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Tumour-stage mycosis fungoides initially misdiagnosed as Langerhans cell histiocytosis

Sir,

Mycosis fungoides, initially presenting in tumour stage, is rare. Langerhans cells can be associated with cutaneous T-cell lymphomas, and when numerous may form the nodular clusters that can mimic Langerhans cell histiocytosis and mask an underlying cutaneous lymphoma. Here we report such a case.

A 54-year-old diabetic man with a history of adenoid cystic carcinoma in the right maxillary sinus 5 years previously, treated with surgery and concurrent chemoradiotherapy at that time, received regular follow-up for right maxillary osteoradionecrosis. He presented to the Plastic Surgery Department with a progressively enlarging mass of the right little finger for 6 months. The mass measured 4.5×4×4 cm and the overlying skin was ulcerated with multiple non-healing wounds (Fig. 1A). On the adjacent palmar skin, there was erythema with some tiny vesicles and scales, reminiscent of dyshidrotic eczema (Fig. 1A). He denied loss of sensation and range of movement was normal. No evidence of bony involvement was seen on the right hand radiograph. Laboratory data including biochemistry and complete blood counts were normal. The patient underwent an excision of the mass. Pathologically, the overlying skin of the mass revealed focal ulceration (Fig. 1B). The mass was composed predominantly of lymphocytes and histiocytoid cells (Fig. 1C). The lymphocytes showed mild atypia; the histiocytoid cells, forming multiple nodules, possessed ovoid to spindle-shaped nuclei with grooving and moderate to abundant amount of cytoplasm, infiltrating the dermis and subcutis (Fig. 1C, inset). Focal spotty necrosis and increased

mitotic figures were found (~13/10 HPF). Immunohistochemically, CD3 highlighted small T cells with mild atypia, and CD20-positive cells were patchy in distribution. The ovoid/spindle cells were positive for S100 (Fig. 1D), CD1a (Fig. 1E), Langerin (Fig. 1F), and BRAF V600E (Fig. 1G). The Ki-67 proliferative index was 40–50% in the highest area. Based on these features, the case was initially reported as Langerhans cell histiocytosis with atypical features.

Subsequent to the above diagnosis, the patient came to the Department of Dermatology, where multiple erythematous patch, plaque and nodular skin lesions over the trunk and four extremities were found. He also noted the dyshidrotic dermatitis-like lesions for 10 years. With a tentative clinical diagnosis of mycosis fungoides, multiple biopsies were performed on skin lesions of the extremities. Histopathologically, the right palmar skin showed dyshidrotic dermatitis with epidermotropism by atypical lymphocytes (Fig. 1H). The nodule of left lateral foot also showed dense infiltration of atypical lymphocytes with scanty to moderate amount of cytoplasm and cerebriform nuclei infiltrating the dermis and subcutis (Fig. 1I). Some eosinophils were seen. Immunohistochemically, these cells were CD3⁺ (Fig. 1J), CD7⁺, CD25⁺ (Fig. 1J inset), and dominantly positive for CD4 compared to CD8. They were however negative for CD20 and BRAF V600E. These features were consistent with mycosis fungoides in tumour phase.

In context of the skin biopsy findings, the morphology of right little finger mass was reviewed. Atypical lymphoid cells with mild nuclear irregularities were identified, which infiltrated the dermis and subcutis associated with many Langerhans cells, histiocytes and eosinophils. The atypical lymphocytes were CD3⁺, CD20⁺, CD5⁺, CD4⁺, focally CD25⁺, and focally CD30⁺. CD7 and CD8 were negative. *In situ* hybridisation for Epstein–Barr virus encoded RNA (EBER) was negative and the Ki-67 proliferative index was high (~50%). The background Langerhans cells, positive for BRAF V600E by immunostaining (Fig. 1G), were negative for BRAF V600E mutations assessed by PCR-based methods as well as negative for cyclin D1 immunohistochemically. Instead, analysis of *TRB* and *TRG* rearrangements showed a monoclonal pattern (Fig. 2A), similar to that in the right posterior thigh skin lesion (Fig. 2B). The case was finally reported as mycosis fungoides (tumour stage) with atypical Langerhans cell hyperplasia. A computed-tomography (CT) scan of the chest revealed bilateral lung nodules. Lung needle biopsy showed metastatic adenoid cystic carcinoma, and bone marrow aspiration and biopsy were negative; neither biopsy showed Langerhans cell histiocytosis or lymphoma. The patient was stage T3N0M0, IIB according to the American Joint Committee on Cancer (AJCC) 8th edition staging system for primary cutaneous lymphoma. He subsequently received radiotherapy 3000 cGy in 10 fractions to the right 3rd finger and left lateral sole skin, and 3900 cGy in 13 fractions to the right 5th finger. The tumours resolved gradually. He also underwent psoralen and ultraviolet A (PUVA) therapy for plaque lesions on right upper arm and left flank area at the dermatology clinic. In the recent follow-up, a new skin plaque was seen on the left heel.

Mycosis fungoides (MF), an indolent cutaneous T-cell lymphoma of skin resident memory T cells (TRM), is confined predominantly to the skin as patches and plaques.¹ The aetiology and pathogenesis of MF is multifactorial and

Fig. 1 Gross and microscopic findings of the finger mass and other skin lesions. (A) Mass of right little finger, measuring $4.5 \times 4 \times 4$ cm, shows ulcerated overlying skin with multiple non-healing wounds. Note erythematous lesions with some tiny vesicles and scales on the palm, which are reminiscent of dyshidrotic eczema. (B) Microscopically, the epidermis is focally ulcerated and covered with an inflammatory exudate (H&E). The underlying mass is composed of mixed lymphocytic and histiocytoid cell infiltrates. (C) The lymphocytes show only mild atypia (left, H&E). The nodular proliferation comprises of ovoid to spindle cells (right) with abundant cytoplasm and nuclear folds or grooves (inset). (D–G) Immunohistochemically, the ovoid/spindle cells are strongly positive for (D) S100, (E) CD1a, (F) Langerin, and (G) BRAF V600E stains. (H) Histopathological sections of the right palmar lesion show spongiotic psoriasiform dermatitis with microvesicular pustules and several foci of lymphocytic epidermotropism (H&E). These aggregated lymphocytes, forming microabscesses, possess hyperconvoluted nuclei, consistent with dyshidrotic mycosis fungoides (inset). (I) The nodular lesion of left lateral foot shows a diffuse infiltrate, consisting predominantly of highly atypical lymphocytes admixed with some histiocytes and eosinophils (H&E, high power). The lymphocytes are small to medium-sized, possess scanty to moderate amount of cytoplasm and cerebriform nuclei. (J) Immunohistochemically, these atypical cells are $CD3^+$, $CD7^-$, $CD25^+$ (inset), and dominantly positive for CD4 compared to CD8 (not shown).

the specific causative agents and precise pathogenesis are unknown.¹ One of the possible mechanisms explaining prolonged disease development could be that in early MF, host immune-surveillance controls tumour progression by an anti-tumour immune response.¹

Dendritic cells (DCs) play an important role in the induction of immunity and maintenance of anti-tumour immunity. DCs undergo progressive maturation from immature ($CD1a^+/CD83^{low}/DC-LAMP^-$) to mature form ($CD1a^{+/-}/CD83^{high}/DC-LAMP^+$).² The development of anti-tumour cellular immunity depends on tumour cell antigens that are phagocytised by immature DCs, which then present tumour antigens to tumour-specific T cells following maturation. However, DCs also induce IL-10 production with down-regulation of anti-tumour immunity, and induce tolerance to tumour antigens, as mainly seen in tumour stage of MF and

perhaps explaining tumour progression.² Langerhans cells, an immature member of the dendritic cell series, are seen in close apposition with the MF cells suggesting that the malignancy may be stimulated and driven by Langerhans cells triggering MF cells.³

Langerhans cell hyperplasia has been observed in inflammatory dermatoses,⁴ and also in lymphoproliferative disorders, such as lymphomatoid papulosis and MF.⁵ These findings have led Drut *et al.* to speculate that T cells in these lesions emerge as a result of $CD1a^+$ cell signaling.⁴ These $CD1a^+$ cells can form discrete nodules which histologically can resemble Langerhans cell histiocytosis (LCH). More importantly, these Langerhans cells may obscure the lymphocytic infiltrate leading to the misdiagnosis of accompanying T-cell proliferative disorders,⁶ as in the current case. Langerhans cells are intermingled significantly more with

Fig. 2 T-cell receptor genes rearrangement analyses show a similar monoclonal pattern for the finger mass and the skin lesion of right posterior thigh. (A) The right little finger mass contains monoclonal T-cell proliferations on T-cell receptor genes (TCR- γ , left panel; TCR- β , right panel) rearrangement. (B) The right posterior thigh lesion shows a similar monoclonal pattern with the finger mass on T-cell receptor genes (TCR- γ , left panel; TCR- β , right panel) rearrangement. The right palmar lesion is also positive for TCR- β gene rearrangement (not shown).

MF cells in tumour stage than in the patch or plaque stage.² The immunophenotype of hyperplastic Langerhans cells is similar to the cells of LCH, although usually negative for cyclin D1 unlike LCH.⁷ The extent of the Langerhans cell infiltrates, cyclin D1 and/or p53 expression, *BRAF* V600E mutation and the clinical context can be helpful in making this distinction.^{6,8}

LCH has been shown to be neoplastic and monoclonal.^{6,8} *BRAF* V600E mutations in most cases of LCH reinforce the neoplastic nature of the disease. Identification of *BRAF* V600E mutations has important implications for potential risk stratification and treatment.⁸ *BRAF* V600E was detected by immunohistochemistry in the current case, but was discordant with the PCR results, which showed no evidence of *BRAF* V600E mutation. Discordance between *BRAF*

V600E immunohistochemistry and PCR results have been described by others in a small subset of a variety of neoplasms.⁹ The possible reasons for the discordance remain elusive but the scoring criteria for evaluating immunohistochemistry positivity of LCH may play a role. Ballester *et al.* found that using lenient scoring criteria ($\geq 1+$, $\geq 1\%$), the sensitivity and specificity of immunohistochemistry compared with allele-specific real-time PCR were 100% and 18%, respectively.¹⁰ The poor specificity of lenient criteria was attributable to weak (1+) staining in both *BRAF*-mutated and wild-type LCH; thus, the authors suggest using stringent scoring criteria ($\geq 2+$, $\geq 10\%$) to improve the specificity to 100%.¹⁰ In addition, Langerhans cell proliferations are more likely to show this discordance than lesions of other lineages such as melanoma,¹¹ colorectal

carcinoma and papillary thyroid carcinoma.⁹ The excess of Langerhans cells in lymphoproliferative disorders or lymphomas has been shown to be polyclonal and supports the reactive nature of the accumulation of Langerhans cells in such cases.^{5,6}

Regulatory T (Treg) cells are a population of T cells with the CD4⁺/CD25⁺/FOXP3⁺ immunophenotype. Treg cells play a key role in suppression of the immune response. MF tumour cells have been shown to adopt a Treg cell phenotype and function.¹² T-cell lymphomas of Treg lineage, such as MF, are an important population that plays a crucial role in the maintenance of tumour self-tolerance. Therefore, identification of Treg cells is important in MF from a therapeutic point of view.¹²

In conclusion, this current case describes an unusually prominent proliferation of reactive Langerhans cells occurring within tumour stage of MF, where epidermotropism of atypical lymphocytes was inconspicuous, and initially leading to a misdiagnosis of LCH and under-diagnosis of MF. The Langerhans cells admixed with tumour cells, although positive for BRAF V600E by immunohistochemistry, showed no evidence of V600E mutation by PCR, consistent with the reactive nature of these Langerhans cells. Thus, positive immunostaining for BRAF V600E needs to be confirmed by PCR. Awareness of proper clinical context and histological features with a high index of suspicion can help prevent an under-diagnosis of cutaneous T-cell lymphomas.

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Report of a classic primordial odontogenic tumour and an unusual mixed odontogenic tumour with features of primordial odontogenic tumour: diagnostic implications

Sir,

Primordial odontogenic tumour (POT) is a newly defined entity in the 2017 World Health Organization (WHO) classification of head and neck tumours as a mixed epithelial and mesenchymal odontogenic tumour.¹ To date, only 16 cases have been reported.² Given the small number of reported cases, the full clinicopathological spectrum of this tumour remains to be defined. Herein, we report the first Chinese case of POT with classic morphological features and an unusual mixed odontogenic tumour with features of POT, with the aim of further characterising the clinicopathological features of POT.

Case 1 was a 2-year-old boy who presented with a painless swelling of the right maxilla of 2 weeks duration. Computed tomography revealed a well-defined radiolucent lesion measuring 2.5×2.2×2.1 cm, enclosing the crown of the unerupted right first deciduous molar. It caused expansion and perforation of cortical bones (Fig. 1A). Surgical enucleation of the lesion was performed under general anesthesia. Macroscopically, the tumour was yellowish, lobulated, solid, with irregular, smooth surface and surrounded by a capsule (Fig. 1B). Histologically, the tumour exhibited classic histological features of POT consisting of predominant mesenchymal proliferation enveloped by columnar, inner enamel-like epithelium (Fig. 1C–E). There was no evidence of recurrence 11 months after surgery.

Case 2 was a 12-year-old girl who presented with a painless right maxillary swelling for 2 months. Panoramic radiography revealed a well-defined, unilocular radiolucent lesion in the right posterior maxilla, extending from the second premolar to the floor of the maxillary sinus and the tuberosity. The roots of the upper right second premolar and first molar were resorbed (Fig. 1F). Surgical excision of the lesion was performed under general anesthesia. The gross specimen was described as a multilobulated, whitish, solid mass measuring 3.5×2.5×2.5 cm. Histological examination