Invisible dermatoses: clues and pitfalls to diagnosis

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Abstract

The phrase "invisible dermatoses" has been used in two different contexts: 1) Invisible dermatoses to the clinician, i.e., skin diseases with no significant clinical features, 2) invisible dermatoses to the pathologist, i.e., clinical evident skin diseases that show subtle or hidden histological features resembling normal skin. The list of such diseases, originally comprising only few entities, has been gradually expanded over decades and now is a large one. This paper will focus on entities that fall into this category of subtle or "invisible" dermatoses histopathologically and offers to the dermatopathologist a strategy for their diagnosis, based mainly on proper awareness, recognition of subtle features, liberal use of special stains, immunofluorescence and immunohistochemistry and proper clinicopathologic correlation. The presentation of a series of "invisible dermatoses" will hopefully familiarize the reader with the diagnostic problems and pitfalls associated with and unique to the interpretation of biopsies from this category of dermatoses.

Keywords histopathology; invisible dermatoses; pitfalls

Introduction

In Dermatopathology, correlation of clinical features and histopathologic findings are more crucial for a proper interpretation of sections than in other medical fields. This is especially important in the diagnosis of inflammatory skin diseases where, more often than not, it is necessary to combine the clinical picture with the microscopic findings if a final accurate diagnosis is to be obtained. Ideally, a clinical examination of the skin should be made by the same competent person who then interprets the histopathologic sections. This concept was elegantly expressed by Unna in the statement that "The dermatologist should always consider the clinical picture with the eye of the microscopist and the histologic findings with the eye of a clinician".

The clinicopathologic correlation in "invisible dermatoses" is no exception as it is always a challenge. Braunstein and Rabinowitz first proposed that invisible or subtle dermatoses encompass a group of skin diseases that are characterized by obvious clinical manifestations which show a very subtle or hidden histopathologic picture.[1] However, as their clinical appearance is often pathognomonic, these dermatoses usually go unbiopsied. There may be several reasons for a biopsy being performed in the presence of this dermatosis group, including the lack of skill to make a clinical diagnosis. Routinely, their deceptively bland histological features may be misinterpreted by the general pathologist as nonspecific changes. Indeed, it must be evidenced that a diagnosis of subtle or invisible dermatoses may be challenging even to a well versed, experienced dermatopathologist. Moreover, there may be a need to make repeated biopsies, examine multiple sections, use special stains, carry out particular investigations, like immunofluorescence and/or histochemistry and clinicopathologic correlations. It is paramount to provide extensive clinical information, as certain clinical clues may prompt a closer examination of subtle histologic signs in specific skin compartments, e.g. dermis, epidermis, stratum corneum, adnexal structures etc.

Although this group of dermatoses accounts for almost 10% of skin biopsies, standard dermatology and dermatopathology textbooks generally neglect the issue and few authors have systematically discussed the question.[1–5] The original list of such diseases included only a few entities, that have been expanded over time. An updated list of invisible dermatoses, classified according to the specific skin compartment, is shown in Table 1.

As it is beyond the scope of this paper to address the clinical and histological features of all subtle or invisible dermatoses, only some examples, with the related histopathologic pitfalls in diagnosis, are briefly presented. Indeed, this paper aims at increasing awareness about this group of dermatoses.

Approach to the slide

When a skin specimen resembles *normal skin*, there are two possibilities: either it is a true-invisible dermatosis or a false-invisible dermatosis. Numerous factors may be involved in the latter, including sampling errors like, improper site, scant material, a too superficial sample, laboratory errors during specimen preparation, i.e. embedding or cutting at the microtome. Firstly, this possibility is to be ruled out by a careful review of the technical procedures, i.e. examination of the paraffin block housing the tissue, performing additional sections, etc. Then, several strategies may be adopted to obtain a better diagnosis of an apparently healthy skin sample and the order depends on the individual case. These include:

1. a critical analysis of the clinical data;
2. a systematic analysis of the sample to identify pathological changes or obtain helpful clues for diagnosis.
3. performing multiple level cuts;
4. using special stains and/or immunohistochemical techniques;
5. comparing the pathologic area under investigation to the adjacent skin, if available;
6. clinical examination of the patient, whenever possible, or, alternatively, obtaining clinical images of the skin disorder under examination. This last step is paramount and may be tie and cost effective.

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Invisible dermatoses classified according to the level of the pathologic changes in the skin

Epidermis and cornified layer
Superficial mycoses (tinea, tinea nigra)
Superficial bacterial infections (erythrasma, pitted keratolysis)
Subcorneal haemorrhage (black heel)
Scabies
Creeping eruption (larva migrans)
Granular parakeratosis
Punctate keratoderma
Punctate keratosis of the palmar creases
Ichthyosiform dermatoses
Peeling skin syndrome
Porokeratosis
Circumscribed acral hypokeratosis.
Acquired aquagenic keratoderma
Superficial pemphigus
Confluent and reticulated papillomatosis (Gourgerot and Carteaud)
Becker nevus
Mucosal lentigo
Clear cell acanthoma
Early actinic keratosis
Sunbun
Notalgia paresthetica
Vitiligo and albinism
Piebaldism
Hypopigmented macules in sclerosis tuberosa
Cafè au-lait macules
Ephelid
Early Mycosis Fungoides

Dermis
Macular amyloidosis/lichen amyloidosus
Primary systemic amyloidosis
Haemochromatosis
Ochronosis
Cryiasis
Amyodaron/mynocline pigmentation
Dermal melanocytoses
Teleangectasia macularis eruptiva perstans
Onchocerchiasis
Nevus flammeus, angioma serpiginosum, nevoid unilateral teleangectasia
Cutaneous collagen vasculopathy
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
Fabry disease
Calciphylaxix
Livedo reticularis
Intravascular lymphoma
Urticaria
Indeterminate leprosy
Mucinoses and scleredema
Scleroderma
Mucopolysaccaridosis
Piezogenic papule
Anetoderma
Striae distensae
Fibroelastolitic papulosis
Pseudoxanthoma elasticum
Superficial dermal elastolysis
Mid-dermal elastolysis
Perifollicular alastolysis
Cutis laxa
Acrokeratoelastoidosis
Connective nevus
Elastic nevus and Buschke-Ollendorf syndrome
Atrophoderma of Pierini-Pasini

Hypodermis
Lypoatrophy

Adnexa
Anidrotic ectodermal dysplasia
Argyria
Alopecia areata and telogen effluvium
Traction alopecia and trichotillomania
Lafora disease
Eccrine-angiomatous nevus
Acquired aquagenic keratoderma
Hair bulb haemosiderosis[a]

[a] This term is used here for the first time by the author to describe the clinical and pathologic findings of a putative novel pigmentary dermatosis (see the text for detailed description).

Table 1

Analysis of clinical data

Most likely the major limitation is the lack of appropriate clinical information when interpreting the biopsies of skin inflammatory diseases. Indeed, a founded clinical suspicion may prompt the dermatopathologist to search for significant alterations of the suspected disease in what seems to be an almost normal section. Moreover, sampling and/or laboratory errors may be detected by a critical evaluation of the clinical data. Therefore, it a must that the clinical data accompanying any skin biopsy be as complete as possible and include the patient's personal data, the disease duration, site and distribution of the lesions, as well as a clinical differential diagnosis.

Systematic analysis of the slide

Should no clinical data be available, then the only path open is that of examining all the skin layers systematically in search of clues. Firstly, the slide is to be examined at a low magnification, to evidence any architectural changes and identify any relationships between the various skin components. Once these steps have been completed, careful scrutiny at higher magnification can be done, starting from the stratum corneum, working down to the subcutis, in search of subtle changes.

Performing serial sections

Although punch or shave biopsies are practical and straightforward, they do have drawbacks, which may be depend on either the kind of skin lesion that has been biopsied (superficial basal cell carcinoma, porokeratosis, livedo reticularis) or the technician's skill (the bioptic material has not been reached by the blade of the microtome). Noteworthy, the early and later stages of some dermatoses (e.g, pemphigus vulgaris and foliaceous) and

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