] Diffuse cutaneous mastocytosis is rare form of pediatric mastocytosis, and can manifest as an eruption of papules, erythematous plaques, bullae, and erythroderma followed by skin thickening and pigmentation changes.[6] The diagnosis of DCM in children, especially those presenting as bullous eruption (namely, diffuse bullous cutaneous mastocytosis), is a challenge for clinicians and symptoms can mimic other bullous eruptions. Other than DCM, the bullous eruption in infants and children can also develop in either acquired or inherited bullous disorders, such as linear IgA bullous dermatosis in childhood (LABD), staphylococcal scalded skin syndrome, juvenile bullous pemphigoid, and epidermolysis bullosa simplex.

We present a DCM case in a child initially managed as LABD because of its similar clinical symptoms and features of linear IgA deposits on the basement membrane in direct immunofluorescence (DIF) examinations. This case report emphasizes the importance of comprehensive clinical, histological and DIF examinations in managing children with acquired bullous eruption. Moreover, clinicians should consider DCM as one of the differential diagnoses of infants or children presenting with bullous lesions.

Case Report

A 1.5-year-old boy was brought to our center with blisters on his face and body, starting three days before the admission. Six days earlier, the patient had fever, cough, and runny nose. The patient was treated with paracetamol and amoxicillin for two days by a general practitioner (GP). After the fever receded, flaccid blisters developed on his face and body.

In past medical history, the patient had experienced a similar complaint one month before. At that time, the complaint was not treated and he self-improved within two weeks. The patient also had a history of recurrent urticaria with unknown causes. There was no family history with a similar condition.

Dermatological examination revealed tense blisters with clear fluid in various sizes scattered on the face and back. Several skin-colored papules and skin erosions were also found on his body (Figure 1). Nikolsky's sign, Darier sign, and dermographism were negative during examination. Neither lymph node enlargement nor hepatosplenomegaly were found.

Based on clinical examination, the working diagnosis established at that time was LABD, and the therapy given was normal saline (0.9% sodium chlo-

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ride) gauze dressing on the top of bullae followed by silver sulfadiazine 1% cream applied twice daily to areas experiencing erosion. At this appointment, skin biopsy was considered, but the parents refused. Four months later, the patient came back with the appearance of rashes that felt very itchy. The lesions had emerged on the chest and spread to the back and extremities. At this appointment, no new blisters had developed. Dermatology examination revealed wheals and hyperpigmented patches, distributed on the face, chest, back, and abdomen (Figure 1). The patient was still managed as LABD and was given methylprednisolone 4 mg tablets twice daily for seven days and cetirizine 2.5 mg daily.

Two weeks later, the symptoms were improved, but there were still new erythematous wheals on the back, face, and chest. During the examination,

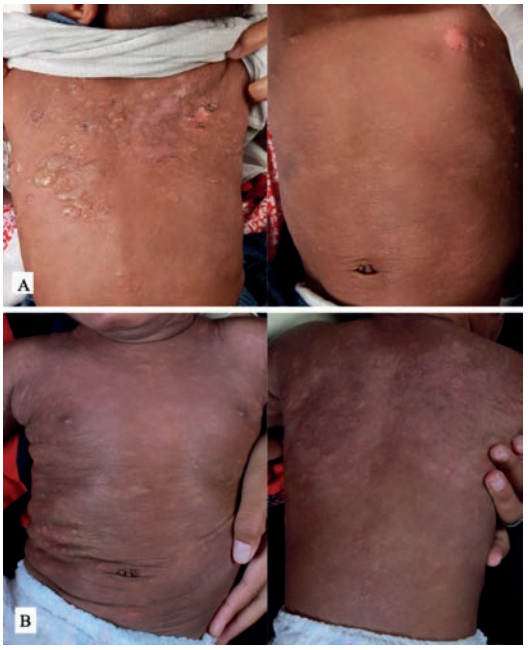

Figure 1. Clinical picture of the patient at initial visit: blisters and erosion distributed on the trunk (A), and the development of new urticarial plaques after blisters resolution (B).

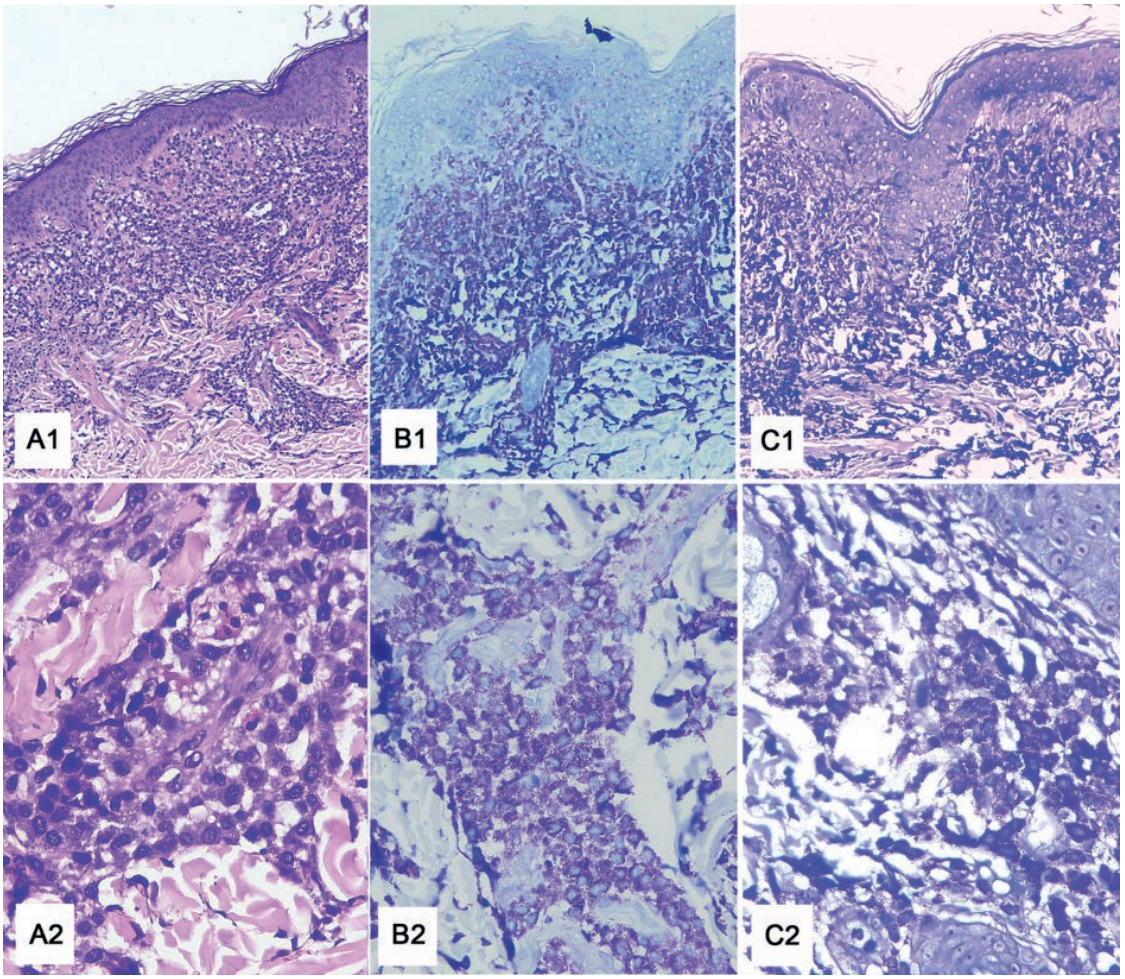

Figure 2. Histopathology staining with hematoxylin-eosin (A1, A2), Toluidine blue (B1, B2), and Giemsa (C1, C2), showed massive infiltration of mast cells in the epidermis and dermis.

more erythematous patches and wheals were found with hyperpigmented patches distributed on the face, chest, back, and abdomen. There were no signs of Darier nor dermographism. At this point, the parents agreed to give consent for the skin biopsy procedure for the patient.

Histopathological examination with hematoxylin-eosin (HE) staining from urticarial lesions taken from the back area showed basket weave-type orthokeratosis, spongiosis, acanthosis, and elongation of rete-ridge in the epidermis. Infiltration of inflammatory cells, consisting of lymphocytes, a few eosinophils, histiocytes, and a large number of mast cells, was found in the upper dermis, perivascular, and surrounding the skin appendages. Neither a subepidermal cleft nor any neutrophil were seen. Additional staining using Giemsa and toluidine blue showed a large number of mast cells in the dermis layer (Figure 2). These findings support the diagnosis of cutaneous mastocytosis.

DIF examination using IgA, IgM, IgG, and complement antibodies (C3) was done on the patient's skin tissue taken from the same area and revealed linear IgA deposits the basement membrane. The staining for IgM, IgG, and C3 were negative (Figure 3).

Based on the clinical and supporting examination, the diagnosis of cutaneous mastocytosis was made in this patient. The therapy given was cetirizine 2.5 mg per day and topical moisturizer. Two weeks later, there were no new lesions had developed, and the treatment was continued with the application of topical moisturizer twice daily. However, new blisters reappeared one week later. The patient went to a GP and received oral prednisone 2.5 mg per day for one month. Up to two weeks after the patient stopped taking oral prednisone, there was no any sign of relapse.

Discussion and Conclusions

Cutaneous mastocytosis is a disease caused by the release of mast cell mediators and/or mast cell infiltration in the skin tissue. Physiologically, stem cell factors (SCF) binding to the Kit receptor in the extracellular area activate mast cells. This binding increases the proliferation and extends the lifespan of mature mast cells and triggers the release of mast cells' mediators. In about 60% to 80% of mastocytosis cases, somatic mutations of the gene encoding the Kit protein cause autocrine dysregulation and activation of Kit in the absence of the SCF ligand.[7,8] The excessive activation of Kit protein leads to the involvement of internal organs other than the skin.[7]

Most of the patients with cutaneous mastocytosis do not meet all of the criteria for systemic mastocytosis, in which there is a massive infiltration of mast cell in various organs, including the bone marrow and liver. Although internal organ involvement is rare, cutaneous mastocytosis is often accompanied by gastrointestinal symptoms and anaphylaxis.[7] We did not find any sign of internal organ involvement in our case.

Skin biopsy is crucial in diagnosing cutaneous mastocytosis. Histopathological examination of DCM reveals a large number of mast cell infiltrations in the perivascular, interstitial, or nodular patterns found in the upper papillary and reticular dermis.[9] In our case, histopathological examination showed abundant mast cell infiltration, mainly in the upper dermis. Thus, the diagnosis of cutaneous mastocytosis could be confirmed.

The clinical findings in our patient are consistent with DCM and the histopathologic examination supported the diagnosis. However, we did not perform bone marrow analysis, *KIT* mutation, and serum tryptase to exclude systemic involvement of mastocytosis. Theoharides and colleagues suggested that children presenting with skin lesions typical for DCM without any clinical signs of hepatosplenomegaly and lymphadenopathy do not require bone marrow biopsy and evaluation.[7] In contrast, mastocytosis in adults is often associated with systemic involvement. Of note, patients with systemic mastocytosis may not show any skin involvement.[7,10] Lange and colleagues suggested that serum tryptase evaluation is necessary as a consideration before performing bone marrow biopsy in pediatric mastocytosis cases.[11]

At the early onset, we managed our

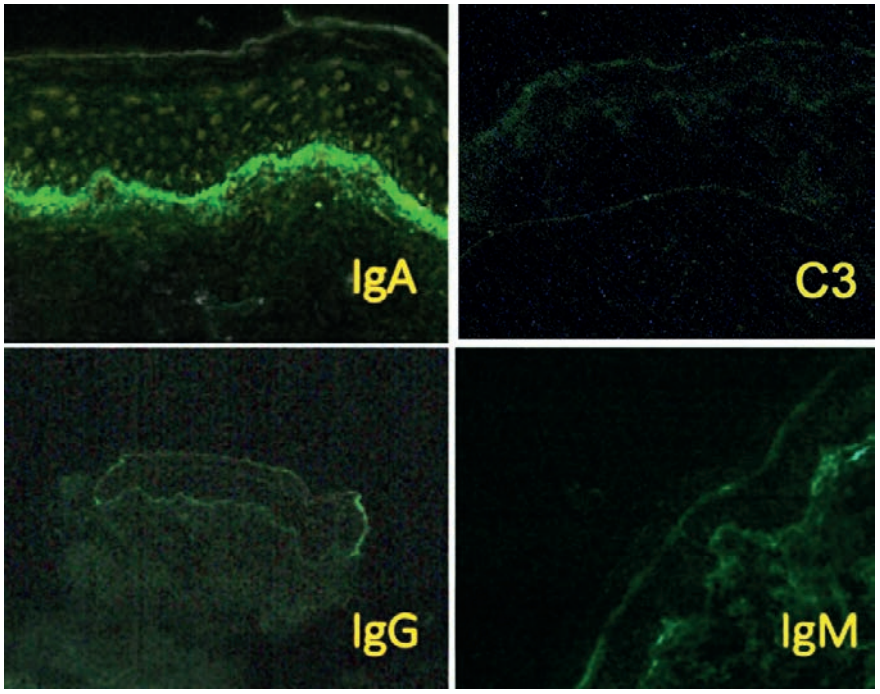

Figure 3. Immunofluorescent staining showed linear Immunoglobulin A (IgA) deposition in the basement membrane.

patient as LABD due to the similarity of skin lesions. Nevertheless, following the blister resolution, urticarial plaques developed at the same locations as the former lesions. The absence of a subepidermal cleft with infiltration of neutrophilic inflammatory cells and the presence of many mast cell infiltrating in the histopathology examination excluded the diagnosis of LABD.

Linear IgA deposition on the basement membrane is a key finding from direct immunofluorescent examination in LABD.[12] Various inflammatory dermatoses, such as dermatitis herpetiformis and Henoch-Schoenlein purpura, and bullous lupus erythematosus, can also exhibit IgA deposition. Even though the role of IgA in the subepidermal blister formation remains unclear, it is assumed to involve neutrophilic infiltration mediated by IgA.[13] Interestingly, in our patient, DIF examination revealed linear deposits of IgA on the basement membrane. Whether the IgA deposition is caused by the inflammatory process in cell mast degranulation of coincidence with LABD remains unknown. Slavescu and colleagues have reported a case of bullous cutaneous mastocytosis accompanied by findings of IgM deposits in the basement membrane.[14] Nevertheless, until now, there is no reported case of linear IgA deposition on the basement membrane in patients with cutaneous mastocytosis.

The management of cutaneous mastocytosis in children is comprised of non-pharmacological and pharmacological therapies. Non-pharmacological management includes avoiding various triggers such as skin friction, exposure to high temperatures such as hot baths, and vigorous physical activities. Other known precipitating factors include fever, teething, diet, vaccinations, and substances that can trigger mast cell degranulation such as non-steroidal anti-inflammatory drugs, anticholinergics, aspirin, narcotics, polymyxin B sulfate, and alcohol.[1]

Pharmacological management of pediatric mastocytosis includes topical and systemic therapies. For topical treatment, corticosteroid cream can be used along with the local care of skin with a moisturizer. Treatment with H_1 and H_1 antihistamines, oral disodium cromolyn, and leukotriene receptor antagonists can be considered as drug choices for severe to moderate pediatric cutaneous mastocytosis.[15] Oral glucocorticoid is recommended for diffuse cutaneous disease refractory to topical treatment, but the supporting evidence is scarce.[16] In our case, the symptoms improved after the administration of antihistamines and moisturizer. Oral corticosteroid given by a GP for one month resulted in a good therapeutic response as well.

Cutaneous mastocytosis commonly occurs in early life and can improve during puberty. Generally, this disorder is benign and has a favorable prognosis.[17] Nevertheless, 15-30% of cutaneous mastocytosis in children will persist in adults and have systemic involvement.[18] In our patient, improvement occurred after administration of antihistamines, but complaints returned when the drug was stopped. After receiving oral corticosteroids from a GP for one month, the skin lesions improved and did not recur within two weeks after discontinuation of oral corticosteroids. Antihistamines act as a competitive antagonist on histamine receptors and help the stabilization of mast cell activity.[19] Whereas, corticosteroids can decrease the number of mast cells in vitro, but they do not have any effect on the release of degranulated mast cells products.[20]

In summary, we report a DCM case of an otherwise healthy 1.5-year-old boy who was initially managed as LABD. The diagnosis of DCM was confirmed by clinical and histopathological examinations using HE, Giemsa, and toluidine blue staining. This case underscores that DCM should be admitted as a differential diagnosis of an acquired bullous eruption in infants or children and can present with bullous eruptions alongside the linear IgA deposition on the basement membrane that imitates LABD.

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Nd:YAG laser in association with pulsed dye laser for the treatment of PHACES syndrome

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Abstract

The acronym PHACES stands for posterior fossa malformations, hemangiomas, arterial anomalies (cardiovascular or cerebrovascular), coarctation of the aorta/cardiac defects, eye abnormalities, and sternal defects. The characteristic dermatological clinical manifestation of PHACES syndrome is a segmental and extensive hemangioma, usually on the face. A combined therapy with 1,064 nm Nd-YAG/595-nm pulsed dye laser was performed in a young 15-year-old patient with PHACES syndrome, who presented a hemangioma on the left side of the face, located in the periorbital region. A first session with Nd-YAG laser (2,5 mm spot size, fluence 100 J/cm^2, pulse duration 7 ms) for the treatment of teleangectasias and subsequently, three treatment sessions with pulsed dye laser (12 mm spot size, fluence 7 J/cm^2, pulse duration 0,5 ms, repetition rate 0,6 Hz), once every 2 months, were performed. No postoperative complications were recorded, except for transient purpura after the pulsed dye laser sessions. The vascular lesion had a decrease in size bigger than 75%, and these results was maintained 6 months after the last treatment. Combined therapy Nd-YAG/pulsed dye laser is an effective and noninvasive procedure for hemangiomas in patients with PHACES syndrome.

Introduction

PHACES syndrome is a neurocutaneous condition characterized by posterior fossa malformations, hemangioma, arterial anomalies, coarctation of the aorta/cardiac defects, eye abnormalities, and sternal malformations. PHACES syndrome is a non-hereditary condition and its etiology and pathogenesis are not fully known. Fetal and embryonic developmental defects have been suggested.[1]

PHACES syndrome predominantly affects the female sex (M:F = 1:9) and it is observed in 2% to 3% of infantile haemangiomas (IHs) cases. IHs associated with PHACES syndrome are typically extensive (>5cm in diameter) and segmental, and they can present as teleagectasias, solitary lesions, papules or confluent plaques.[2] Hemangiomas in PHACES syndrome are most commonly located on the face, but cases involving other regions, such as occipital area, trunk, upper thoracic and proximal upper limb regions have also been described.

The treatment of the syndrome requires a multidisciplinary approach involving the cardiologist, neurologist and dermatologist. Systemic propranolol and steroids, surgery and laser therapy can be used to treat hemangiomas.[3] 595nm pulsed dye laser (PDL) and 1064 nm Nd:YAG-laser represent two laser systems very effective in the treatment of vascular anomalies such as HI. The combined use of these two lasers have been proposed in the treatment of HI, with good clinical results.[4]

Case Report

In this study we present the case of a 15 years-old girl affected by PHACES syndrome. At the age of one y.o., the patient underwent corrective surgery for aortic coarctation. Physical examination showed IH covering the left periocular region. Patient reported that IH appeared two months after birth, it grew for the first year of life and only partially spontaneously regressed up to current form. Cranial computed tomography documented the presence of angiomatous formation localized mainly on the lateral side of the eye which extended to the tear gland and to the ipsilateral eyelid region. Magnetic resonance angiography did not detect malformative alterations of the examined districts. Extracutaneous manifestations included headache, myopia and glaucoma.

Informed consent regarding the possible risks such as scars, discoloration, or hyperpigmentation of the procedures and the use of photographs for scientific reasons was obtained. This study was approved by ethical committee Calabria Centro with reference number 373/2019. Facial hemangioma was treated with 1,064 nm Nd:YAG laser Synchro Replay (Deka Medical Lasers, Italy)followed by 595-nm PDL Synchro VasQ (Deka Medical Lasers, Italy) the first used on telangiectasias and the second on the entire surface of the hemangioma respectively. Device characteristics are reported in Table 1.

The parameters used were 2,5 mm spot size, fluence 100 J/cm2, pulse duration 7 ms for Nd:YAG laser, and 12 mm spot size, fluence 7 J/cm2, pulse duration 0,5 ms, repetition rate 0,6 Hz for PDL.

A first session of Nd:YAG laser treat-

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Consent to publication: Photo-content and consent for publication was obtained by the parents of the patient.

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ment was performed without prior application of a local anesthetic with follow up and retouching after 40 days. The first treatment session with PDL, preceded by the application of topical anesthetic (Lidocaine/Tetracaine cream), was performed 40 days after the treatment session with Nd:YAG laser. A total of three PDL treatment sessions, once every 2 months, and a single session of Nd:YAG laser were performed; the size and appearance of the IH gradually and slowly improved after each treatment session. Antibiotic cream was applied topically to the treated area after each session. During the laser treatment, no severe side effects were observed; transient purpura lasting less than 15 days occurred after PDL treatment sessions. Photographs were taken before and at the end of all treatments ; the results were assessed by evaluating the reduction in IH size and classified as 0-25% (I), 26-50% (II), 51-75% (III) and 76-100% (IV). Postoperatively, the patient was seen at 4 weeks, and 6 months after last treatment.

Four weeks after the last treatment, the hemangioma showed a strong improvement (IV) in size, thickness, and appearance, and the result remained stable after 6 months (Figures 1 and 2).

Discussion and Conclusions

Several types of lasers can be used for management of HIs, including argon laser, PDL and Nd:YAG laser,[5] acting on intravascular oxyhemoglobin and resulting in vascular injury.

PDL produce pulses of visible light at a wavelength of 585 or 595 nm, which is primarily absorbed by oxyhemoglobin, destroying blood vessels selectively and keeping the overlying skin intact.

PDL represents the gold standard therapy for vascular lesions such as superficial hemangiomas, port-wine stains, and telangiectasias but it has also proven effective for treating vascular dependent lesions, or non-vascular lesions. In fact, PDL acts selectively on the abnormal vessels of the lesions to be treated and causes selective thrombosis with the consequent destruction of the supply of nutrients to the lesions.[6]

While PDL reaches 0.75-1 mm in depth, Nd:YAG laser, whose 1064 nm wavelength light is absorbed by oxyhemoglobin, melanin and water, is able to penetrate 5-6 mm deep into the tissues, representing the most efficient vascular laser system in terms of skin penetration.[7,8] Therefore, combined therapy using Nd:YAG-laser and PDL is very effective in the treatment of vascular lesions. and it is important to start the treatment with the Nd:YAG because PDL therapy causes post-treatment edema, which could influence the effectiveness of the treatment with Nd:YAG, since its light is also absorbed by the water. Transient purpura is the main side effect that occurs immediately after PDL treatment and correlates with the effectiveness of the treatment; this visible side effect disappears within 1-2 weeks and then the reduction in the number

Table 1. Device characteristics.

Technical specifications	Synchro VasQ DEKA	Synchro Replay DEKA
Wavelength	Dye Laser 595 nm	Nd:YAG Laser 1064 nm
Spot size (mm)	3-12	2.5-24
Max fluence J/cm^2	33	1500
Pulse duration (ms)	0.3-40	0.2-300
Number of pulses per shot	1	up to 3
Emission control	Foot and finger switch	Foot and finger switch
Repetition rate	up to 1 Hz	up to 10 Hz

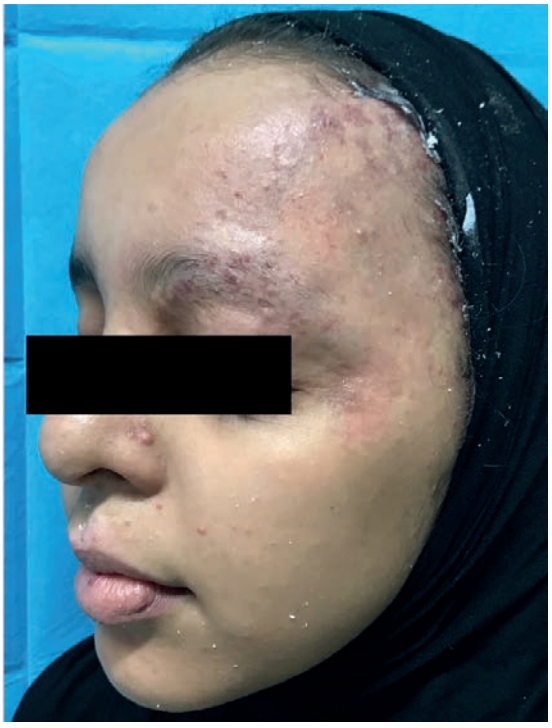

Figure 1. Facial hemangioma before treatment.

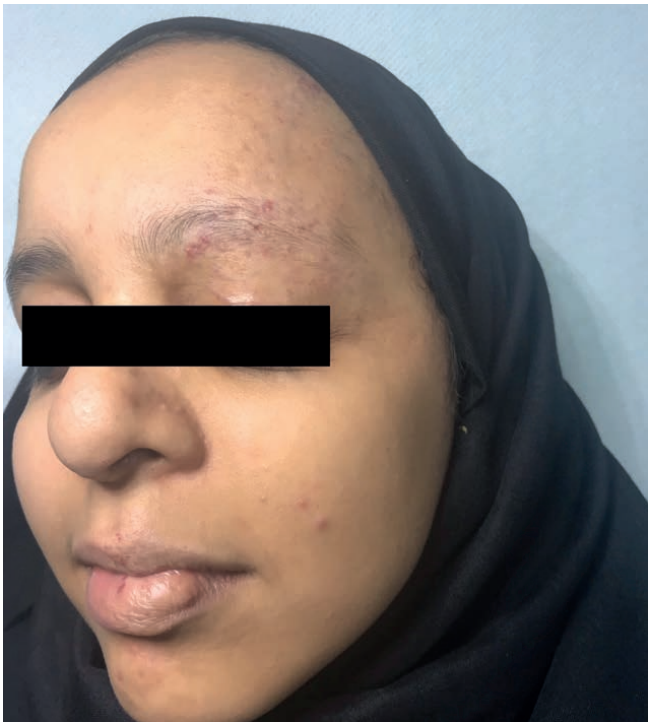

Figure 2. Facial hemangioma 6 months after therapy.

and size of vessels will start.[9]

Although different recent works report the effectiveness of combined PDL and Nd:YAG-laser in the treatment of hemangiomas,[4] this is to our knowledge the first time that this combination technique is proposed in the treatment of this rare cutaneous condition. Our results demonstrate that Nd:YAG laser in conjunction with PDL is a well-tolerated and effective therapy in patients with facial hemangiomas in the context of PHACES syndrome, and represents a promising alternative to other medical and surgical treatments. In fact, the different wavelengths of light emitted by these two laser systems manage to reach vascular structures at different levels of depth within the tissues, and their synergistic action allows to obtain excellent aesthetic results, with minimal incidence of side effects.

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Transformation of a myelodysplastic syndrome to acute myeloid leukemia and concurrent necrotizing sweet syndrome

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Abstract

The Sweet's syndrome, is an inflammatory skin disorder characterized by extensive infiltration of neutrophils in the dermis with extension to the subcutis, known as acute febrile neutrophilic dermatosis. It may occur as a paraneoplastic syndrome. To our knowledge, there are currently few reports about transformation of a myelodysplastic syndrome to acute myeloid leukemia and concurrent necrotizing Sweet syndrome in the literature. Herein we describe an unusual case in a young patient with these characteristics that evolved to a fatal outcome.

Introduction

The Sweet's syndrome (SS), is an inflammatory skin disorder characterized by extensive infiltration of neutrophils in the dermis with extension to the subcutis, known as *Acute febrile neutrophilic dermatosis.*[1]

The clinical spectrum of manifestations is wide, some of the most representative characteristics are tender skin lesions, erythematous plaques, papules or nodules located in extremities, neck and head, usually accompanied by fever and neutrocytosis.[2] Some of the clinical conditions related to this syndrome include infections, autoimmune diseases, inflammatory bowel diseases, vaccines, pregnancy, certain medications, neoplasms and idiopathic.[3]

Paraneoplastic syndromes are clinical clues that neoplasms cause in places outside their primary location and that are directly associated with them or with their metastases. They may occur accompanying an established cancer or as the first sign of malignancy or its recurrence.[4]

The malignancy-associated Sweet's syndrome (MASS) can occur as a paraneoplastic syndrome in patients with solid tumors such as carcinomas of the genitourinary tract, breast, and gastrointestinal tract or related to hematologic condition including myeloproliferative, lymphoproliferative, and myelodysplastic disorders. Among the hematologic malignancies most commonly associated with Sweet's Syndrome is Acute Myeloid Leukemia (AML).[5]

Herein, we report a case of Myelodysplastic Syndrome (MS) that evolved to AML with concurrent SS as a skin paraneoplastic condition.

Case Report

A 23-years-old female patient, with a history of marijuana addiction for one year, tobacco and alcohol consumption since the age of 17, three abortions before 10 weeks of gestation, previously diagnosed in May 2012, with Human Papillomavirus (HPV) infection by cervical cytology and aplastic anemia by bone marrow aspiration (BMA). She received treatment with Antithymocyte Globulin for 2 cycles (May 2012 and April 2014) and posteriorly Cyclosporin A, with subsequent liver toxicity, changing to Mycophenolate Mofetil and Danazol, with a partial response, requiring multiple hospitalizations and transfusion support, with more than 40 units of globular packages, complicating with transfusional hemosiderosis, treated with Deferasirox. In May 2015, she presented cellulitis of the right thoracic limb, with spontaneous resolution and a secondary atrophic scar. In November 2015, she began with asthenia, adynamia and fever up to 41ºC, predominantly in the evening and a nodular lesion of 3 cm diameter in the upper inner quadrant (UIQ) of the right breast, which increased in size progressively, with very painful violaceous skin lesions, evolving to confluent blisters and later ulceration with non-purulent secretion and necrosis (Figure 1A). She was treated with Dicloxacillin, Piperacillin / Tazobactam and Carbapenemic. In the absence of improvement, stage IIIB breast cancer was suspected, so she was referred in December 2015 to a tertiary level hospital. Upon admission, it was documented the lesion in the right breast, with bleeding nipple, as well as confluent blisters and edema on the outer side of the left thigh (Figure 1B,C). The patient had a non-reactive viral

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Key words: Necrotizing Sweet syndrome, Myelodysplastic syndrome, Acute myeloid leukemia.

Contributions: OVL: formulating the research problem and medical clinical evaluation. AOA: medical clinical evaluation. NPD: dermatologist. MJQR: pathologist. IOG: writing the first original draft, review and editing. ECA: data collection and review of literature. MPCD: critical review of the manuscript. GM: writing, critical review of the manuscript and corresponding author.

Conflict of interest: The authors declare no conflict of interests.

Ethics approval: We obtained the approval of local Ethics comitee.Personal data from the patient are not revealed in the manuscript

Consent to publication: Due to the fact that the patient died,we obtained consent to publication from her relatives.

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panel for HIV, HCV, HBV. A breast skin biopsy revealed a neutrophilic inflammatory infiltrate with no evidence of vasculitis (Figure 2). Treatment with systemic steroid was started, with excellent response and remission of lesions. Imaging tests were performed, as chest x-ray and Thoracoabdominal computed tomography, finding hepatosplenomegaly, the final diagnosis was necrotizing Sweet's syndrome. A month later, a new BMA was performed, finding dysplasia of more than 50% of the cells of the erythroid and granulocytic series, as well as absent megakaryocytes, diagnosing MS. The patient persisted with transfusion support with globular packages and treatment with Mycophenolic Acid. On November 2016, the patient was hospitalized for a 2-week course consistent with fever, anemia and purpuric syndrome, low cardiac output data, syncope, and acute kidney injury. BMA congruent for AML with absent megakaryocytes, 7% adult neutrophils, 2% young neutrophils, 1% lymphocytes, 77% normoblasts, 13% myeloid blasts and 58% myeloid blasts. Immunophenotyping: 32.6% HLA-DR, 29.2% CD34, 36.5% Glycophorin, 2.08% Glycophorin A/34, 28.6% CD117, 53.8% CD13, 51% CD33, 12,7% CD64, 1.9% CD7 and 31.6% CD22. Management began with anti-tumor lysis measures, hemoderivatives, and leukapheresis. Five days after admission, the patient presented respiratory failure, requiring mechanical ventilatory support, progressing to multiple organ failure culminating in death, with final diagnoses of AML subtype M2, aplastic anemia and Sweet's Syndrome.

Discussion

We described a case in a young patient with aplastic anemia that evolved to myelodysplastic syndrome and further to acute myeloid leukemia with necrotizing Sweet syndrome as a paraneoplastic expression of the latter. This hematologic disorder is the most common associated malignancy, being important to carry out the differential diagnosis since breast cancer was initially suspected.[5]

Hematologic disorders represent more than 15-20% of MASS, being AML and MS the most common.[6]

Few cases coincident with MS, AML and SS have been reported in the literature as the case of a 15-year-old girl who presented these three entities with FLT3 and NPM1 type A mutations. Risk factors for MASS in AML encompass deletion of chromosome 5 or 5q, presence of FLT3 mutations, and AML with myelodysplasia-related features. Unfortunately, our patient did not have a karyotype due to a rapid adverse clinical course.[7]

Pourmoussa and Kwan reported another case of an extremely rapid transformation from MS with concomitant SS to AML, in an elderly patient.[8] Our patient also followed that sequence with a fatal ending. Myelodysplastic Syndrome can evolve into AML, which often leads to a poor prognosis.

The outlook of SS is little known, with an incidence of 2.7 at 3 cases/100,000 in the general population.[9] The diagnosis of SS associated with MS with transformation to AML has a low incidence and it is scarcely described in the literature, but of importance in the diagnostic suspicion.

In Mexico, a recent multicenter study identified that AML presents at a younger age in comparison with developed countries, with a median age of onset of 47 years, however this patient presented AML at an earlier age.[10]

SS related to hematological neoplasia may present prior to or concomitant to the primary diagnosis, that means a paraneoplastic event, in the patient occurred concomitantly with acute myeloid leukemia, similar to that reported by Mo *et al.*[11]

Necrotizing SS or acute necrotizing neutrophilic dermatosis is an infrequent and severe variant, distinguished by aggressive skin lesions that can easily simulate and be mistaken for necrotizing soft tissue infections such as necrotizing fasciitis or pyoderma gangrenosum. It is characterized by hyperpyrexia, neutrophilia and painful skin lesions that can be single or multiple, be vesicular, pustular, bullous or ulcerative, and mainly necrosis.[12]

The term Necrotizing SS proposed in 2012 and to date only 4 cases have been reported worldwide, in which patients had concealed hematological diseases and histopathological findings with necrosis of the fascia and fat, simulating necrotizing

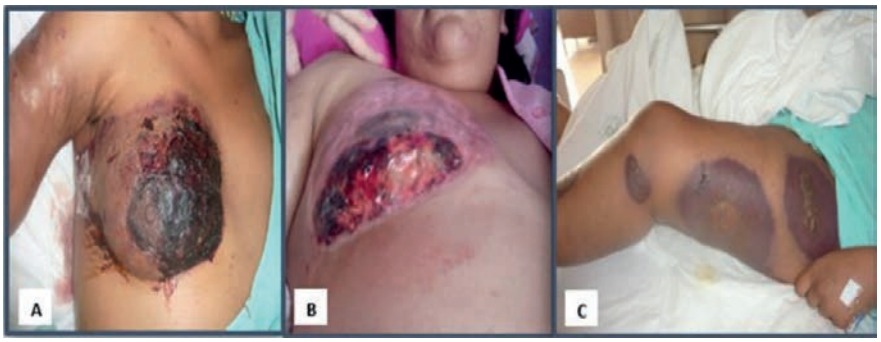

Figure 1. A) Cutaneous necrosis of the right breast. B) Erythematous violaceous plaque with undefined edges, ulcerated with perilesional edema and purpuric raised edges, central blisters, erosion and bleeding nipple; 1C. Lesions on the outer side of the left thigh characterized by confluent blisters and peripheral edema.

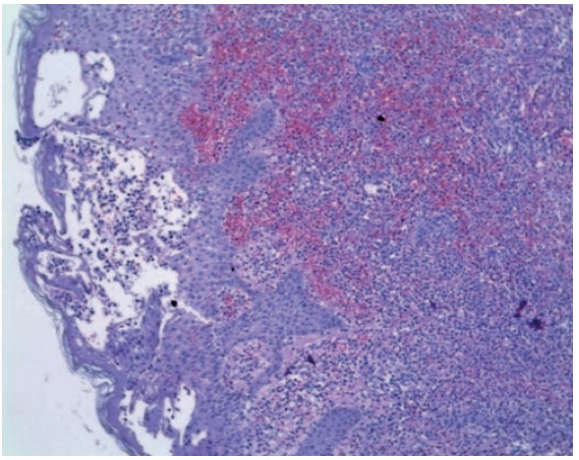

Figure 2. Superficial and deep neutrophilic dermatosis, with spongiform pustules, secondary neutrophilic vascular reaction in small vessels, and added purpuric phenomenon.

fasciitis. Previous cases were males with a median age of 57.5 years of onset, all of them with underlying hematological diseases, however the present case was in a very young woman with an aggressive clinical course.[13]

This entity may be confused with other pathologies, among the most common differential diagnoses that mimic SS are bacterial, mycobacterial, fungal, and parasitic infections. To avoid this, a biopsy should be considered to detect characteristic features consistent with SS.[5] This disease has a low incidence and is little described in the literature. Communications of fatal outcomes of Sweet's syndrome are uncommon, as it is depicted as an idiopathic chronic systemic inflammatory response syndrome or as in this case, related to malignancy with a fatal outcome in a young patient.[1,14]

Conclusions

Sweet syndrome is a rare entity that may appear as a sign of malignancy, as in the present case, in a young patient with fatal outcome. It is necessary to have a high index of suspicion to recognize it and identify the underlying disorder.

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The association between activity levels and skin moisturising function in adults

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Abstract

Factors associated with skin moisture retention include age and lifestyle, such as diet and sleep efficiency. However, the impact of exercise habits on skin moisturising function is unclear. We surveyed 86 participants from a Japanese university about their activity levels using the International Physical Activity Questionnaire. We also examined their skin moisturising function, measuring stratum corneum (SC) hydration levels and transepidermal water loss (TEWL). Comparisons of participants' activity levels, SC hydration, and TEWL, accounting for their gender and age differences, revealed activity levels significantly related to differences in SC hydration levels. Results of multiple comparisons showed increased activity relates to significantly higher SC hydration − the higher the activity levels, the higher the hydration. No difference was found in TEWL. The results suggest exercise habits can prevent dry skin. The findings may be useful for the prevention and treatment of dry skin and promoting the benefits of exercise.

Introduction

Skin problems can develop regardless of age, and skin problems can range from acne in young people to dryness in the elderly. These conditions may cause mental anxiety and physical issues such as itchiness, thereby negatively affecting one's quality of life (QoL).[1,2] Keeping the skin in good condition is important for both physical and mental health. It is, therefore, important to maintain proper skin conditioning.

Important functions of the skin include moisture retention, which regulates the release of water from the inside of the body to the atmosphere, and the barrier function, preventing chemicals and microbes from the environment from entering the body.[3] The stratum corneum is important to both the moisturising and barrier functions.[4] Skin problems are caused by disruption of the skin barrier function[3] moisturising and barrier function are strongly related.[4] Trans-Epidermal Water Loss (TEWL) and stratum corneum (SC) hydration are useful for measuring the skins' moisturising and barrier functions.[3,5] In previous studies, researchers have examined these indicators and have identified several factors that affect these functions (*e.g.* daily skincare habits, bathing habits, smoking, rest, diet, etc.).[6-13]

However, the association between skin moisturising and barrier function and exercise is not well understood. Known effects of exercise on the skin are blood flow motion increases[14] and changes in skin temperature.[15] It is also known that SC hydration increases temporarily immediately following a single high-intensity exercise session but significantly decreases after 120 minutes to a level lower than before the bout of exercise.[16] On the other hand, compared to occasional, single sessions of exercise, a long-term endurance exercise habit yields improvements to the exerciser's skin structure, such as to the stratum corneum thickness.[17,18] The decrease in SC hydration after exercise is caused by sweating, which causes the stratum corneum to swell, increasing the outflow of hydro-soluble natural moisturising factors.[16] This effect of SC expansion on SC hydration is transient.[16] The short-term and long-term effects of exercise on the skin moisturising function need to be interpreted separately. It is not clear whether the impacts on the skin differ according to the term of endurance exercise or the intensity of endurance exercise.

Therefore, it is necessary to examine the effects of medium- to long-term exercise habits on the skin moisturising and barrier functions. This study examined the relationship between exercise habits and skin moisture retention and barrier function in the last month. If the relationship between the moisturising function of the skin and the level of exercise is clarified, a new option for exercise instruction will emerge as a method for preventing skin trouble in clinical practice.

Materials and Methods

Study design

This cross-sectional, observational study was conducted in Japan from July to October 2019.

Participants

We recruited students and staff from X University to ensure the participant group represented a wide range of ages. However, those with chronic skin diseases such as atopic dermatitis were excluded. Thus, a total of 86 participants without skin disorders were thus recruited. This study was conducted as part of a health check-up program to modify lifestyle habits. All participation was voluntarily.

Data collection

This study analysed two skin moisturising function parameters based on data from self-administered questionnaires concerning participant exercise habits. We confirmed that no responses had been omitted when collecting the questionnaires. All participants completed these in a room set to a

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Key words: Lifestyle, exercise, skin physiological phenomena, skin ageing.

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Contributions: RO, YS, and HA conceived and designed the study. RO contributed to obtaining and analysing the data. RO, YS, and HA drafted and revised the manuscript. All the authors critically reviewed and approved the submitted version of the manuscript.

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Ethics approval and consent to participate: This study was conducted after gaining permission from the research ethics committee of University Graduate School of Nursing (Approval No. 2019-29). Consent was obtained before submission.

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temperature of 20-22°C, with humidity levels measuring between 40-60%. Skin moisturising function parameters were measured after 20 minutes of rest in the room where the questionnaire was answered.

The self-administered questionnaire included questions regarding sex, age, and exercise habits. Exercise habits were measured using the Japanese version of the International Physical Activity Questionnaire-short version (IPAQ-SF).[19] Reliability and validity were previously confirmed.[20] The intensity of exercise was divided into three activity levels according to the responses to IPAQ. The questionnaire was analysed according to the guidelines.[21]

Skin moisturising functions were evaluated based on TEWL and SC hydration. TEWL measurements were taken from the centre point of each participant's right forearm (8 cm point on the palm side from the elbow fossa centre). This method was used due to the ease of obtaining stable values.[8] All measurements were performed for 20 seconds; the average value from the last 10 seconds was used as data. The Tewameter TM300 was used for this purpose (Courage + Khazaka electronic GmbH, Köln, Germany).

To influence the measurement index,[8] we requested that participants adhere to the following three rules:

i. Do not apply body cream or similar substances to the measurement site for at least 12 hours prior to the measurement.
ii. Do not consume caffeinated beverages (e.g., coffee or tea) or smoke for at least three hours prior to the study.
iii. Do not engage in strenuous exercise for at least one hour prior to the study.

Ethical consideration

This study was conducted after gaining permission from the research ethics committee of University Graduate School of Nursing (Approval No. 2019-29). Participants were informed that they had the right to decline participation and could withdraw from the study at any time. Participation was completely voluntary, and all participants received both oral and written information about the study purpose, contents, and extent. They were assured that all responses were confidential. Specifically, participant confidentiality was protected by giving each participant a unique code number prior to data collection and analysis. Also, collected questionnaires were kept in a locked cabinet. Consent checkboxes were included on each questionnaire form; participant consent was indicated by checking the respective boxes before submitting the forms.

Data analysis

All data were calculated by a web application named langtest.jp at http://langtest.jp (accessed July 1, 2020).[22] Descriptive statistics were presented as means and standard deviations (SD) for continuous variables, while numbers (%) were used for categorical variables.

Differences between activity level (Low, Moderate, or High) and skin moisturising function were examined using Kruskal–Wallis test. Pairwise comparisons were completed using the Mann-Whitney U test and the Holm adjustment to control for Type I errors across tests. We deemed *p*-values less than 0.05 to be significant.

Results

Table 1 shows participants' characteristics and skin function, and Kruskal-Wallis test results. Data from all 86 participants were included in the analyses. Many of the participants were women (83.7%). The median (Min, Max) age was 30.0 (20, 62) years. There was no difference in age between activity levels (p=0.92) and no difference in TEWL (p=0.22). However, there was a statistically significant between activity level in SC (p<0.001).

To the difference of each group gender ratio were large, confirmed that there was no difference in the skin moisturising function between the genders (Table 2). Since there was a significant difference in SC between activity levels, a pairwise comparison was performed. Figure 1 shows the distribution of SC in each group. All pairwise comparisons were statistically significant (Table 3). The higher the activity level, the higher the SC. The Effect size [95% CI] was large between Low and High (r = 0.52[0.26, 0.70]).

Discussion

We investigated the association between activity level and skin-moisturising function using a self-administered ques-

Table 1. Characteristics and skin function of participant.

Characteristics and skin function (n=86)	Total sample (n=34)	Low level (n=42)	Moderate level (n=10)	High level	P-value
Age, median (min, max)	30.0 (20, 62)	33.0 (20, 57)	29.5 (20, 62)	28.0 (21, 56)	0.92
Gender, n (%)					
Male	14 (16.3)	3 (8.8)	6 (14.3)	5 (50.0)	
Female	72 (83.7)	31 (91.2)	36 (85.7)	5 (50.0)	
SC, median (min, max)	38.5 (22.7, 56.1)	34.4 (24.3, 48.8)	39.9 (22.7, 53.4)	46.5 (35.1, 56.1)	<0.001
TEWL (g/h/m^2), median (min, max)	4.96 (2.42, 8.95)	4.86 (2.42, .95)	4.80 (2.56, 7.13)	6.06 (2.71, 8.43)	0.22

Kruskal-Wallis test.

Table. 2. SC and TEWL between genders.

	Male (n=14)	Female (n=72)	z-value	P-value
SC, median (min, max)	40.5 (27.8, 53.4)	38.25 (22.7, 56.1)	-1.176	.240
TEWL (g/h/m^2),median (min, max)	4.62 (2.42, 8.35)	4.99 (2.56, 8.95)	-1.234	.217

Mann-Whitney's U test.

Table 3. Comparison of SC between each group.

	z-value	P-value	Effect size (r) [95% CI]
Low-Moderate	-2.722	0.01	0.31 [0.09, 0.50]
Low-High	-3.417	<0.01	0.52 [0.26, 0.70]
Moderate-High	-2.415	0.02	0.34 [0.07, 0.56]

Mann-Whitney's U test.

tionnaire about exercise habits and by examining two kinds of skin moisturising and barrier function. The results suggest that active people have moist skin.

In previous studies, long-term endurance exercises habits have been shown to improve skin structure,[17,18] but, after a single endurance exercise, SC hydration is reduced.[16] However, these studies did not clarify the association between exercise habits and skin's moisturising function. An important finding of this study is that exercise habits may improve skin moisturising function and that higher-intensity exercise may promote the skin-moisturising function.

This study results showed the moderate- and high-activity level habit groups have high skin moister levels than the low-activity level habit group. This result suggests that exercise habits may improve skin moisturising function. Declines in skin functions, such as skin moisturising and barrier function, are thought to be driven by pronounced mitochondrial DNA deletions.[23] Therefore, it is necessary to stimulate mitochondrial biosynthesis to improve skin function. Endurance exercise induces IL-5, and IL-5 promotes biosynthesis mitochondria; thus, skin construction improves.[18] Skin construction is associated with SC hydration.[4] The moistened skin of active individuals may be due to improved skin structure due to mitochondrial biosynthesis. Exercise habits can improve the structure of the skin and improve the skin's moisturising function. However, it is not clear what type of exercise is most effective for this purpose. The IPAQ used in this study does not provide specific exercise details. Therefore, it is not clear whether the participants' exercise was endurance exercise or not. Possible differences in the effects of different types of exercise, such as endurance training compared to strength training, on skin moisturising function should be investigated. Additionally, results from previous studies have suggested that diet and sleep efficiency also affect skin moisturising function.[12,13] Thus, further studies with adjustments for factors such as dietary habits and sleep are needed, as exercise may also improve sleep conditions.[24]

One of the factors in the lack of relationship between activity level and TEWL may be that participants in this study were not older, and not had skin diseases. TEWL depends on physical structures such as the lamellar bodies of the stratum corneum, [25] the structure of which is deteriorated by chronic dermatitis and ageing.[26,27] Therefore, the healthy adults who participated in this study had healthy stratum corneum structure with no factors that could worsen its structure. Exercise improves the structure of the stratum corneum in older adults,[18] but this may only be effective for those with originally deteriorated stratum corneum structure. Future studies should be conducted in the elderly and people with skin diseases to clarify the relationship between TEWL and activity levels.

The results of this study suggest that exercise may increase SC hydration. SC hydration has an association with skin barrier function.[4] Therefore, as exercise raises SC hydration, exercise may prevent skin problems. Hence, studies should also be conducted to determine if the increases SC hydration resulting from exercise can prevent the development of skin problems.

There are several limitations to the present study. First, cross-sectional studies cannot prove causality. Therefore, further investigation by a prospective study is necessary. Second, our study participants were limited to people belonging to one university, and the group was mostly comprised of women. Thus, studies with diverse participant groups are necessary. Despite these limitations, this study results provide evidence of an association between activity level and SC hydration. Further research will help to raise awareness of the exercise to dermatology patients and people living in the community.

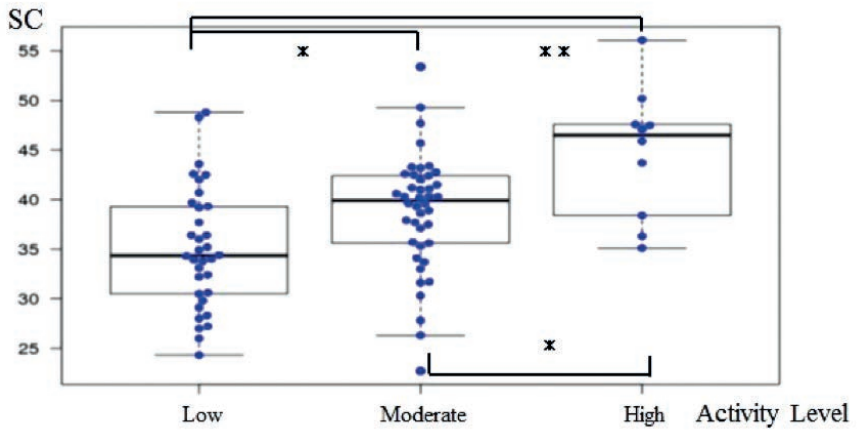

Figure 1. Distribution of SC in each group. *<0.05 and **<0.01.

Conclusions

People with higher activity levels are likely to have higher SC hydration than those with lower activity levels—the higher the activity level, the higher the SC hydration. Exercise improves the skin's ability to retain moisture and may prevent future skin problem. Further studies into this relationship may help in the treatment of dry skin and related skin problems.

These results, along with those from future studies with diverse participants, may assist dermatologists and primary care doctors in advising their patients about skin problems and hydration. They may also be used in public service announcements and health-related promotional materials describing the benefits of regular exercise.

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Ethnicity is a major determinant of the pattern of dermatological diseases among pilgrims during the *Hajj* in 2019

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Abstract

The authors aim to explore the pattern and demographics of dermatological disorders occurring during Hajj 2019. Clinical records from three major public healthcare facilities in Al-Madinah Al-Munawara were retrieved for the period July-August, 2019. Collected data included age, gender, nationality, and dermatological complaints. 550 records were retrieved. Patients were 282 (51.3%) males and 268 (48.7%) females with a mean age of 58.3±12.6 years. Most patients were Asians (n=320, 58.2%), and Africans (n=183, 33.3%). Accidents (n=226, 41.1%), and infections (148, 26.9%) were the most common complaints. Asians and Africans had significantly: more accidents and less infections (P=0.002, P=0.027 respectively). They were the only category affected by exacerbations of auto immune diseases. Asian and African pilgrims are mainly affected by traumatic dermatologic conditions. Preventive awareness programs should target these ethnicities to reduce their higher rates of accidents. Other ethnicities need programs that promote hygienic practices and target infections.

Introduction

Hajj (Pilgrimage) is one of the five obligatory religious rituals required from all Muslims if they have the physical and financial ability to meet its demands. The ritual takes place in certain parts of the city of Makkah during five specific days of the last month of the Hijri (Lunar) year. Under normal circumstances more than 2 million people of various ethnicities and different age groups practice this ritual in a characteristic mass gathering.[1] The enormous number of people gathering under harsh weather conditions is often associated with ensuing adverse health conditions and emergency situations particularly when crowding and lack of hygienic standards act as additional confounders.[2]

Various health problems may be encountered during Hajj season, posing major challenges to the healthcare system. Among these health problems, dermatologic conditions stand out as a poorly investigated category which necessitates further studies to clarify their nature and impact on the healthcare system. Skin diseases are a major cause of consultations in primary care.[3] They are the third most frequent disease category encountered in primary care among pilgrims next to respiratory and gastrointestinal diseases.[4] More recent studies report that they are the second most frequent disease category.[5] This may indicate that there is a changing trend in the epidemiology of skin diseases over the years favoring increased prevalence.

Studies investigating skin diseases among pilgrims are scarce and relatively old dating more than a decade ago.[4,6] Further, none investigated patients during other stages of Hajj season when many pilgrims opt to visit Al-Madinah which is the second most holy city in Islam, to pray in the second most holy mosque (Al Masjid Al Nabawi) and visit the tomb of Prophet Mohammad.[7] During this visit most pilgrims often feel worn out, due to fatigue and disturbed sleep associated with long distance travel which increases their susceptibility to various diseases. It is important to explore the recent trends in epidemiological aspects of skin diseases taking into consideration: its high frequency among pilgrims, anticipated impact on healthcare system and pilgrims' quality of life.

Therefore, we conducte this study to explore we conducte this studypattern and distribution of dermatologic conditions affecting pilgrims during their visit to Al-Madinah in Hajj season and investigate possible association with important demographic factors like age, gender and ethnicity.

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Key words: Al Madinah; Hajj, Pilgrims, Dermatological diseases, Ethnicity.

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Materials and Methods

Three major public healthcare facilities (two hospitals and one primary healthcare center) within Haram area (close to Al-Masjid Al-Nabawi) participated in the study during July-August, 2019. These facilities were allocated by the Ministry of Health for providing treatment to pilgrims. Clinical records of patients attending dermatology and emergency departments were included. All pilgrims with any skin condition that presented to any of these three centers were enrolled in this study. Records of patients who were residents in Al-Madinah were excluded as they were not pilgrims. Collected data included: age, gender, ethnicity, diagnosis of the dermatological condition, and its duration (onset) in days.

The research was conducted in complete accordance with the principles of the World Medical Association Declaration of Helsinki. Ethical approval was obtained

from Institutional Review Board, General Directorate of Health Affairs in Al-Madinah, reference #H-03-M-084.

Statistical analysis

Data were coded and analyzed using IBM SPSS software for windows (SPSS version 21 software, Armonk, NY: IBM Corp). Descriptive statistics were conducted to describe frequencies and percentages. Chi-square test was used to estimate statistical significance of difference between groups of age, gender and ethnicity. Statistical significance was considered at P≤0.05.

Results

A total of 550 clinical records were retrieved from the three healthcare facilities. Mean age of patients was: 58.3±12.6 years, age range was: 11-90 years. There were 282 (51.3%) males and 268 (48.7%) females. Patients were seen in these healthcare facilities within 1-28 days from the onset of the symptoms with a mean (SD) duration of: 2.24 (2.5) days. Most patients were from Asia and Africa, and they were distributed as follows: Asia (n=320, 58.2%), Africa (n=183, 33.3%), Europe (n=20, 3.6%), North America (n=12, 2.2%), South America (n=12, 2.2%) and Australia (n=2, 0.4%). The pilgrims were affected by different dermatologic conditions including accidents (n=226, 41.1%), infections (n=148, 26.9%), eczema (n=66, 12%), burns (n=54, 9.8%), allergies (n=30, 5.5%), exacerbations of autoimmune diseases (n=26, 4.7%) as presented in Table 1.

Cross tabulation (Table 2) of gender and age groups (<60 and ≥60 years) with various skin conditions did not show significant variations between elderly and the younger pilgrims nor between males and females regarding the occurrence of various conditions with P value >0.05. However older age group was more prone to: infections (28%), autoimmune diseases (3.5%) and connective tissue diseases (2.1%).

Pilgrims were categorized into three ethnic categories based on their numbers: African, Asian, and others (North America, South America, Europe and Australia). African and Asian pilgrims had significantly: more accidents and less infections than other pilgrims (P=0.002, 0.027 respectively) (Table 3).

Regarding the time that elapsed from onset of signs and symptoms till the time the patients were seeking treatment, it was found that these conditions were of acute nature as 60.4% of patients presented for medical attention on the same day of the complaint, and more than 90% presented within 4 days.

Discussion

Hajj could be associated with development of adverse health incidents like skin diseases; investigating which will help organize healthcare services so that neither pilgrims' spiritual activities are disturbed, nor services of the healthcare system are jeopardized. Only few studies investigated the epidemiology of skin complaints among pilgrims,[6,7] which highlights the need for further and recent studies.

There were no significant differences between males and females in all categories of skin conditions, however, females showed a slight predilection for accidents and exacerbations of connective tissue diseases. While it is difficult to interpret the higher prevalence of accidents among females, higher prevalence of connective tissue disease exacerbations could be attributed to the established correlation between this category of diseases and the female gender, particularly for bullous diseases and SLE.[8]

Pilgrimage is highly competitive and governments give priority to older people, this explains why the mean age of patients stands high at: 58.3 years. Pilgrims from Asia and Africa were the most commonly affected ethnic groups with skin diseases. These diseases were mostly due to accidents. The vulnerability of other ethnic groups to accidents may be explained by differences in safety measures they practice. Asians constitute the largest proportion of pilgrims each year. The large numbers associated with overcrowding during the practice of Hajj rituals may pose health risks for the older and vulnerable age groups. Mass movements of pilgrims can increase susceptibility to accidents like falling, stampede, and traffic accidents, which may be aggravated by language and culture barriers.[9] It is

Table 1. Types of skin diseases encountered in pilgrims.

Accidents	Infections	Eczema	Burns	Allergies	AID exacerbations
- Skin cut wounds/abrasions - Open fractures - Displaced nails	- Bacterial: pyoderma, abscesses, cellulitis, furuncles - Viral: herpes labialis, zoster - Fungal: tinea cruris, tinea pedis, pityriasis versicolor	- Contact dermatitis - Atopic dermatitis - Xerotic eczema, intertrigo - March blisters - Dry lips and dry skin	- Sun exposure - Walking shoeless - Holding hot objects - Spills of hot water	- Drugs - Insect bites - Food	- Pemphigus vulgaris - Bullous pemphigoid - Psoriasis - SLE

AID: Autoimmune diseases; SLE: Systemic lupus erythematosus.

Table 2. Cross tabulation showing differences between genders and age groups for the various conditions and significance level.

	Disease categories, number (%)						
	Accident	Burn	Infection	Allergy	Eczema	AID	CTD
Age groups							
<60 years	109 (41.8)	26 (10.0)	67 (25.7)	16 (6.1)	33 (12.6)	6 (2.3)	4 (1.5)
≥60 years	117 (40.5)	28 (9.7)	81 (28.0)	14 (4.8)	33 (11.4)	10 (3.5)	6 (2.1)
P value	0.761	0.507	0.914	0.659	0.534	0.418	0.634
Gender							
Female	119 (44.4)	12 (4.5)	22 (8.2)	29 (10.8)	71 (26.5)	8 (3.0)	7 (2.6)
Male	107 (37.9)	18 (6.4)	32 (11.3)	37 (13.1)	77 (27.3)	8 (2.8)	3 (1.1)
P value	0.124	0.325	0.216	0.407	0.830	0.918	0.174

AID: Autoimmune disease exacerbations; CTD: connective tissue disease exacerbations

not always possible to limit the numbers of pilgrims. Hajj season of 2020 was a very special case associated with corona virus disease-2019 (COVID-19), whereby very minimal numbers of pilgrims were allowed to perform Hajj to prevent spread of the virus. However, it was evident that limited numbers have allowed for the highly organized rituals mitigating the risk of developing accidents. Plans to organize the movement of pilgrims can take into consideration implementation of relevant legislations to mandate registration with organized campaigns and employment of easily readable multi-language signs for pilgrims to read and follow. It is also recommended to provide rest areas and different means of transport particularly for elderly pilgrims. Providing education on Hajj rituals and increasing awareness on proper behaviors in mass gatherings should be initiated in home countries before the start of Hajj journey.

Skin infections among pilgrims are one of the most commonly reported skin problems.[10] This might be due to: overcrowding, heat, humidity, and insufficient hygienic practices which all contribute to compromised immunity and opportunistic infections. Viral herpetic infections were common among pilgrims being associated with extremes of age, and weakened immunity arising from fatigue, lack of sleep, and stressful conditions. Adverse environmental conditions that are common during pilgrimage like: heat, sun exposure, thirst, crowding, traffic congestions and language barriers all represent major sources of stress.[11] Patients who have recurrent episodes of oral herpes infections and who are expected to travel to sunny areas, can be advised to use a short oral course of acyclovir or famciclovir to suppress viral activation.[12] On the other hand, zoster should be identified and treated within the first 72 hours of infection to prevent the debilitating complication of post-herpetic neuralgia. A highly effective vaccine is available against this infection, and it is usually administered to susceptible patients in two doses separated by two to six months.[13]

Bacterial infections also affected pilgrims such as pyoderma.[10] The predisposing factors include poor hygiene, trauma and overcrowding which allow easy spread of pathogens. It is important to address these predisposing factors and apply appropriate preventive measures because treatment may be difficult, and prognosis may be worsened by antibiotic bacterial resistance.[10] Other bacterial skin infections reported in this study include cellulitis, an infection that may be complicated by diabetes mellitus.[14] Although most of these infections are responsive to antibiotics, care should be taken so as not to overprescribe antibiotics for pilgrims and consequently encourage the development of bacterial resistance and other side effects of antibiotics.[15]

Fungal infections were in the form of tinea infections including tinea cruris, tinea pedis. and pityriasis versicolor. Tinea cruris characteristically affects pilgrims due to the warm, humid weather conditions, and wearing Ihram clothes, which are wrapped around their bodies. Tinea pedis may also be associated with excessive sweating and insufficient drying of skin following ablution. Prevention is the most important means to reduce incidence of these infections by following hygienic practices, wearing cotton clothes,[16] and avoid sharing clothes and towels.

Eczema accounted for only 12% of all skin disorders. Higher percentages of 23.8% and 24.8% were reported among pilgrims during their stay in Makkah where the weather is humid and warmer.[8,7] March blisters are also reported. These could hinder the pilgrims' movement and affect their ability to meet their rituals.

Sun burns were reported in this study. These are preventable, and pilgrims can be advised to avoid sun from 10 am to 4 pm, wear protective clothes, avoid walking shoeless, and use sunscreens and umbrellas.

Allergies (urticarial) were the fifth most common documented skin disorder. Previous studies reported that it is the fourth most common skin disorder.[7] It is important to highlight the importance of taking a thorough medical history from patients regarding the history of allergies and to exclude a positive history of food or drug allergy before prescribing any medications particu-

Table 3. Ethnicity in association with various dermatological findings.

	Ethnicity, n (%)			P value
	African	Asian	Others	
Accidents				0.002*
No	105 (57.4)	180 (56.3)	39 (83.0)	
Yes	78 (42.6)	140 (43.8)	8 (17.0)	
Burns				0.192
No	168 (91.8)	289 (90.3)	39 (83.0)	
Yes	15 (8.2)	31 (9.7)	8 (17.0)	
Infections				0.027*
No	132 (72.1)	243 (75.9)	27 (57.4)	
Yes	51 (27.9)	77 (24.1)	20 (42.6)	
Allergy				0.613
No	173 (94.5)	304 (95.0)	43 (91.5)	
Yes	10 (5.5)	16 (5.0)	4 (8.5)	
Eczema				0.809
No	162 (88.5)	282 (88.1)	40 (85.1)	
Yes	21 (11.5)	38 (11.9)	7 (14.9)	
AID			0.418	
No	178 (97.3)	309 (96.6)	47 (100.0)	
Yes	5 (2.7)	11 (3.4)	0 (0.0)	
CTD				0.563
No	180 (98.4)	313 (97.8)	47 (100.0)	
Yes	3 (1.6)	7 (2.2)	0 (0.0)	

AID: Autoimmune disease exacerbations; CTD: connective tissue disease exacerbations. *Statistically significant difference.

larly antibiotics and nonsteroidal anti-inflammatory drugs.[17]

Fortunately, the rate of acute exacerbations of autoimmune diseases like pemphigus vulgaris in this study was very low. Hajj long journey may be stressful to some pilgrims. This stress is likely to play a role in triggering flare in autoimmune diseases.[18] Although autoimmune vesiculobullous diseases are rare, they may have severe clinical manifestations, and treatment in the form of immunosuppressants should be prompt and aggressive to prevent complications.[19] Further, many of these patients are considered immunocompromised because of prolonged intake of immunosuppressants like corticosteroids which can have adverse effects by complicating the clinical outcomes.[20]

The study has limitations being retrospective in nature with the possible occurrence of unknown potential confounders.

Conclusions

It seems that pilgrims from Asia and Africa, who are the majority of pilgrims, are mainly prone to dermatological accidents, followed by infections, eczema and burns. Most of these diseases are preventable by employing safety measures, implementing hygienic standards and applying protective measures against adverse weather conditions. Public health measures, and international collaboration in monitoring pilgrims' numbers and initiating awareness programs prior to Hajj season are a priority. Utilization of social media in the respective countries can also be considered.

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Erythema ab igne masking cutaneous metastasis of colorectal adenocarcinoma

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Abstract

Skin metastasis commonly manifest as subcutaneous or intradermal violaceous nodules that coalesce with a firm rubbery appearance. Few cases reported an erythema *ab igne*-like appearance in the presence of internal malignancy. We report a case of metastatic colorectal adenocarcinoma with erythema *ab igne*-like presentation. We also review cases of erythema *ab igne* in association with internal malignancy.

Introduction

Although skin is the largest organ of the human body, cutaneous metastasis is quite uncommon with an incidence of 5.3%.[1] It is particularly rare for colorectal adenocarcinoma to metastasize to the skin.[2,3] Morphologically, cutaneous metastasis commonly manifest as subcutaneous or intradermal violaceous nodules that coalesce with a firm rubbery appearance.[4-6] Other reported manifestations include erythematous, plaques, bullous, and ulcerative lesions.[4-6] However, to the best of our knowledge, erythema *ab igne*-like presentation has never been reported as a feature of cutaneous metastasis. We report a case of colorectal adenocarcinoma cutaneous metastasis with erythema *ab igne*-like morphology.

Case Report

A 60-year-old female known to have sigmoid adenocarcinoma with peritoneal and omental metastasis on chemotherapy presented with a two-month history of a progressive and asymptomatic periumbilical lesion. On examination, there was a solitary, red-brown, reticular, indurated, periumbilical plaque (Figure 1). The morphology of the plaque was vaguely suggestive of erythema *ab igne*. The patient gave a history of applying heat pad on the abdomen for 3 months to relieve the associated pain. Given the presence of induration and internal metastases, a skin biopsy was preformed to rule out cutaneous metastasis. Histopathological examination revealed cutaneous metastatic carcinoma consistent with colonic adenocarcinoma. The neoplastic cells were strongly positive for CK20 and negative for Chromogranin (DAK-A3) (Figure 2). The patient died a month later due to the metastatic adenocarcinoma.

Discussion

Malignancies, especially of colorectal origin, rarely metastasize to the skin. In two large studies, only 3 (0.1%) out of 2538 and 18 (4.4%) out of 413 colorectal cancer patients had cutaneous spread.[2,7] It is infrequently reported as the presenting sign of an occult colorectal cancer in only 0.05% of patients.[8] In addition it indicates an advanced stage and dismal prognosis, occurring years after diagnosis.[9,10]

Recognizing cutaneous metastases remains a challenge for clinicians due to the wide spectrum of presentations. The most commonly reported presentation of cutaneous metastasis of any malignancy is nodular lesions. Other less frequent presentations include inflammatory erythema, ulcers, plaques, blisters, and teleangectasia.[4-6] We report an atypical morphological manifestation of erythema *ab igne* with an underlying cutaneous metastasis that diag-

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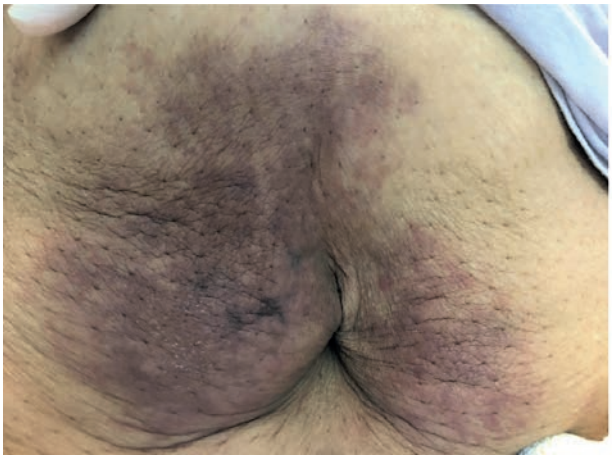

Figure 1. Periumbilical erythema *ab igne*.-like lesion.

nosed based on biopsy. A thorough search in the literature resulted in only 11 reports of incidental *ab igne* lesions, mostly with history of heat exposure, in patients diagnosed with malignancy (Table 1).[11-17] Interestingly, most patients were elderly males with gastrointestinal cancer. Erythema *ab igne* was observed mainly on the back followed by the abdomen which possibly reflect common sites of heat application. In addition, erythema *ab igne* lesions were the first sign of an occult internal malignancy in 50%. However, due to lack of a skin biopsy and positive history of heat application, secondary cutaneous malignancy was not shown in any of the reports.

Jones *et al.* suggested an explanation to the relation between erythema *ab igne* and malignancy. They hypothesized that erythema *ab igne* is the result of frequent application of heat to manage the pain associated

Table 1. *Ab igne* in the presence of history of malignancy.

Author, year	Age	Gender	Primary malignancy organ	Skin lesion site	Lesion detection	Heat exposure	Survival
Mok *et al*. 1984[12]	68	F	Pancreas	Back	Before Dx	No	Died
Ashby *et al*. 1985[13]	67	F	Breast	Buttock and thigh	Not mentioned	No	Died
Ashby *et al*. 1985[13]	84	M	Lung	Abdomen	Not mentioned	No	Died
Ashby *et al*. 1985[13]	38	M	IgG myeloma	Back	Not mentioned	Radiation therapy	On palliative
Ashby *et al*. 1985[13]	78	M	Rectal	Perineum and buttock	Before Dx	Yes	On palliative
Ashby *et al*. 1985[13]	65	F	Renal	Abdomen	4 months after Dx	Yes	No mention
Halliday *et al*. 1986[14]	45	M	Gastric	Abdomen and back	Not mentioned	Yes	No mention
Mac Hale *et al*. 2000[15]	36	F	Rectal	Back	Before Dx	Yes	Succumbed
Mac Hale *et al*. 2000[15]	34	M	Unknown primary	Abdomen and back	Before Dx	Yes	Succumbed
Molina *et al*. 2010[16]	45	M	Colorectal	Perineum and buttock	Before Dx	Yes	Improved
Bunick *et al*. 2014[17]	66	F	Pancreas	Back	Before Dx	Yes	No mention
Present patient	60	F	Rectal	Abdomen	After Dx	Yes	Died

Dx: Diagnosis.

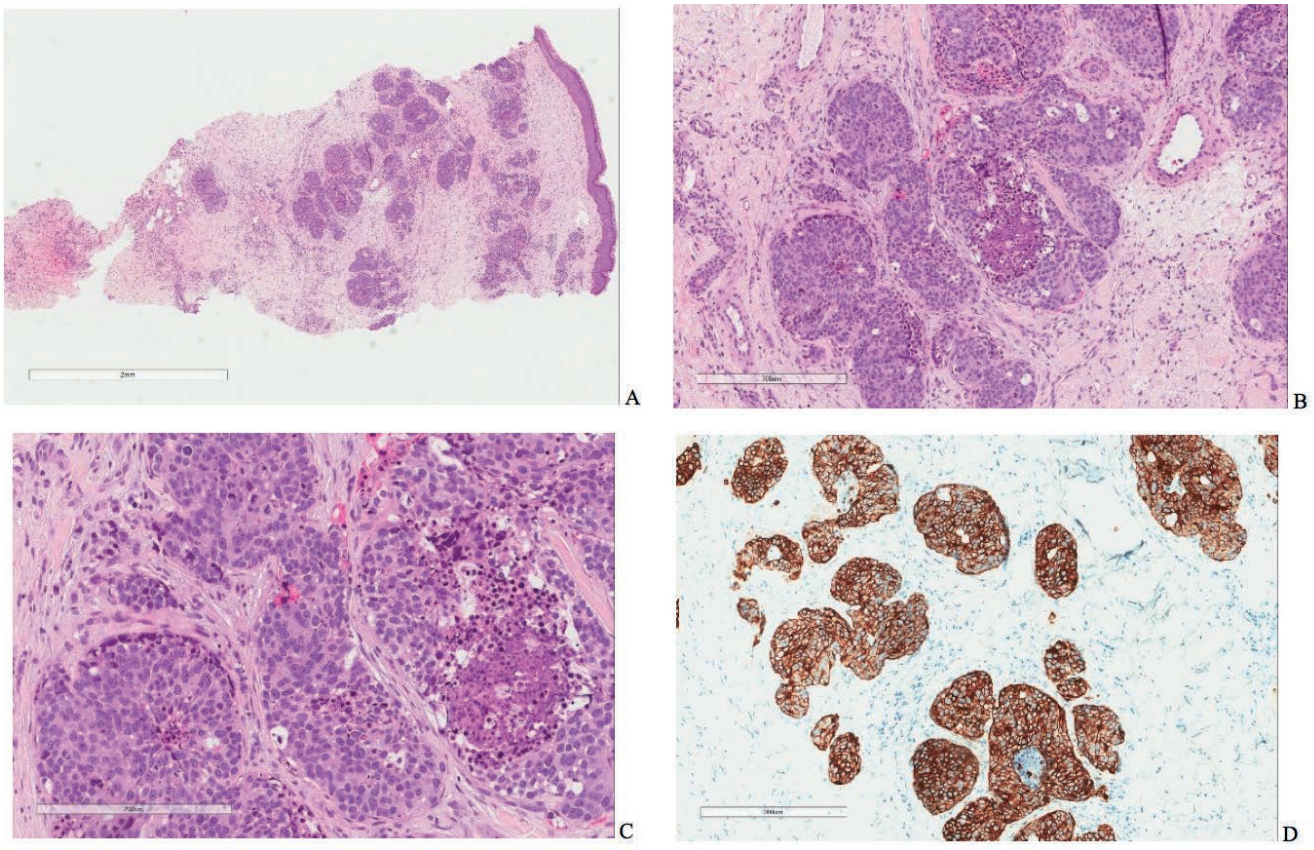

Figure 2. A) Sample composed of epidermis with underlying dermis and subcutaneous fat shows adenocarcinoma extending from upper dermis toward subcutaneous fat. B) The adenocarcinoma islands are composed of cohesive small glands with scattered areas of necrosis. C) The tumor cells are uniform irregular with large nuclei and several mitoses. The area of necrosis is also seen. D) The tumor cells express strong cytokeratin (CK) 20 immunostaining.

with occult internal malignancy.[11] Our patient used heat pads for the same purpose and the erythema *ab igne* masked the underlying cutaneous metastasis.

Conclusions

We report a rare case of colorectal adenocarcinoma cutaneous metastasis diagnosed based on biopsy that morphologically presented as erythema *ab igne*. By sharing this report, we aim to stress the wide range of presentation of cutaneous metastases, and to bring awareness to the possibility of metastasis when encountering erythema *ab igne* in cancer patients.

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The effect of COVID-19 emergency in the management of melanoma in Italy

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Abstract

The COVID-19 pandemic has severely hampered the functioning of any health system, absorbing a considerable amount of resources and with the threat of widespread infection in the health services. The present survey has been carried out in Italy to evaluate if and how COVID-19 also affected skin melanoma management. We enrolled 13 Italian centres highly qualified in the diagnosis and care of skin melanoma. We compared a set of information evaluating the amount of activity for melanoma performed during February-April 2020 with the same quarter in 2019. The number of new melanoma diagnosis, biopsies, wide local excisions, overall pathology reports decreased. However, the most severe cases seem promptly managed with sentinel lymph node biopsies, new systemic treatments (north) and the total number of (advanced) treated patients (centre-south). The COVID-19 experience has underlined the need to exploit the help which may come from telemedicine.

Introduction

The COVID-19 pandemic has caused, in addition to the specific effects, also a significant obstacle to the normal functioning of Health Services not directly related to the diagnosis and treatment of these patients. This effect due to rules to avoid infection spread in the health sector has recently been underlined, for its globality and severity, also by the World Health Organization.[1]

Substantially all types of services have suffered this backlash from the pandemic, with negative consequences for patients, even those suffering from serious diseases. The WHO states that 42% of the 155 countries investigated reduced or stopped the services aimed at cancer patients due to Codiv-19. In Italy, the first two cases of COVID-19 occurred on January 23rd. Subsequently, the infection spread with high intensity, especially in some northern regions, leading to measures of severe social distancing maintained from March 9th to May 18th 2020.[2] Such actions caused an almost 80% blockade of general dermatological activities in both public and private sector.[3] Some dermatologic centres implemented rules for the assessment of the presence/absence of SARS2 infection in patients, prioritising their care according to the severity of diseases.[4] We aimed at evaluating the extent of a COVID-19 effect in Italy on the activity of a series of services dedicated to the diagnosis and treatment of skin melanoma by comparing an epidemic period with a previous one.

Material and Methods

The following Italian centres were involved: the Hospital of national importance and high specialization (ARNAS) Garibaldi of Catania, the Istituto Fisioterapico Ospedaliero (IFO) of Rome, the AOU of Sassari, the Medical Oncology of University of Bari, the IRCCS Tumour Institute "Giovanni Paolo II" of Bari, the IRCSS IRST Romagna, the University of Parma, the Department of Pathological Anatomy of AUSL Romagna, the National Cancer Institute of Naples, the University of Florence, the Dermatological Clinic of the University of Turin, the IRCCS Foundation the National Cancer Institute of Milan and the Immuno-Oncology Centre-University Hospital of Siena.

A quarter (February-April) preceding the pandemic (relating to the year 2019) and one in the pandemic (the year 2020) were considered.

For both periods the participating centres were asked to collect data relating to: number of first visits; number of biopsies performed; number of wide local excisions; number of sentinel lymph node biopsies; number of new systemic medical therapies; number of total patients being treated.

The data concerned with cases before melanoma diagnosis: first visits, biopsies; cases with a positive biopsy for melanoma: wide local excision; cases with a positive biopsy for melanoma and indication for lymph node evaluation: sentinel node biopsy; cases of newly or previously diagnosed melanoma with advanced stage or evolved from earlier stages: the beginning of systemic medical therapies; finally, the total number of patients (with advanced melanoma) in therapy.

The participating centres are in the northern Italian regions, most affected by the pandemic (Lombardy, Emilia Romagna, and Piedmont) and in central (Tuscany and Lazio) and southern regions (Sicily, Puglia, and Sardinia) where the number of cases was sensibly lower.

The comparison of the extent of the cases between 2019 and 2020 was made assuming that the observed events had a cumulative distribution of Poisson.

Results

In Italy (Table 1) during February-April 2020 we observed, a substantial reduction (-31.3%) in the number of first visits, in the number of biopsies (-36.5%) and wide local excisions (-22.9%) in comparison to 2019. Total histological diagnoses also decreased by about a quarter, and the new therapies dropped by about a fifth (-20.8%). On the contrary, no decrease in the sentinel node biopsies count and a reduction, within the limits of significance, in the overall number of patients currently being treated was observed.

By evaluating the northern and central-southern services separately, we observed a homogeneous reduction in the number of

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first visits, biopsies, wide local excisions and total histological diagnoses. In both areas, the number of sentinel lymph node biopsies did not decrease. Notably, there were two differences: the number of new systemic therapies did not reduce significantly in the north but did so (-23.7%) in the centre-south, and the total number of patients under treatment remained stable in the centre-south, while it shrank in the north (-14.0%).

Discussion

This survey had the aim of quantifying the effect of the COVID-19 pandemic in Italy in the management of cutaneous melanoma. The participating centres allowed comparisons of thousands of observations to provide a robust evaluation.

The comparison between the February-April 2019 and 2020 quarters takes for granted some assumptions:

i. the stability of the population (from which cases originate). In 2019 the Italian resident population counted up to 60,359,546 inhabitants, according to National Institute of Statistics and, to 60,362,432 in 2020 (www.demoistat.it);
ii. the incidence of melanoma is not decreasing;5
iii. that stability in the two periods of the staff and the overall work capacity of the participating Services.

With this premise, we can affirm that in Italy - during the COVID-19 epidemic – we observed a substantial reduction in some of the elective activities of a group of highly specialised centres for cutaneous melanoma. In particular, there was a contraction of first visits and, consequently, of the biopsies that follow a melanoma suspicion and the wide local excisions following the histological confirmation of the biopsy. In the same way, histological diagnoses have decreased, presumably according to the decline in general diagnostic clinical activity.

The diminution of first visits and the ensuing diagnostic process can determine a temporal delay in melanoma diagnosis and a stage shift leading to more advanced melanomas with a worse prognosis. This risk has been underlined by the scientific community,[6-8] which has led to recommendations for optimising the resources, directing them more to the most severe forms.[9,10] Such strategies apply to both melanoma and non-melanoma skin cancer patients for whom standard[11] and advanced[12,13] clinical and instrumental synopsis is essential.

A Spanish study estimated that the diagnostic delay of three months, related to the blocking of the activities of the COVID emergency, resulted in the melanoma stage T1 (≤1 mm), which represents the majority of diagnosed melanoma, a decrease in the percentage of early diagnosis from 40% to 27%. On the contrary, the T4 stage (>4 mm) doubled from 16% to 30%.[14] This latter stage represents has an estimated average increase in Breslow thickness greater than 0.50 mm per month.[15] In the present study, the analysed centres seem to have accomplished the need for optimising the available resources during the COVID emergency. There was no decrease in sentinel node biopsies, aimed at evaluating the possible lymph node extension in newly diagnosed melanoma with severe prognostic figures. Moreover, in the north, where the COVID-19 epidemic was more devastating, there was a decrease in the number of patients being treated (mainly patients with more advanced forms of melanoma who need systemic therapy). Still, this decrease did not concern the treatment of new patients in the quarter 2020 (similar in number to 2019), pointing at the ability to treat timely the most severe patients. On the contrary, in the centre-south, there was a decrease in new therapies but not in the treated patients, which remained stable.

The reduction or closure of the hospital and/or private outpatient activities for the COVID emergency[1,2] has indeed delayed dermatological triage for suspected melanoma. Likewise, also the access to general medicine clinics suffered a blockage or marked reduction, also due to the limitation or absence of adequate spacing and containment measures that prevented appropriate triage also for all cancer prevention activities.[1,2]

Telemedicine support would have been useful for consultation between general medicine clinics and dermatological structures. Oncological teledermatology has become part of clinical practice even if more evidence is needed.[16] However, in Italy, such a technique is still in a pioneering stage,[17] also due to technological shortages and medico-legal restrictions.[18]

During the COVID pandemic, an Australian randomised study showed the usefulness of teledermatoscopy managed directly by trained patients, who sent images of suspected lesions straight to the dermatological reference centre, reporting a sensitivity higher than 75% and a specificity above 87%.[19] In Italy, the Istituto Superiore di Sanità strongly recommended during the COVID emergency to strengthen the implementation of telemedicine services. Telemedicine can turn to be very useful for both providing health services and for monitoring people in quarantine, including those with chronic disease as invasive melanoma, who need continuity of care.[20]

Conclusions

In Italy, the COVID-19 epidemic significantly affected the management of skin melanoma. The number of new melanoma diagnosis decreased in February-April 2020 in comparison with 2019. This shrunk activity may bring about a delay in melanoma diagnosis. However, the most severe cases seem promptly managed with sentinel

Table 1. The number of analysed melanoma diagnosis and treatment actions, for a quarter in 2019 and 2020, percentage variation in 2020 in comparison with 2019, for Italy as overall and for north and centre-south Italy.

Actions	Italy				North		Centre-South	
	Feb-Apr 2019	Feb-Apr 2020	%	P	%	P	%	P
First visits	6.711	4.613	-31.3	<0.01	-37.0	<0.01	-25.6	<0.01
Biopsies	4.458	2.829	-36.5	<0.01	-26.4	<0.01	-46.1	<0.01
Wide local excision	1.072	827	-22.9	<0.01	-11.5	<0.01	-38.5	<0.01
Sentinel lymph node biopsy	376	400	+6.4	0.90	+4.2	0.72	+8.2	0.89
Overall pathological diagnosis	3.156	2.386	-24.4	<0.01	-14.6	<0.01	-33.9	<0.01
Start new systemic therapy	409	324	-20.8	<0.01	-12.7	0.10	-23.7	<0.01
Overall patients in therapy	1.734	1.667	-3.9	0.054	-14.0	<0.01	+1.9	0.74

lymph node biopsies, new systemic treatments (north) and an overall number of treated (advanced) patients (south) stable. The COVID-19 experience has underlined the need to exploit more the help which may come from technology (*e.g.* Teledermatoscopy).

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Inflammatory seborrheic keratosis resolution after hyperbaric oxygen therapy: Case presentation and pathophysiology review

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Abstract

Seborrheic keratosis (SK) is a common epidermal tumor, consisting of a benign proliferation of immature keratinocytes. The natural history of SK is a slow progression over time and complete remission is not expected. The article presents the first case of a complete resolution of a large (2.5 cm diameter) SK lesion after hyperbaric oxygen therapy (HBOT). In addition to the case presentation, the pathophysiology of SK and the potential beneficial physiological effects of HBOT are reviewed and discussed.

Introduction

Seborrheic keratosis (SK) is a common epidermal tumor, consisting of a benign proliferation of immature keratinocytes. Clinically, SK manifests as solitary or multiple, well demarcated brownish papules or plaques with a verrucous surface, that predominantly localizes at the head, neck and trunk areas.[1] Since the tumor slowly grows, in many cases the lesion is surgically removed due to cosmetic reasons or because the lesions are traumatized and become symptomatic.[2-5]

In this article we report an unexpected full resolution of a large SK lesion in a patient treated by hyperbaric oxygen therapy (HBOT) due to hemorrhagic cystitis. In addition to the case presentation, the pathophysiology of SK and the potential beneficial physiological effects of HBOT in the setting of SK will be reviewed and discussed.

Case Report

A 74 years old man was admitted for HBOT due to chronic late post radiation hemorrhagic cystitis (grade 3-4 RTOG). In addition, on his left temple, he had a slowly growing SK lesion, known for about 24 months prior to the treatment. The SK presented as a red non-tender demarcated lesion, 2.5 cm diameter in size, with clear boundaries and occasional mild oozing (Figure 1A).

The lesion was diagnosed as inflammatory seborrheic keratosis and was scheduled for surgical removal after the intendent HBOT.

The medical history of the patient included prostate cancer (Glisson score 6), diagnosed 13 years prior to his admission, that was treated with radiation. Since he had chronic unremitting hemorrhagic cystitis, he was referred to HBOT. In addition to the cystitis, he had type-II diabetes mellitus, hypertension, osteoporosis, gastroesophageal reflux, hyperlipidemia, s/p resection of craniopharyngioma in 2019 and a fractionated stereotactic radiation therapy, gait disturbance with parkinsonism and a primary unspecified kidney tumor.

The HBOT protocol used for his hemorrhagic cystitis included a total of 56 hyperbaric sessions, five days per week of 90 minutes 100% oxygen at 2 ATA with five-minute air breaks every 20 minutes. The treatment went well with no significant side effects and the clinical symptoms of the hemorrhagic cystitis resolved.

Surprisingly, in addition to the resolution of the cystitis, there was a full resolution of the 2.5 cm seborrheic keratosis lesion (Figure 1B). During a follow-up, 16 weeks after the last hyperbaric session, the skin was still intact without any sign of recurrence.

Discussion and Conclusions

SKs are common epidermal tumors that usually develop after the age of 50. Skin aging and cumulative UV exposure are considered to play a major role in SK pathogenesis and seem to cause increased expression of amyloid precursor protein (APP),[6] which is a marker of cellular senescence and chronic inflammation, particularly in human keratinocytes (Figure 2 summarizes the pathophysiology cascade of SK).[7]

APP expression has been evaluated in SKs *versus* normal skin by different methods and it was found that APP and its downstream products (*i.e.* amyloid-β42) are highly expressed in SK lesions as compared to the adjacent normal skin tissues.[8] Similar to growth factors and tumor growth factor alpha (TGF-α), APP can induce proliferation of epidermal keratinocytes, and contribute to mitochondrial dysfunction and oxidative phosphorylation.[7] In addition to the skin, APP is highly expressed and has a pathophysiology role in many of the age-related diseases such as Alzheimer's disease, atherosclerosis, Parkinson and macular degeneration.[9-11] HBOT utilizes 100% oxygen in an environmental pressure higher than one absolute atmosphere (ATA) to enhance the amount of oxygen dissolved in body's tissues. Repeated intermittent hyperoxic exposures have been shown to induce physiological effects which normally occur during hypoxia in a hyperoxic environment,

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Contributions: KES & SE wrote the first draft of the article and treated the patient presented. ME reviewed and worked on the final version of the manuscript.

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including stem cells proliferation, generation of new blood vessels (angiogenesis) and enhanced tissue regeneration.[12-16] The direct effect of HBOT on keratinocytes was evaluated by the use of monolayer cultures including dermal fibroblasts, keratinocytes and melanocytes.[17] It was found that repeated HBOT sessions at a pressure of 2 atmospheres, as was used in our treatment protocol, inhibits keratinocytes proliferation.[17] In addition, in another study it was demonstrated that HBOT ameliorates APP and amyloid beta (Aβ) plaques in the brain of Alzheimer prone mice.[18] With regards to UV related injury, it was found that pretreatment with HBOT significantly reduces UV-A induced apoptosis and proliferation in hairless SKH1-E mice.[19] Hence, as summarized in Figure 2, HBOT has the potential to intervene and revert the pathophysiological processes responsible for the development of SK lesions.

In our patient, the SK lesion at a diameter of 2.5 cm had a complete remission after HBOT (Figure 1).

The natural history of SK is a slow progression over time and complete remission is not expected. The only available treatments for SK include surgical removal, cryosurgery, curettage, electrodessication, shave excision or laser therapies (CO2, YAG).[3-5] To the best of our knowledge, this is the first reported case of complete resolution of SK without local intervention. Had the lesion not been so large in size and not at such a notable location, we would have probably missed HBOT's effect on the lesion. Until this case, we have not monitored SK lesions in patients treated at our center, and the skin lesions have not received the attention they deserve. By presenting this unique case, we hope that awareness of the potential beneficial effect of HBOT on SK lesions will increase and prospective clinical trials on different types of SK will be initiated. These studies may potentially shed additional light on the pathophysiology of SK and may help in developing noninvasive biological interventions, such as HBOT, to treat it.

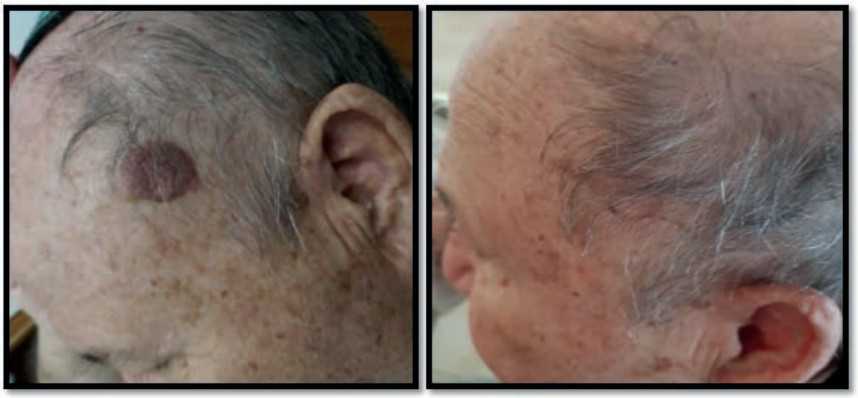

Figure 1. The skin before and after hyperbaric oxygen therpy. A) before treatment; B) after treatment.

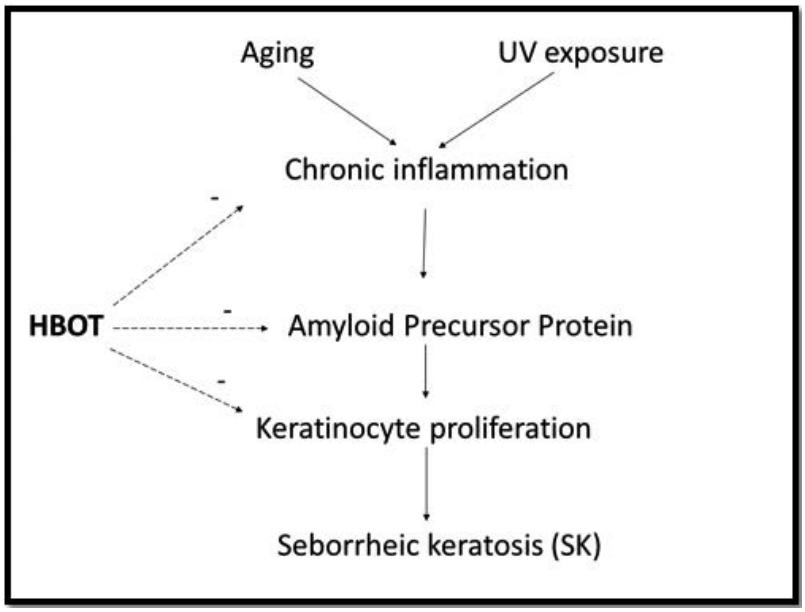

Figure 2. The pathophysiology cascade of seborrheic keratosis and the biological effect of hyperbaric oxygen therapy.

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Successful treatment of idiopathic knuckle pads with a combination of high-dose salicylic acid and urea topical keratolytics: A case report

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Abstract

Knuckle pads are benign subcutaneous and usually hyperkeratotic fibromas for which no specific treatments exist. Unspecific treatments are, most of the time, ineffective and a wait-and-see policy is often recommended to patients. However, especially in adolescents, knuckle pads are often poorly tolerated for cosmetic reasons, potentially causing embarrassment and social anxiety. Here we present the case of a young adult successfully treated with a combination of high-dose salicylic acid and urea topical keratolytics. In addition, we provide ideal diagnostic images obtained via high-resolution ultrasonography and histological features that can be used by medical practitioners to better distinguish knuckle pads from other proximal interphalangeal/metacarpophalangeal joint diseases as also from other diseases inducing swelling of periarticular soft tissues.

Introduction

Knuckle pads (KPs) or Garrod's nodules are benign subcutaneous fibrotic nodules located in the extensor surface of feet and/or more frequently in finger joints.[1-3] Clinically, they are well-circumscribed, non-compressible, freely movable, wart-like lesions involving mostly the dorsal aspect of proximal interphalangeal (PIP) and more rarely metacarpophalangeal (MCP) joints.[4,5] Usually, KPs are painless, asymptomatic (*i.e.* no functional effects on the joints like reduced flexibility or alterations of tendons), and characterized by a progressive and gradual growth that leads them to reach their final size (up to 40 mm in diameter).[2,4,5] Primarily (idiopathic) KPs are the most common in children and young adults, while in older patients KPs are often associated with fibrosing disorders like Dupuytren's contracture, Peyronie's disease, and Ledderhose disease (*i.e.*, plantar fibromatosis). Secondary (acquired) KPs, instead, appear following the recurrence of frictional/traumatic events involving the joints, like those typical of some professional and athletic activities.[2,3,5] The diagnosis is clinical with warts, xanthomas, rheumatoid nodules, gouty tophi, neurofibromas, Bouchard's and Heberden's nodes, synovial cysts, and retained foreign bodies reported as a differential diagnosis.[2] In the case of diagnostic doubt, ultrasonography, histology (if sonography is not clear definite), and plain radiograph enhance the information gathering process reducing the risk of misdiagnosis.[2–4] On ultrasound, KPs appear as noncompressible, dome-shaped, hypoechoic nodules with absent or peripheral vascularization at Doppler analysis, while histology reveals increased (myo-)fibroblasts proliferation often associated with hyperkeratosis.[1-4,6]

Owing to the absence of specific and effective treatments, a stressful wait-and-see approach is usually recommended.[1,4] Surgery has also been used, usually without leading to an aesthetic improvement with recurrences, post-operational loss of joint flexibility, scars, and keloids as possible side effects.[1,6,7] Recently, few treatments are turning out to be effective, but they are mostly based on case reports and are often moderately to highly invasive.[1,3,5] *Case reports*-based treatments are associated with a low level of evidence and, especially in painless and non-pathogenic conditions, priority should be given to non-invasive methods. Previous reports have shown conflicting results regarding the use of keratolytics in the treatment of KPs,[1,3,7,8] usually without leading to complete resolution. On the contrary, we report here a potential resolutive treatment for idiopathic KPs based on the combination of two common keratolytics, *i.e.,* urea and salicylic acid, administered at high dosages.

Case Report

A 15-years-old healthy boy developed nodules on PIP joints of the left-hand fingers (fifth finger excluded; Figure 1A), as also in all the fingers of both feet since autumn 2011 (Figure 2). No traumatic events were reported and the family history as also the patient's medical history did not suggest a possible genetic predisposition for KPs or fibrosing disorders.

From July 2012 to August 2013, the patient received independent KP diagnosis by dermatologists and a hand surgeon. All dermatologists prescribed several types of therapies, while the surgeon proposed a surgical intervention, emphasizing the risk of possible recurrence as well as other side effects such as scars and loss of joint flexibility. Therapies were several and mainly based on 5% urea cream application for 3 months, 25% urea cream application for 40 days, different wart removal products (*i.e.,* lactic acid, glycolic acid, and salicylic acids) for 40 days, and

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cryotherapy. All ended unsuccessfully. In mid-2014, resigned, the patient stopped treating the lesions which remained unchanged in shape and size.

Ultrasonographic and histologic features of Knuckle pads

Recently, ultrasound (hereafter, US) and histological investigations were performed on the refractory right big toe KP (Figure 2; black arrow) and, based on these new findings, the original diagnosis was confirmed. US (13 MHz operating frequency) of the plaque revealed a subcutaneous, uncompressible, and hypoechoic fibroma, while Doppler-mode US showed the absence of internal vascularization (see Supplementary Files SF_1). Sometimes, high-resolution US investigation might be necessary in order to increase the resolution of the diagnostic images. In dermatology, the optimal observation of surface structures – as KPs are – is usually reached with transducers working between 18 and 24 MHz.[9] For this reason, we provided here a series of US images of KPs (see Supplementary Files SF_2) acquired at high resolution (15-18 MHz operating frequency), thus expanding the current knowledge on the ultrasonographic characteristics of such nodules.[2,4,10-12] Histological examination showed dermal fibrosis and the predominance of the stratum corneum layer (Figure 3).

Resolutive therapy

At the end of 2017, the patient autonomously decided to restart a new treatment combining the active ingredients of those therapies that had worked partially and momentarily (*i.e.,* urea and salicylic acid). He also decided to administer topically high-dose urea/salicylic acid preparations, as well as to increase the frequency of urea treatments. The administration of those keratolytics was not suspended after 40-90 days of treatment as originally recommended. Novel therapy was based on two applications per day of 25% urea-based emollient-keratolytic cream, one overnight application per day of 40% urea-based emollient-keratolytic cream, and one application per day of 30% salicylic acid ointment. The three major KPs (*i.e.*, left-hand thumb and big toes) were treated overnight under occlusion at least five times a week. Great attention was paid to not causing trauma to the nodules both during the removal of dead skin and in daily life. Depending on the size of the KPs, 4 to 6 months were required for the total or quasi-total removal of the lesions. All the four KPs of the hand disappeared completely, with great cosmetic and psychological benefit (Figure 1B). All feet KPs disappeared or were greatly reduced both in diameter and thickness (Figure 2), with no recurrences observed after years from the end of the treatment. The only KP partially refractory to the therapy was that of the right big toe that was anyway lowered by a few millimeters.

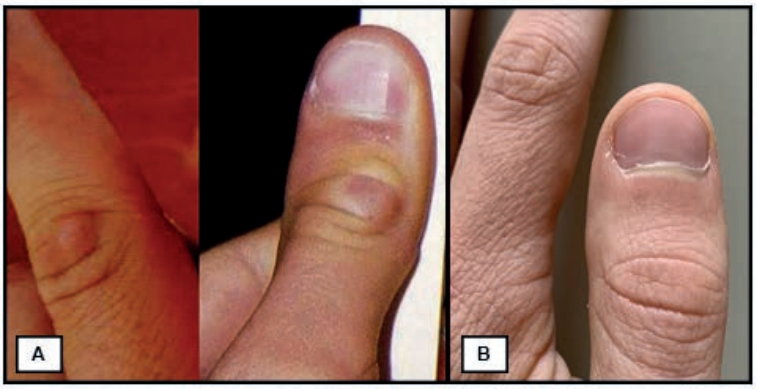

Figure 1. Knuckle Pads on proximal interphalangeal joints of the left-hand fingers before resolutive treatment, A). Situation at the end of the resolutive topical therapy based on 25-40% urea and 30% salicylic acid keratolytics B).

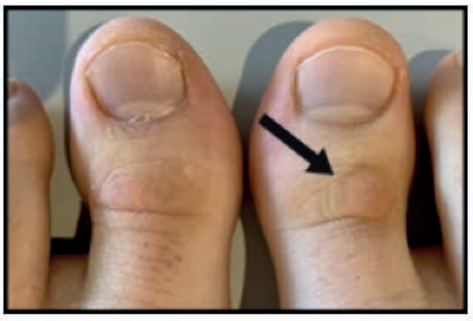

Figure 2. Knuckle Pad (black arrow) on the right big toe partially refractory to the keratolytic treatment. The Knuckle Pad that was originally present on the left big toe completely disappeared after treatment.

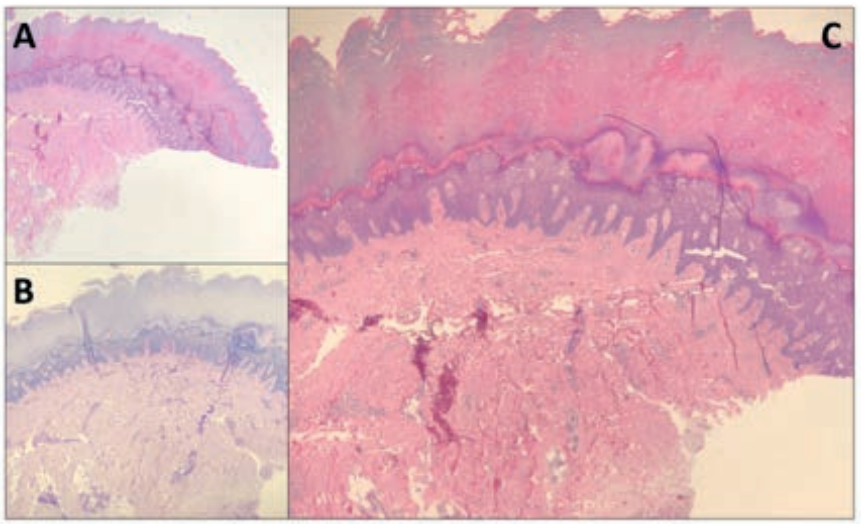

Figure 3. Knuckle Pad histological examination: A) Hematoxylin-eosin (H&E) staining shows the histological architecture with mild dermal fibrosis and the predominance of the corneum layer; B) Periodic acid-Schiff (PAS) staining shows the dermal-epidermal interface and the dermal adnexa (original magnification: 8x); C) H&E, central detail of A, at a higher magnification (original magnification: 20x).

Discussion and Conclusions

Knuckle pads are recognized as refractory cutaneous lesions and usually, they do not disappear over time whether they are treated or not. Spontaneous resolution of primarily KPs has never been described, although in rare cases they can become smaller without disappearing.[6] In the case of acquired KPs, they may disappear after elimination of the source of friction/trauma.[3] Few case studies reporting after-treatment resolution of KPs have been reported in scientific literature and are often based on incisive therapies mostly carried out after several more or less moderate attempts to cure them. In clinical practice, there are many reports of refractory cases finally treated with high-dose and/or long-lasting therapies. Besides, in KPs treatment, what works for one patient often does not work in another, suggesting a possible heterogeneous pathogenesis and indicating that many attempts should be made in trying to resolve this condition. However, in clinical practice the trail-an-error approach is non-optimal, and the definition of gold standard therapies must remain a priority. Moreover, especially in painless non-pathogenic disorders, like Garrod's nodules, patients should start being treated with non-invasive therapies, possibly avoiding surgery, or leaving it as a last resort. Here, alongside high-resolution ultrasound and histologic images of KPs, we have presented a possible novel keratolytic-based first-line therapy which has proven to be resolutive, painless, and risk-free. Additionally, we can conclude that ultrasonography should be considered as the ideal front-line tool for diagnostic imaging of KPs, and the detailed images we have provided in this manuscript perfectly complement what is summarized in important published works on that topic.[2,10-12] To conclude, this knowledge not only can make physicians familiar with the typical ultrasonographic appearance of KPs, thus potentially reducing the risk of misdiagnosis, but it can also play a role in medical education about this "forgotten skin condition".

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Acral pityriasis rosea: A rare variant of pityriasis rosea

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Letter

Pityriasis rosea (PR) is a common, self-limited inflammatory skin condition, usually affects the trunk and proximal extremities. A variety of atypical manifestations of PR have been recognized ranging from the difference in the morphology, distribution, and course. Herein, the rare form of acral PR in an adult has been illustrated as the 29-year-old Thai female who presented with generalized erythematous papules and plaques with peripheral collarette scales on the trunk and extremities, prominently on the hands and feet (Figures 1-3). The face and mucous membranes were spared. The patient denied associated systemic symptoms such as fever. There was no history of genital ulceration. The provisional diagnosis of PR was initially made due to the presence of fine collarette scales, the oval morphology of the lesions, and the Christmas-tree distribution. Secondary syphilis, erythema annulare centrifugum and psoriasis were also considered as the differential diagnoses.

The rapid plasma reagin (RPR) and treponema pallidum particle agglutination (TPPA) assays were both negative. Blood test for anti-HIV was not collected. Histopathology showed spongiotic dermatitis with lymphocytes. Superficial perivascular infiltration with lymphocytes and extravasation of red blood cells were observed without an evidence of plasma cell (Figure 4). Hyperkeratosis and parakeratosis were also noted. All histologic findings supported the diagnosis of PR. Despite the treatment with moderate potency topical corticosteroids and the four-week course of oral roxithromycin, the disease continued to progress. A short course of oral prednisolone (0.5 mg/kg/day) was added which finally led to a complete resolution. There was no recurrence on the 3-month followed-up period.

Acral, or palmoplantar, PR can affect patients of all ages but there have been more reports in adults. The morphology of acral PR varied from scaly plaques to vesicles, however, the latter were usually categorized as vesicular PR variant. Although acral PR had been defined as primary and secondary eruptions confined to the acral parts, the rash on the other locations, e.g. the trunk and distal extremities, usually coexist.[1] To date, there have been less than ten published cases of acral PR in English literature.[1-5] It is difficult to delineate the clinical pattern of acral PR due to an insufficient number of cases. In general, acral PR would be diagnosed when the palmoplantar areas were involved where the rash can either limited to the acral sites or extended beyond the palms or soles. The management of acral PR was identical to those of the classic disease. The course and prognosis were unaffected in this variant.

Criteria for diagnosis of PR were proposed by Chuh *et al.*[1] comprised three

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Key words: Pityriasis rosea; acral; palmoplantar; atypical.

Contributions: The authors contributed equally.

Conflict of interest: The authors declare no potential conflict of interest.

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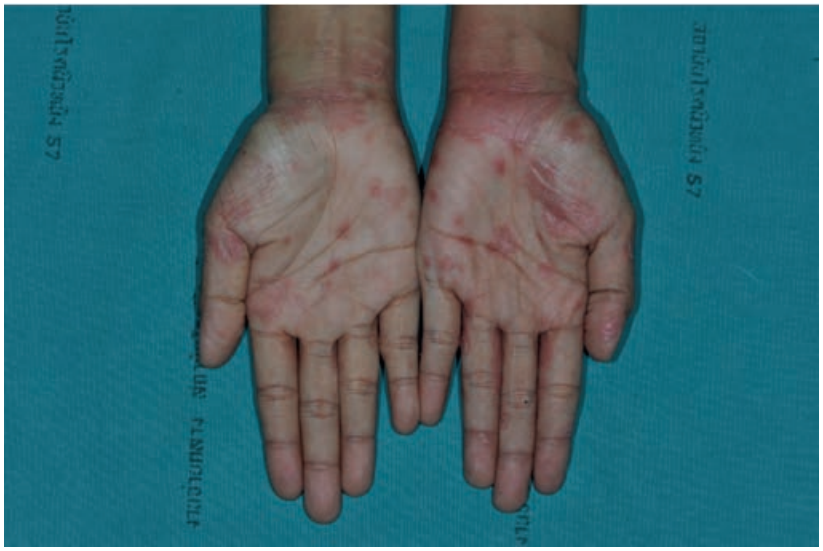

Figure 1. Typical erythematous papules with collarette scales on the palms.

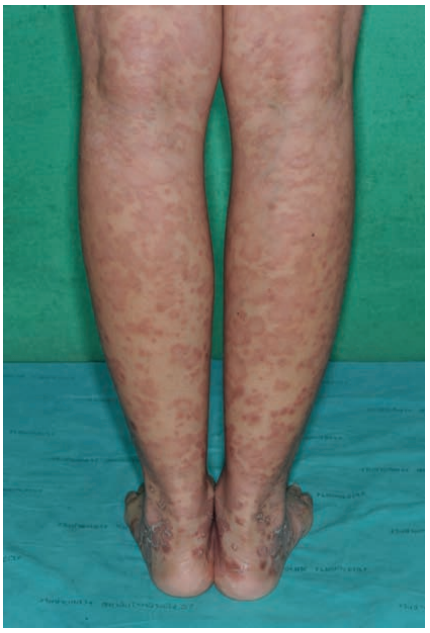

Figure 2. The generalized eruption was evidenced on the entire legs.with collarette scales on the palms.

major components as follows; the "essential", "optional", and "exclusional" clinical characteristics. The diagnosis of PR would be established by fulfilling all the essential features plus at least one of the optional features. In brief, the "essential" clinical presentation for PR must include scaly circular eruptions with two lesions at the minimum showing peripheral collarette scale plus at least one of these following "optional" features; (i) truncal and proximal extremities involvement with less than 10% of lesions on the distal limbs, (ii) most lesions distribute along the ribs, and (iii) the presence of a herald patch. Pityriasis rosea would be unlikely if any "exclusional" features present including multiple vesicular lesions, predominant palmoplantar distribution, and clinical or serological tests indicate secondary syphilis. These criteria seem to be applicable for typical PR but not for other atypical forms since the exclusion criteria would ultimately rule out certain types of atypical PR such as acral and vesicular variants. It is thus crucial to revise the above diagnostic criteria to minimize the potential of the underdiagnosis of some atypical PR subsets.

In summary, acral PR accompanied by the typical PR eruptions distributed in a disseminated pattern was reported. The existed criteria may facilitate the diagnosis of classic PR but fail to diagnose acral PR. The strong clinical clue for acral PR is the presence of collarette scales within the periphery of typical PR lesions which could be observed either on the palmoplantar surfaces or other locations. Herald patch is also pathognomonic that can be generally observed in up to 80 % of PR cases while palmoplantar herald patches were reported in a few patients.[4-7] As the appearance of palmoplantar lesions may indicate secondary syphilis, serological tests should always be investigated in virtually all suspected cases.

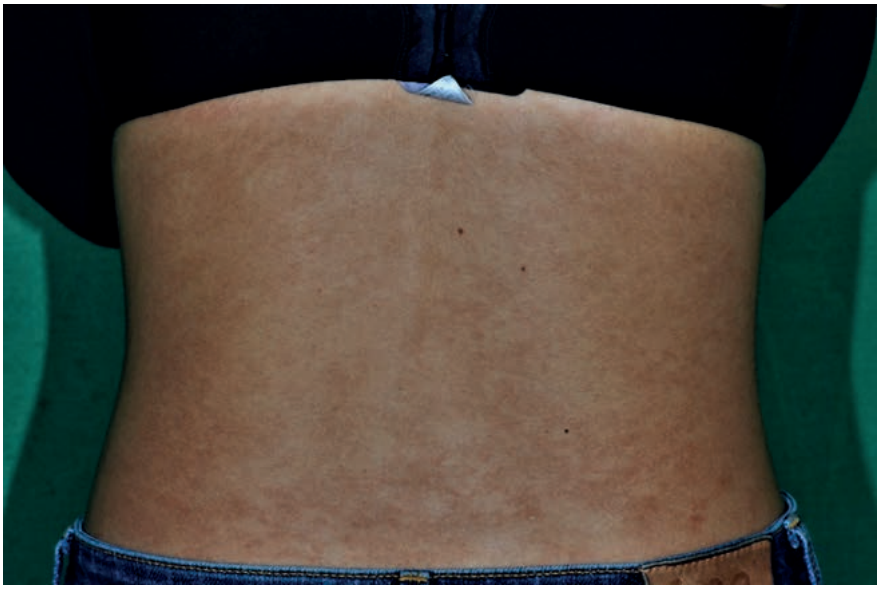

Figure 3. The rash distributed along cleavage lines of the back or a "Christmas tree" distribution.

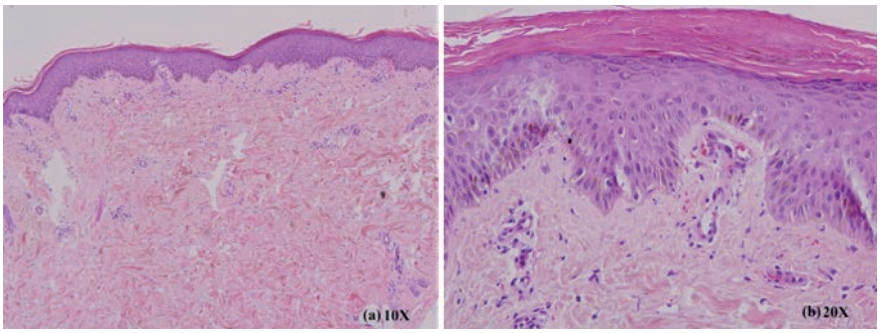

Figure 4. a) The section displayed mild acanthotic epidermis with hyperkeratosis and focal parakeratosis. There was superficial perivascular infiltration on the upper dermis. b) Lymphocytic infiltration and extravasation of red blood cells were evident. (Hematoxylin and eosin stain).

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In Memory of Raffaele Gianotti

Prof. Raffaele Gianotti ("Raf" for friends) was born on July 7th,1959 in Milan (Italy). His father, Prof. Ferdinando Gianotti (1920-1984), was a famous pediatric dermatologist that gave his name to the "papular acrodermatitis of childhood" (Gianotti-Crosti Syndrome).

Raffaele graduated cum laude in Medicine in 1985 at the University of Milan. In 1988 he completed the residency in Dermatology and in 1992 he got also his second specialization in Surgical Pathology. Soon after in 1993, he made a fellowship in Dermatopathology by Bernie Ackerman in New York. Back again in Milan, he started the work of his life of in Dermatopathology with a full researcher position at Istituto di Scienze Dermatologiche Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena. Between 2000-2005 he collaborated with H. Kutzner in Friedricshafen (Germany) on Lampyris101, an automatized software for the diagnosis of inflammatory skin diseases. In 2005, he also got the International Board Certification in Dermatopathology.

As academic, he published over 135 scientific papers on various topics on inflammatory and neoplastic skin diseases and reached an H-index of 27 (source: Scopus, last visited April 5, 2021). Particularly, he was recently very active in describing the histological features of COVID-19 infection in the skin and became very popular reporting the first proved Italian patient affected by COVID-19.[1-4]

Raf was also author of Dermosprint (https://www.dermosprint.com/), a freely available Dermatopathology collection with contributions by worldwide best dermatopathologists.

He passed away on March 27, 2021 at the age of 61.

In his memory, we decided to publish posthumous in Dermatology Reports an editorial that Raf wrote for Dermosprint.

Ciao Raf!
Rest in peace.

Cesare Massone,[1]Antonio Perasole[2]
[1]Dermatology Unit, Galliera Hospital, Genoa (Italy)
[2]Consultant Pathologist at Lifebrain s.r.l. Limena, Padua (Italy)

Raf Gianotti with both his work & hobby: dermatopathology and motorbike.

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And... who is the best of all times in diagnosing melanocytic lesions?

Raffaele Gianotti

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***published posthumous**

A question came to my mind as I was writing about Ackerman and sharing all the thoughts of legends like LeBoit, Kutzner, and Weedon: "Of all times, who has been and who is the best dermatopathologist in the field of melanocytic lesions?" I am not talking about charisma, the number of index publications, awards received or the lectures held around the world. What I mean is who, sitting at the microscope, never misses a diagnosis, or if you prefer, makes the least wrong calls. How often have sports reporters asked themselves: "Who was the best tennis player of all time? And ... the football player? And ... the F.1 driver?" If nowadays Dante Alighieri wrote the Divina Commedia, written in a language typical of the 1300s, you could barely find it on the shelves of a supermarket. It is impossible to answer who's best when comparing individuals from different times.

Dear reader, be honest and admit to yourself that at least once in your life, you couldn't help thinking you were better at diagnosing than your colleague that works in a lab or a department hundreds of kilometers away from your workplace, whom you come across at a surgical pathology congress or inter-regional gatherings.

It is hard to determine who nowadays is the most gifted in examining a histological section on the controversial issue of Spitz nevus and spitzoid melanoma. What if I told you that my friend and colleague Giuseppe a fellow pathologist at a peripheral hospital of suburban town has an extremely high score in melanocytic lesions? Would you believe it? It could be true, but it is impossible to prove! In our job, there are no "scores", no timer running to measure up against, and no championship that rewards the best athlete of the year based on actual results.

Several years ago, 26736 melanomas were examined in an Australian study. It was established that only 4% of the patients with a Breslow index above 0.75 mm would not survive 20 years since the disease was first determined. I always asked myself: "How many of these four patients, before passing to a better place, manage to contact the pathologist who, perhaps ten years earlier, made a diagnosis of Spitz lesion?". In light of this study, you could decide to diagnose all of the histologic sections for pigmented lesions, even in presence of melanoma, as melanocytic nevus, as long as they don't go beyond the fateful 0.75 mm. Probably no more than a single patient, or none at all, would contact the dermatopathologist who made the diagnose maybe it would be just one patient out of a whole pathologist carrier. And ... how about the patients who were mistakenly diagnosed with melanoma. No further news from them, whose only trouble will be to have frequent nightmares of the "sword of Damocles" in the shape of a melanoma hanging from the ceiling and falling to hit them in the middle of the forehead.

Can we learn from our mistakes when facing melanocytic lesions? Almost impossible! Only in the rare event that a patient dies due to metastatic spreading of the disease, one can be sure to have missed a melanoma. Meanwhile, it is quite different when we talk about cutaneous lymphomas and inflammatory conditions. Patients do not disappear, they will come back to you. It is a slow diagnostic process. We can learn from our diagnostic errors by comparing the previous histologic slide with a second biopsy, and make a new diagnosis that better describes the clinical progress. A surgeon's performance is easily evaluated because results occur shortly after the surgery. With melanocytic lesions, it is not possible. "One shot only" a diagnosis of Spitz is made and ... then the patient disappears. The studies regarding melanoma vs nevus are based on very rare and complex cases with a thickness larger than 0.75 mm. They have relatively short follow-ups, rarely exceed fifty cases, and the histological slides have been evaluated only by the pathologists who wrote the report. Others can only acknowledge the report, but they cannot deeply internalize a personal diagnosis, be it right or wrong. So we cannot know who among Dr. Riccardo from Rome, Dr. Erica from Pasadena, Dr. Federico from Genoa or Dr. Arianne from Hannover have under- diagnosed melanoma cases or over-diagnosed melanocytic nevi every so often.

A statistical theorem called "Single shoot theory" was developed by Russian mathematicians to train Olympic rifle shooting athletes, a discipline in which our friends from the east have always been masters. These Olympic competitions are held on sixty shots and the theorem relies on convincing the athletes to be constantly super-focused as if it was not a single competition of sixty shots, but sixty one-shot competitions. What is the meaning of all this? Quite simply: an average shooter at the fifteenth shot could be faring on a slightly better score than an Olympic athlete who momentarily lost focus. However, at the end of the competition, the champion would still finish up "miles" ahead of an average shooter. Likewise, in a hypothetical competition with Bernie Ackerman, if we had conflicting opinions on a single complex case, I could be the one that's ahead. But stretch our competition on a year's work, thousands of difficult cases examined, and I would be embarrassingly behind in the number of correctly diagnosed cases. Think about this when you send a complex case in consultation to a more expert colleague and his diagnosis wasn't convincing. That case could be your 15th shot, so remember to learn from the mistakes of the more experienced. "a mistake is an error, but an error is not always a consequence of carelessness or indifference. On the contrary, mistakes can be made when great care has been exercised." Bernie Ackerman

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MERCOLEDÌ 15 SETTEMBRE 2021

SALA AUDITORIUM		AULA MAGNA	
14.30	CORSO DI DERMATOSCOPIA	14.30	CORSO DI LASERTERAPIA
16.15	ADOI-SIDELF		

SESSIONE INAUGURALE

17.30	SALUTI PRESIDENTI E AUTORITÀ	
18.00	LETTURA MAGISTRALE Il farmaco: da sintetico al biotecnologico	Giovan Battista De Sarro
18.30	LETTURA MAGISTRALE STORICO-CULTURALE Calabria tra storia e natura: un paradiso abitato da diavoli?	Dino Vitale
19.00	Cocktail di benvenuto	

GIOVEDÌ 16 SETTEMBRE 2021

SALA AUDITORIUM		AULA MAGNA	
8.45	CHIRURGIA DERMATOLOGICA	8.45	DERMATOLOGIA PEDIATRICA: DALLA CLINICA... UNA LEZIONE!
11.00	MELANOMA UPDATE 2020	11.00	ORTICARIA
		11.30	DERMATITE ATOPICA
13.00	LUNCH SESSION ACNE, ROSACEA, IDROSADENITE: NEWS	13.00	LUNCH SESSION DERMATOLOGIA ALLERGOLOGICA
15.00	NON MELANOMA SKIN CANCER	15.00	MALATTIE DERMO NEUROGENETICHE E MALATTIE RARE
		16.15	LETTURA
16.30	BIOINGEGNERIA TESSUTALE E MEDICINA RIGENERATIVA	16.45	LGBT E DERMATOLOGIA
17.15	LE USTIONI AMBULATORIALI	17.15	DERMATOLOGIA PSICOSOMATICA

VENERDÌ 17 SETTEMBRE 2021

SALA AUDITORIUM		AULA MAGNA	
8.45	DERMATOPATOLOGIA CLINICA CLINICA E PATOLOGIA: INSIEME PER VINCERE	8.45	PSORIASI
10.45	DERMATOSI IMMUNOMEDIATE LE DERMATOSI IMMUNO-MEDIATE AL TEMPO DEL SARS COVID-2		
12.00	MALATTIE BOLLOSE	12.00	LETTURA MAGISTRALE
		12.30	SMALL MOLECULES: WHAT'S NEWS?
13.00	LUNCH SESSIONE ANNESSI CUTANEI	13.00	LUNCH SESSIONE PSORIASI
			FOTOTERAPIA
15.00	CORSO DI TRICOLOGIA	15.00	PSORIASI
16.00	DERMATOLOGIA INFETTIVA E TROPICALE		
16.30	DERMATOLOGIA INFETTIVA E TROPICALE		
17.00	MST		

SABATO 18 SETTEMBRE 2021

SALA AUDITORIUM		AULA MAGNA	
8.30	NEWS DERMATOLOGICA E SESSIONE GIOVANI	8.30	ISPLAD UP-GRADING HIGH TECH IN DERMATOLOGIA PLASTICA
9.45	STORIA DELLA DERMOVENEREOLOGIA	9.45	DERMATOSI EMO-LINFOPROLIFERATIVE E KAPOSI I LINFOMI CUTANEI: dalla clinica alla istologia e ritorno
11.00	SESSIONE CONGIUNTA ADOI - ADMG	11.00	TELEMEDICINA
12.30	SALUTI E CHIUSURA DEL 58° CONGRESSO NAZIONALE ADOI		

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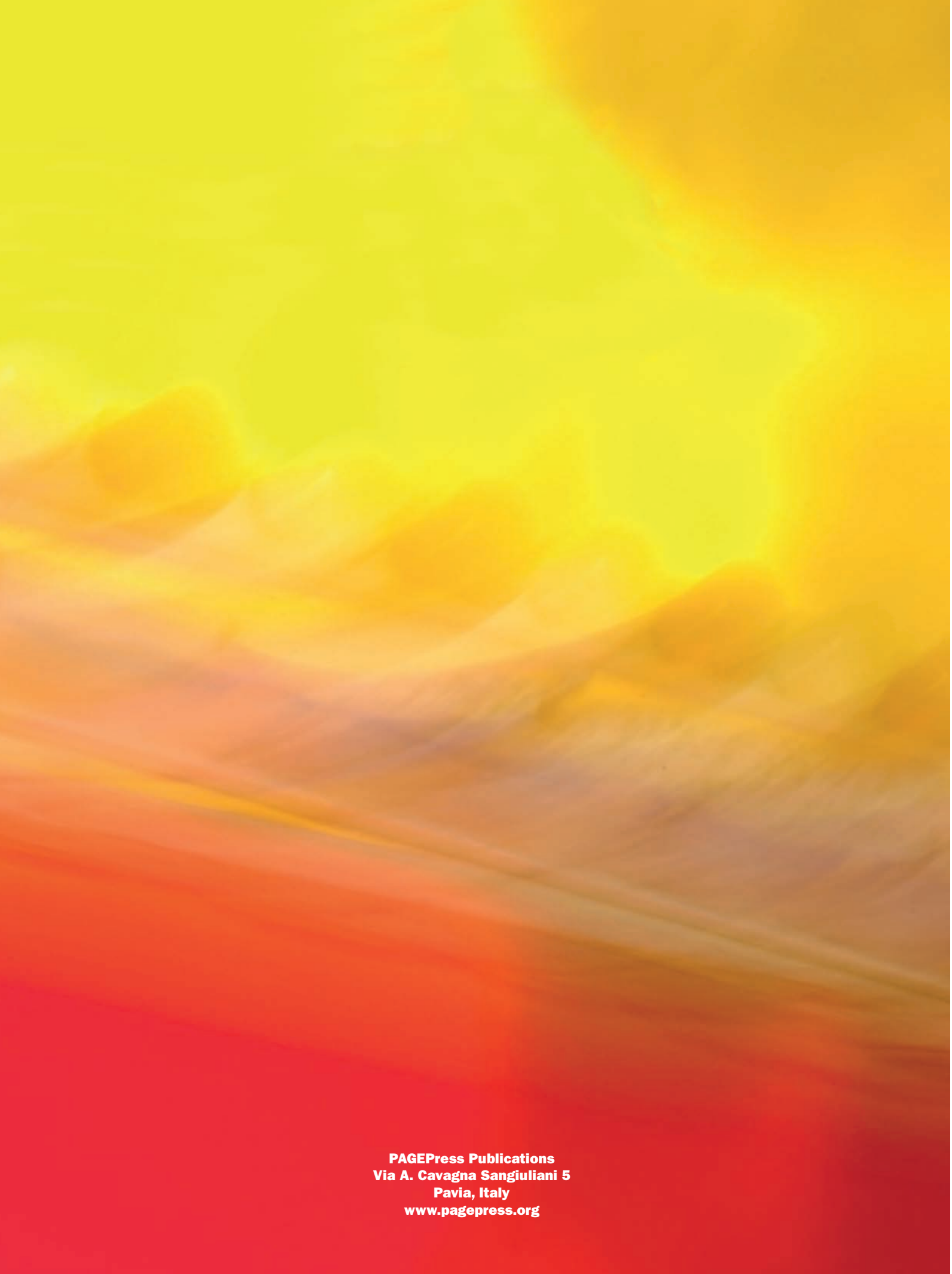

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