europass Curriculum Vitae

26/6/23

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Patente di guida: B

## ULTERIORI INFORMAZIONI

Pubblicazioni

- Castelli E, Orlando E, Pardo N, Turdo A, Pistone G, Bongiorno MR. Nodular morphea keloidal type: A rare case with paradigmatic histopathology significantly accompanied by a flawless surgical scar. J Cutan Pathol. 2020 Dec 1. doi: 10.1111/cup.13810. Epub ahead of print. PMID: 33258515.
- Pistone Giuseppe, Pardo Nicola, Caputo Valentina, Castelli Elena, Cunale Salvatrice, Gurren Rosario, Bongiorno Maria Rita. A Case of Moderate Hidradenitis Suppurativa and Psoriasis Treated with Secukinumab. Ann Dermatol. 2018 Aug;30(4):462-464. doi: 10.5021/ad.2018.30.4.462. Epub 2018 Jun 27. PMID: 30065588; PMCID: PMC6029963.

Poster a Congressi

- XX Giornate di Terapia in Dermovenereologia, Catania 2022. Efficacia e sicurezza a lungo termine di Sonidegib in pazienti pluripatologici con BCC localmente avanzato. G. Licata, N. Pardo, M. Fazzitta, D. Rizzo, L. Zichihi.
- 24th World Congress of Dermatology, Milan 2019. A very rare case of nodular morphea uncovered by a well-defined surgical wound. E. Castelli, E. Orlando, G. Pistone, S. Cunale, G.M. Garbo, N. Pardo, M.R. Bongiorno.

Partecipazioni a Congressi

- Congresso Annuale AIDNID 2018, Catania. Ruolo della Capillaroscopia nella malattia di Anderson-Fabry.
- 24th World Congress of Dermatology, 10-15 June, Milan 2019.
- PSOMOT 2018 (PSOriasis Management of patients Over Time), Berlino 26/28 ottobre 2018.
- PROGETTO DI FORMAZIONE BLENDED Generating Real World Evidence (GREv)_Milano 29/30 giugno 2017.
- Ultrasonografia in Idrosadenite suppurativa 2.0 Firenze 11 marzo 2017
- Journeé Dermatologique de Paris 2015, 8-12 Decembre 2015, Paris.

Relatore a Congressi

- Brodalumab e Psoriasi – INNOVAZIONI TERAPEUTICHE IN DERMATOLOGIA – 16 novembre 2019. Palermo.
- Terapia medica dell'idrosadenite suppurativa e trattamento delle sovrainfezioni batteriche con antibiotici topici – TRADIZIONE E INNOVAZIONE NELLA TERAPIA DELL'IDROSADENITE SUPPURATIVA – 03 marzo 2017, Palermo
- Terapia medica dell'idrosadenite suppurativa e trattamento delle infezioni cutanee sostenute da germi sensibili – LE MALATTIE INFIAMMATORIE DELLA CUTE – 19 dicembre 2017 Palermo.

ALLEGATI

- Allegato 1 copia delle pubblicazioni scientifiche
- Allegato 2 copia dei poster

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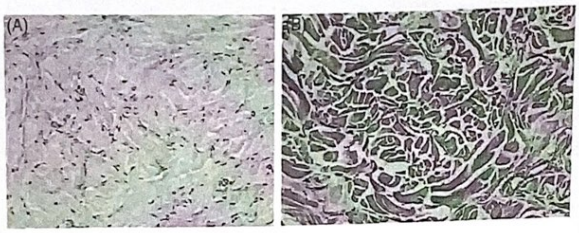
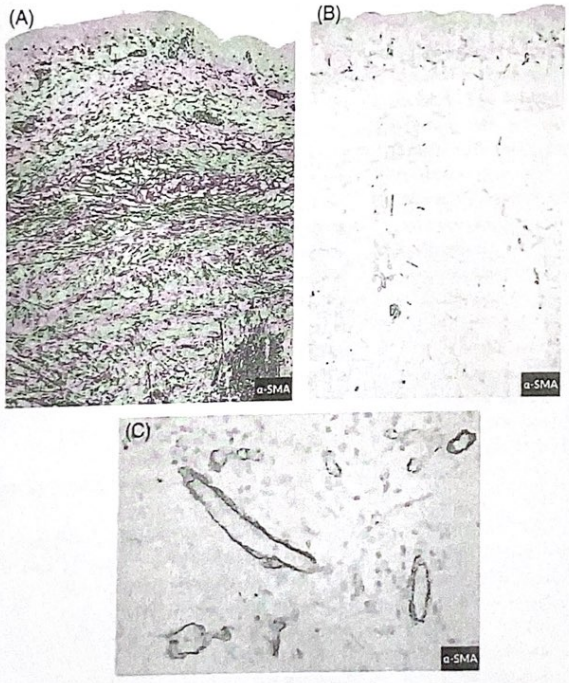
COVER QUIZLET

Elena Castelli, Elisabetta Orlando, Nicola Pardo, Alice Turdo, Giuseppe Pistone, Maria Rita Bongiorno

Figures 1 and 2 are depicted on the journal cover.




*Your diagnosis?*

Discussion follows on page 000

# Nodular morphea keloidal type: A rare case with paradigmatic histopathology significantly accompanied by a flawless surgical scar

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**KEYWORDS:** bland surgical scar, nodular/keloidal morphea, unusual immunohistochemical features

## 1 | INTRODUCTION

Nodular morphea is a rare variant of localized scleroderma, clinically and histopathologically characterized by cutaneous nodules or plaques associated or superimposed to the flat lesions of classic morphea.[1-3] Accordingly, the association of such outgrowths with systemic sclerosis is designated as nodular scleroderma.[4-6] Sometimes these lesions appear as firm, erythematous and irregularly curvy plaques resembling keloids or hypertrophic scars, thus characterizing keloidal morphea or keloidal scleroderma.[7-10] These mystifying features can make the diagnosis challenging, especially in the absence of a well-documented medical history. Here we report a case of keloidal morphea with multiple histopathologically typical nodules in the absence of clinical or laboratory signs of scleroderma, whose clinical diagnosis was suggested by a concomitant normally cicatrized scar from quadrantectomy.

## 2 | CASE REPORT

A 50-year-old Caucasian woman presented with multiple firm, linear or arciform, erythematous and slightly pigmented asymptomatic plaques, of 2-3 cm in diameter and 2-10 cm in length, localized on clinically normal skin, at the sternal and pectoral regions, and at the shoulders (Figure 1A, B). The lesions had slowly but relentlessly multiplied over the past thirty years without being preceded by local injury or inflammation, and had been diagnosed as spontaneous keloids soon after their first appearance. However, our clinical examination revealed in addition a thin, inconspicuous surgical scar at the right breast (Figure 1A ), which represented the outcome of a quadrantectomy with post-surgical radiotherapy, performed 10 years before for a ductal carcinoma in situ. This contrasting finding disproved the diagnosis of spontaneous keloids, suggesting instead the possibility of nodular morphea. The patient was otherwise healthy and her drug history was negative. Her blood cell count and hematocrit were in the normal range. The inflammatory parameters (CRP: 6 mg/L; reference range: <8 mg/L, ESR: 5 mm/h; reference range: 1-13 mm/h) and laboratory screenings for autoimmune diseases (ANA: 1/80; reference range: ≤ 1/80, anti-dsDNA IgG, anti-centromere, anti-Scl-70, anti-SS-A, anti-SS-B: negative) were unremarkable.

A biopsy taken from a lesion at the right shoulder showed the following features: beneath a slightly acanthotic epidermis, the dermis was remarkably thickened extending into and partly replacing the subcutaneous fat, with relative upward reposition of the eccrine glomeruli (Figure 2A). There was atrophy and peripheral dislocation of the pilo-sebaceous units with hypertrophy of the arrector pili muscles. The papillary dermis showed a felt-like texture, replaced at a lower level by a disordered intertwining of hypereosinophilic collagen bundles, with a few perivascular foci of lympho-histiocytic infiltrate (Figure 2B). In the deep reticular dermis and around the sweat glomeruli, the collagen bundles were swollen and homogenized with reduction and focal effacement of the interfascicular spaces. These findings were therefore highly indicative of scleroderma diagnosis.

On this background, a wide twine of thick hypereosinophilic collagen bundles occupied the mid dermis, intermingled with variable numbers of roughly spindled cells (Figures 2B,C). The cells were either sparsely strewn between the collagen bundles or gathered together in densely cellular ribbons, which predominated over the collagen component (Figure 2D). Most of them had plump nuclei and large cytoplasm, while others were spindle-shaped with elongated tapering nuclei. Notably, a focally localized vague nodular pattern resulted from the close interweaving of haphazardly

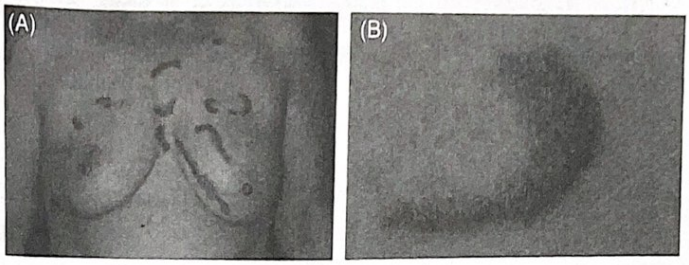


**FIGURE 1** A, Multiple linear and arciform, erythematous and slightly pigmented plaques, localized on apparently normal skin, at the sternal and pectoral regions, and at the shoulders in concurrence with a bland quadrantectomy scar at the right breast. Biopsy site at the right shoulder (arrow). B, Detail of an arciform plaque

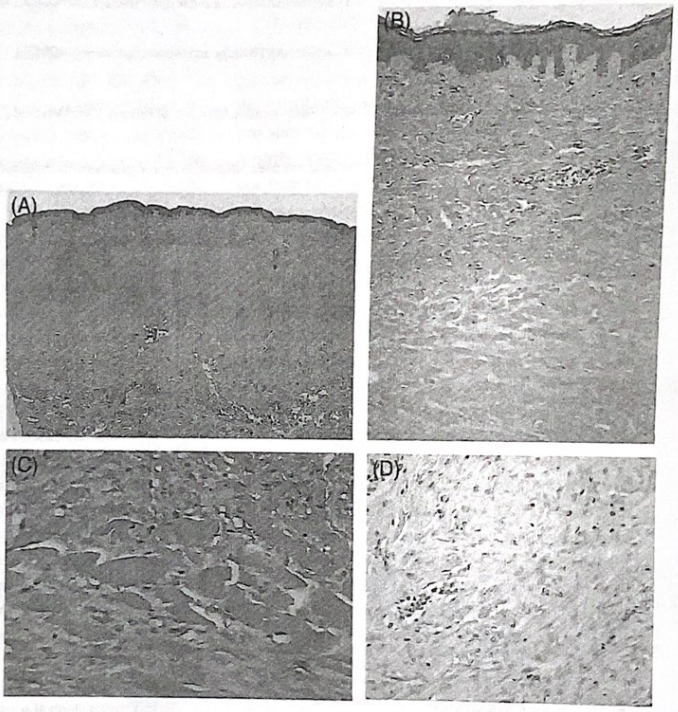


**FIGURE 2** A, Panoramic view of a plaque of the right upper arm, showing remarkably thickened dermis at expense of the subcutaneous fat with relative upward reposition of the eccrine glomeruli and peripheral dislocation of the pilo-sebaceous units (H&E, X40). B, Felt-like texture of the papillary dermis, twining of the collagen bundles in the superficial reticular dermis, wide weave of broad hyaline and hypereosinophilic (keloidal) collagen bundles in mid dermis, intermingled with roughly spindled cells (H&E, X100). C, Detail of the keloidal collagen bundles (H&E, X250). D, Ribbons of interwoven plump spindle cells with large cytoplasm, in the spaces between the collage bundles (H&E, X250)

oriented collagen bundles with hypereosinophilic, Weigert-positive elastic fibers encased in between (Figure 3A,B).

Most cells exhibited immunohistochemical expression of vimentin (Figure 4A) but were negative for α-smooth muscle actin (α-SMA) (Figure 4B,C), thus being identifiable as fibroblasts. CD34-positive dendritic cells were not detected in the tissue. Instead, these antibodies marked pericytes and endothelial cells revealing the presence of numerous slit-like capillaries and venules compressed by the fibroplasia. The morphological and immunopathological analysis, supported by the patient clinical history, suggested the diagnosis of keloidal morphea.

## 3 | DISCUSSION

Nodular morphea is a rare form of localized scleroderma with less than 50 cases reported.[1-3] It is clinically characterized by one or more raised lesions that usually occur in association with classic morphea, developing on the affected areas or on apparently normal skin. Similar abnormal growths can arise in the course of generalized scleroderma, thus distinguishing a form of the disease specified as nodular scleroderma.[4-6]

These growths usually appear as nondescript protuberances, histopathologically composed of sclerodermatous tissue,[1-6] but

sometimes they show specific clinical and histopathological characteristics of keloids.[7-13] In this case, they have a firm consistency and an uneven surface with arciform or irregularly curvy contours, which can protrude outward with pseudopod-like projections. Older and larger plaques may have a geographic outline.[10] From the histopathological point of view, these lesions appear as endo-exophytic formations composed of haphazardly interweaving, broad, homogenous, and brightly eosinophilic collagen bundles, accompanied by a variable number of fibroblasts and/or myofibroblasts, which are sometimes crowded around fibrotic hypocellular areas.[9-11] The elastic fibers between the bundles are usually fragmented or absent. These formations, which show the typical histopathologic features of keloids, usually stand out against the background of a thickened, hypocellular dermis characterized, as expected in scleroderma, by faintly eosinophilic, swollen collagen bundles with effacement of the interfascicular spaces, conserved elastic fibers, and peripheral dislocation of the adnexa.[10] A few foci of perivascular and periadnexal lymphocytic infiltrate are present in recent lesions. This association and/or overlapping of keloidal overgrowths with classical morphea characterizes the special form of the disease that has been recently designated as keloidal morphea. The latter can be considered either a distinct form or a variant of nodular morphea.[12,13]

**FIGURE 3** A, Nodular formation resulting from closely interweaving and haphazardly oriented collagen bundles with fragmented hypereosinophilic elastic fibers in between (H&E, ×100). B, Weigert-positive elastic fibers in the interfascicular slits of a nodular formation (Weigert method, ×100)

**FIGURE 4** A, Extensive expression of vimentin in the cell population of the newly-formed tissue (×40). B, Expression of α-SMA in venules, capillaries and sweat gland glomeruli (×40). C, Detail of 4B showing α-SMA positivity in the pericytes of venules and capillaries (×250). A-C, Horseradish-Labeled-Polymer technique with diaminobenzidine + chromogen/substrate

Our case meets the criteria for the clinical and histopathological diagnosis of a keloidal type of nodular morphea.[1-13] In fact, it is characterized by firm keloidal-like plaques not related to a side effect of the radiotherapy, which was administered several years after their first appearance. The previous diagnosis of true spontaneous keloids is hardly plausible because of the concomitant inconspicuous surgical scar from quadrantectomy, and is barely consistent with our patient's Caucasian ethnicity. Caucasians, in fact, are noticeably less prone to develop spontaneous keloids than Africans, and suffer from these skin overgrowths still more rarely than from nodular morphea.

**TABLE 1** Differential diagnosis between keloidal morphea, wound healing disorders and cutaneous mesenchymal tumors

| Diagnosis | Clinical features | Histopathologic features | IHC |
|---|---|---|---|
| Keloidal morphea | Firm raised lesions with geographic contours, associated to classic morphea | Keloidal collagen aggregation on the background of classical scleroderma characterized by swollen, smudgy collagen bundles and effacement of the interfascicular spaces | Reported: α-SMA+[8,20] α-SMA −[19] CD34−[19] Our case: α-SMA− CD34− |
| Keloids | Firm raised lesions with geographic contours | Broad hyaline, hypereosinophilic bundles replacing the normal collagen with few spindled cells in between | Reported: mainly α-SMA−[24] mainly α-SMA+[25] |
| Hypertrophic scars | Firm raised lesions, limited to the initial boundaries of the injury | Nodules of fibrillar collagen intermingled with spindled cells | Reported: mainly α-SMA+[24, 26] mainly α-SMA−[25] |
| Dermatomyofibroma | Firm red brown plaques or nodules, sometimes resembling keloids, on shoulder, axilla, abdomen of young adults | Fascicles horizontally oriented in the absence of keloidal collagen | Vimentin+ α-SMA− CD34−[18] |
| Cutaneous adult myofibromas/ Myopericytoma | Sometimes multiple nodules Distal extremities of middle aged adults | Concentric, perivascular proliferation of ovoid, plump, spindled to round myoid cells | α-SMA+ mainly CD34−[18] |
| Solitary fibrous tumor | Solitary nodule simulating a cyst mostly on the head and neck | Short fascicles of spindled and ovoid cells sometimes arranged with storiform configuration; dilated vessels with staghorn contours | Vimentin+ α-SMA− CD34+[18] |

Abbreviation: α-SMA, α-smooth muscle actin.

Our findings of negative autoimmune serology are consistent with the literature data. In fact, in classical morphea, variable ANA positivity (18-68%) and, less frequently, the presence of anti-dsDNA and anti-ENA antibodies have been reported.[14,15] Furthermore, the uncommon association of sclerodermatous nodules with classical morphea is rarely complicated by multi-organ involvement and only anecdotally accompanied by ANA positivity.[16] Conversely, these nodules are usually associated to systemic sclerosis with multi-organ involvement and serological signs of autoimmune disease. These observations raise the question whether nodular morphea may herald systemic sclerosis, but, to our knowledge, this kind of progression has not been reported.

Histopathologically, our diagnosis is supported by the presence of bulky bundles of brightly eosinophilic keloidal collagen on a background of typical swollen and smudgy sclerodermatous collagen. The collagen bundles are interwoven in broad twines and nodules with fragmented elastic fibers encased in between.[8] These features allow the differential diagnosis with both common morphea and plain keloids. Another element in favor of our diagnosis is the rich cellular population focally gathered in long ribbons, which predominates over the collagen component. This finding does not match any classic description of authentic keloids, whereas it has been reported in acknowledged cases of keloidal morphea.[10-19] This population of large cells with plump nuclei and spindle-shaped elements with tapering nuclei should be histopathologically differentiated from a few cutaneous mesenchymal tumors that may simulate keloidal overgrowths. The clinical and histopathological differential diagnoses are reported in the Table 1.[18]

The absence of α-SMA-positive myofibroblasts in our specimens conflicts with the diffuse α-SMA expression usually found in classical scleroderma, while it is narrowly comparable with the variable α-SMA positivity detected in the few immunohistochemically documented reports of nodular scleroderma.[6-11,18,19] The contemporary absence of dendritic cells and myofibroblasts does not reflect the inverse correlation between the extent of CD34-negativity and the α-SMA-positivity reported in scleroderma.[20] These discrepancies may depend on the phase and the severity degree of scleroderma, as suggested by recent morphological studies that highlight progressive increase of myofibroblasts paralleling the evolution of the disease.[21] On the other hand, the studies on hypertrophic and keloidal scarring supply various and contrasting results on the presence and the extent of fibroblastic and myofibroblastic population in these forms of wound healing.[22-25]

In conclusion, we have reported a rare case of multiple keloidal morphea, in the absence of any clinical and serological evidence of common scleroderma. Our histopathologic investigation was prompted by the clinical observation of a concomitant normal surgical scar and revealed a typical morphological picture with unconventional immunohistochemical features.

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CASE REPORT

# A Case of Moderate Hidradenitis Suppurativa and Psoriasis Treated with Secukinumab

Pistone Giuseppe, Pardo Nicola, Caputo Valentina, Castelli Elena, Curiale Salvatrice, Gurreri Rosario, Bongiorno Maria Rita

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Hidradenitis suppurativa (HS) is a disorder of the apocrine gland causing a chronic, recurrent and painful inflammation. It is a disabilitating condition and, though many therapeutic options are available, the response is often ineffective in most cases and patients can present many recurrences with physical and psychological sequelae. Recent data had shown increased interleukin (IL)-17 serum levels in patients with HS. Psoriasis is a chronic immune-mediated inflammatory disorder and new evidences have shown the role of Th17 cells in its pathogenesis and the therapeutic efficacy of anti-IL-17 antibodies. We present a case of a patient suffering from psoriasis and HS successfully treated with anti-IL-17 antibodies for both conditions. This is the first case report of HS treated with secukinumab. **(Ann Dermatol 30(4) 462~464, 2018)**

**-Keywords-**
Hidradenitis suppurativa, Interleukin-17, Psoriasis

## INTRODUCTION

Hidradenitis suppurativa (HS) is a disorder of the terminal follicular epithelium in the apocrine gland-bearing skin, characterized by a chronic, recurrent and painful inflammation in areas of the apocrine sweat glands, most commonly the axillary, inguinal, and anogenital regions.

It is a disabilitating chronic inflammatory disease with major negative impact on quality of life and significant comorbidities.

Though many therapeutic options are available, the response is inadequate in most cases and patients can present many years of recurrent outbreaks that have major physical and psychological sequelae.

Recent publications confirm the presence of increased interleukin (IL)-17 serum levels in patients with HS and there is a base for treatment with secukinumab[1].

We successfully treated a patient with HS and psoriasis. This is the first case report of HS treated with secukinumab.

## CASE REPORT

A 37-year-old white man was referred to the Department of Dermatology, University of Palermo (Italy) with a twenty-years history of psoriasis and eleven of HS.

He had received many treatments with several systemic agents: a combination of Rifampicin and Clindamycin and Cyclosporine with poor response. From April 2015 to September 2016, the patient received infliximab infusions (5 mg/kg) with partial improvement of both diseases and frequent recurrences.

In November 2016, skin examination revealed erythematous plaques with sharp boundaries and covered with pearlescent squamae on the trunk and extremities in a generalized distribution (Fig. 1A, B).

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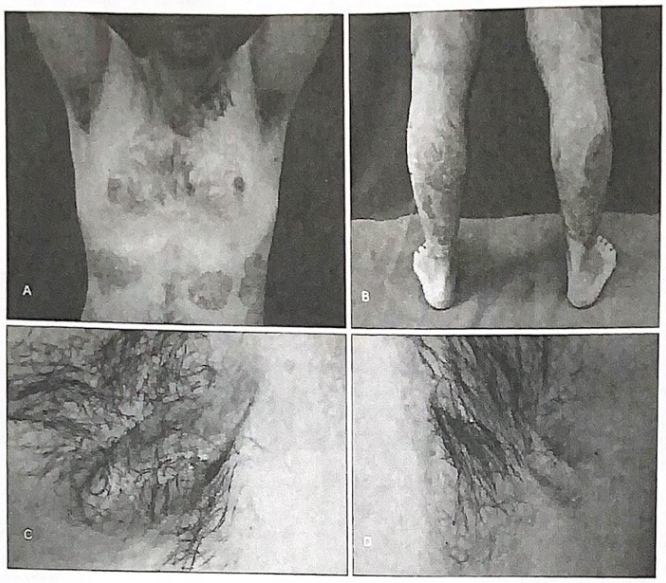

**Fig. 1.** (A, B) Erythematous plaques covered with squamae on the trunk and extremities; (C) reddish painful abscesses with a sinus tract of the right axilla; (D) erythematous lesions with hypertrophic scars at the left axilla.

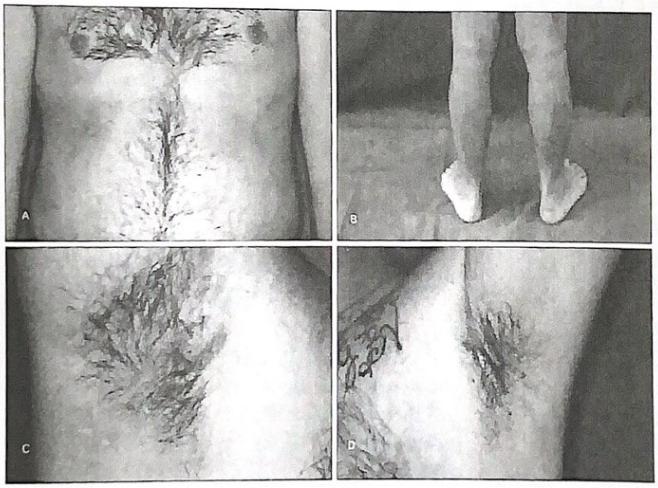

**Fig. 2.** (A~D) Regression of the abscesses and improvement of psoriatic lesions.

In the right axillary region were found reddish painful abscesses with a sinus tract (Fig. 1C). The lesions caused considerable pain, resulting in severe discomfort and a substantial negative effect on quality of life. Slightly raised erythematous lesions with hypertrophic scars were present at the left axilla. The patient had secondary stage of HS according to the Hurley staging system (Fig. 1D).

Before treatment, the patient underwent comprehensive laboratory investigations, including complete blood cell count; chemistry panel; tuberculosis (Quantiferon-TB Gold test; Cellestis Limited, Carnegie, VIC, Australia), human immunodeficiency virus, and hepatitis B and C screening; and chest X-ray.

After comprehensive information he received the first sub-

cutaneous injection of secukinumab according to the psoriasis regimen, 300 mg subcutaneously in weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter. Within two weeks there was a good reduction in inflammatory activity with regression of erythema, pain and flattening of abscesses as well as a significant improvement of psoriasis skin lesions (Fig. 2).

## DISCUSSION

Both HS and psoriasis are considered chronic inflammatory diseases due to immune dysregulation. The high prevalence of psoriasis patients diagnosed with HS suggests the existence of common pathogenic links[2].

The pathogenesis of HS is complex and it remains unclear. Genetic factors, hormones, smoking, obesity, bacterial infection, and alteration of antimicrobial peptides that regulate cutaneous innate immunity, have been implicated. Recent studies revealed increased expression of a broad range of cytokines in lesional HS skin, including IL-17[3]. Psoriasis is a chronic immune-mediated inflammatory disorder and new evidences revealed a role of Th17 cells as proximal regulators of psoriatic skin inflammation; the therapeutic efficacy of IL-17 blockade has provided clinical confirmation of the central role of this cytokine in the pathophysiology of psoriasis. Recent studies revealed an increased number of IL-17-producing cells and IL-17 expression in lesional and perilesional skin of patients with HS and psoriasis[4]. The use of systemic biologic therapy with anti-tumor necrosis factor (TNF)-alfa has shown a favorable safety profile in the treatment of plaque psoriasis and psoriatic arthritis, preventing the articular disability, through an early diagnosis[5,6]. The new molecule secukinumab, is a fully human monoclonal immunoglobulin G1 $\kappa$ antibody that selectively inhibits the ligand IL-17A and its downstream effects by preventing it from binding to the IL-17 receptor[7]. Considering that IL-17 acts synergistically with TNF-alfa, and that HS and psoriasis are associated with metabolic syndrome with increased risk for development of cardiovascular disease, the use of anti-IL-17 agents in the treatment of our patients is justified[8]. Therefore, secukinumab represents a new therapeutic option for patients with recalcitrant HS.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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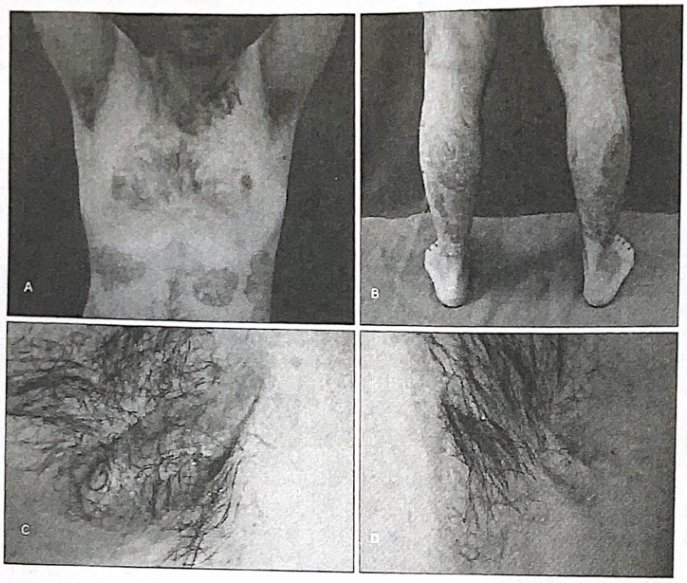


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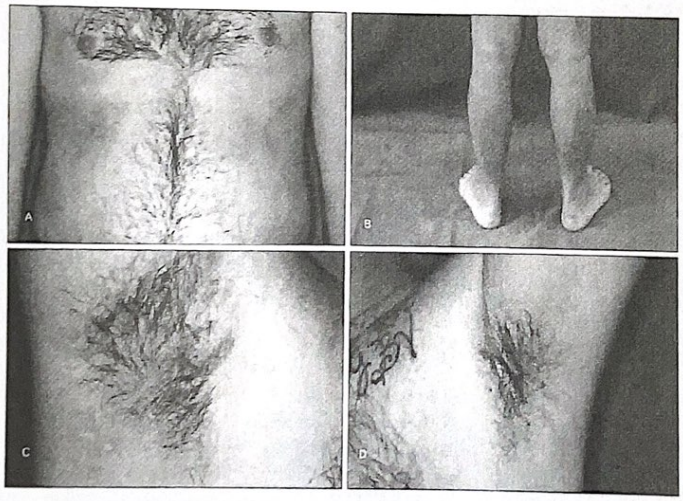


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# A very rare case of keloidal morphea uncovered by a well-defined surgical wound

**E. Castelli, E. Orlando, G. Pistone, S. Curiale, G.M. Garbo, N. Pardo, M.R. Bongiorno**

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## Background

Keloidal morphea also known as nodular morphea or keloidal scleroderma is a rare variant of morphea, clinically characterized by thick, erythematous, arciform and polycyclic nodules or plaques resembling keloids or hypertrophic scars. Such lesions can occur in association with systemic sclerosis (SSc), with morphea or much more rarely, as a solitary form in the absence of other clinical manifestations[1]. This variable and insidious clinical presentation can make the diagnosis extremely difficult. We present a case of keloidal morphea in a 50-year-old female, who developed the disease without other clinical symptoms.

## Observation

A 50-year-old woman presented with a 30-year history of firm, linear and arciform erythematous plaques, which had slowly but relentlessly developed on the sternum area, breasts and shoulders (Fig. 1A, Fig. 1B). The patient denied a previous history of surgery or trauma at the affected sites and reported that a clinical diagnosis of spontaneous keloids had been made soon after the appearance of the first cutaneous manifestations. The drug history was negative. At skin examination, a thin, inconspicuous surgical scar from an old quadrantectomy at the right breast was in patent contrast with the previous diagnosis of spontaneous keloids, and raised the possibility of keloidal morphea. The patient was otherwise healthy and laboratory screening for autoimmune diseases was unremarkable. The histological examination of a bioptic specimen taken from the right upper arm showed the following features (Fig. 2) :

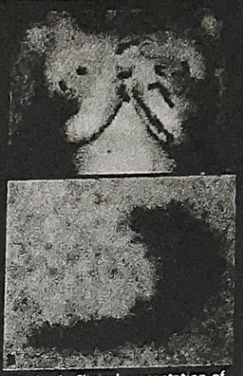

**Fig. 1 - A.** Clinical presentation of keloidal morphea - **B.** Lesion from the right shoulder.

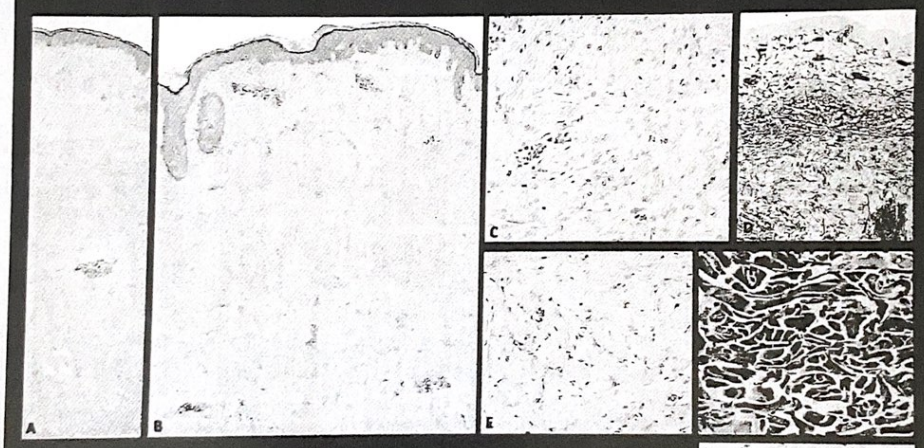


Fig.2: Beneath a normal epidermis, the dermis was remarkably thickened, extending into the subcutaneous fat with peripheral dislocation of the pilo-sebaceous units and relative upward reposition of the eccrine glomeruli (A). Around the sweat glomeruli and in the deepest reaches of the lesion, the hypereosinophilic sclerotic dermal bundles became swollen and homogenized with effacement of the interfascicular spaces. A sparse perivascular and periadnexal lympho-histiocytic infiltrate was present (B). On this background, a gathering of roughly spindled cells, bound together in sweeping ribbons, occupied the mid dermis, intermingled with hypereosinophilic keloidal collagen bundles (B-C). These cells showed prominent nucleoli and thickened nuclear membranes (C). They exhibited extensive immunohistochemical expression of vimentin but were negative for smooth muscle actin (D), thus being identifiable as fibroblasts. Focally, a vague nodular pattern resulted from the close interweaving of haphazardly oriented collagen bundles with hypereosinophilic, Weigert – positive elastic fibers encased in between (E-F). In this pattern, occasional "free floating" hyaline collagen bundles, rimmed by histiocytes were detectable (floating sign) (G). These features as a whole were consistent with the diagnosis of nodular/keloidal scleroderma. **A: Hematoxilin &Eosin (H&E), microphotographic map, X4 . B: microphotographic map, X10. C: H&E, X25. D: Immunostain for Vimentin, X4. E: H&E, X25. F: Weigert-Masson's method for elastic fibers, X25. G: H&E, X4.**

## Discussion

Keloidal morphea is a rare form of scleroderma with less than 50 cases previously reported. Because of its rarity and misleading morphology, it may be clinically misdiagnosed as keloidal scars, mucinosis, apocrine cystadenoma or even chronic folliculitis. Such challenging diagnosis may be facilitated only by the concurrence of an autoimmune disease, when it is detected. In our exceptional case, the diagnostic suspicion was raised by the keloid-like lesions observed by us in a patient with a normal surgical scar and no risk for keloids. After accurate collection of the medical history, the final diagnosis was prompted by the histologic observation, which demonstrated a focus of keloidal collagen overproduction by a hyperplastic fibroblast population, superimposed on the typical alterations of scleroderma. These findings indicated a highly cellular form of nodular/keloidal scleroderma, and allowed the differential diagnosis from several other similar lesions, in the absence of clinical and laboratory signs of systemic or localized scleroderma[1,2]

*1 Kassira S, Jaleel T, Pavlidakey P, Sami N. Keloidal Scleroderma: Case Report and Review. Case Rep Dermatol Med. 2015;2015:635481*

*2 Cooper C, Winston Adam I, Rubin, Rosalie Elenitsas, Glen H. Crawford. Nodular scleroderma: a report of 2 cases. Am J Dermatopathol. 2008 Aug;30(4):385-8*

# Ruolo della capillaroscopia nella malattia di Anderson-Fabry

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U.O.C. di Dermatologia e Malattie Sessualmente Trasmesse, DI.BI.M.I.S., A.O.U.P. "P. Giaccone" di Palermo, Università degli Studi di Palermo

## Introduzione

La malattia di Anderson-Fabry è un raro disordine da accumulo intralisosomiale, X-linked, causato dalla mutazione del gene GLA che codifica per l'α-galattosidasi A. La mancanza di questo enzima comporta il deposito di globotriaosilceramide (Gb3) all'interno degli endoteliociti. In età giovanile, la malattia determina la formazione degli angiocheratomi (Ak) a livello cutaneo (Fig.1), tuttavia, in età più avanzata, la compromissione clinica assume un carattere sistemico con danno cardiovascolare, renale, cerebrale, oculare e vestibolo-cocleare. Il progressivo danno vascolare cutaneo e sistemico è stato valutato in sei pazienti attraverso la capillaroscopia periungueale.

**Fig.1** – Numerosi angiocheratomi in un paziente affetto da malattia di Anderson-Fabry (a-b).

## Risultati

L'esame ha mostrato una **ridotta visibilità** in 4 casi su 6, in tutti i casi riconducibile al linfedema degli arti superiori, una condizione spesso osservata tra i pazienti affetti da questa malattia. Tale fenomeno, tuttavia, non impediva l'osservazione morfo-funzionale dei capillari in nessun caso in esame. L'**architettura dei capillari** era alterata in 5 casi su 6, ma soltanto in 2 casi è apparsa fortemente irregolare (Fig.2a-b). Tutti i pazienti presentavano una **ridotta densità dei capillari** seppure, in 4 casi su 6, di grado lieve e moderato (Fig.2c). L'indagine mostrava inoltre, in tutti i pazienti, entità variabili di alterazione con **capillari dilatati** (Fig.2d), **capillari tortuosi** ed **ectasie** dell'ansa capillare e del versante venoso (Fig.2e). In 5 pazienti erano presenti **microemorragie** periungueali (Fig.2f) mentre i **capillari ramificati** sono stati osservati in 4 pazienti su 6 e solo due di questi presentavano capillari a cespuglio (Fig.2g). La formazione di **rouleaux**, che conferisce tipicamente un aspetto granuloso al flusso è stata osservata in 4 pazienti su 6 (Fig.2h). Nessun'altra alterazione capillaroscopica è stata riscontrata.

## Metodi

Obiettivo di questo studio è stata la valutazione delle manifestazioni cliniche (Tab.) e l'analisi dei relativi pattern capillaroscopici per mezzo di un videodermatoscopio 30x, 150x a luce UV. Nove parametri indicativi di alterazione capillaroscopica sono stati presi in considerazione: ridotta visibilità, architettura irregolare dei capillari, ridotta densità di capillari, capillari dilatati, ectasie venose, microemorragie, capillari tortuosi, capillari ramificati e rouleaux.

| Pz. | Sesso | Mutazione gene GLA | Acroparestesie | AK | Anomalie cardiache | Anomalie urinarie | Sintomi uditivi |
|---|---|---|---|---|---|---|---|
| 1 | M | c658C>T | + + + | + + + | + + + | + + – | + + – |
| 2 | F | c658C>T | + – – | + + + | + – – | + + – | + – – |
| 3 | M | c946delG | + + + | + + + | + + + | – – – | + + – |
| 4 | M | c946delG | + + + | + + + | – – – | – – – | + + + |
| 5 | F | c946delG | + + + | – – – | – – – | + – – | + + – |
| 6 | F | g.7446G>A | + + – | + + + | + + + | – – – | + – – |

**Tab.** – Grado di compromissione clinica dei pazienti studiati.

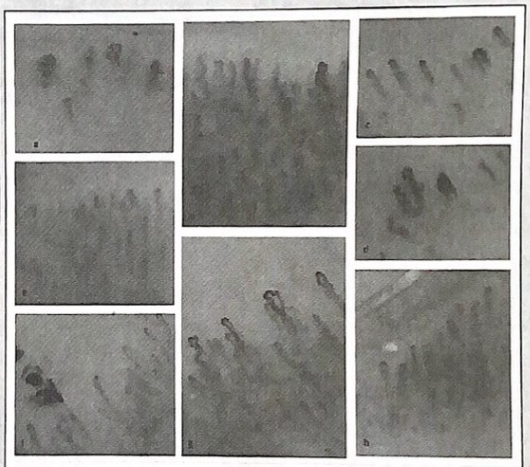

**Fig. 2** – Architettura irregolare dei capillari (a-b), ridotta densità dei capillari (c), capillari dilatati (d), ectasie venose (e), microemorragie (f), capillari ramificati e a cespuglio (g), rouleaux (h).

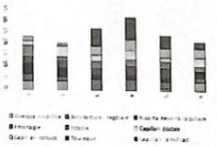

**Fig.3** – Gravità del singolo parametro capillaroscopico analizzato per ogni paziente studiato, espressa mediante un punteggio da 0 a 5.

## Discussione

Tutti i pazienti studiati presentavano anomalie del pattern capillaroscopico, dato compatibile con il progressivo danno del microcircolo tipico di questo disordine da accumulo lisosomiale (Fig.3). Le alterazioni capillaroscopiche più comunemente osservate sono state l'architettura irregolare, i capillari dilatati e l'aumentata tortuosità dei capillari. Nei pazienti di sesso maschile è stato osservato un grado più severo di alterazioni: ciò potrebbe essere giustificato dalla condizione di emizigosi che contraddistingue i maschi affetti e che generalmente comporta un maggiore rischio di complicanze del microcircolo sistemico rispetto alle pazienti di sesso femminile che presentano due cromosomi X. In questo studio non è stato possibile mettere in correlazione l'entità della compromissione multisistemica con il grado di alterazione dei capillari periungueali; tuttavia, la presenza di rouleaux, indicativi di un deficit funzionale del microcircolo cutaneo e di capillari ramificati è stata messa in evidenza nei maschi che presentavano danni vestibolo-cocleari di grado severo ed acroparestesie persistenti. Saranno comunque necessari ulteriori studi per confermare questa correlazione. Alla luce di queste osservazioni, non va escluso il potenziale ruolo di questa tecnica nel predire alcune delle complicanze del paziente affetto da malattia di Fabry, soprattutto per i maschi emizigoti. Inoltre, a nostro giudizio, un confronto del pattern capillaroscopico con il relativo quadro clinico, potrebbe essere utile per migliorare la valutazione dell'efficacia della terapia enzimatica sostitutiva e per stabilire se intraprenderla nelle femmine eterozigoti asintomatiche.

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# Efficacia e sicurezza a lungo termine di sonidegib in pazienti pluripatologici con BCC localmente avanzato

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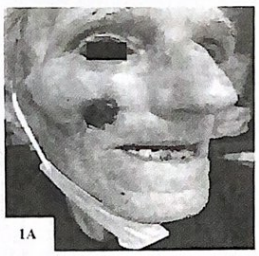
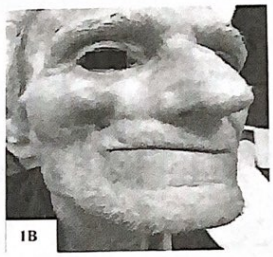
## INTRODUZIONE

arcinoma a cellule basali (BCC) rappresenta quasi l'80% dei tumori della pelle e la sua gestione terapeutica riveste un ruolo importante interno delle unità operative di dermatologia. Sebbene la maggior parte dei BCC siano di dimensioni piccole o intermedie, con margini ben finiti e possano essere trattati chirurgicamente o con procedure conservative, in una piccola percentuale di pazienti, essi possono progredire so uno stadio localmente avanzato (laBCC) o metastatico (mBCC). I laBCC rappresentano un'entità non chiaramente definita, in quanto non inca una standardizzazione circa i criteri di definizione e di diagnosi. In linea generale, è possibile definire i laBCC come tumori estesi con una scita distruttiva dopo multiple recidive, spesso localizzati nelle aree della testa e del collo, non sono suscettibili di intervento chirurgico ativo o di radioterapia. In questi casi la terapia medica di prima scelta è rappresentata dagli inibitori della via di segnalazione di Hedgehog ): sonidegib e vismodegib. Riportiamo due casi clinici di pazienti con pluricomorbidità e laBCC trattati con successo con sonidegib

## CASO I

ziente maschio di 85 anni affetto da ipertensione arteriosa, diopatia ischemica cronica, IRC, DM II e pregresso ictus ebrale. Giungeva alla nostra attenzione nel Maggio 2022 per la senza di BCC tipo *ulcus rodens* in regione zigomatica destra (fig ). Il paziente era stato sottoposto a plurimi interventi chirurgici n successiva recidiva locale. Veniva eseguita RMN del massiccio ciale con riscontro di ispessimento del tessuto sottocutaneo in le sottorbitaria con aspetto pseudonodulare e dimensioni ssime di 20 mm in prossimità dell'osso mascellare. Tenuto nto delle comorbidità riportate e delle numerose recidive st-chirurgiche, il caso veniva sottoposto a discussione ultisciplinare, in presenza del chirurgo maxillo-

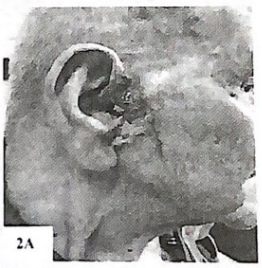

1A

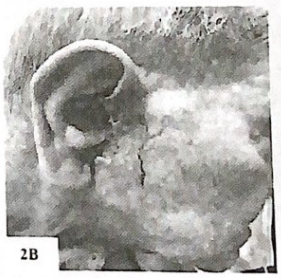

1B

ciale e del radioterapista, nella quale si decideva di trattare il paziente con sonidegib 200 mg cp, 1 cp/die alterni. Dopo due mesi di terapia si ervava un aggravamento del quadro clinico con formazione di soluzione di continuità con il cavo orale; si decideva pertanto di incrementare posologia a 200 mg cp, 1 cp/die, con progressivo miglioramento con chiusura della soluzione di continuità nel corso del follow-up. Dopo 6 si dall'avvio della terapia si osservava una remissione clinica completa (**fig 1B**).

## CASO II

ziente maschio di 92 anni affetto da ipertensione arteriosa, IRC, egresso carcinoma polmonare nel 2016. Giungeva alla nostra enzione per la presenza di un BCC nodulare presente da circa 3 ni in regione pre-auricolare destra, confermato ologicamente, e andato incontro a progressivo aumento rfo-volumetrico, ulcerazione e sanguinamento (**fig 2A**). Veniva eguita RMN del massiccio facciale che evidenziava un essimento delle cute e della cartilagine auricolare a livello del go, con estensione al tessuto sottocutaneo e parziale iltrazione della parotide. Si integrava con PET che evidenziava tologico accumulo del tracciante in sede pre-auricolare, in enza ulteriori reperti nei restanti distretti corporei esaminati.


2A


2B

opo aver discusso il caso in riunione mutidisciplinare, si decideva di iniziare terapia con sonidegib 200 mg cp, 1 cp/die alterni. Dopo 5 mesi di rapia si osservava una risoluzione quasi completa della neoplasia (**fig 2B**).

ntrambi i pazienti, nonostante le multiple comorbilità e le fragili condizioni cliniche, hanno ben tollerato il trattamento farmacologico, tt'ora in corso, senza significative alterazioni dei parametri bioumorali (emocromo, funzionalità epatica e renale, CK, amilasi e lipasi) valutati corso di follow-up.

## DISCUSSIONE

iscontro di laBCC non è infrequente nella pratica clinica. Si tratta solitamente di tumori con un lungo decorso clinico, recidivati dopo multipli ttamenti chirurgici e che spesso presentano istotipo aggressivo ed infiltrazione perivascolare o perineurale. Ad esserne interessati sono rattutto pazienti immunosoppressi o con pluricomorbilità. In questi casi, nei quali sia il trattamento chirurgico che quello radioterapico o controindicati o non più applicabili, gli inibitori di Hh (sonidegib e vismodegib) rappresentano una strategia terapeutica valida e sicura. idegib è piccola molecola orale che agisce in modo selettivo come antagonista del recettore SMO, fondamentale per il corretto zionamento della via di segnalazione Hedgehog, iper-espressa nei BCC. Attualmente indicato per il trattamento di laBCC o mBCC alla dose rnaliera di 200 mg, garantisce una risposta clinica totale o parziale soddisfacente, con un elevato profilo di sicurezza. La sicurezza e la lerabilità del sonidegib sono state valutate nel trial clinico di fase 2 in doppio cieco BOLT. Tale studio ha dimostrato che non è necessario un iustamento della dose in pazienti con compromissione renale, in quanto l'eliminazione renale del farmaco è trascurabile; allo stesso modo, n sono necessari particolari accorgimenti in pazienti con compromissione epatica o con più di 65 anni. Le più comuni reazioni avverse sono presentate da: spasmi muscolari, alopecia, disgeusia, affaticabilità, nausea, dolore muscoloscheletrico, diarrea, perdita di peso, diminuzione l'appetito, mialgia e dolore addominale. La tossicità muscolare, con conseguente aumento della creatina chinasi (CK), è l'effetto collaterale frequente: si raccomanda un monitoraggio periodico dei livelli di CK per tutta la durata del trattamento e la sua sospensione nel caso di lli di CK >5 x ULN. Va sottolineato inoltre che sonidegib condivide gli stessi eventi avversi di vismodegib, seppur questi sembrino, nei ienti in terapia con sonidegib, meno frequenti e con un tempo di insorgenza leggermente più lungo, probabilmente a causa di un diverso filo farmacocinetico, rendendolo meglio tollerato.

## CONCLUSIONI