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Histopathological Diagnosis of Early Stage of Malignant Melanoma

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1. Introduction

Macroscopically, malignant melanoma (MM) is diagnosed by the so-called ABCDE rule(asymmetry, border irregularity, color variation, diameter generally greater than 6 mm, and elevation)[1)]. Nowadays, D may stand for dark color. In addition to this, the dermoscope has been an indispensable tool to diagnose MM, allowing MMs of less than 4 mm in diameter to be found. Therefore, D may also stand for dermoscopic structure[2)].

There are variations in approaches for the histopathological diagnosis of MM. By putting them in order according to the clinical ABCDE rules, they are as follows: Asymmetry (including asymmetrical silhouette and color imbalance), Buckshot scatter (= pagetoid spread), Cytological atypia, Deep mitosis, Enclosing (= surrounding) lymphocytes, Fibrosis, and Gainsaying (= no) maturation. Moreover, the diagnosis will be made by adding the specific findings related to the site of the body such as palms, soles, subungual region, genital area, oral cavity and conjunctiva[2)].

In general, the pathological diagnostic clues of MM in situ are as follows:

1. single melanocytes predominance and irregular distribution of nests,
2. cytological atypia (larger than the normal melanocytes, abundant cytoplasm, distinct nucleoli), and
3. pagetoid spread of melanocytes.[3)]

We chose three important conditions in early stage lesions of MM, which are difficult to be applicable to the above clues of MM in situ. They are (1) early stage of lentigo maligna pattern of maligna melanoma in situ, (2) early stage of melanoma in situ on volar skin, and (3) Spitzoid or nevoid melanoma without invasion beyond the mid-dermis.

Here, in this session, we describe these three conditions. In particular, we describe No (2) item, which is common in the Japanese, in detail. Moreover, although immunostainigs are not useful for the differential diagnosis between MM and benign lesion, we selected some useful immunohistochemical findings which serve to differentiate them.

2. Lehtigo maligna (early stage of lentigo maligna pattern of maligna melanoma *in situ*)

Lentigo maligna (LM=early stage of lentigo maligna pattern of maligna melanoma in situ) is clinically only found on chronically sun-exposed areas of elderly people. Macroscopically,

changes of asymmetry, border irregularity, color variation in the ABCDE rule and dermoscopically irregular reticular pigment network are important findings for their diagnosis. Histologically, in typical LMs, three of the diagnostic clues of MM in situ described above are used for the diagnosis of LM. In the early lesions of LM, melanocytes do not show buckshot scatter (pagetoid spread) and alignment along the basal layer. Their nuclei are hyperchromatic, and show slight cytological atypia and few mitoses. Single melanocytic proliferation is present broadly[4], continuously[3], or generally (almost diffusely)[5], and is lentiginous along the basal layer.

However, in earlier stages of LM the distribution is not lentiginous but sparse. The diagnostic clues for the early stage of LM are follows: 1) melanocytes are irregularly distributed (Fig. 1); 2) melanocytes lose their polarity of nuclei against the basement membrane (Fig. 2); and 3) melanocytes show a rather large shape, hyperchromatic nuclei and clear halo with moth-eaten appearance of nuclei (Fig. 3). Although these large melanocytes in LM are needed for differentiating them from activated melanocytes in benign lesions (lentigo senilis, lichen planus-like keratosis, lichenoid actinic keratosis and so on), benign lesions have neither loss of polarity nor a moth-eaten appearance. In addition, benign lesions usually show vacuolar degeneration and pigment incontinence.

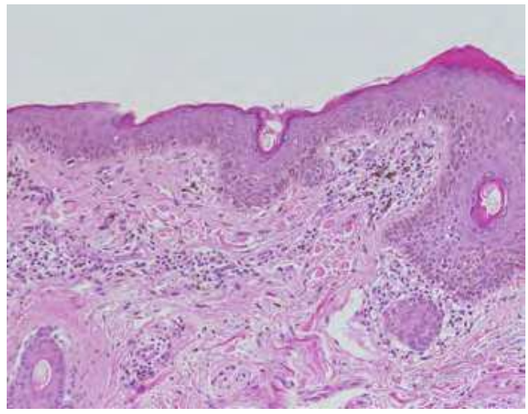


Fig. 1. Early stage of lentigo maligna (low power view): The distribution of melanocytes is irregular.

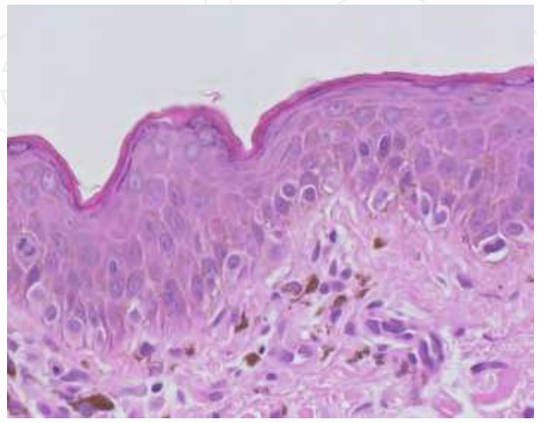


Fig. 2. Early stage of lentigo maligna melanoma (middle power view): Melanocytes lose their polarity of nuclei against the basement membrane.

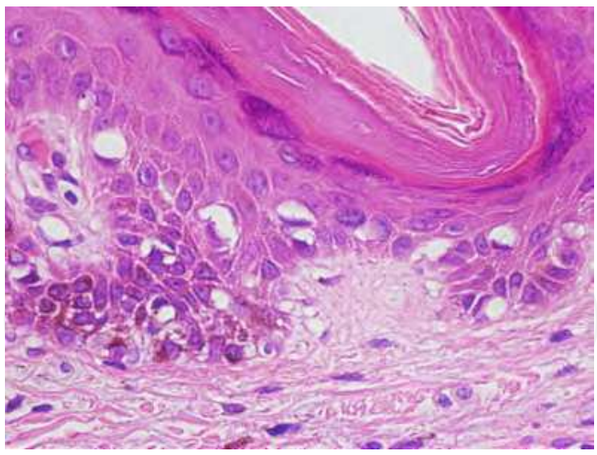


Fig. 3. Early stage of lentigo maligna melanoma (high power view): Melanocytes show a rather large shape, hyperchromatic nuclei and clear halo with moth-eaten appearance of nuclei. They also show hyperchromatic nuclei and loss of polarity against the basement membrane.

3. Early stage of melanoma *in situ* on volar skin

Histopathological criteria of early stage of melanoma in situ on volar skin have been thought to be so far as follows:

1. melanocytes arranged as solitary units predominate over melanocytes in nests[6];
2. irregular distribution of nests are frequently seen[3]; nests of melanocytes vary in size and shape[6];
3. slight cytological atypia is seen[3];
4. single cells often extend irregularly far down to the eccrine duct epithelium[3,6]; and
5. pagetoid spread of melanocytes is seen, especially an ascent up to the granular layer[3,6].

Moreover, on the sole, benign melanocytic lesions are frequently observed to have melanocytes ascending up to the granular layer. As in the early volar MM in situ, when only a few melanocytes show slight nuclear enlargement and slight cytological atypia, such a lesion has been called atypical melanosis of the foot[7]. However, nowadays these lesions are thought to be an early stage of MM in situ. With the recent development of dermoscopy for the diagnosis of MM in situ on the sole, it is important to find the melanocytes present on the crista profunda intermedia[8]. We found 5 cases of MM in situ from the review of 145 cases of melanocytic nevi on the sole previously diagnosed[9]. Separately from these five cases of MM in situ, we chose 14 cases of MM in situ on the volar skin in our institution. Resected specimens of these cases were cut perpendicularly against for cutaneous secant (the direction of skin crista and furrow, Fig. 4). The diagnoses of these cases were confirmed after clinicopathological conference. By the detailed observation of melanocytes on the crista profunda intermedia as pointed out by Ishihara et al[8], we found important findings about the distribution pattern and cytological atypia. In the early lesion, the melanocytes on the slope of rete ridges on the crista profunda intermedia exist without a continuous pattern, showing irregular intervals of each melanocyte and loss of polarity of nuclei against the basement membrane (Fig. 5). The nuclei are larger than those of normal melanocytes, show hyperchromatic nuclei, and have large nucleoli (Fig. 6). These findings are reported in our report[9].

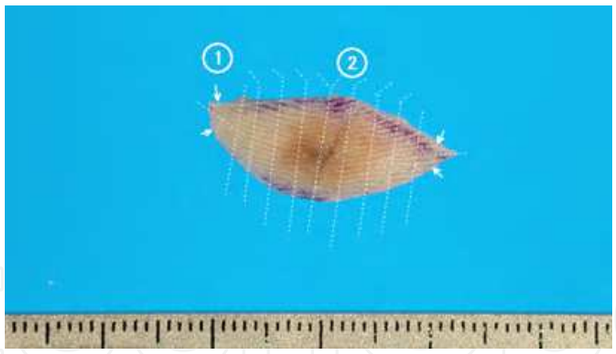


Fig. 4. How to cut the specimen of pigmented lesion on the volar skin. Lesions should be cut perpendicularly for cutaneous secant (the direction of skin crista and furrow).

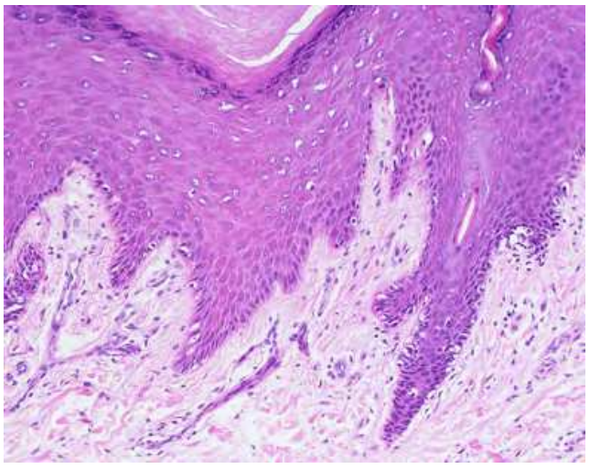


Fig. 5. Early lesion of MM in situ on the volar skin (low power view). Melanocytes on the slope of rete ridges on the crista profunda intermedia exist without continuous pattern, with irregular intervals of each melanocyte and loss of polarity of nuclei against the basement membrane.

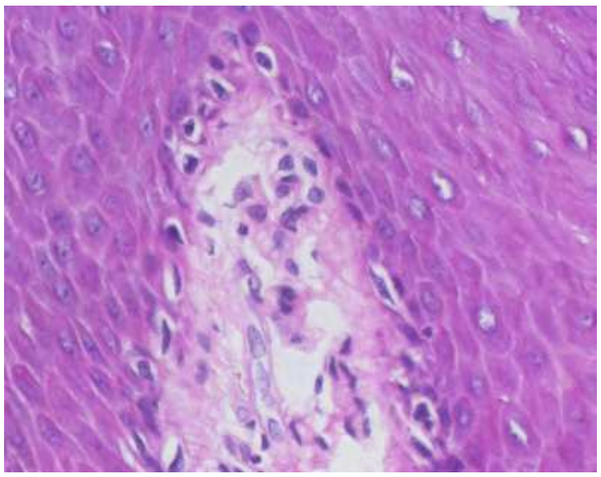


Fig. 6. Early lesion of MM in situ on the volar skin (high power view). The nuclei are larger than those of normal melanocytes, show hyperchromatiic nuclei, and have large nucleoli.

4. Spitzoid or nevoid melanoma without invasion beyond the mid-dermis

Melanocytic proliferative disorders include only melanocytic nevi and malignant melanomas. Therefore, the diagnosis of MM could be based on an exclusion of benign pigmented nevi. The differential points between Spitz nevi or compound nevi and early stage of MMs in this group are deep existence of high cellular density without maturation (Fig. 7), deep mitosis (Fig. 8) and jagged lesional base (Fig. 9). In addition, many well-formed large Kamino bodies favor a diagnosis of Spitz nevus [3].

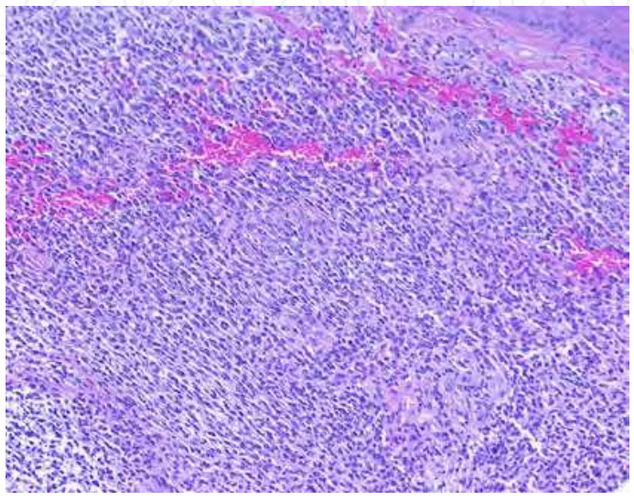


Fig. 7. Nevoid melanoma (middle power view). High cellular density without maturation is present.

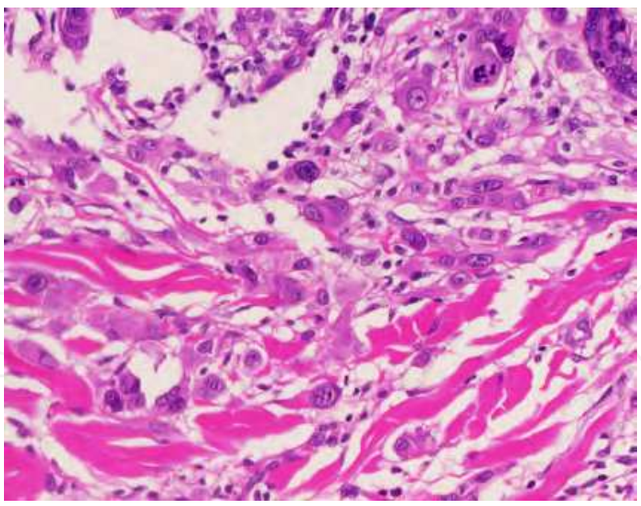


Fig. 8. Spitzoid melanoma (high power view). Deep mitosis is present.

5. Useful findings of immunostaining

Regarding the immunohistochemistry in the diagnosis of MM, combined immunohistochemical stains may be used to gain useful information in the diagnosis of early stage of MM. In Spitz nevus, nevoid nevus, blue nevus, melanocytic nevus and normal

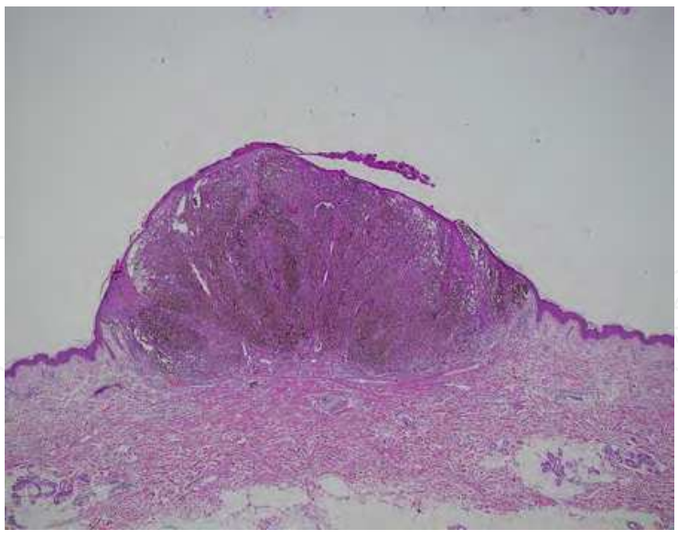
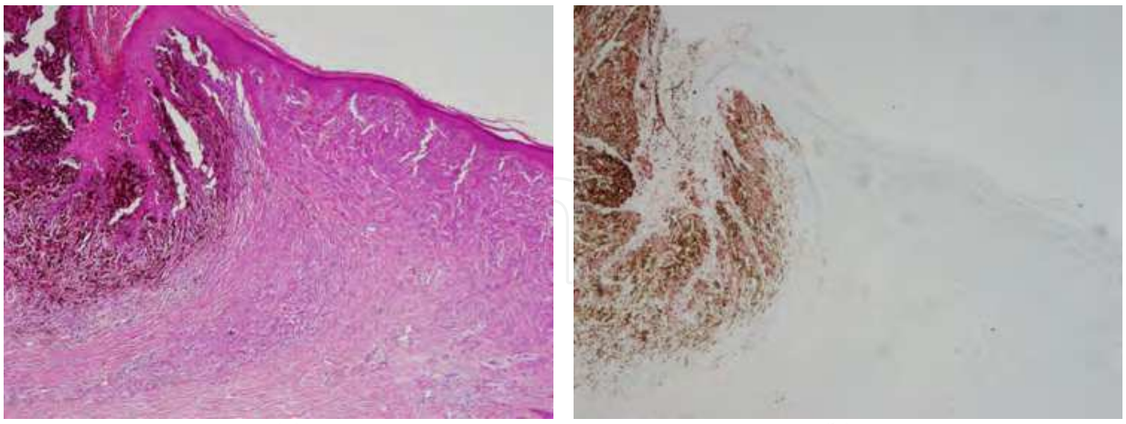


Fig. 9. Spitzoid melanoma (low power view): There is a jagged lesional base.

melanocyte, S-100 protein and Melan-A are diffusely positive. Furthermore, we must know that S-100 protein is positive for Langerhans cells, and melan-A is positive for melanophages. MM and blue nevus are diffusely positive for HMB-45 (Fig. 10, left), but normal melanocytes and benign melanocytic nevi are negative (Fig. 10. right). In Spitz nevus, nevoid nevus and activated melanocytic lesion are usually positive for HMB-45. Especially, the upper portion of these lesions is strongly positive for HMB-45, but the lower portion of these lesions is weakly positive or negative (Fig.11). This finding is indicative for maturation of melanocytes. Namely, melanocytes in the epidermis are positive but melanocytes in the dermis are negative. MIB-1 is also useful for seeking deep mitosis, which favor a diagnosis of MM (Fig.12).



(a) (b)

Fig. 10. (a) Combined case with Spitzoid melanoma (left) and intradermal melanocytic nevus (right). (b) The Spitzoid melanoma is positive (left) but intradermal melanocytic nevus is negative for HMB-45 using alkaliphosphatase (right).

HMB-45 has been known to be positive for MM except for desmoplastic/spindle cell melanoma[2]. However, early stage of MMs rarely shows this specific feature. In general,

desmoplastic/spindle cell melanoma usually exists in the dermis and has little epidermal change. In differentiation between spindle cell melanoma and pigmented spindle cell nevus (Reed), it is useful to find maturation.
In immunohistochemical summary, combination of S-100 protein (high sensitivity for melanocytic lesions), melan-A (high specificity for melanocytic lesions), HMB-45 and MIB-1 is useful for making a diagnosis of early stage of MM.

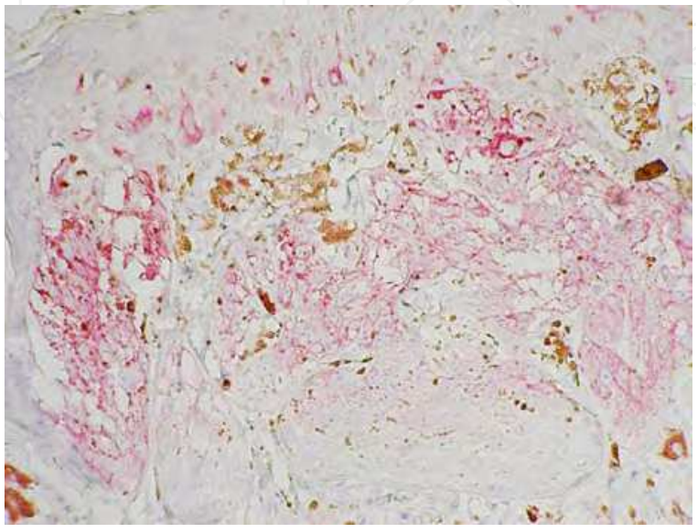


Fig. 11. Spitz nevus: The upper portion of these lesions is strongly positive, but the lower portion is weakly positive or negative (HMB-45 using alkaliphosphatase.

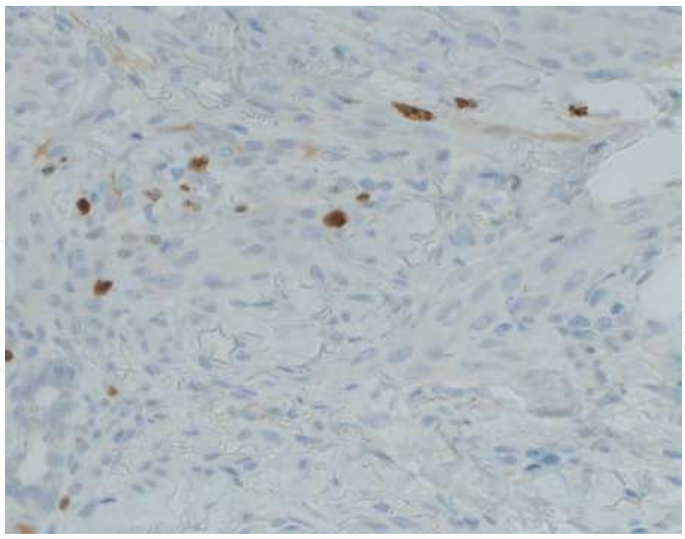


Fig. 12. Spitzoid melanoma: MIB-1 is positive for the lower part of the lesion.

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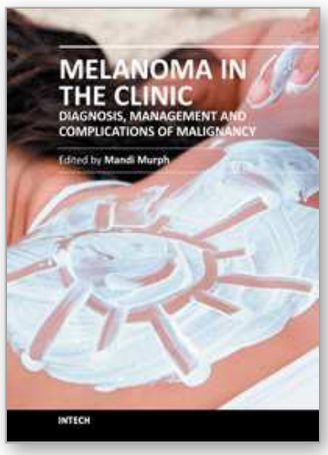

Melanoma in the Clinic - Diagnosis, Management and Complications of Malignancy

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This book provides an excellent overview of how melanoma is treated in the clinic. Since oncologists and clinicians across the globe contributed to this book, each area also explores the unique burdens that geographical areas experience from melanoma subtypes and how these are treated in different settings. It also includes several chapters that illustrate novel methods for diagnosing melanoma in the clinic using new technologies, which are likely to significantly improve outcomes. Several chapters cover surgical techniques and other present very rare or challenging clinical cases of melanoma and how these were treated. The book is geared towards informing clinicians and even patients how melanoma arises, what tools are available and which decisions need to be made by patients and their families in order to treat this devastating disease.

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