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Nasal-type NK/T-cell Lymphoma with Palatal Ulcer as the Earliest Clinical Manifestation: A Case Report with Literature Review

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Abstract Extranodal nasal natural killer (NK)/T-cell lymphoma is a very rare kind of lymphoma, Oral cavity involvement of extranodal natural killer/T-cell lymphoma, nasal type is extremely rare, and its clinicopathologic features are also poorly understood. Recently, we experienced an unusual case of Epstein-Barr virus-associated, extranodal NK/T-cell type with a unhealed palatal ulcer as the earliest clinical feature. It is a challenge for oral medicine specialists to make the early diagnosis for this special type of tumor.

Keywords Epstein-Barr virus · Granzyme B · Immunohistochemistry · NK/T-cell lymphoma · Ulcer

Introduction

Extranodal nasal natural killer (NK)/T-cell lymphoma is a very rare kind of lymphoma characterized by strong association with Epstein-Barr virus infection, with very aggressive clinical behavior and poor prognosis. Natural killer (NK)/T-cell lymphoma, nasal type, is a distinct subtype of non-Hodgkin's lymphoma, which is very rare in North America and Europe but rather common in Asia and South America [1]. Clinically, it frequently occurs in middle-aged men, and usually presents as a localized disease involving the head and neck [2]. The diagnosis of it mainly relies on the histopathology and immunohistochemical examination. The typical immunophenotype of neoplastic natural killer cells in this entity is as follows: CD2+, CD56+, surface CD3-, cytoplasmic CD3epsilon+, and cytotoxic granule-associated protein positive. Nasal-type NK/T-cell lymphoma is the commonest type of CD56+ lymphoma occurring outside the nasal or nasopharyngeal region. It is morphologically and immunohistochemially identical to nasal NK/T-cell lymphoma.

Oral cavity involvement of extranodal natural killer/T-cell lymphoma, nasal type is extremely rare, and its clinicopathologic features are also poorly understood. It is a challenge for oral medicine specialists to make the early diagnosis for this special type of tumor. To the best of our knowledge, until now none of typical cases that primarily occurred on oral mucosa without any nasal symptom or other signs has been reported. Recently, we experienced an unusual case of Epstein-Barr virus-associated, extranodal NK/T-cell type with a unhealed palatal ulcer as the earliest clinical feature. The immunohistochemistry demonstrated a characteristic phenotype expressing CD3epsilon, CD56, granzyme B, and KI67(+, 80–90%). However, the tumor cells are negative for CD20. In this case, we describe the clinical presentation and discuss the diagnostic work-up of this rare entity to highlight the importance of immunophenotypic profiling for making an early and actual diagnosis.

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More importantly, we emphasize the primary role of the oral medicine specialists and dentists in the diagnosis process and the possible necessity of referral to an otolaryngologist to prevent misdiagnosis.

Case Report

A 63-year-old previously healthy chinese woman presented to the West China Hospital of Stomatology, with serious palatal ulceration by an area of 4*5 cm for about a month (Fig. 1). The mucosa of the hard palate necrotized partly and the large ulceration formed. However, no bony destruction or perforation were observed through systemic examination. Hematoxylin and Eosin Staining had revealed prominent ulceration and necrosis in a local hospital. After the regular topical and general anti-inflammation treatment, the palatal ulcer did not show any sign of healing. The patient's situation continued to worsen, even gradually presented with intermittent haematemesis after that. She had developed spike fevers and fatigue for three weeks before admission, accompanied by occurance of intermittent haematemesis for five times. The total volume of blood loss was about 400 ml. Extensive investigations on the fever and haematemesis, including evaluations for chest CT scan, gastroscope, abdominal ultrasound, as well as blood cultures, were all negative except for the chronic superficial gastritis. The complete blood count showed asphaerinia (HGB: 92 g/L, RBC: 3.27*1012/L, HCT: 0.28 L /L), leukopenia (WBC: 1.59×10 9 /L), and thrombocytopenia (PLT: 56×10 9 /L). Serum alanine aminotransferase was 99 IU/L, aspartate aminotransferase 218 IU/L, lactate dehydrogenase 573 IU/L, and hydroxybutyric acid dehydrogenase 480 IU/L.

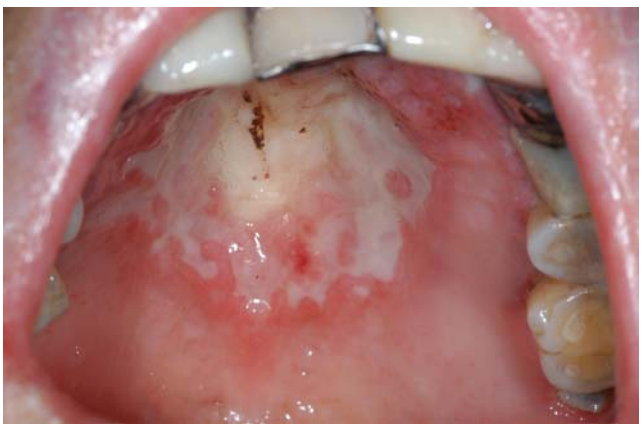


Fig. 1 Serious palatal ulceration and necrosis with an area of 4*5 cm. The mucosa of the hard palate necrotized partly and the large ulceration formed. However, no bony destruction or perforation observed through systemic examination. ('published with the patient's consent')

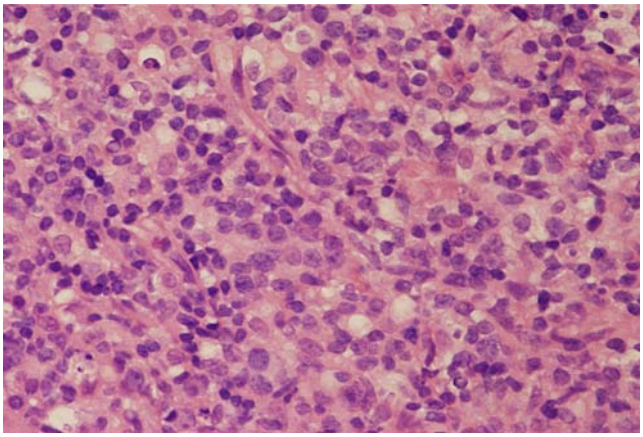


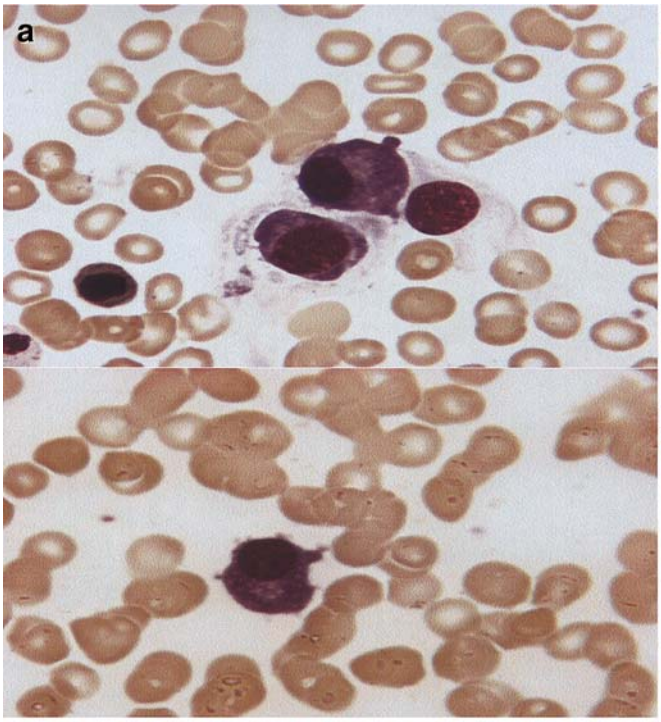
Fig. 2 Sections of the biopsy specimen obtained from the oral palatal ulceration **a** Haematoxylin and eosin staining revealed a diffuse infiltration of large and medium-sized lymphoma cells with irregular nuclear contours. The chromatin is fairly dense. (×200)

Haematoxylin and eosin staining of the second palatal biopsy made in our hospital revealed a diffuse infiltrate of large and medium-sized lymphoma cells with inconspicuous nucleoli, and moderately abundant clear cytoplasm. A few small, normal-appearing lymphocytes, plasma cells, and eosinophils were also noted. (Fig. 2).

Immunohistochemical staining of bone marrow showed a normocellular marrow with trilineage hematopoiesis. Meanwhile, the bone marrow aspirate revealed no typical changes among granulocyte series with only relative abundant pale cytoplasm in erythrocytes (Fig. 3a).

Nasal cavity/nasopharynx also did not present typical clinical features and symptoms in the absence of lymphadenopathy according to the patient's chief complaint. However, the hibateral nasal cavity was lined with crust after a complete endoscopic examination of the nasal cavity. No necrotic or malodorous debris was observed. After we got a negative result of lymphoma from a bone marrow biopsy, extensive diagnostic work-ups were carried out. A corona-CT of the nasal part revealed a soft tissue mass in the walls of maxillary sinus, ethmoid sinus, frontal sinus, and right sphenoid sinus. Finally the nasal malignant lymphomas or nasal type NK/T-cell lymphoma presented in the palatal mucosa was suspected.

Fig. 3 **a** The bone marrow aspirate revealed relatively abundant pale cytoplasm in erythrocytes. Level of BM granulocyte are not low, but easy to see plasma cell **b** The nuclear staining pattern of Ki-67 expression was evaluated and the quantified Ki-67 expression (the percentage of Ki-67-positive cells to tumor cells) was 80%–90%. (original magnification: ×200) **c** Immunohistochemical staining using an anti-CD3εantibody identified intracytoplasmic reactivity in neoplastic cells. (×100) **d** Immunohistochemical stain for CD56. Note diffuse membranous positivity for CD56. (×100) **e** Immunohistochemical staining revealed being positive for granzyme B. (×200) **f** *In situ* hybridization with a specific RNA probe demonstrated strong EBER-1 expression in neoplastic cells. (×100)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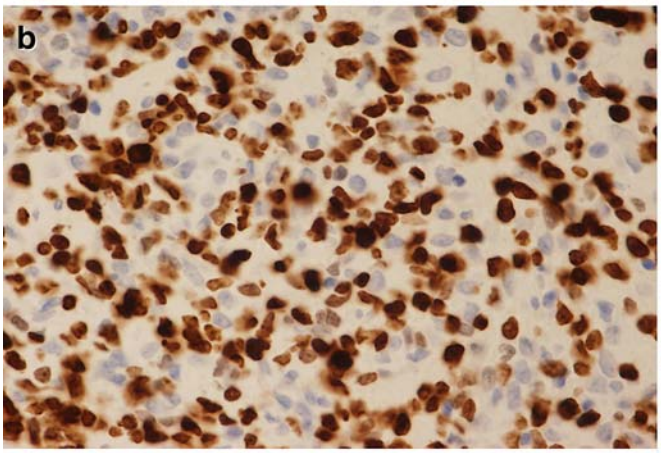
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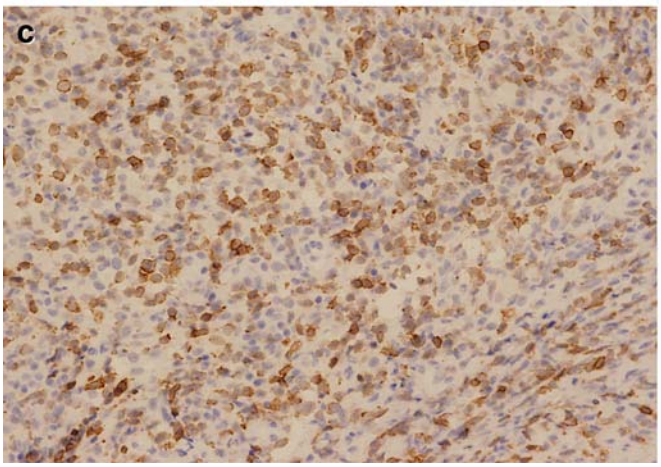
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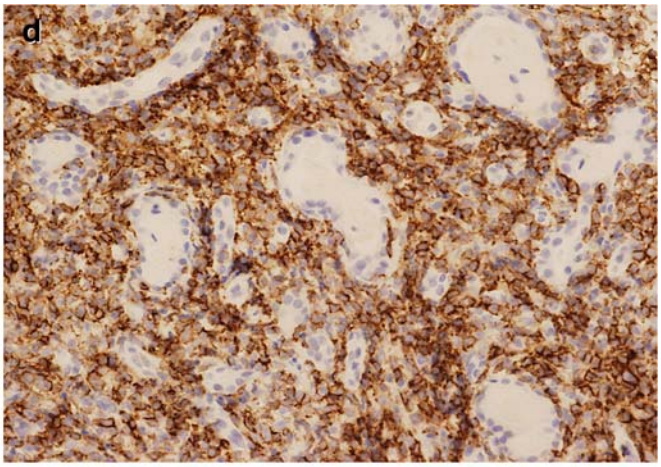
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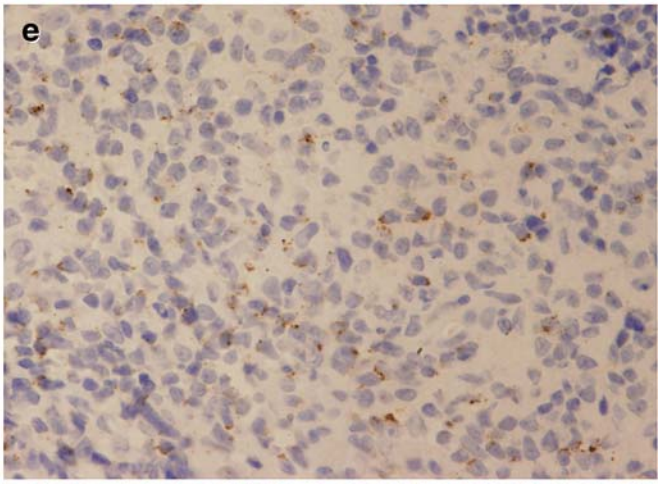
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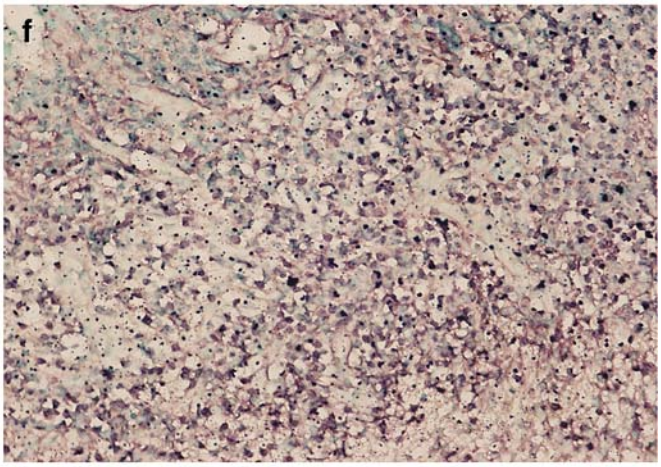
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Immunohistochemical studies were performed on paraffin sections of both right nasal vestibule and the top palate necrosis tissue. Both of the sections of the biopsy specimen showed the same results. The cell proliferation marker, Ki67, was positive in virtually every cell (80–90%) (Fig. 3b). The cells showed strong cytoplasmic staining with poly-CD3[epsilon] (Fig. 3c), cytoplasmic and membranous staining with CD56 (Fig. 3d), as well as being positive for granzyme B (Fig. 3e), but negative for CD20. We also performed *in situ* hybridization using an EBV-encoded small nuclear RNA (EBER)-1 probe. EBER-ISH was strongly expressed by the tumour cells (Fig. 3f). From these results, the patient was finally diagnosed as nasal-type extranodal NK/T-cell lymphoma (invasive, WHO).

Discussion

In the recent World Health Organization (WHO) classification of hematopoietic and lymphoid neoplasms, two major neoplasms deriving from mature NK/T cells are recognized: the nasal/nasal-type T/NK-cell lymphoma and the aggressive NK cell leukemia/lymphoma [3]. Nasal NK/T-cell lymphomas are more common in Asia and South America than in Europe or North America. These tumors often present intranasally, and have been reported to spread to multiple extranodal sites including the gastrointestinal tract, lung, skin [4–6], even involving in the spine [7]. Progression of the disease may also lead to septal perforation and result in destruction of the hard palate, and the prognosis of these lymphomas is usually poor.

Generally, NK/T-cell lymphomas originated at other sites but nasal cavity/nasopharynx do not present with the relatively specific signs and symptoms associated with disease progression. So there are possibilities for misdiagnosis or delayed diagnosis in such cases. Sometimes, it is also difficult to make histological diagnosis precisely, because tumors imbedded in large necrotic areas and neoplastic infiltration may be admixed with small lymphocytes, plasma cells, eosinophils, and histiocytes, and thus the entity could be misdiagnosed as chronic inflammation. In the present case, according to relatively nonspecific signs, symptoms, and the HE staining of the first palatal biopsy in another hospital, the patient was diagnosed as serious oral ulcer by oral maxillofacial surgeon and pathologist in that hospital. After regular topical and general anti-inflammation treatment, the palatal ulcer did not show any sign of healing. The patient's situation continued to worsen, even presented gradually with intermittent haematemesis after that. Extensive diagnostic work-ups were carried out, including gastroscope, abdominal ultrasound, bone marrow aspirate, as well as blood cultures. The patient was finally diagnosed as nasal-type extranodal NK/T-cell lymphoma according to a corona-CT of the nasal part and immunohistochemical studies. One point of interest in our case report is that the primary unhealed necrosis ulcer occurred in the oral cavity albeit without any nasal symptom or other signs. In addition, the patient in our case reported here was a healthy and immunocompetent woman when the palatal ulcer appeared initially. However, in previously reported cases, NK-like T-cell lymphomas have typically been described in the setting of immunosuppression and organ transplantation [8]. That is the other characteristic of our case distinguished from cases reported previously.

To avoid a delayed diagnosis, the oral medicine specialists should be careful when evaluating a patient with serious palatal ulcer. Examining the nasal cavity or even repeated biopsy are both necessary. Otherwise, an endoscopic examination is essential for detecting any mucosal or structural abnormality of the nasal cavity with no typical clinical symptoms, but with the formation of refractory palatal ulceration. Meanwhile, the primary role of the otolaryngologist in the management of patients with sinonasal malignancy is to make an early diagnosis.

Immunohistochemical and molecular genetic early diagnosis is of crucial prognostic relevance. The NK-cell phenotype of the neoplasm is highlighted by the expression of the NK cell marker CD56 [9], with absence of surface CD3. In addition, the cells express cytoplasmic CD3epsilon+, characteristically expressed by NK cells and some cytotoxic T cells. There is a great deal of overlap between markers of NK-cell differentiation and those for CD8+ T-cell differentiation (cytotoxic T-cells), including being positive for granzyme B, which is consistent with our report. Otherwise, previous reports have shown that the bone marrow involvement based on morphologic examination is rare.

Ki-67 is a nuclear antigen expressed by dividing cells. Thus, the percentage of Ki-67-positive cells reflects the proportion of actively proliferating tumor cells. A recent study in peripheral T-cell lymphoma showed a positive correlation with poor prognosis [10]. It was also reported by Kim S. J. et al. [11]. that High Ki-67 was associated with a worse overall survival (OS; P=0.021) and disease-free survival (DFS; P=0.044). In multivariate analysis, Ki-67 expression and primary site of involvement were found to be an independent prognostic factor for OS and DFS in patients with extranodal NK/T-cell lymphoma (P<0.05).

EBV has been associated with a variety of lymphoproliferative disorders including B-cell, T-cell neoplasms, Hodgkin lymphoma, and NK-cell lymphomas [12]. More than 80% of B-cell lymphomas and 30% of T-cell and NK/T-cell lymphomas are EBV positive in Japan [13]. As seen in this patient, the case reported herein was positive for

EBER transcript in almost all tumor cells. In addition, EBV-associated latent membrane protein was also positive, indicating that EBV may play a role in the pathogenesis of the disease.

In summary, we report a most unusual aggressive patient with NK/T-cell lymphomas that primary occurred in oral mucosa. This case highlights the need for a better understanding of the molecular biology technique. And the role of our oral medicine specialists of referral to an otolaryngologist to prevent misdiagnosis should also be noted.

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