Vitiligo: To Biopsy or Not To Biopsy?

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The histopathologic diagnosis of vitiligo is classically understood as the absence of melanocytes and melanin in the skin biopsy.[1] It is difficult for a pathologist to establish the absolute absence of melanocytes and melanin in a skin biopsy. Therefore, we need to take into consideration many variables when we face the possibility to biopsy a vitiligo lesion.

The basis of the clinical diagnosis of vitiligo is the appearance of achromic lesions in periorificial and acral areas; however, sometimes it is difficult to differentiate between an achromic or hypochromic lesion. Although Wood light is of great help in these circumstances, it still can be difficult to make the diagnosis with certainty.

In other cases, the lesions do not present a classic distribution of vitiligo, and other differential diagnoses are considered. For example, if we see a single hypochromic or achromic lesion in a young child, then the main differential diagnosis would be achromic nevus. If there are multiple lesions, then we may consider progressive macular hypomelanosis, postinflammatory hypopigmentation, and hypopigmented mycosis fungoides. In genital lesions, the differential diagnosis between initial lichen sclerosus and vitiligo also can be considered. Finally, we must always bear in mind that both sarcoidosis and Hansen disease can appear as achromic or hypochromic lesions.

The histologic diagnosis of vitiligo in a completely constituted lesion implies the total loss of melanocytes and melanin in the epidermis. Additional histologic findings are described at the edge of the advanced border, such as the presence of melanocytes that have increased in size with large dendrites and lymphoid infiltrate. In perilesional skin, vacuolated keratinocytes and Langerhans cells have increased in number and repositioned in the basal layer, with visible degeneration of nerves and sweat glands. Lymphocytes also can be found in contact with the melanocytes.[2] It is important to note that in addition to these histologic findings, it is common to find spongiosis, mononuclear superficial perivascular inflammatory infiltrate, and melanophages in biopsies of vitiligo.[3]

Given that ensuring the absence of melanocytes is central to diagnosis and melanocytes can be difficult to identify or differentiate from repositioned Langerhans cells in the basal layer with hematoxylin and eosin stain, immunohistochemical techniques must be performed every time we are dealing with vitiligo biopsies. Although there are no studies comparing the diagnostic value of the different immunohistochemical techniques in vitiligo, dihydroxyphenylalanine (DOPA) seems to be a good option, as it will only mark active melanocytes. Human melanoma black 45 (HMB-45), anti-TYRP1 (Mel-5), and antimelanoma gp 100 antibody (NKI/beteb) also have been used. Some authors recommend the use of pan melanoma because it includes 3 markers—HMB-45, tyrosinase, and Mart-1. Currently, SRY-related HMG-box10 (SOX10) seems to be a good option, as it is a nuclear marker that makes it easier to differentiate melanocytes from pigmented keratinocytes.[4]

Establishing a complete absence of melanocytes in the lesions or finding there are melanocytes but they are inactivated is key to evaluating the pathogenesis of vitiligo and directly affects the histologic diagnosis and eventually even the treatment. Le Poole et al[5] used a panel of 17 monoclonal antibodies and a polyclonal antibody in lesions of 12 patients with vitiligo without identifying the presence of melanocytes. They concluded that there are no melanocytes in lesions of vitiligo.[5]

In a subsequent study with a larger number of patients, Kim et al[2] found melanocytes that marked with NKI/beteb and Mart-1 in 12 of 100 patients with vitiligo. They also showed melanocytes by electron microscopy in lesional skin of 1 of 3 patients with vitiligo.[2] Tobin et al[6] managed to grow melanocytes from skin with vitiligo and confirmed the presence of melanin in basal keratinocytes

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of lesions of stable vitiligo. From this evidence we can conclude that the absence of melanocytes and melanin in the epidermis confirms the diagnosis of vitiligo; however, the opposite is not true—that is, the presence of melanocytes or melanin in a skin biopsy does not rule out the diagnosis of vitiligo.

Taking this information into consideration, we can understand that if our differential diagnosis is a dermatosis that requires the evaluation of the number of melanocytes as a fundamental diagnostic clue (eg, postinflammatory hypopigmentation), the biopsy will probably not be useful. On the other hand, when our differential diagnosis has characteristic diagnostic findings independent of the number of melanocytes or the presence of melanin, the biopsy will be useful (eg, hypopigmented mycosis fungoides).

Thus, we can understand why the histologic differentiation between vitiligo, pityriasis alba, postinflammatory hypopigmentation, and progressive macular hypopigmentation is difficult. The histology images of these 4 diseases may show different degrees of melanocyte and melanin decrease, spongiosis, and in the superficial dermis melanophages and mononuclear inflammatory infiltrate.[7]

Nevus depigmentosus also may generate diagnostic confusion with vitiligo. Although it is unilateral and usually congenital, it can appear as late as 3 years of age, leading to an initial clinical differential diagnosis of vitiligo. The histologic findings in this nevus also overlap with vitiligo. The characteristic findings are presence of melanocytes and decreased pigment in the keratinocytes compared with perilesional skin. Therefore, a biopsy is not a solution to this diagnostic dilemma.[8]

In all the differentials named, the solution to the diagnostic doubt is not based on the histologic findings but on the clinical evolution of the patients. In cases of vitiligo, the lesions will become more evident in the evolution. They will eventually disappear in pityriasis alba, postinflammatory hypopigmentation, and progressive macular hypopigmentation and will remain unchanged in nevus depigmentosus. It is important, especially when we are dealing with concerned parents/guardians, to convey the importance of assessing the evolution of the disease as the main diagnostic procedure. Even though a biopsy is minimally invasive, it is usually stressful on children, it may leave sequelae, and above all it will not contribute to the diagnosis in this clinical context.

There are other clinical circumstances in the scenario of hypochromic or achromic lesions in which the biopsy will be useful: If we consider an initial genital lichen sclerosus vs vitiligo. In lichen sclerosus the biopsy will show dermal hyalinosis and interphase changes; absence of both will support vitiligo. If we need to differentiate hypopigmented mycosis fungoides from vitiligo, we will find an infiltrate of pleomorphic lymphocytes in the epidermis and dermis in the former and an absence of these findings in vitiligo. Finally, if we find granulomas in a biopsy of an achromic or hypopigmented lesion, we may be dealing with hypopigmented sarcoidosis or Hansen disease.

It also is important to choose the best site to perform the biopsy to have the best chance at diagnosing vitiligo histologically. As already described, in the edges and in the perilesional skin we can find remnant melanocytes, Langerhans cells, and interphase changes that do not allow us to clearly evaluate the main change that is the loss of melanocytes and melanin. In fact, a biopsy of the edge of a vitiligo macula can lead to confusion. For example, if the differential diagnosis is lichen sclerosus and the image we see in the biopsy of the edge of a vitiligo lesion is an interface reaction, we can interpret it as a finding that favors lichen sclerosus. In this way, it is better to biopsy the center of a well-constituted vitiligo lesion where we have the best chance to assess the absence of melanin and melanocytes.

The vitiligo differential diagnosis can be divided into 2 groups: entities that are difficult to differentiate from vitiligo histologically (ie, pityriasis alba, postinflammatory hypopigmentation, progressive macular hypopigmentation, nevus depigmentosus) and entities that are easily distinguishable from vitiligo histologically (ie, lichen sclerosus, mycosis fungoides, sarcoidosis, leprosy). If our differential diagnosis was found in the first group, the final diagnosis should be based on the evolution of the patient. If it was in the second group, a biopsy of the center of the lesion will be useful and may allow us to reach a definitive diagnosis.

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