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SHORT COMMUNICATION

A Case of Extranodal Natural Killer/T-cell Lymphoma Mimicking Refractory Behçet's Disease

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Extranodal natural killer cell (NK)/T-cell lymphoma (ENKL) is a rare type of non-Hodgkin's lymphoma. With a strong aetiologic link to Epstein-Barr virus (EBV), the incidence of ENKL is higher in Asia and South America compared with Western regions.

Behçet's disease (BD) is an immune-mediated small vessel vasculitis presenting with ulceration of mucous membranes and ocular symptoms. Involvement of lymphoma in BD is only infrequently reported. Herein, we report a case of ENKL that proved to be a diagnostic challenge as its symptoms mimicked refractory BD.

CASE REPORT

A 39-year-old woman had a 2-month history of skin lesions on her arms and legs, along with a year-long history of recurrent orogenital ulcerations and a 2-month history of uveitis. Skin biopsy from a hard subcutaneous nodule of the arm (Fig. 1a) revealed septal panniculitis and fat necrosis, suggestive of erythema nodosum (Fig. 1b). According to the criteria of the International Study Group for Behçet's Disease, the patient was initially diagnosed with complete BD (1).

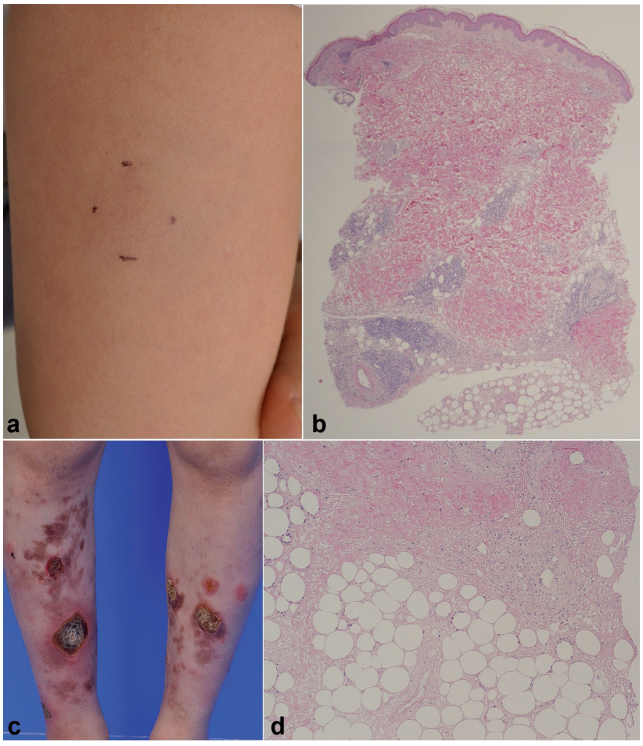

Fig. 1. (a) Subcutaneous nodule on the arm suspicious for erythema nodosum in a Behçet's disease patient. (b) H&E analysis of a biopsy from the patient's arm revealed septal panniculitis with fat necrosis at 40× magnification. (c) Deterioration of skin lesions with ulceration and necrosis over a period of 1 year. (d) Lymphohistiocyte inflammation near vessels of subcutis (H&E 400×).

The patient's BD, however, ran an unusual course with uncontrolled uveitis and cutaneous symptoms despite intense treatment with systemic steroids, colchicine, azathioprine, and mycophenolate mofetil. Within one year, skin lesions deteriorated with ulceration and necrosis (Fig. 1c), but only modest lymphocytic, perivascular inflammation in subcutis was found upon rebiopsy (Fig. 1d). Even high-doses of steroid and infliximab were ineffective in controlling uveitis and eventually, the patient also complained of chronic rhinorrhoea, headache, and facial palsy, which were considered manifestations of BD.

The disease continued to progress rapidly and after one month an atypical ulcer on the hard palate was detected (Fig. 2a). The biopsy specimen revealed focal atypical lymphoid cell infiltration with extensive necrosis in the background (Fig. 2b). Histological examination revealed atypical-looking cells in angio-destructive patterns. Immunohistology analysis revealed cells positive for CD3, CD56, granzyme B. In addition, EBV-encoded RNA (EBER) was also positive. We then undertook a retrospective review of the skin pathology previously diagnosed as erythema nodosum. There were pleomorphic, atypical cells (Fig. 3a) staining positive for CD3, granzyme B, and EBER (Fig. 3b, c). The overall histological findings led to a final diagnosis of ENKL.

Furthermore, positron emission tomography–computed tomography (PET-CT) showed possible involvement of lymphoma in the soft tissue, spleen, liver, retroperitoneal lymph nodes, and nasal cavity. A regimen of ifosfamide, methotrexate, etoposide, and prednisolone (IMEP) plus L-asparaginase was initiated, but shortly after the first cycle, the patient died of septic shock.

DISCUSSION

According to the WHO classification, NK/T-cell lymphoma is classified into extranodal and leukaemia type with further subdivision into nasal, extranasal, and leukaemia type (2). Although the nasal type comprises 75% of ENKL, extranasal involvement of skin, salivary glands, gastrointestinal tract, soft tissues, and kidneys (3).

Diagnosis of NK/T-cell lymphoma is aided by morphological, immunohistochemical, and molecular examination. Histological features include variably sized pleomorphic cells with angiocentric infiltration, mimicking vasculitis and fibrinoid changes caused by cytokines and tumour cell cytotoxic molecules (3). As in our case, the underlying BD led to biased interpretation of the pathological findings. Evolution of skin lesion from an erythematous subcutaneous nodule to an ulcerative lesion was likely due to vessel destruction by tumour cells. A case of ENKL, initially misdiagnosed

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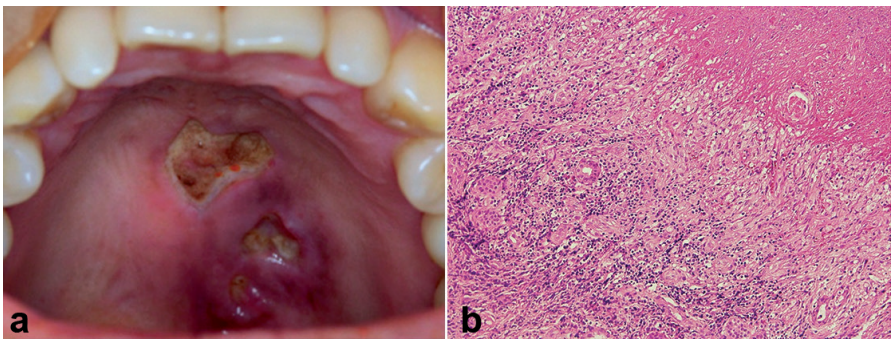

Fig. 2. (a) Atypical ulcer on hard palate. (b) Multiple pleomorphic cells in an environment of extensive necrosis (H&E staining 200×).

as pyoderma gangrenosum (4), and another case of ulcerative skin lesion diagnosed as angiocentric T-cell lymphoma (5), illustrate similar presentation (Fig. 1c, d).

The characteristic ENKL immunophenotype is $CD2^+$, $CD56^+$, surface $CD3^-$, cytoplasmic $CD3\varepsilon^+$, and positive cytotoxic molecule (granzyme B, TIA-1, perforin) (6). CD56 is an NK cell marker; however, absence of CD56 from nasal vestibule does not rule out a possibility of ENKL. Often, extensive nasal area necrosis and inflammation requires pathological confirmation, necessitating re-biopsy. Also, a possibility of ENKL with T-cell lineage cannot be excluded, but examination of betaF1 expression and T-cell receptor gene arrangement studies would be necessary for confirmation (7).

The presence of BD in our patient was clear. Recurrent orogenital ulcers were present one year before the onset of extranasal lymphoma of skin. Furthermore, eye involvement of BD was typical posterior uveitis that was unrelated to ENKL because no ocular or periocular mass, which is a frequent ocular manifestation of ENKL, was found (8). Because the patient never presented with skin pathology compatible with BD, the appropriate final diagnosis would be incomplete type of BD (orogenital ulcer, uveitis) with ENKL initially presenting in the skin.

Until now, approximately 20 published reports have identified an association of BD with lymphoma, but only anecdotal cases of ENKL with BD have been reported (9, 10). It is unknown why malignancy arises in BD patients. A role for the use of immunosuppressive agents during BD treatment has been suggested (9). However, since our patient did not undergo rigorous systemic treatment before the first occurrence of lymphoma, this explanation seems unlikely.

Thus, our case provides an educational example of how manifestations of skin pathology involved in lymphoma could be mistaken as refractory systemic vasculitis in BD. When BD symptoms persist, even with intensive systemic treatment, other diagnoses including malignancy should be investigated in clinical practice.

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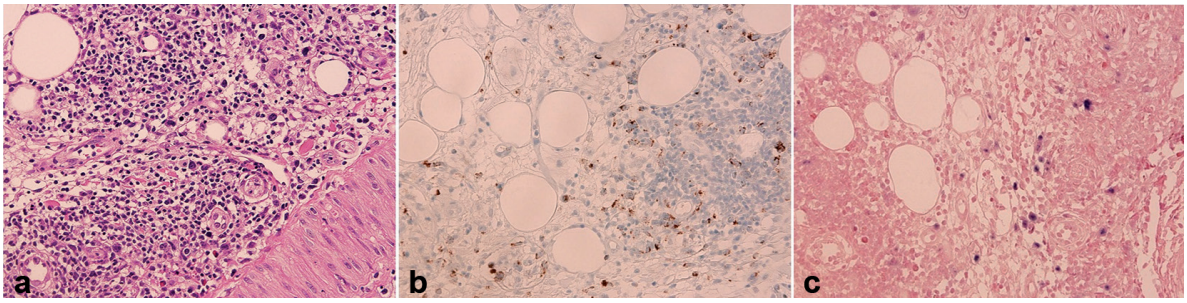

Fig. 3. Retrospective review of skin. (a) Different-sized atypical cells with hyperchromatic, irregular nuclei (H&E staining 400×). (b) Granzyme B staining (200×). (c) Epstein-Barr virus *in situ* hybridization (200×).