

Pigmented Epithelioid Melanocytoma: Immunohistochemical Profiles of Tumour-infiltrating Histiocytes

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Pigmented epithelioid melanocytoma (PEM) was first described by Zembowickz et al. (1) as a distinctive group of melanocytic tumours, with a more favourable prognosis than conventional melanoma. The typical histopathological findings of PEM are proliferation of epithelioid, pleomorphic, atypical cells with heavy pigmentation in the dermis, and the aggregation of histiocytes in the center of the tumour (1–3). Because PEM is a relatively new and rare category of skin cancer, reports are limited. We describe here the dermoscopy findings of a case of PEM and investigate the immunohistochemical profiles of the tumour-infiltrating histiocytes.

CASE REPORT

A 77-year-old Japanese woman consulted our outpatient clinic with a 2-year-history of a blue-black nodule on her right hand. On her first visit, physical examination disclosed a blue-black nodule on the dorsal part of her right hand, 13 mm in diameter (Fig. 1A). Dermoscopy revealed blue-whitish monotonous features with a focal red-black area and a clear border (Fig. 1B). We excised the tumour with a 20-mm surgical margin. Histological examination revealed proliferation of epithelioid, pleomorphic, atypical cells with heavy pigmentation in the dermis (Fig. 2A). At the periphery of the tumour, epithelioid, pleomorphic, atypical cells were positive for Melan A and HMB-45 staining. At the center of the tumour, an aggregation of histiocytes, which were positive for CD68 and negative for Melan

A, was prominent (Fig. 2B, C). From the above findings, the patient was diagnosed with PEM. Because PEM was reported to have a favourable prognosis compared with conventional malignant melanoma, we employed immunohistochemical staining for CD163, MMP9, and Foxp3, which we have previously reported as markers for M2 macrophages, as well as angiogenic factors and functional markers for myeloid-derived suppressor cells (MDSC) and regulatory T cells (Tregs), respectively, in the tumour microenvironment (7). CD163⁺ macrophages were found to be scattered in the CD68⁺ area, (Fig. 2D). MMP9 was negative in the CD68⁺ area (data not shown), and few MMP9⁺ cells were observed in the peripheral site of the tumour (data not shown). Few Foxp3^{high+} regulatory T cells were observed (data not shown).

DISCUSSION

PEM has features very similar to those previously described as “human animal-type melanoma” and “epithelioid blue naevus of Carney complex” (1–3). Although histological findings are indispensable for the diagnosis of PEM, sometimes it takes a long time to achieve a final diagnosis, or the findings can be histologically misread as malignant blue naevus or melanoma, which can lead to unfavourably extensive excision. Therefore, another diagnostic tool is necessary for the diagnosis of PEM. Dermoscopy is a valuable, non-invasive, widely used technique that has improved the diagnostic accuracy for skin cancer (9). It allows *in vivo* observation of the skin, with visualization of the morphological structures in the epidermis and papillary dermis, which are not otherwise discernible to the naked eye. In the present case, we observed a focal red-black area in the blue-whitish monotonous tumour, which might be connected with the aggregation of histiocytes and be a characteristic dermoscopy finding for PEM. Comparative dermoscopy studies on a series of PEM are needed, however, to support our description.

Interestingly, previous reports also suggested a favourable prognosis for PEM, although PEM is reported to be associated with frequent lymph node metastases. Indeed, Zembowicz et al. (1) reported that lymph node metastasis was detected in 11 of 24 cases (46%). Remarkably, their 5-year follow up data suggested that distant metastases of PEM are rare (less than 1%) (2),

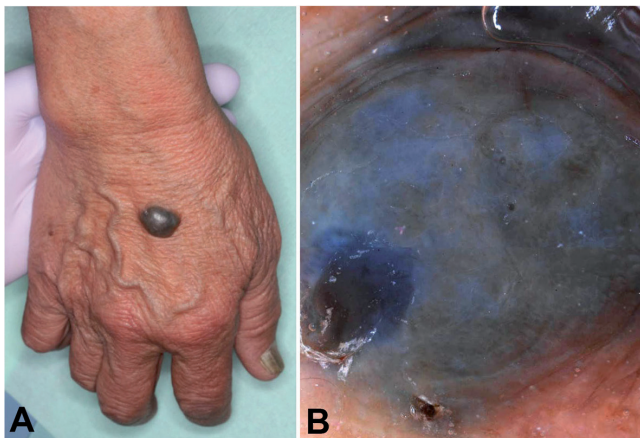


Fig. 1. (A) A blue-black, nodule 13 mm in size on the dorsal part of the right hand. (B) Blue-whitish, monotonous features with a focal red-black area and clear border.

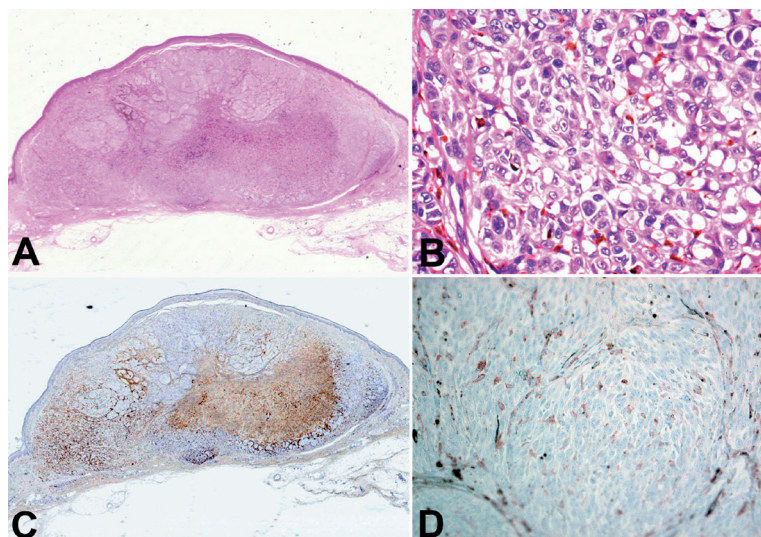


Fig. 2 (A) Proliferation of epithelioid, pleomorphic, atypical cells with heavy pigmentation in the dermis. (B, C) At the center of the tumour, was a prominent aggregation of histiocytes, which were positive for CD68 and negative for Melan A. (D) Paraffin-embedded tissue sample was deparaffinized and stained using anti-CD163 Ab. The sections were developed with new fuchsin (red) (original magnification: (A, C) $\times 5$, (B) $\times 400$, (D) $\times 200$).

and they concluded that PEM has a more favourable prognosis than conventional melanoma. However, there is no report that describes a possible reason for the favourable prognosis of PEM.

For the above reason, we employed immunohistochemical staining for PEM, focusing especially on tumour-infiltrating lymphocytes. Together with other suppressor cells, such as regulatory T cells (Tregs), CD163⁺ M2 macrophages are reported to promote an immunosuppressive environment in the tumour-bearing host (4, 5). As we reported previously, the expression of MMP9 on immunosuppressive macrophages in the tumour microenvironment contributed to tumour invasion and metastasis (5–7). These reports suggest that increased numbers of MMP9⁺ cells, especially expressed CD163⁺ M2 macrophages around the tumour might contribute to the poor prognosis of various types of skin tumour by establishing immunosuppressive tumour microenvironment, together with the induction of angiogenic factors, such as vascular endothelial growth factor. In addition, more recently, we demonstrated the effect of Tregs on immunosuppressive macrophages, MDSC, as having a suppressive function through the increase in the expression of B7H1 in melanoma models (8). Concerning our present case, the majority of tumour-infiltrating histiocytes/macrophages were CD68⁺ CD163⁻ MMP9⁻ macrophages. In addition, few Foxp3^{high+} Tregs were observed. The absence of immunosuppressive cells, such as Foxp3^{high+} Tregs, CD163⁺ M2 macrophages and MMP9⁺ cells, might connect with the favourable prognosis of PEM compared with conventional malignant melanoma. Since we did not directly assess the suppressive function of these infiltrating Tregs and M2 macrophages, further analysis of the mechanisms underlying this phenomenon may offer fundamental insights

into the mechanisms of PEM. Such clarifications will need to be addressed in future investigations.

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