Approach to the so-called "Invisible Dermatosis": When Subtle Histopathological Findings Guide Diagnosis

Mar Llamas-Velasco, PhD,† Noelia Pérez-Muñoz, MD,‡§ Eduardo Rozas-Muñoz, PhD,¶ Rosa Ballester, MD,‡ Rodolfo Posada, MD,‡ and Maite Fernández Figueras, PhD‡§*

Abstract: Invisible dermatosis is a concept that can be applied either to clinical or histopathological findings. We will focus on the dermatopathological aspect of this invisible dermatosis that can be seen as dermatosis with subtle histopathological findings that are mandatory to known to stablish the diagnosis. With a proper approach facing in depth the different skin layers from stratum corneum to subcutaneous tissue combined with some especial stains, special investigations and mostly a proper clinicopathological correlation, the problem of missing out a diagnosis can be decreased. We will review the general aspects for diagnosis and the peculiar findings of an in-depth review of them because it is important to note that minor changes on a skin biopsy do not mean it is disease free. We will review classic clues, we will add some new useful ones, and we will also provide a guide on the special stains helpful, such as periodic acid–Schiff when facing fungi, orcein-Giemsa and van Gieson when altered elastic fibers are suspected, or Pearl and Masson Fontana when an altered skin pigmentation is suspected.

Key Words: invisible dermatosis, subtle dermatosis, special stains, clinicopathological correlation, minor changes

(*Am J Dermatopathol* 2023;45:801–811)

INTRODUCTION

In a visible organ such as the skin, we can face many dermatoses with subtle or hidden features that makes the diagnosis a challenge. This so-called invisible dermatosis can be applied either to the clinicians, as stated by Albert Kligman,[1,2] or to the ones with difficulty to find histopathological features, as proposed by Bernstein and Helwig, because they encompass a group of diseases that can be easily missed by the pathologists.[3,4]

Regarding the first group, authors emphasized generalized pruritus where many underlying causes, such as invisible mycosis fungoides, can be found[5] and diseases where "clinically uninvolved skin" is not completely normal like in psoriasis, pemphigus or lupus, or the areas of recently healed skin that may favor the subsequent appearance of different dermatosis acting like a "*locus minoris resistentiae*."[6] This idea will fit with the concept of disease scar, such as psoriasis,[7] and also with the presence of different dermatosis in areas previously involved by herpes zoster reactivation.[8] We will not review this first group to focus on the second one.

Thus, in dermatopathology, the concept of invisible dermatoses can be defined as lesions where the skin biopsy microscopically resembles normal skin or present minimal changes that apparently cannot justify the clinical presentation, usually evident. It is considered that this group represents as much as 10% of the skin biopsies.[9] Based on this definition, we can make it synonym of dermatosis with subtle dermatopathological findings where a diagnostic protocol is needed to avoid missing the diagnosis; as they have been named "*nothing diseases*" to highlight the diagnostic challenge when facing them.[10]

As in every other biopsy, when we are facing this group of dermatoses, it is necessary to give a quick look to all the sections looking for abnormal and elusive findings that can be only present in sections located focally or even at the edge of the preparation. This first approach provides also an overview to the tissue landscape. It allows to evaluate the degree of actinic damage or the presence of subtle edema or mucin deposition, as well as tenues differences in the collagen texture or changes in the expected size of amount of every layer component from stratum corneum to subcutaneous tissue.[9]

Analyzing previously stated histopathological findings, we can obtain information about the exact biopsy location, an impression useful either if location was not provided or even if it can act as a clue for some dermatosis. For instance, we can know whether a biopsy was taken from the palm or the dorsum of the hands depending on the presence of many sweat glands or hair follicles, respectively. In addition, if we have a stratum corneum mimicking the one in acral areas appearing in an arm biopsy, we are facing the "*hairy palm*" clue to suspect chronic eczema or lichenification (Fig. 1).

When major changes are not apparent in this first glimpse, it will be necessary to look for more subtle alterations and odd or unexpected findings. It is also important to try to compare the pathologic area and the adjacent skin, if available or to consider to ask for serial sections to check whether the lesion is already included in the slides we are reviewing.[9]

In addition, correlation with the clinical information is essential and often the quickest way to reach the diagnosis,

From the *Faculty, Department of Dermatology, Hospital Universitario de La Princesa, Madrid, Spain; †Universidad Autónoma de Madrid, Madrid, Spain; ‡Faculty, Department of Pathology, Hospital Universitari General de Catalunya-Quirónsalud, Sant Cugat del Vallès, Barcelona, Spain; §Universitat International de Catalunya, Sant Cugat del Vallès, Barcelona, Spain; and ¶Dermatology Department, Hospital San Pablo, Coquimbo, Chile.

The authors declare no conflicts of interest.

Correspondence: Mar Llamas-Velasco, PhD, Department of Dermatology, Hospital Universitario La Princesa, C/Diego de León 62, CP 28006 Madrid, Spain (e-mail: mar.llamasvelasco@gmail.com).

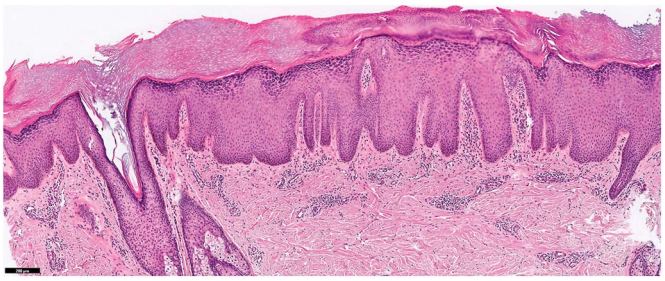

FIGURE 1. Regular acanthosis and hypergranulosis are seen as well as a dense and eosinophilic compact stratum corneum. A hair follicle is observed, pointing out to chronic friction to explain the stratum corneum resemblance to the one usually found in acral skin.

especially in the case of metabolic or deposition diseases. If clinical data are missing and after careful review of all the epidermal layers, we are still facing a such subtle dermatosis that we cannot point out and it is mandatory to check the clinical history or contact the clinicians.

Many invisible dermatosis present alterations in the corneal layer. Therefore, the top of the specimen is the best place to start a methodical examination of each anatomical level, keeping in mind the most common causes of "*invisible dermatosis*" for each one. In this article, we will review some of them within the involved layer (Table 1).

CORNEAL LAYER

We can find increased thickness, focal detached areas, and presence of endogenous or exogenous material as main findings in our first step for diagnosis.

Thickened or more compact corneal layer might be the only manifestation of a congenital or acquired ichthyosis that in the case of ichthyosis vulgaris is characterized by the absence of the granular layer.[11] In contrast with the obvious clinical appearance of granular parakeratosis, histopathologically, there is only slight hyperkeratosis with intracorneal persistence of keratohyalin (Fig. 2).

In guttate psoriasis, the corneal layer findings may also be very subtle and the presence of foci of neutrophils within parakeratotic areas is a useful clue for the diagnosis. In fact, the combination of these features in the corneum stratum with the psoriasiform hyperplasia have been named as the "*Ñ sign*" and are considered a visual clue for the diagnosis of psoriasis.[12] Some epidermal findings such as focal hypogranulosis and suprabasal mitosis are useful findings to add if we find the typical psoriasis' stratum corneum findings (Fig. 3).

The lack of the stratum corneum can be a subtle clue for superficial pemphigus or staphylococcal scalded skin syndrome, and we should look for acantholytic cells and follicular involvement. Even a more subtle separation above stratum granulosum without acantholysis is the guiding sign for peeling skin syndrome, a rare, autosomal, recessively inherited ichthyosiform genodermatosis, that can be related to mutations encoding transglutaminase-5 and reported by Fox.[9,13] (Fig. 4).

TABLE 1. Invisible Dermatosis to the Pathologist

Location	List of Diagnosis
Corneum layer	Fungal or bacterial infections (tinea, pityriasis versicolor, tinea nigra, erythrasma, and pitted keratolysis)
	Scabies
	Guttate psoriasis
	Terra firma-forme
	Ichthyosis vulgaris
	Granular parakeratosis
	Circumscribed acral hypokeratosis
	Graft-versus-host disease
Epidermis	Secondary syphilis
	Plane warts
	Pityriasis rosea
	Guttate psoriasis
	Parapsoriasis and early mycosis fungoides
	Porokeratosis and punctata keratoderma
	Ichthyosiform dermatitis (peeling skin syndrome)
	Lupus erythematosus
	Large-cell or clear-cell acanthoma
	Pigmentary lesions such as vitiligo, hypomelanosis of Ito
	Becker nevus
	Confluent and reticulated papillomatosis
Dermis	Indeterminate leprosy
	Cutaneous leishmaniosis
	Granuloma annulare
	Mastocytosis
	Macular amyloidosis
	Urticaria
	Pseudoxanthoma elasticum, anetoderma, nevus elasticus
	Scleroderma/atrophoderma of pasini and pierini
	Scleredema of Buschke, other mucinosis
	Argyria
	Pigmentary lesions such as dermal melanosis, haemochromatosis
	Metastatic deposits
	Blue nevi
Periadnexal diseases	Argyria
	Anhidrotic ectodermal dysplasia
	Mercury pigmentation
	Alopecia areata
	Acquired aquagenic keratoderma
Subcutaneous tissue	Lipoatrophy

Acral circumscribed hypokeratosis shows a diminishment of the thickness of the normal stratum corneal of the acral area. With a proper biopsy, if the entity is known, it is difficult to miss it as we can see the sharp stair between normal thickness stratum to the involved one.[14]

Corneal changes in *terra firma-forme* dermatosis and confluent and reticulated papillomatosis, also known as *Gougerot–Carteaud* syndrome, are very subtle.[15] In both processes, there is also a slight acanthosis with papillomatosis, with loose orthokeratotic hyperkeratosis (Fig. 5).

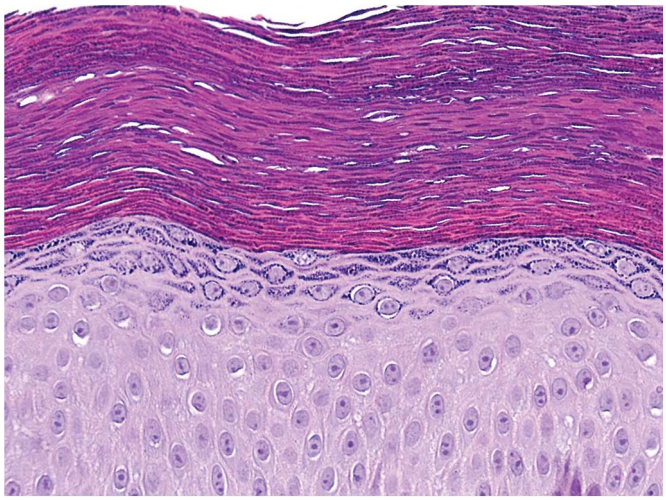

FIGURE 2. Normal epidermis with persistence of small basophilic granules that correspond to keratohyalin granules in the corneum layer.

The presence of keratin whorls in *terra firma-forme* is a quite characteristic finding.[16]

Superficial mycosis must be also considered. Tinea incognito can have a minimal inflammatory response and scant parakeratosis.

Small "*dots and tiny tails*" are a clue for the diagnosis on hematoxylin–eosin sections. The "*sandwich sign*" that is the presence of spores in between an upper layer of orthokeratotic and a lower layer of parakeratotic stratum corneum can be a hint, where refractility of spores can be helpful by moving the condenser[17] (Fig. 6). Additional stainings such as Gomori or periodic acid-Schiff (PAS) are mandatory when this possibility is considered and always of help if nothing is seen. Sometimes a process as seeming as pityriasis versicolor characterized by the presence of a large amounts of fungal structures that has been compared with "*meatball and spaghetti*" can be missed if we do not analyze thoroughly the specimen. Often because a misleading information sends our sight to the wrong place (Fig. 7).

Similar pattern can be found in erythrasma, a superficial bacterial infection caused by *Corynebacterium minutissimum*, where we will find many coccobacilli within the alternating

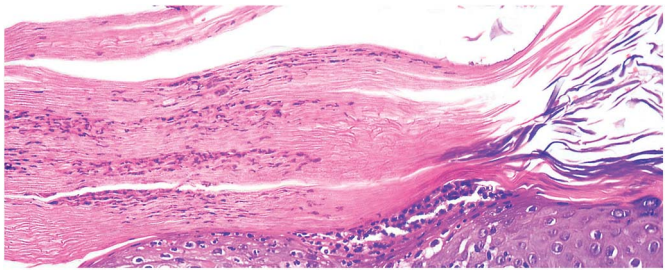

FIGURE 3. Alternating parakeratotic corneum layer, with foci of neutrophils within the parakeratotic areas, is close to loose normal orthokeratotic corneum layer. Additional clues are the neutrophils within the epidermis (Munro microabscesses).

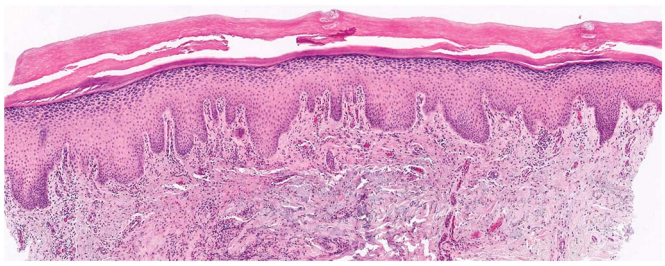

FIGURE 4. Regular psoriasiform hyperplasia with a subtle but constant separation above stratum granulosum in a peeling skin syndrome, produced by a mutation in transglutaminase 5.

basket-weave orthokeratosis and compact eosinophilic orthokeratotic hyperkeratosis within the stratum corneum.

Finally, in pitted keratolysis, there is a superficial bacterial infection by different types of *Corynebacteria*, mostly in soles, and here, histopathology shows an irregular loss of the cornified layer with irregularly distributed spaces filled by the infecting organisms.

Entering parasites, scabies tends to cause an inflammatory reaction rich in eosinophils, except in immunocompromised patients or when the biopsy has been taken from the advanced edge of the burrow. In these cases, the inflammation may be limited to scattered eosinophils. A superficial shave biopsy may contain the useful clues, eggs, feces, or adult worm if we are lucky[18]; but more frequently subtle signs such as superficial depressions indicating a burrow, the nuggets, or the mite are hints of its presence; sometimes, we can observe few fragmented remains such as broken eggs with a pink pigtail appearance that appears as curled pink structures (Figure 8).[19]

As mentioned before, step sections might be of great help because they may change completely the appearance of the biopsy, and up to half of the cases, we can identify typical clues, although many histopathological patterns, including

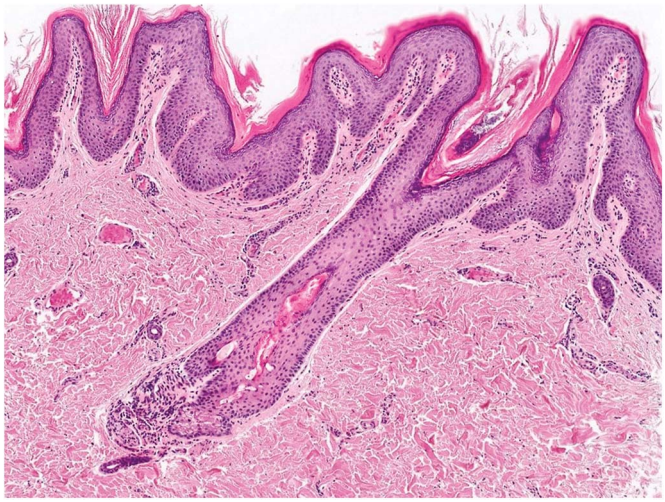

FIGURE 5. Papillomatous epidermis with subtle basal hyperpigmentation. Mostly loose orthokeratotic hyperkeratosis although it is more compact in some areas.

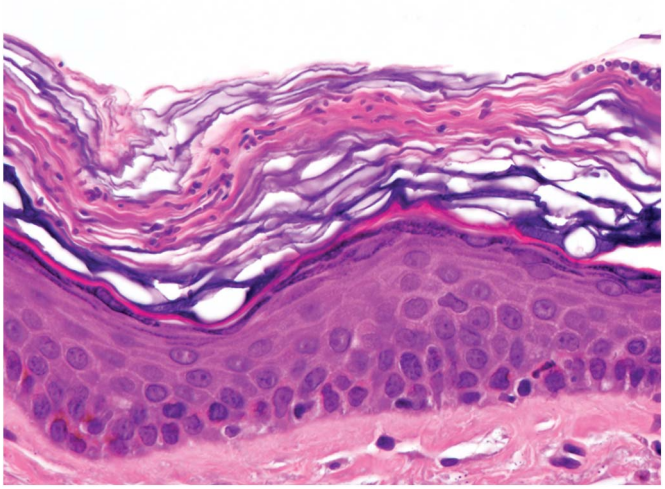

FIGURE 6. Sandwich sign, a clue for dermatophytosis is observed. A parakeratotic layer of stratum corneum with a high number of hyphae is seen.

even thrombosis and vasculitic damage may be present in scabiosis[20]

Sometimes, cornoid lamella, the pathognomonic histopathological finding of porokeratosis, is included in this group as diagnostic sensitivity varies according to the site of the biopsy and the orientation of the biopsy during inclusion as it must be orthogonal to the edge of the porokeratotic lesion. Same happens with keratoderma, as punctata, where histology evidences a spire of parakeratosis with a reduced or missing granular layer. In our experience, cornoid lamella presents a very typical aspect as a small column of parakeratosis overlying an epidermis with vacuolar changes and dermal lymphocytic infiltrate.[21] If there are doubts on the

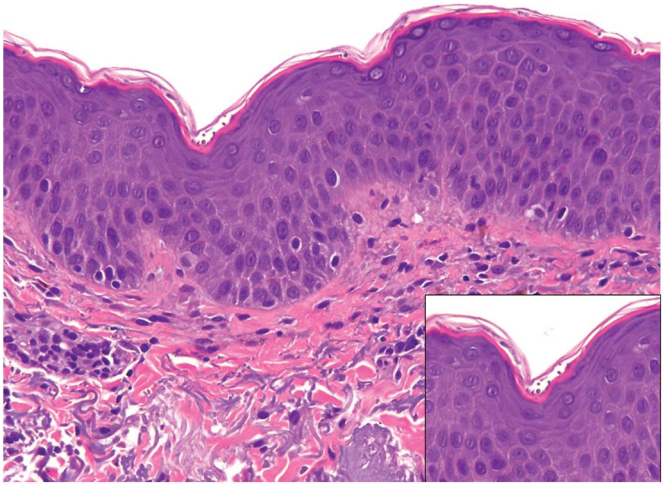

FIGURE 7. Subtle parakeratotic corneum layer overlying epidermis is seen. In between the parakeratotic layer and the orthokeratotic layer, round and elongated structures, named as meatball and spaghetti, typical from pytiriasis versicolor are observed. Inset, detail of a diagnostic area.

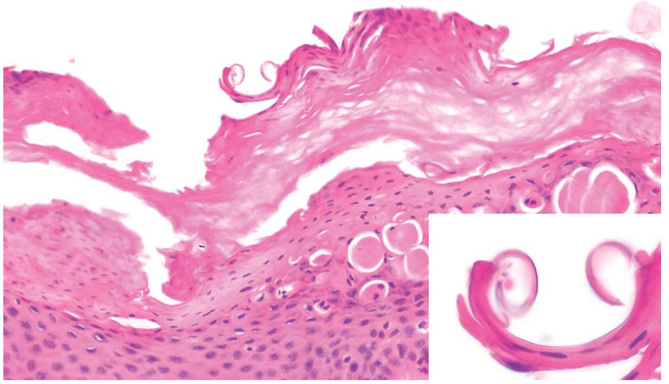

FIGURE 8. Pigtail appearance within a hyperkeratotic and parakeratotic stratum corneum overlying an spongiotic dermatosis with some hints of necrosis due to scratching. Inset in the right down corner, detail of the pigtail structure.

presence of cornoid lamella, PAS staining highlights it, making easier the diagnosis.[22]

Acquired aquagenic keratoderma is clinically very distinctive with whitish and edematous confluent patches located on the fingers and palms after contact with water, but histopathology is subtle, just showing a paler stratum corneum with dilated acrosyringia and a dermal hyperplasia of the secretory and ductal components.[23]

Finally, accidental staining by silver nitrate causes clinically striking areas of pigmentation that can simulate melanoma metastasis or satellitosis (Fig. 9). This situation is especially common among physicians, and one of the most rewarding experiences for a dermatopathologist is giving good news relieving the stress of a clinician. On microscopic examination, we can find coarse pigmented granules dispersed throughout the corneal layer.[24]

Clinically similar to the previous scenery, again a patient with a worrisome and recently appeared, pigmented, mostly black lesion in the acral area can correspond to the

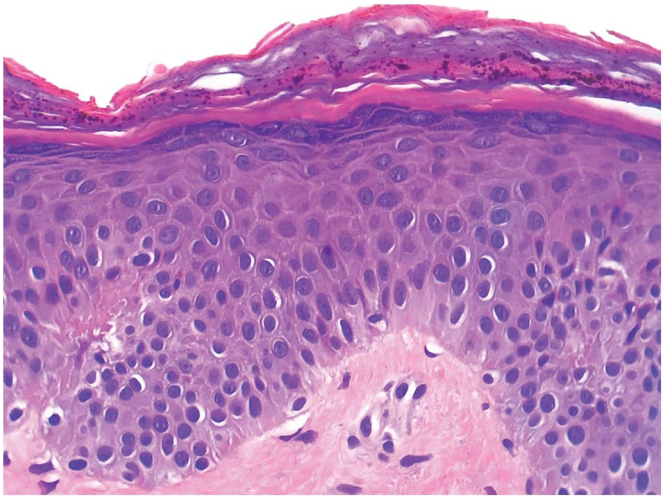

FIGURE 9. Coarse and irregular brownish to black pigment granules in parakeratotic stratum corneum.

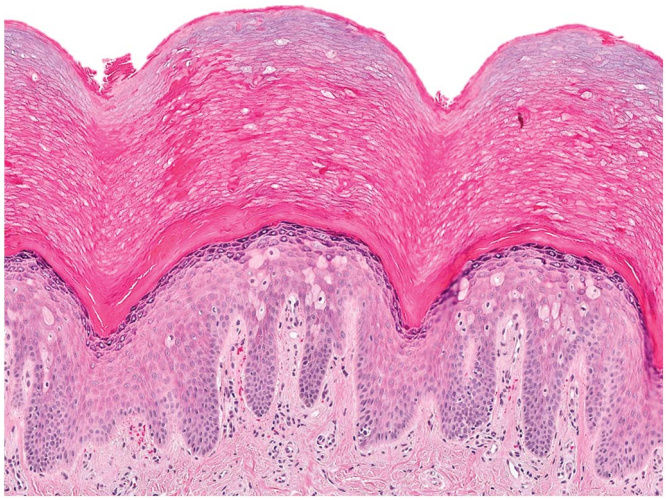

FIGURE 10. Epithelioid pale cells with centrally located nuclei surrounded by a clear halo are intermingled within the keratinocytes in the different layers of the epidermis. No pigmentation in the corneum layer, that is orthohyperkeratotic. There is a slight dilatation of the vessels in the dermal papillae as well as slight red cell extravasation.

presence of hemorrhage in the corneal layer, the so-called, black heel or "*talon noir*."[25] Skin biopsies of this entity are becoming rarer because dermoscopy is very useful to avoid the clinical suspicion of melanoma.[26]

EPIDERMIS

As we have stated before, ichthyosis vulgaris is characterized by the absence of the granular layer along with a thickened corneum layer and flat warts may present an increased granular layer with coarse keratohyalin granules and even koilocytes.

Large-cell acanthomas and actinic keratosis can be missed in the context of an aged or sun-damaged skin. This can happen also with incipient and atrophic actinic keratosis

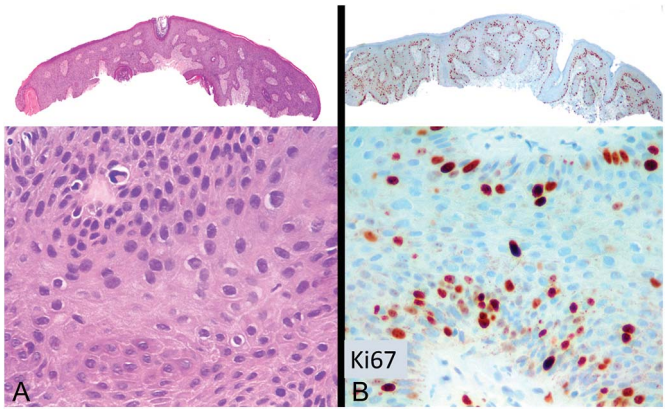

FIGURE 11. A, HE panoramic (up) and HEx10 (down). Flat lesion with slight hyperplasia and few atypical keratinocytes, without clear koilocytes. B, Ki67 staining. Panoramic (up) and Ki67 × 10 (down). Ki67 stained nuclei in different layers of the epidermis. HE, hematoxylin and eosin staining.

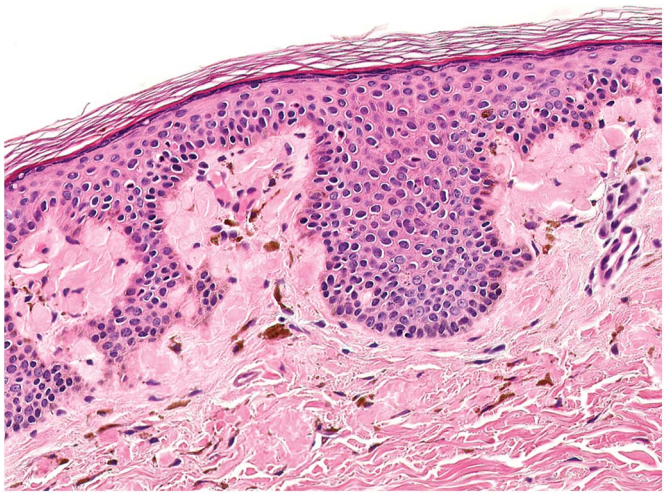

FIGURE 12. Pink nodular deposits of keratin-derived amyloid is seen filling up the dermal papillae and intermingled with hemosiderophages.

where few atypical basal keratinocytes and parakeratosis in an actinically damaged skin can be the only features found. Despite basal cell carcinoma being the more frequent tumor in humans, sometimes very small tumors that are diagnosed with dermoscopy and not cut in the proper area can appear as normal skin before serial cuts. *Derm dotting*, a technique to mark areas of interest to ensure they are examined under microscope, may decrease this problem.[27] When a clinician suspects basal cell carcinoma and nothing is in the slide but solar elastosis, basal cell carcinoma or actinic keratosis usually will appear in serial sections.

Subtle pigmentary changes, such as early vitiligo or *ce au lait* spots can be difficult to evaluate microscopically, but their clinical presentation is so characteristic that clinicopathological correlation can help and, in some cases, can be easily made and confirmed using any melanocyte staining SOX-10, MiTF, or Melan-A.

Although clinically vitiligo is usually evident, it can be confused with postinflammatory hypopigmentation. Immunostaining with Melan-A, or with Masson Fontana, to evaluate degree of melanin content, comparing uninvolved and lesional skin can be helpful.[9,28]

In another rarely biopsied dermatosis, guttata hypomelanosis, there is a diminishment of the basal pigmentation and melanocytes are preserved.[29]

Pityriasis versicolor, previously reviewed here, can be included also in the differential diagnosis of vitiligo, but histopathologically, there are "*meats and balls*" in the corneum layer and epidermis is usually uninvolved or present with slight perivascular lymphocytic infiltrates.

Early stages of mycosis fungoides including the hypopigmented variant can show only barely noticeable rows of slightly atypical T lymphocytes at the dermo–epidermal junction.[30] Other histopathological features such as atypical lymphoid cells with larger nuclear size, presence of haloed atypical lymphocytes in the epidermis, and alignment of those single atypical dermis are helpful.[31] The presence of the wiry

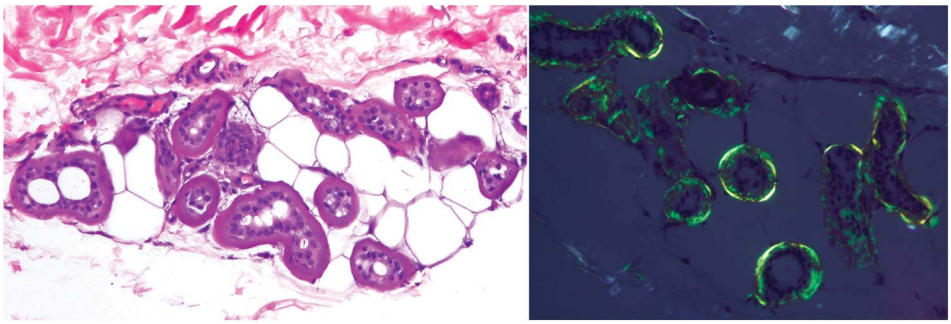

FIGURE 13. A, Amyloid material surrounding the basal layer of eccrine glands. B, Congo red green apple color birefringency.

collagen bundles in the papillary dermis is also a diagnostic aid, usually present in no so subtle cases. Pagetoid dyskeratosis in the acral skin is a really tricky diagnosis if the entity is not known (Fig. 10). Although pagetoid dyskeratosis can seem as an incidental finding in several skin conditions,[32] it can appear in acral lesions like fast-appearing well-defined areas of pigment showing a parallel ridge pattern in dermoscopy and thus mimicking melanoma.[33,34] Some authors' hypotheses consider that the origin of pigmentation that tend to occur in areas of microtrauma are areas of microhemorrhages, only visible when stained using benzidine stain. In any case, the presence of these squamous cells with clear halo within the epidermis, typical of pagetoid dyskeratosis, with the absence of proliferation of melanocytes is a very good clue for the diagnosis of the clinically pigmented forms in the acral areas.

Flat warts are also usually included here, and hypergranulosis and koilocytes are usually seen. Some early or regressing genital human papilloma virus infections lack the typical papillomatous silhouette and show only minimal acanthosis with scant parakeratosis. When in doubt, when facing a diagnosis of flat seborrheic keratosis either condyloma, mostly in the genital area, a ki67 staining can demonstrate hotspots of hyperproliferation at the upper levels of the epidermis that are the best areas to find koilocytes, a hallmark of the process[35] (Fig. 11).

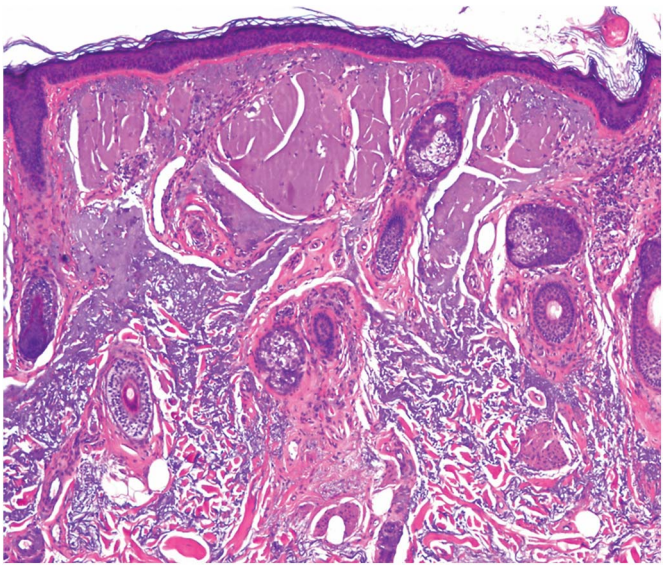

FIGURE 14. Adult colloid milium. Severe solar elastosis and nodules of hyaline material with artifactual cracks can be seen in papillary dermis.

The presence of enlarged bluish-hue granular keratinocytes can be also a clue for human papilloma virus infection, epidermodysplasia verruciformis-like, that can appear also in immunosuppressed patients.[36]

Multinucleated keratinocytes can appear not only as a results of viral infections (herpes simplex, herpes varicella-zoster, or measles) but also to chronic rubbing.[37] In acute physical sun damage apoptotic keratinocytes, the so-called, sunburn cells can be observed either in previously healthy skin or overlying preexisting nevi.[38]

Pityriasis rosea is rarely biopsied as clinically is pretty characteristic and their main histopathological features are the presence of spongiotic foci in epidermis with red cell and lymphocytic exocytosis and the presence of red blood cells extravasated in the underlying dermis, which are very useful hints for making an accurate diagnosis.[10]

Grade I graft versus host disease, requires clinic–pathological correlation as can appear in a very subtle way, just showing some satellite cell necrosis and a subtle vacuolar change.[39]

There are certain dermatosis characterized by slight acanthosis and basal hyperpigmentation, with elongated epithelial ridges that are flattened and fused together as Becker nevus; and other where papillomatosis is the main feature, such as confluent and reticulated papillomatosis of *Gougerot and Carteaud*.

DERMIS

Papillary Dermis

The presence of scattered melanophages below a normal epidermis without more pigmented basal melanocytes is a common hint that indicates the existence of a previous inflammatory process. It can be associated with apoptotic bodies if it follows lichenoid damage or with coarse eosinophilic aggregates of homogeneous material in macular amyloidosis (Fig. 12). In the latter process, a positive immunostaining for keratins, specially CK5 and 34βE12, is the more sensitive immunostaining for diagnostic purposes.[40]

Thick collagen bundles, perpendicular to the epidermis, are typical of lichenification, and wiry collagen can be a companion sign in mycosis fungoides. Lesions resembling

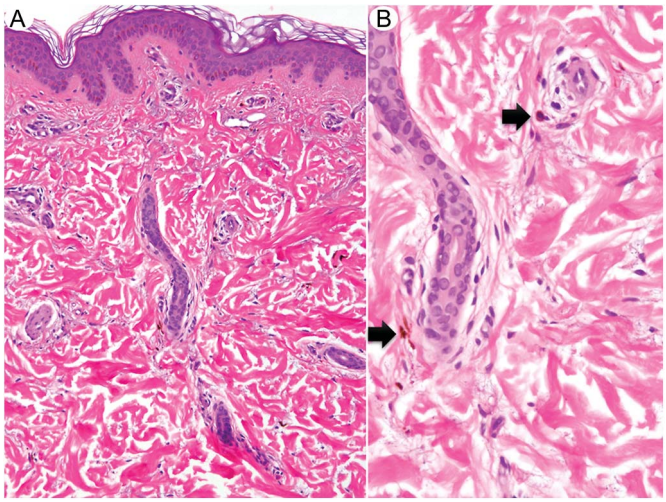

FIGURE 15. Few elongated and pigmented melanocytes are within the dermis, mostly located surrounding adnexal structures and vessels. See black arrows in the right image.

clinically a pseudoxanthoma elasticum can look histologically like normal skin and a histochemical stain for elastic fibers, with orcein-Giemsa or van Gieson, might be necessary to demonstrate the existence of elastolysis of the papillary dermis.

Secondary syphilis is included in some reviews of invisible dermatosis as it may mimic many clinic–pathological entities, a mix of lichenoid and psoriasiform patterns combined with specific clues such as plasma cell infiltrates can guide the immunohistochemistry or the serological tests for proper diagnosis[10] In our opinion, histopathological findings are not subtle usually in secondary syphilis but are of wide range.

Reticular Dermis

Main groups of invisible dermatosis diagnosis here are some infections, deposit dermatosis, and either dermal melanocytosis or other pigment deposition.

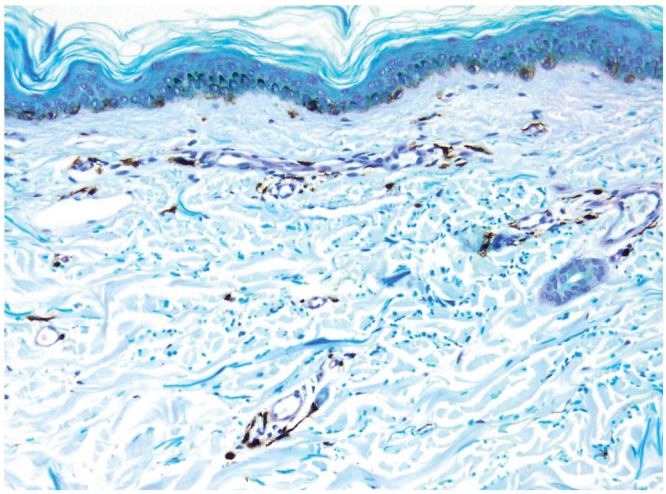

FIGURE 16. C-kit staining, where an increased number of positively stained cells, that correspond to mastocytes, are located surrounding the vessels.

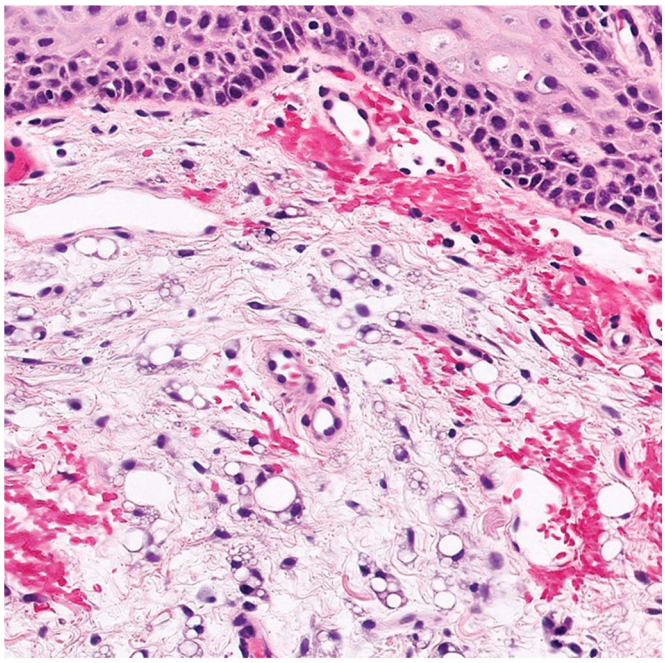

FIGURE 17. Irregular in size empty vacuoles, sometimes grouped in the dermis, as well as blood cells extravasation after silicone injection.

Indeterminate leprosy requires a high degree of awareness because the main clues for diagnosis are the lymphocytic infiltrates extending into the arrector muscles and located surrounding perineural and periadnexal areas.[40]

Small amyloid depositions can be also difficult to detect in the reticular dermis, especially inconspicuous accumulations within the basal membranes of sweat glands (Fig. 13A) and blood vessels as the ones that may appear in patients with

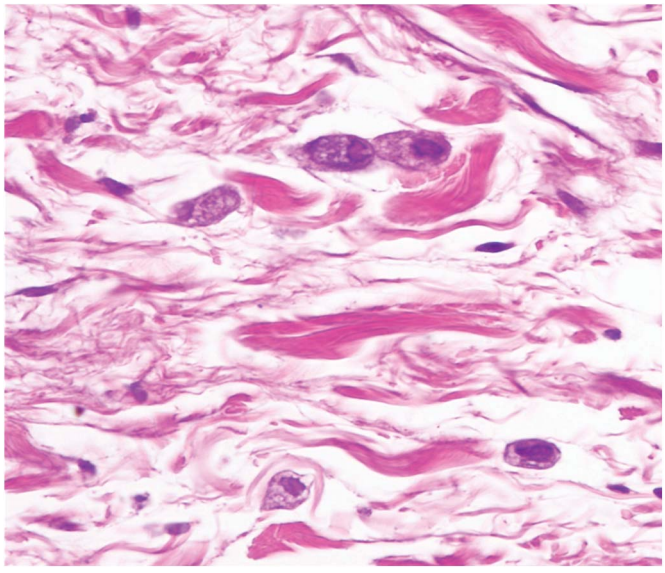

FIGURE 18. Isolated histiocytoid atypical cells in the dermis in a patient with breast carcinoma.

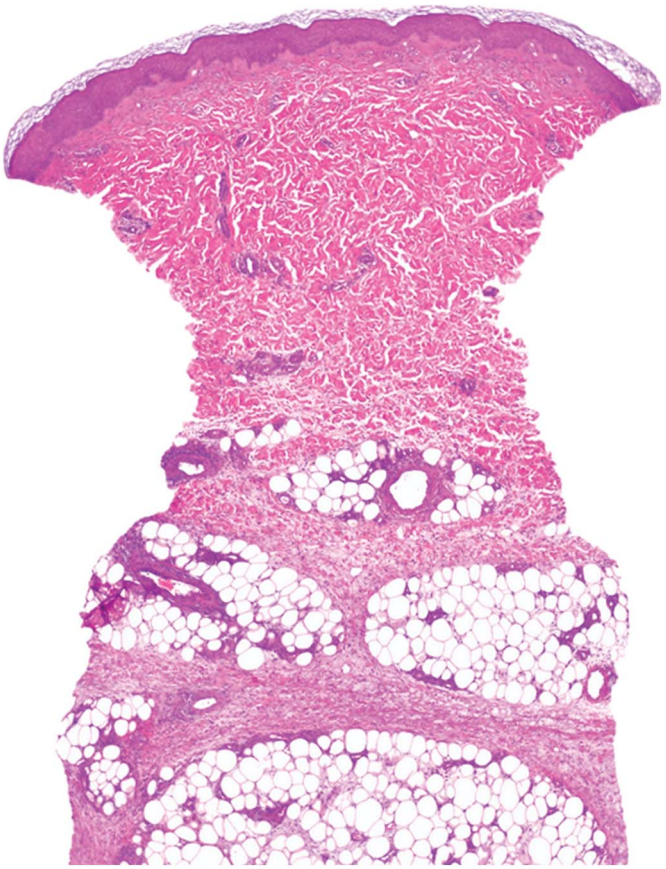

FIGURE 19. Enlarged and fibrotic septae with hemorrhage and lipophagic necrosis within the fat lobules.

chronic hemodialysis.[41] Congo red staining is mandatory when this pathology is clinically or histologically suspected (Fig. 13B).

Apart from amyloid, deposition of other immunoglobulin components and porphyria can also cause PAS + thickening of the basal membranes that will be negative for amyloid stains. There are also lesions, named as *colloid milium*, clinically presenting as yellowish papules in sun-exposed areas, where we can see an hyaline and amorphous slightly basophilic material, with irregular fractures, and negative for Congo red.[42] Here, histopathological features, to our eyes, do not fit within invisible dermatosis, but it is an important differential diagnosis from amyloid and it can also be the only finding in some small lesions that are sent as basal cell carcinomas (Fig. 14).

Melanophages below the superficial vascular plexus that can be the only change evident in erythema dyschromicum perstans or *ashy dermatitis* that is a late-stage lichen planus pigmentosus.[10]

Macrophages containing iron are histologically similar but can be distinguished because they stain positive for Pearls. A predominantly perivascular hemosiderin deposition point toward a previous episode of vascular damage like in lichen aureus while predominant peri-eccrine iron accumulation is typical of idiopathic hemochromatosis.[43]

Some blue nevus and many cases of dermal melanocytosis (Fig. 15) will only show slender melanocytes and can be easily missed. It is important to remember that there are a wide group of congenital and acquired dermatosis all of them characterized by pigmented dendritic melanocytes in the reticular dermis. Ota, Ito nevus, Mongolian spot, and acquired dermal melanocytosis can be easily highlighted using Melan-A staining.

Filaria infections do not always generate intense eosinophilia, and thus, it might be necessary to search for them in consecutive sections because of their small size.

Elastic fibers can be also altered in the reticular dermis either in nevus elasticus or mid dermal elastolysis that has several forms of clinical presentation.

A "busy dermis" can be the results of an increase in the density of mastocytes, histiocytoid cells, or mesenchymal cells or being even related with neoplastic processes such ductal breast carcinoma metastasizing to the skin.

Urticaria and mastocytosis should be included in the differential diagnosis of invisible dermatosis. Spindle-shaped mastocytes are difficult to recognize, especially after degranulation. They are previously named as telangiectatic and macular type and it is particularly difficult to assess because there is an increase in the number of mast cells surrounding the vessels that can be surrounded by a focal oedema. Special stains such as Giemsa stain or Leder stain are helpful to demonstrate the metachromatic granules but immunohistochemistry using CD117 (c-kit) is more used nowadays and easy to interpret (Fig. 16). The presence of basal hyperpigmentation, vascular dilatation, and eosinophils also support the diagnosis.

Urticaria can be in the differential diagnosis, and sometimes, there is some dilated vessels and few eosinophils to recognize an urticaria in the adequate clinical context. The presence of neutrophils within the dilated vessels can be added as another useful sign for early urticaria biopsies.[44]

Skin biopsy showed few eosinophils in 2 of 12 cases of nonepisodic angioedema with eosinophilia, although eosinophilic

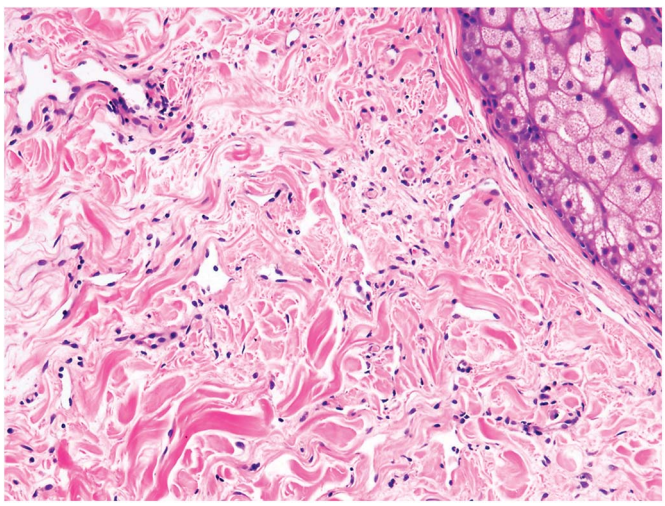

FIGURE 20. A busy dermis with too many vessels dissecting collagen bundles can be seen in this early Kaposi sarcoma.

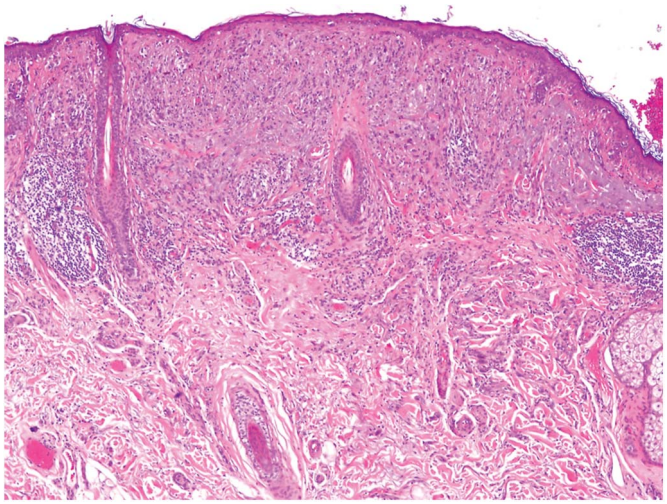

FIGURE 21. Nests and fascicles of atypical cells with few pigment within the dermis. IHC led to the diagnosis of melanoma.

dermatitis and even eosinophilic and granulomatous panniculitis are other described patterns in angioedema.[45]

There are also some deposits that may produce hyperpigmentation while histopathological findings are subtle. First of them, argyria, may produce confusion with melasma and lichen planus pigmentosa. The detailed examination of the skin to find round and brownish small granules surrounding eccrine glands is useful for the diagnosis. On the one hand, hydroxychloroquine-induced hyperpigmentation usually is similar to postinflammatory hyperpigmentation. On the other hand, amiodarone-induced pigmentations is characterized by yellowish–brownish granules of lipofuscin within the macrophages of papillary dermis and the ones surrounding capillary vessels.[29] Finally, ochronosis, clinically can be similar, shows very evident findings with irregular brownish enlarged collagen bundles. Within this type of pigmentary changes, Fontana Masson and Pearls staining are helpful to determine whether melanin or ferric deposits are present.

Collagen and elastic tissue abnormalities are within the dermatosis usually with quite subtle histopathological findings that includes different entities with elastic fiber destruction such as "*striae distensae*," anetoderma, elastolysis of the mid dermis, or perifollicular elastolysis; as well as elastic nevus, when elastic fibers are incremented. The different staining of collagen bundles in the different laboratories make comparison even more tricky. When there is a hypoplastic dermis, epidermis seems to be closer to subcutaneous tissue. In the opposite case, we can have collagenomas where normal or thick collagen bundles may present as a hazardous distribution in the dermis. This collagen anomalies' dermatopathological features have been recently reviewed.[46]

Cells with histiocytic appearance sprinkled within the dermis can appear in multiple circumstances including infections with histiocytes containing leishmania histoplasma that in immunosuppressed patients do not generate a specific inflammatory response. Some drug reactions can show macrophages slightly enlarged after use of granulocyte–macrophage colony-stimulating factors[47]; and some patients with hydroxyethyl starch-pruritus can present HES-laden vacuoles in the macrophages as a subtle clue for diagnosis.[48] Free-life amoebas, mainly *Balamuthia mandrilaris*, can be misinterpreted as histiocytes and are very difficult to identify in the absence of clinical suspicion.[49]

Filler reactions, especially silicon that has a marked tendency to migrate and can be detected far away from the location where it was injected (Fig. 17).

Another possibility is a subtle interstitial metastatic spread of a tumor with histiocytoid appearance, for instance, from melanoma or breast carcinoma (Fig. 18).

Mucin deposition in the dermis, associated or not with a fibroblastic proliferation can be subtle but a clue for the diagnosis of a dermal mucinosis. Interstitial granuloma annulare with mild collagen degenerative changes is better appreciated using staining for elastic fibers that tend to be wiped out from the center of the lesions and mucin can be a clue for its diagnosis. Autoimmune-related lesions, such as *Gottron papules*, sometimes can present with basal cell vacuolation, thickened basement membrane, and a scarce lymphocytic infiltrate along with mucin deposition.[50]

Finally, the absence of nerve endings in what seems to be an otherwise normal and representative biopsy is a clue for leprosy. In addition, although it is not routinely performed in many dermatopathological laboratories, skin biopsy can be used for the diagnosis of peripheral neuropathy by using specific antibodies with bright-field immunohistochemistry or immunofluorescence technique to investigate unmyelinated fibers innervating the epidermis of hairy and glabrous skin, large myelinated fibers supplying specialized corpuscles in glabrous skin, and autonomic fibers innervating sweat glands, blood vessels, and arrector pilorum muscles.[51]

SUBCUTANEOUS TISSUE

Fat tissue penetrating to the upper portion of the dermis is typical of nevus lipomatosus that often diagnosed clinically as neurofibroma. Foci of fat necrosis with lipogranulomas and slight sclerosis are the earliest changes in lipodermatosclerosis while septal thickening maybe the only remain of a previous nodosum erythema (Fig. 19).

Atrophic subcutaneous tissue can be observed also after corticosteroids injection[52] where sometimes there is also an overlying skin depigmentation. In addition, it can also be the main sign for a Parry Romberg, where a sonographic comparison of the degree of adipose tissue in symmetrical areas is a good way of confirming the diagnosis and even of evaluation the treatment response.

The presence of adipose tissue too close to epidermis can also be a clue for some dermatosis. It can appear in focal dermal hypoplasia, also known as Goltz–Gorlin syndrome. In some series of skin biopsies of these patients, it was a more consistent sign, the reduction and fragmentation of elastic fevers, where orcein elastic staining was mandatory for finding this subtle sign.[53]

When there is a hair miniaturization, hair shafts can be located not in subcutaneous tissue but in higher layers because this has been considered even as a new histopathological clue for frontal fibrosing alopecia.[54]

Coming back to the skin of the scalp, there are also a group of entities named hypotrichosis simplex where there is a low number of normal-appearing hair shafts in the adipose tissue and quantification of the hair shafts and their types in a scalp biopsy is mandatory to make the diagnosis.[55]

To end up this part is important to remember the possibility of lipomatous metaplasia appearing as a band of adipocytes in the superficial reticular dermis and related to several inflammatory and tumoral disorders not to confuse this reaction pattern with some of the previously explained diagnosis.[56]

INVISIBLE NEOPLASMS

There is a short list of benign and malignant tumors that should always be kept in mind when facing an "invisible dermatosis." The first to consider should be macular Kaposi sarcoma (Fig. 20) that in an early stage can show some dilated and congestive capillary-like structures, scattered vascular clefts, and slight lymphoplasmocytic infiltrate with minimal red blood cell extravasation or iron deposition. A clue for the diagnosis is the neoplasm tendency to proliferate along the adnexal structures. An HHV8 immunostaining will provide the final diagnosis.

Early angiosarcomas can also be extremely deceptive and totally devoid of atypia. To find some endothelial piling, c-myc staining or a ki67 positivity in more than 10% of endothelial cells can be subtle hints for the diagnosis.[57]

Desmoplastic melanomas (Fig. 21) and desmoplastic squamous cell carcinoma and sclerosing basal cell carcinomas can simulate scars that can be specially misleading when previous surgical procedures have been performed in the same location justifying the sclerotic reaction. Amelanotic lentigo maligna can also be found b using immunohistochemistry for melanocytic lesions such as Melan-A, HMB45, or SOX10.[58]

Some cases of breast cancer metastasis can be a challenge as tumoral cells may appear quite isolated intermingled with collagenous bundles or within a sclerotic stroma, and sometimes, immunohistochemistry is needed to highlight their presence and confirm their origin.

Sclerosing syringomas can remain underdiagnosed as sclerosis predominates over the secretory gland-likes elements. Something similar can happen in the atrophic and paucicellular variants of dermatofibromas where a superficial biopsy may only show the typical epidermal induction associated with these tumors.

Finally, skin lymphomas may be very inconspicuous and appear as "pruritus." As the number of malignant cells in the skin biopsy is usually very low in these cases, clinicopathological correlation and peripheral blood cytometry are need to get a proper diagnosis[59,60]

CONCLUSIONS

In summary, as in Alhumidi et al[61] article, when up to 46.9% biopsies with subtle findings remained undiagnosed, lack of awareness of subtle clues, and inadequate specimens, inappropriate biopsies from inactive or treated lesions or inadequate lesions selected to biopsy are the commoner causes of a histopathological report of "unspecific dermatosis."

Thus, to face invisible dermatosis is a relatively common situation and, basically, the best-known protocol to approach this type of biopsies is to study in depth every skin layer despite a "all-normal" first impression in the panoramic view.

The presence of just a few eosinophils, a slight thickening of the basal membranes or a funny coloration in the corneal layer can be enough to point toward the correct diagnosis. The presence of foreign body giant cells or fibrosis in the deepest portion are an alert that should make considering a deeper seated or underrepresented lesion. Step sections are in these cases mandatory and, in general, the best cost/benefit technique in dermatopathology. Sometimes what seems to be normal skin in the first sections becomes a clear-cut intradermal nevus or basal cell carcinoma.

We have reviewed many of this dermatosis to increase their diagnostic awareness and we provide the main steps to minimize this type of reports.

1. Correlation with the clinical history is mandatory
2. A methodical examination of the hematoxylin and eosin staining sections knowing the pathologies typical at each level may lead the diagnosis
3. Step sections in hematoxylin and eosin staining are the most cost-effective technique
4. Special stains (fungal, Congo red, and elastic staining) can be helpful in many sceneries.
5. Combining previous steps, we will be able to get a diagnosis in most cases.

REFERENCES

1. Kligman AM. The invisible dermatoses. *Arch Dermatol*. 1991;127:1375–1382.
2. Rietschel R, Lewis C. Invisible dermatoses. *Cutis*. 1978;21:378–380.
3. Brownstein MH, Rabinowitz A. The invisible dermatoses. *J Am Acad Dermatol*. 1983;8:579–588.
4. Bernhard JD. Invisible dermatoses versus nonrashes. *J Am Acad Dermatol*. 1983;9:599–600.
5. Pujol RM, Gallardo F, Llistosella E, et al. Invisible mycosis fungoides: a diagnostic challenge. *J Am Acad Dermatol*. 2002;47:S168–S171.
6. Bickers D. In locus minoris resistentiae-or not? *J Invest Dermatol*. 2004;123:vii.
7. Benezeder T, Wolf P. Resolution of plaque-type psoriasis: what is left behind (and reinitiates the disease). *Sem Immunopathol*. 2019;41:633–644.
8. Requena L, Kutzner H, Escalonilla P, et al. Cutaneous reactions at sites of herpes zoster scars: an expanded spectrum. *Br J Dermatol*. 1998;138:161–168.
9. Tomasini C. Invisible dermatoses from the perspective of the dermatopathologist: new observations. *G Ital Dermatol Venereol*. 2017;152:500–515.
10. Mysore V. Invisible dermatoses. *Indian J Dermatol*. 2010;76:239.
11. Wells R, Kerr C. The histology of Ichthyosis. *J Invest Dermatol*. 1966;46:530–535.
12. Camporro ÁF, Roncero-Riesco M, Revelles-Peñas L, et al. The ñ sign: a visual clue for the histopathologic diagnosis of psoriasis. *JAMA Dermatol*. 2022;158:451–452.
13. El Hanbuli HM, Elmahdi MH, Kamal N. Peeling skin syndrome: a pathologically invisible dermatosis. *J Microsc Ultrastruct*. 2019;7:141.
14. Pérez A, Rütten A, Gold R, et al. Circumscribed palmar or plantar hypokeratosis: a distinctive epidermal malformation of the palms or soles. *J Am Acad Dermatol*. 2002;47:21–27.

15. Berk DR, Mutizwa MM. Comment regarding the histopathology of terra firma-forme dermatosis. *J Cutan Pathol*. 2012;39:300–301.
16. Lora V, Ardigò M, Catricalà C, et al. Terra firma-forme dermatosis. *J Cutan Pathol*. 2014;41:141–143.
17. Gottlieb GJ, Ackerman AB. The "sandwich sign" of dermatophytosis. *Am J Dermatopathol*. 1986;8:347–350.
18. Martin WE, Wheeler CE, Jr. Diagnosis of human scabies by epidermal shave biopsy. *J Am Acad Dermatol*. 1979;1:335–337.
19. Kristjansson AK, Smith MK, Gould JW, et al. Pink pigtails are a clue for the diagnosis of scabies. *J Am Acad Dermatol*. 2007;57:174–175.
20. Elwood H, Berry RS, Gardner JM, Shalin SC. Superficial fibrin thrombi… and other findings: a review of the histopathology of human scabietic infections. *J Cutan Pathol*. 2015;42:346–352.
21. Vargas-Mora P, Morgado-Carrasco D, Fustà-Novell X. Porokeratosis: a review of its pathophysiology, clinical manifestations, diagnosis, and treatment. *Actas Dermo-Sifiliogr*. 2020;111:545–560.
22. Ziemer M, Haeusermann P, Janin A, et al. Histopathological diagnosis of graft-versus-host disease of the skin–an interobserver comparison. *J Eur Acad Dermatol Venereol*. 2014;28:915–924.
23. Rongioletti F, Tomasini C, Crovato F, et al. Aquagenic (pseudo) keratoderma: a clinical series with new pathological insights. *Br J Dermatol*. 2012;167:575–582.
24. Ondrasik RM, Jordan P, Sriharan A. A clinical mimicker of melanoma with distinctive histopathology: topical silver nitrate exposure. *J Cutan Pathol*. 2020;47:1205–1210.
25. Hafner J, Haenseler E, Ossent P, et al. Benzidine stain for the histochemical detection of hemoglobin in splinter hemorrhage (subungual hematoma) and black heel. *Am J Dermatopathol*. 1995;17:362–367.
26. Zalaudek I, Argenziano G, Soyer HP, et al. Dermoscopy of subcorneal hematoma. *Dermatol Surg*. 2004;30:1229–1232.
27. Romero JM, Muñoz NP, Sánchez AC, et al. Derm dotting: una técnica novedosa para mejorar la precisión diagnóstica de lesiones cutáneas. *Actas Dermosifiliogr*. 2019;110:193–196.
28. Le Poole IC, van den Wijngaard RM, Westerhof W, et al. Presence or absence of melanocytes in vitiligo lesions: an immunohistochemical investigation. *J Invest Dermatol*. 1993;100:816–822.
29. Carlotti A. Invisible dermatoses. *Ann Dermatol Venereol*. 2009;136:152–159.
30. Pimpinelli N, Olsen EA, Santucci M, et al. Defining early mycosis fungoides. *J Am Acad Dermatol*. 2005;53:1053–1063.
31. Massone C, Kodama K, Kerl H, et al. Histopathologic features of early (patch) lesions of mycosis fungoides: a morphologic study on 745 biopsy specimens from 427 patients. *Am J Surg Pathol*. 2005;29:550–560.
32. Santos-Briz A, Cañueto J, del Carmen S, et al. Pagetoid dyskeratosis in dermatopathology. *Am J Dermatopathol*. 2015;37:261–268.
33. Llamas-Velasco M, Gallo E, Fraga J. Hyperpigmented asymptomatic macule in a fingertip with suspicious dermoscopic pattern—quiz case. *Arch Dermatol*. 2012;148:247.
34. Loidi L, Mitxelena J, Córdoba A, et al. Dermoscopic features of pagetoid dyskeratosis of the palm. *Actas Dermo-Sifiliogr*. 2014;105:804–805.
35. Gardner KM, Crawford RI. Distinction of condylomata acuminata from vulvar vestibular papules or pearly penile papules using ki-67 immunostaining. *J Cutan Med Surg*. 2019;23:255–257.
36. Berk DR, Bruckner AL, Lu D. Epidermodysplasia verruciform-like lesions in an hiv patient. *Dermatol Online J*. 2009;15:1.
37. Sweeney SA, Sulit DJ, Adams EG, et al. Grape cells (multinucleated keratinocytes) in noninfectious dermatoses: case series and review of the literature. *Am J Dermatopathol*. 2015;37:e143–e146.
38. Laethem AV, Claerhout S, Garmyn M, et al. The sunburn cell: regulation of death and survival of the keratinocyte. *Int J Biochem Cell Biol*. 2005;37:1547–1553.
39. Häusermann P, Walter RB, Halter J, et al. Cutaneous graft-versus-host disease: a guide for the dermatologist. *Dermatology*. 2008;216:287–304.
40. Mysore V, Bhushnurmath SR, Muirhead DE, et al. Frictional amyloidosis in Oman--a study of ten cases. *Indian J Dermatol Venereol Leprol*. 2002;68:28–32.
41. Chao CC, Huang CM, Chiang HH, et al. Sudomotor innervation in transthyretin amyloid neuropathy: pathology and functional correlates. *Ann Neurol*. 2015;78:272–283.
42. Zamora A, Simón M, Sánchez A, et al. Adult colloid milium. An underdiagnosed and difficult to treat entity. *Revista Med del Hosp Gen de Mexico*. 2016;79:21–25.
43. White J, Powell A, Brady K, et al. Severe generalized argyria secondary to ingestion of colloidal silver protein. *Clin Exp Dermatol*. 2003;28:254–256.
44. Llamas-Velasco M, Fraga J, Requena L, et al. Neutrophilic urticaria or urticaria with predominantly neutrophilic inflammatory infiltrate: study of its clinical and histopathologic characteristics and its possible association with rheumatic disease. *Actas Dermo-Sifiliogr*. 2012;103:511–519.
45. Goto K, Ishizaki S, Tanese K, et al. Histological classification and differential diagnosis of nonepisodic angioedema with eosinophilia: a clinicopathologic study of 12 cases with literature review. *Am J Dermatopathol*. 2016;38:124–130.
46. Santos-Alarcón S, López-López OF, Flores-Terry MÁ, et al. Collagen anomalies as clues for diagnosis: Part 2. *Am J Dermatopathol*. 2018;40:79–110.
47. Alvarez-Ruiz S, Penas P, Fernández-Herrera J, et al. Maculopapular eruption with enlarged macrophages in eight patients receiving g-csf or gm-csf. *J Eur Acad Dermatol Venereol*. 2004;18:310–313.
48. Ständer S, Richter L, Osada N, et al. Hydroxyethyl starch-induced pruritus: clinical characteristics and influence of dose, molecular weight and substitution. *Acta Derm Venereol*. 2014;94:282–287.
49. Lehmer LM, Ulibarri GE, Ragsdale BD, et al. Cutaneous balamuthia mandrillaris infection as a precursor to balamuthia amoebic encephalitis (bae) in a healthy 84-year-old californian. *Dermatol Online J*. 2017;23().
50. Smith ES, Hallman JR, DeLuca AM, et al. Dermatomyositis: a clinicopathological study of 40 patients. *Am J Dermatopathol*. 2009;31:61–67.
51. Lauria G, Lombardi R, Camozzi F, et al. Skin biopsy for the diagnosis of peripheral neuropathy. *Histopathology*. 2009;54:273–285.
52. Jacobs MB. Local subcutaneous atrophy after corticosteroid injection. *Postgrad Med*. 1986;80:159–160.
53. Rohdenburg C, Liersch J, Kutsche K, et al. Fragmented elastic fibers in focal dermal hypoplasia (Goltz-Gorlin syndrome) without focal dermal hypoplasia: report of a male case and review of the literature. *Am J Dermatopathol*. 2020;42:653–661.
54. Miteva M, Castillo D, Sabiq S. Adipose infiltration of the dermis, involving the arrector pili muscle, and dermal displacement of eccrine sweat coils: new histologic observations in frontal fibrosing alopecia. *Am J Dermatopathol*. 2019;41:492–497.
55. Willems A, Sinclair R. Diffuse congenital hypotrichosis simplex with associated hair shaft fragility. *Australas J Dermatol*. 2022;63:e96–e97.
56. Googe PB, Tidwell WJ, Rosenberg AE. Lipomatous metaplasia of superficial dermis. *J Cutan Pathol*. 2016;43:120–124.
57. Paolino G, Lora V, Cota C, et al. Early angiosarcoma of the scalp: a clinicopathological pitfall. *Am J Dermatopathol*. 2016;38:690–694.
58. Perera E, Mellick N, Teng P, et al. A clinically invisible melanoma. *Australas J Dermatol*. 2014;55:e58–e59.
59. Henn A, Michel L, Fite C, et al. Sézary syndrome without erythroderma. *J Am Acad Dermatol*. 2015;72:1003–1009. e0011.
60. Shiue LH, Ni X, Prieto VG, et al. A case of invisible leukemic cutaneous t cell lymphoma with a regulatory t cell clone. *Int J Dermatol*. 2013;52:1111–1114.
61. Alhumidi A, Alshamlan N, Alfaraidi M, et al. Invisible dermatosis, diagnostic discrepancy between the general pathologist and dermatopathologist. *J Cutan Pathol*. 2019;46:905–912.