Pitfalls in the diagnosis of lentigo maligna and lentigo maligna melanoma, facts and an opinion

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Received 23 August 2020
Revised 16 September 2020
Accepted 17 September 2020
Published Online First 13 October 2020

To cite: Sina N, Saeed-Kamil Z, Ghazarian D. *J Clin Pathol* 2021;**74**:7–9.

ABSTRACT

Lentigo maligna/lentigo maligna melanoma (LM/LMM) affects chronically sun-damaged skin of the head and neck with a slow radial growth phase. It is characterised by predominantly lentiginous proliferation of small, but atypical melanocytes with occasional upward scatter in an atrophic epidermis. It is not uncommon for pathologists to receive partial or scouting biopsies to assess for LM. This makes the interpretation of symmetry and circumscription of the lesions challenging. Therefore, both cytologic and architectural criteria should be taken into consideration to render an accurate diagnosis of melanoma. Moreover, pathologists should be vigilant to avoid missing invasion, as this can change the treatment plan and prognosis. Herein, we aim to discuss important pitfalls in the diagnosis of LMM and its invasive component. Some of these caveats are differentiating between true invasion versus adnexal involvement by the in situ component or an incidental intradermal nevus, detection of microinvasion and multifocal invasion, and recognition of desmoplastic/spindle cell melanoma component.

INTRODUCTION

Lentigo maligna/lentigo maligna melanoma (LM/LMM) clinically appears as an ill-defined, irregularly pigmented and slow-growing patch reaching a considerable size before coming to attention. In situ lesions are designated as LM, whereas invasive melanomas are called LMM.

The diagnosis of LM could be challenging due to many reasons. First, the anatomic location of LM on functionally/cosmetically sensitive areas frequently leads to initial small biopsies which can be problematic in rendering definitive diagnosis. Second, the size of the lesion defies an excisional biopsy; so, pathologists may receive multiple scouting biopsies. This type of lesion sampling may not be a true representative of the whole lesion and is impossible to be assessed for symmetry and circumscription. Finally, LM should be differentiated from its mimics, including dysplastic nevi, lentiginous nevi, solar melanocytic hyperplasia, pigmented actinic keratosis and benign lichenoid keratosis. In solar melanocytic hyperplasia, a frequent finding in sun-damaged skin, while the number and size of melanocytes are increased, they have regular distribution along the basal layer and remain equidistant without deep extension along the adnexal structures.

The incidental finding of a LM in a wide excision of chronically sun-damaged skin for a different lesion is not uncommon in our setting. Thus, always be aware of the chance of finding LM in a specimen with atrophic epidermis and severe solar elastosis and look for it.

Herein, we focus our discussion on the significance of early recognition of LMM and the pitfalls in the detection of invasion in excisional samples previously diagnosed as LM.

DISCUSSION

Early identification of LM/LMM is of utmost importance in guiding management and predicting prognosis. There is no single conclusive finding for the diagnosis of malignancy in melanocytic lesions and LM/LMM is no exception. Therefore, careful scrutiny of both architectural disorder and cytologic atypia is critical for the diagnosis.

The classic architecture of the radial growth phase of LM manifests as a broad asymmetric lesion with a confluent basal lentiginous growth of somewhat atypical nevoid to small epithelioid melanocytes along the dermal-epidermal junction with occasional nesting and downward extension surrounding adnexal structures, especially hair infundibulum. Upward pagetoid scatter may be only focal and not as striking as in superficial spreading melanoma (figure 1). The neoplastic melanocytes exhibit moderate amounts of faintly pigmented cytoplasm, angulated, enlarged and hyperchromatic nuclei with inconspicuous to small nucleoli. The cytological atypia in LM is variable and can be subtle, especially in early lesions. Helpful classic cytopathological features include discohesive small cells with cytoplasmic retraction artefact, enlarged angulated nuclei and star-burst multinucleated giant melanocytes. Epithelioid melanocytes with dusty cytoplasm and prominent cherry red nucleoli are not common features in LM. Other helpful diagnostic clues include epidermal atrophy and a background of severe solar elastosis.[1]

A less common yet important architectural pattern is the dysplastic nevus-like LM or nevoid LM.[2] The recognition of this pattern is important to avoid misinterpreting LM as a dysplastic nevus. It is characterised by a significant tendency towards nesting and bridging of adjacent elongated rete ridges in a manner similar to that of dysplastic nevus. Such distinction can be challenging, particularly in partial biopsies. Fortunately, the occurrence of dysplastic nevus on chronically sun-damaged skin of the elderly is infrequent. Furthermore, LM lesions are broader with more asymmetry, and only a minority of them account for dysplastic nevus-like morphology. In our practice, on the rare occasions that we render the diagnosis of dysplastic nevus in this population, we require very strict

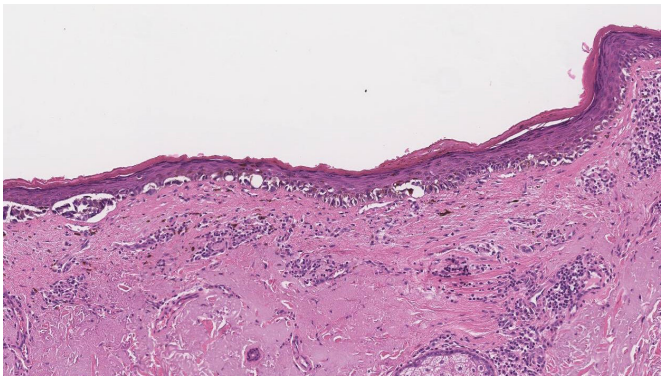

Figure 1 Lentigo maligna, lentiginous proliferation of atypical small melanocytes and their nest formation, also demonstrating separation artefact and dyscohesion within the nests. Of note is the epidermal atrophy, solar elastosis and the absence of prominent upward scatter.

criteria. Immunohistochemical stains such as SOX-10, MiTF and Melan-A can aid in this distinction by demonstrating the degree of confluence of basal lentiginous melanocytes and breadth of the lesion. They can also be utilised to detect occult invasion. However, to diagnose invasion in these immunostained-positive dermal cells, definitive morphological evidence of atypia is a must.

The diagnosis of invasion in LMM is critical because it correlates with both prognosis and treatment plan. As LM involves the head and neck region, any change in the treatment plan may have significant cosmetic and functional impact on the patient.[3] A study showed that forming rows and nests by proliferating junctional melanocytes, subepidermal clefting and lesser degree solar elastosis are the findings in LM that are frequently associated with invasive components.[4] In other words, in foci of LM with striking junctional activity, pathologists should be alarmed of the possibility of invasion. Moreover, the presence of prominent inflammatory infiltrate, especially plasma cells associated with melanophages, is alarming and should prompt ordering deeper levels in equivocal cases to look for the invasion. Of note, despite the slow radial growth phase of LM, a long-term progression rate of 30% to 50% invasion has been documented.[5] In the re-excision of 5% to 52% of biopsy-proven LM cases, the presence of invasion was recognised[1] (figure 2).

The main pitfalls in the diagnosis of invasive component in a biopsy or re-excision of LM sample include:

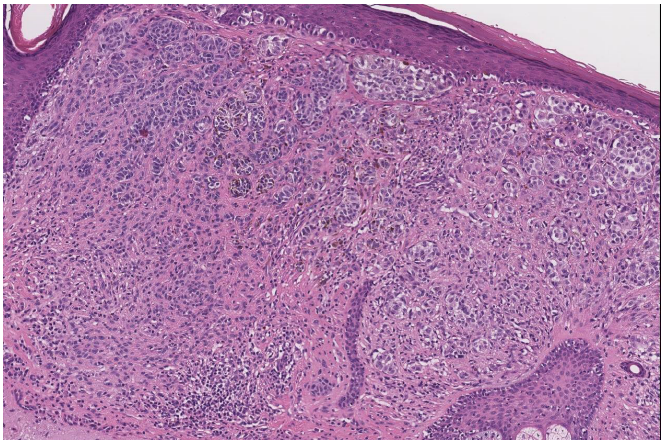

Figure 2 Lentigo maligna melanoma. This invasion was found in a wide re-excision of a lentigo maligna case.

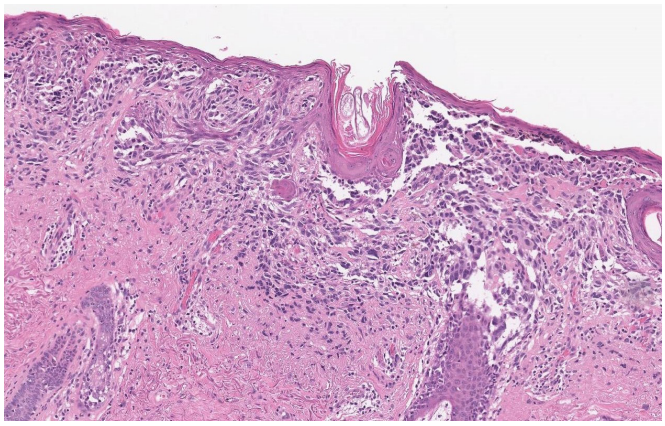

Figure 3 Lentigo maligna melanoma with microinvasion, single units and tiny nests of atypical melanocytes with hyperchromatic nuclei within superficial dermis underneath prominent junctional component. Of note is the significant perifollicular involvement as well.

Diagnosis of microinvasion

Microinvasive melanoma represents an early invasive form with a better prognosis compared with the grossly invasive melanoma. It is characterised by scattered single units and small nests of melanoma cells within papillary dermis which are smaller than their junctional counterparts and, by definition, lack mitotic activity (figure 3). Appreciation of microinvasion, particularly in the presence of severe dermal inflammatory infiltrate, can be hard and sometimes difficult to differentiate from benign intradermal nevic nests. In these cases, although immunostains for melanocytic markers highlight melanocytes within the dermis, they are not helpful for the confirmation of the malignant nature of the melanocytes. Furthermore, HMB45, p16 and MIB1 (proliferation index) immunostains are of no help either, because the dermal component is very tiny and the staining pattern is inconclusive. Best clue in these challenging situations is to compare the cytology of dermal melanocytes with the junctional neoplastic melanocytes and pay attention to cytologic atypia. Moreover, as mentioned before, an eye-catching overlying junctional activity can be in favour of dermal invasion (figures 3 and 4).

Differentiation from an incidental dermal nevus

It is not uncommon to have an incidental dermal nevus in an excision specimen for LM. In these cases, in contrast with the above-mentioned microinvasive melanoma, the dermal nests are usually more than just a few tiny nests. Furthermore, they do not show atypical cytologic features and should exhibit maturation towards the base of the lesion. Demonstration of maturation gradient highlighted by HMB45, retained mosaic staining by P16 and low proliferation index (MIB-1), can help in difficult cases. It should be emphasised though that the morphology remains the gold standard for definitive diagnosis in melanocytic lesions.

Differentiation from adnexal involvement

Adnexal involvement is characteristically found in LM. The neoplastic melanocytes extend along the adnexal structures, especially follicular infundibulum, and this may be very extensive.[6] In some cases, a transected adnexal structure surrounded by neoplastic melanocytes within dermis and without apparent connection to the surface can be misdiagnosed as an invasion. Keeping this in mind, along with examining deeper sections, helps avoid misinterpretation. Furthermore, measuring the

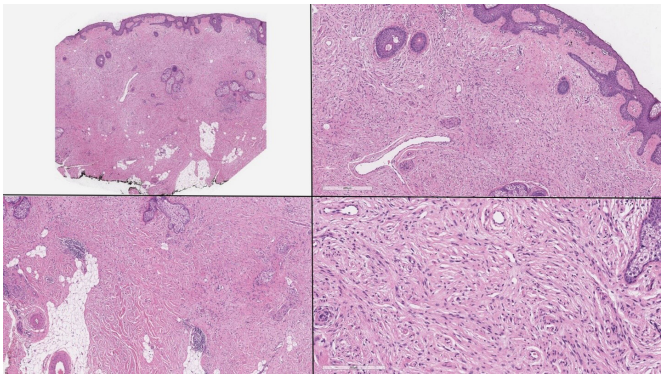

Figure 4 Spindle cell melanoma. On the top left, a biopsy from a cheek lesion showing a focus of in-situ component and busy dermis. On the top right, a closer view of the same case demonstrating focal junctional lentiginous proliferation of dyscohesive melanocytes with nest formation and busy dermis. On the bottom left, lymphocytic aggregates in the deep dermis is noted; and on the bottom right, atypical spindle cells with hyperchromatic nuclei in the dermis is noted.

melanoma thickness adjacent to the involved adnexal structures may lead to an overestimation/underestimation of the melanoma thickness for the same reason. Therefore, if possible, stay away from hair follicles and sweat glands when measuring the depth of the invasion. (figure 2)

Multifocality of invasion in LMM

LM is a broad lesion and it may invade into the dermis in different foci. Careful examination of the entire lesion is necessary to find multifocal invasion. The identification of multifocal invasion is critical not only for the thickness measurement but also for determining the appropriate excisional margins.

Diagnosis of spindle cell melanoma and its differentiation from scar

Desmoplastic melanoma (DM)/spindle cell melanoma, although may arise de novo, has the most common association with LM type among all types of melanoma.[7] Although hypercellular variants may be noted easily, hypocellular DM is hard to differentiate from scar tissue or a benign dermal spindle cell tumour such as neurofibroma or dermatofibroma.

Scattered spindled melanocytes among collagen bundles in DM may have deceptively bland morphology and may be readily mistaken for fibroblasts (figure 4). Helpful clues for the diagnosis include identification of atypical hyperchromatic nuclei, atypical multinucleated giant melanocytes, mitotic activity, extension into deep dermis and subcutis, neurotropism and lymphoid aggregates.[8]

To avoid missing DM, always think about its possible association with LM. To specify the nature of the spindle cells within the dermis, use melanocytic markers such as S100, WT1 and SOX10. It should be noted that most desmoplastic/spindle cell melanomas are negative for the more specific melanoma markers such as HMB45. S100 does not help distinguish DM from Schwann cell tumours.

CONCLUSION

Correct diagnosis of invasion in LMM is critical as in other types of melanoma and sometimes very challenging. The main pitfalls include differentiating microinvasive melanoma from adnexal involvement by in situ melanoma or an incidental benign dermal nevus, the possibility of multifocal invasion and misinterpreting desmoplastic/spindle cell melanoma as scar tissue or other cutaneous spindle cells tumours.

Take home messages

- A careful scrutiny of both architectural disorder and cytologic atypia is critical for the diagnosis of lentigo maligna/lentigo maligna melanoma.
- The presence of microinvasion in lentigo maligna melanoma should be differentiated from adnexal involvement by melanoma in-situ and incidental dermal nevus.
- Desmoplastic melanoma most commonly presents in association with lentigo maligna and should not be misdiagnosed as scar tissue or a benign dermal spindle cell tumour.

Handling editor Runjan Chetty.

Contributors NS, as a clinical fellow in dermatopathology at Toronto General Hospital, wrote the first draft of this Viewpoint based on her supervisor's (DG and ZS-K) guidance and experiences. Then, this paper was reviewed and edited by DG and ZS-K.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer-reviewed.

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