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CASE REPORT

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Early diagnosis of extranodal NK/T lymphoma presenting with oral ulcer and lip swelling by metagenomics next-generation sequencing: a case report

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Abstract

Background Extranodal natural killer/T-cell lymphoma, is a rare, aggressive lymphoma strongly associated with Epstein-Barr virus infection. Its clinical manifestations are often non-specific, and atypical presentations outside the nasal cavity, such as lip swelling or oral ulcers, can mimic benign oral conditions, leading to delayed diagnosis. Histological variability and tissue necrosis further hinder early diagnosis. Metagenomic next-generation sequencing (mNGS) has emerged as a useful adjunct for detecting pathogen-specific nucleic acids when conventional pathology is inconclusive.

Case presentation A 39-year-old man presented with a one-month history of recurrent upper lip swelling and a persistent labial and hard palate ulcer. Examination revealed firm swelling of the upper lip, a U-shaped ulcer on the upper labial mucosa, and an ulcer on the right hard palate. Laboratory tests were normal. Considering the patient's recollection of a prior fish bone injury to the oral mucosa, we performed mNGS on biopsy tissue in addition to routine histopathology. mNGS revealed a high load of Epstein-Barr virus DNA, prompting targeted immunohistochemistry and in situ hybridization, which confirmed the presence of Epstein-Barr virus-encoded RNA in atypical lymphocytes, establishing the diagnosis of extranodal NK/T-cell lymphoma. PET/CT showed a hypermetabolic upper-lip mass without systemic spread. The patient was classified as Ann Arbor stage IE, group A. Treatment with two cycles of pegaspargase, gemcitabine, and oxaliplatin resulted in complete healing of oral lesions, followed by localized radiotherapy. No recurrence was observed at the eight-month follow-up.

Conclusions This case illustrates that extranodal NK/T-cell lymphoma can present with isolated oral lesions, posing significant diagnostic challenges. Incorporating mNGS into the evaluation of suspicious or infection-like oral lesions

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expedite Epstein-Barr virus detection, guide targeted pathological workup, and reduce diagnostic delays, ultimately improving patient outcomes.

Keywords Extranodal NK/T-cell lymphoma, Epstein-Barr virus, Lip swelling, Oral ulcer, Metagenomic next-generation sequencing, Early diagnosis, Immunohistochemistry

Background

Extranodal NK/T-cell lymphoma (ENKTL) is a highly aggressive subtype of non-Hodgkin lymphoma, accounting for approximately 2–10% of cases worldwide, with higher prevalence in Asian and Latin American populations [1]. The neoplasm originates primarily from natural killer cells and is nearly always associated with Epstein-Barr virus (EBV) infection [2]. The disease is characterized by its predominant extranodal presentation, with a striking predilection for the nasal cavity and other sites of the upper aerodigestive tract [3, 4]. The common sites of ENKTL are the nasal cavity and paranasal sinuses, accounting for 60% to 80%, followed by the pharynx, larynx and cervical lymph nodes [2]. Through the expression of viral oncoproteins such as LMP1 during latent infection, EBV activates proliferative and anti-apoptotic signaling pathways, thereby driving tumorigenesis [2, 5]. In a cohort of 107 patients with ENKTL who completed the treatment protocol, 48 patients (44.9%) achieved a complete remission. During follow-up, 60 patients (56.1%) succumbed to the disease due to local recurrence, distant relapse, or disease progression. The mean overall survival was 70.0 months, with a 5-year survival rate of 39.4% [6]. ENKTL exhibits aggressive behavior and rapid progression. The prognosis for patients with advanced-stage disease remains poor, accompanied by high mortality rates, The 5-year mortality rate in the advanced stage (III-IV) is approximately 40% to 60%. The mortality rate is even higher for patients who have not received standardized treatment, with a 1-year mortality rate of over 70% [7]. Underscoring the critical importance of early diagnosis and intervention to improve clinical outcomes [8].

However, the early diagnosis of ENKTL is associated with numerous challenges. ENKTL accounts for 0.2% of all non-Hodgkin lymphomas and 1–2% of all NKTLs [9]. Clinically, its manifestations are highly non-specific; common symptoms such as nasal obstruction and epistaxis are frequently misattributed to chronic sinusitis [10, 11]. Atypical presentations, including lip swelling or oral ulcers, are prone to misdiagnosis as granulomatous cheilitis or other oral mucosal disorders. Histopathologically, ENKTL often demonstrates angiocentric infiltration and a destructive growth pattern. Obtaining diagnostic biopsies can be challenging due to paucicellular tumor infiltration, architectural distortion, or extensive necrosis [12, 13]. Accurate diagnosis of ENKTL is critical for guiding clinical management and currently depends primarily on tissue biopsy. However, histological interpretation is often challenging due to the frequent presence of heterogeneous features and morphological overlap with both benign lymphoid proliferations and other lymphoma subtypes, particularly B-cell lymphomas [14]. The confluence of these factors frequently contributes to diagnostic delays, thereby compromising optimal treatment timing.

Given the limitations of conventional histopathology in such settings, molecular diagnostic techniques have been increasingly explored. In recent years, metagenomic next-generation sequencing (mNGS) has emerged as a valuable tool in the diagnosis of infectious diseases [15, 16]. Similarly, the quantification of circulating cell-free Epstein-Barr virus (EBV) DNA in plasma has provided an objective measure for early detection of lymphoma [17]. Here, we report a rare case of ENKTL initially presenting with lip swelling and oral ulcers, in which mNGS analysis of biopsy tissue revealed high EBV DNA levels, directing targeted pathological work-up and enabling timely diagnosis.

Case presentation

A 39-year-old man presented to the oral medicine department reporting a one-month history of upper lip swelling and a concomitant ulceration of the labial mucosa and hard palate. The symptoms began insidiously without an obvious trigger, and he recalled a history of a fish bone injury to the mouth, although its relevance to the current condition was uncertain. In the preceding month, the upper lip had repeatedly become swollen and erythematous, with fluctuations in severity. He was treated at a local facility with a 7-day course of intravenous levofloxacin and acyclovir, but his symptoms showed no improvement. Examination revealed firm swelling of the upper lip (Fig. 1a), a 30 mm×5 mm U-shaped ulcer on the upper labial mucosa (Fig. 1b) and a 5 mm × 5 mm ulcer with a yellow pseudomembrane on the right hard palate (Fig. 1c). An ulcer was noted at the left maxillary buccogingival sulcus (Fig. 1d). Laboratory tests, including blood routine examination, T-SPOT (tuberculosis infection T-cell test), immunoglobulin levels, complement levels and autoantibody screening, were all within normal range. Given the patient's recollection of a prior local injury from a fish bone, we also subjected the biopsy tissue to metagenomic next-generation sequencing (mNGS) to rule out infectious disease. mNGS analysis of the oral tissue samples using the IDseq™ Ultra platform revealed the presence of EBV DNA with a high

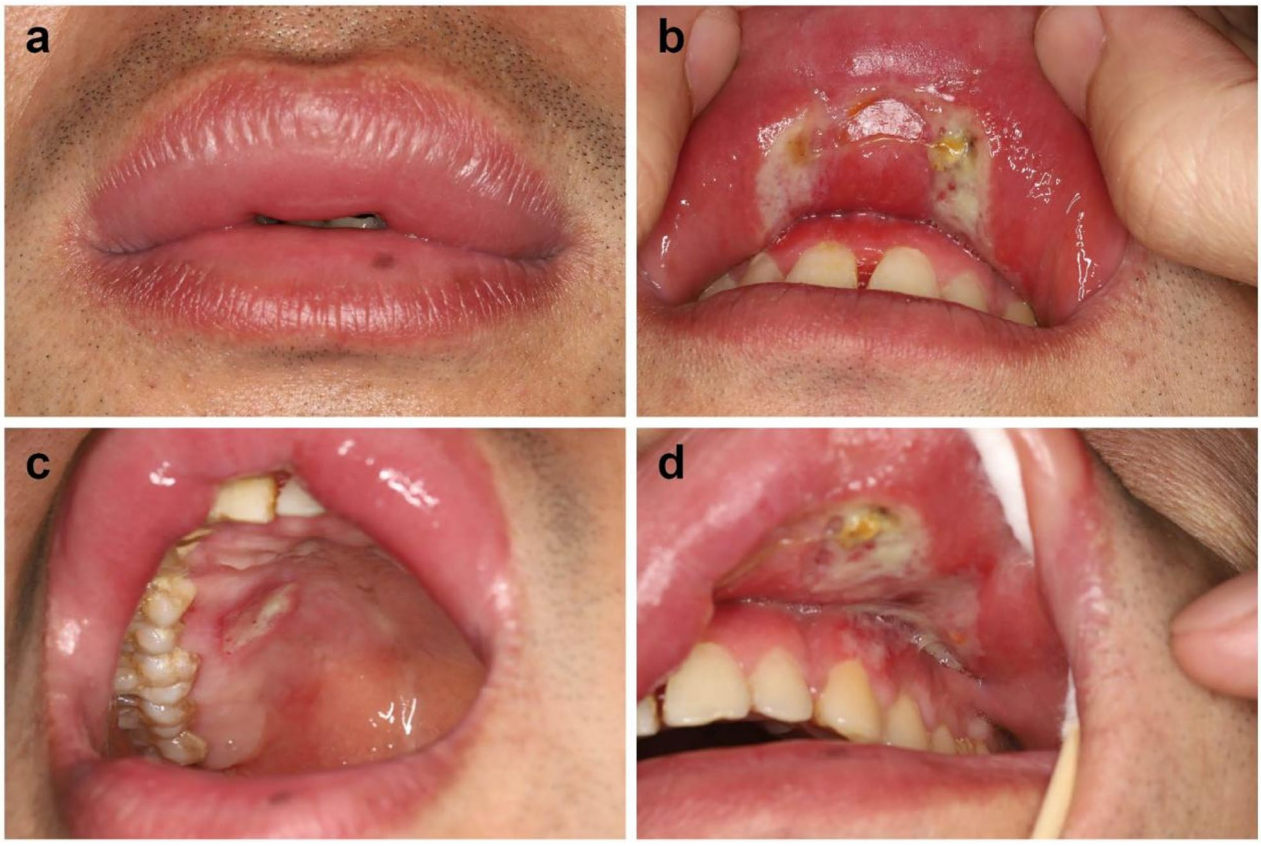

Fig. 1 Clinical photographs at initial presentation. **a** Swelling of the upper lip. **b** A U-shaped ulcer on the inner aspect of the upper labial mucosa. **c** Mucosal ulcer on the right hard palate. **d** Ulceration at the left maxillary buccogingival sulcus

confidence score of 99%, represented by 7,221 specific sequence reads (Fig. 2). Several oral commensal bacterial species were also detected, but no fungal, parasitic, or other pathogenic DNA was identified. Meanwhile, histopathological examination of the biopsy specimens showed parakeratotic hyperkeratosis of the mucosal epithelium with an underlying mixed infiltrate of acute and chronic inflammatory cells in the lamina propria in both the palatal and upper labial mucosa. The palate specimen exhibited areas of epithelial loss with ulcer formation, accompanied by perivascular lymphocytic infiltrates (Fig. 3a-b). In the labial mucosa specimen, some of the infiltrating cells displayed atypical cytologic features, raising concern for possible malignancy (Fig. 3c-d). Considering the high EBV viral load within the lesion, the presence of atypical cytologic features in the upper labial biopsy, and the absence of any history of immunosuppression, extranodal NK/T-cell lymphoma was our leading diagnostic consideration.

To confirm the diagnosis, immunohistochemical staining was performed on the labial biopsy tissue. The lymphocytes were positive for LCA (leukocyte common antigen), CD3, and CD56, with the proliferation index (Ki-67) was approximately 70%, indicating a high proliferative activity. The tumor cells were negative for CK (cytokeratin, AE1/AE3), CD20, S100 and HMB-45. Epstein–Barr virus–encoded RNA (EBER) in-situ hybridization showed scattered positivity in the neoplastic cells (Fig. 4), confirming EBV infection within the neoplastic cells. These findings were diagnostic of ENKTL. For disease staging, whole-body ^{18}F-FDG PET/CT scan was performed. A soft-tissue mass measuring approximately 2.7 cm × 1.5 cm was seen in the upper lip (SUVmax = 19.8) without systemic involvement (Fig. 5). A plasma EBV-DNA quantitative PCR indicated EBV replication in PBMC (860 copies/mL, normal range < 500 copies/mL). The patient also denied any B symptoms (fevers, night sweats, or weight loss). Thus, the lymphoma was staged as Ann Arbor stage IE (localized extranodal disease) and group A (no B symptoms). After two cycles of combination chemotherapy with pegaspargase, gemcitabine, and oxaliplatin (P-GEMOX), the patient's condition improved significantly, with complete healing of the labial and palatal mucosal lesions achieved within two months. ^{18}F-FDG PET/CT scan revealed no elevated glucose uptake in original lesion area. Patient was subsequently transferred to department of radiation oncology and received radiotherapy. CTV_tb was delineated

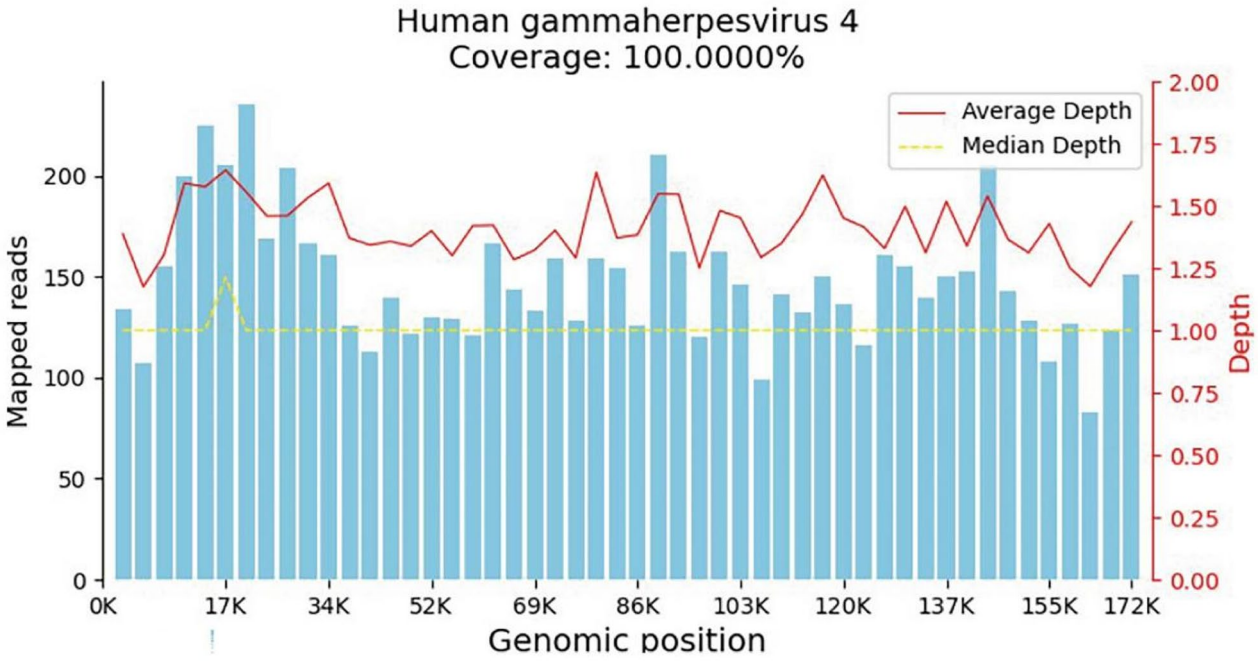

Fig. 2 mNGS analysis of EBV sequences from oral lesion tissue. The X-axis represents the full genome length of Epstein-Barr virus (Human gamma herpesvirus 4). The left Y-axis indicates the number of sequencing reads aligned to the EBV genome, and the right Y-axis shows the average sequencing depth

according to pretreatment PET/CT images, including upper labial mucosa and right hard palate ulceration area. CTV was expanded from CTV_tb with 10 mm margin to include upper lip, gingival mucosa and whole hard palate mucosa. PTV was formed with 3 mm expansion from CTV. Conventional fractionation (2 Gy) of 50 Gy in 25 fractions over 5 weeks was delivered, with concurrent use of low-energy laser therapy to prevent radiation-induced oral mucositis. Two weeks after completion of radiotherapy, patient continued to receive four cycles of P-GEMOX chemotherapy. All treatment completed in November 2025. At the four-month follow-up after diagnosis, there was no local recurrence nor distant metastasis (Fig. 6). At the 8-month follow-up, clinical examination showed complete and sustained healing of both the upper labial mucosal ulcer and the hard-palate ulcer, with no visible signs of local recurrence (Fig. 7). Consistently, the PET/CT scan demonstrated no residual soft-tissue mass or abnormal FDG uptake in the upper lip region and no evidence of distant metabolic lesions (Fig. 8).

Discussion

This case report describes a rare case of extranodal natural killer/T-cell lymphoma (ENKTL) presenting initially with lip swelling and oral ulcers. Given the patient's medical history and symptoms, infectious etiologies were of significant concern. Therefore, in addition to traditional histopathological examination, metagenomic next-generation sequencing (mNGS) was performed. The mNGS results showed a high EBV DNA load with a confidence score of 99%, which greatly assisted in directing subsequent pathological diagnosis toward ENKTL [17]. It is important to clarify that histopathology, immunohistochemistry, and EBER in situ hybridization are the gold standards for confirming ENKTL-NT diagnosis. These techniques are simple to perform, cost-effective, and more accessible in primary care institutions. In contrast, mNGS serves as a crucial auxiliary tool rather than a core diagnostic technique, with its primary value lying in rapidly distinguishing infectious from tumor-related etiologies and shortening the diagnostic cycle—especially in complex cases where clinical manifestations are inconsistent with initial pathological findings.

ENKTL is an aggressive lymphoma closely associated with EBV infection, in which EBV plays a central driving role in pathogenesis: EBV primarily persists in a latent infection state, and its encoded proteins such as LMP1 and EBNA1 can activate the NF-κB pathway, promoting tumor cell proliferation, inhibiting apoptosis, and inducing immune tolerance to create favorable conditions for tumor development [18]. However, EBV-negative cases of ENKTL-NT have been reported. For example, a previously documented EBV-negative ENKTL-NT case was diagnosed through typical histopathological features of angiocentric infiltration, $CD3^{+}CD56^{+}$ IHC phenotype, and exclusion of diffuse large B-cell lymphoma, peripheral T-cell lymphoma, and other mimickers. Its diagnosis relied on comprehensive assessment of pathological morphology and immunophenotype, requiring a more

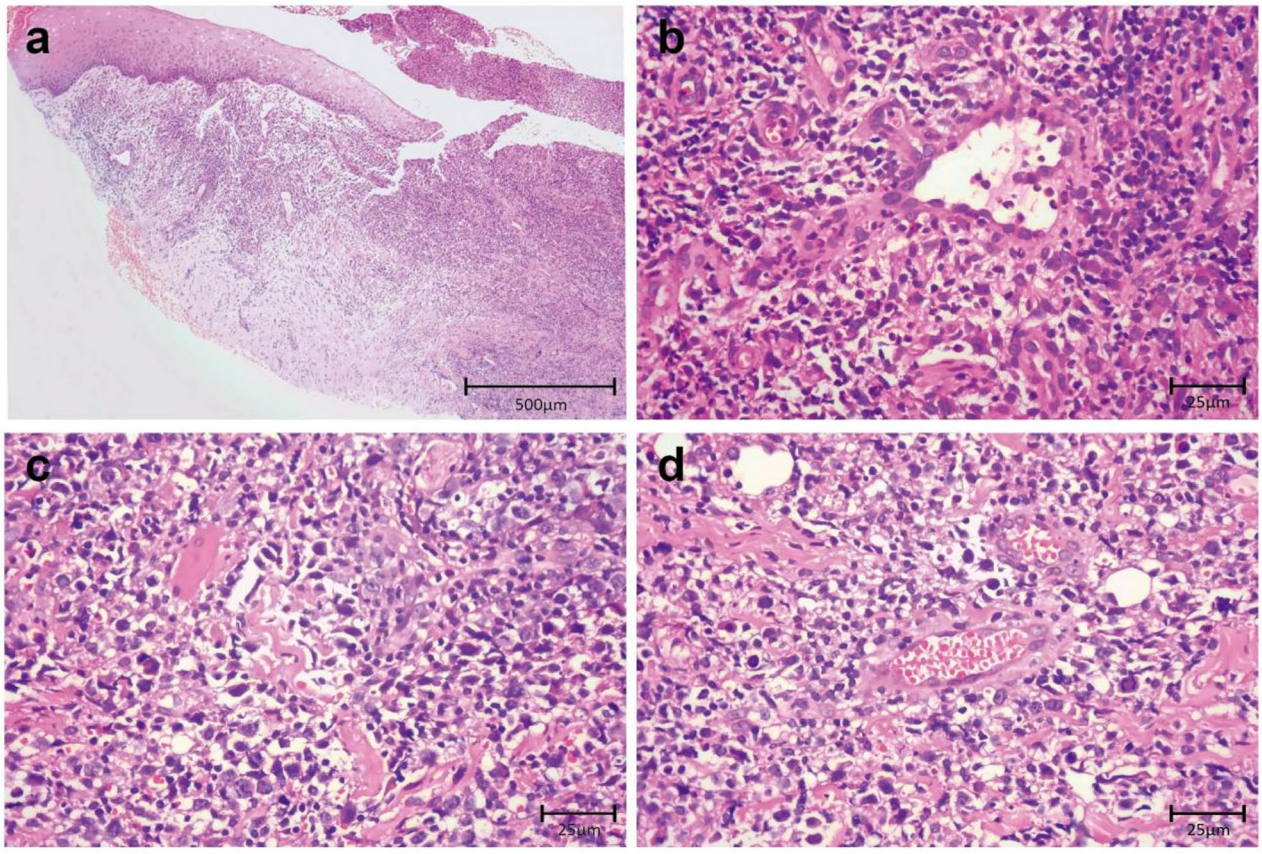

Fig. 3 Representative histopathological images of the patient's lesions. **a** Low-power view of the hard palate lesion showing partial epithelial ulceration with dense inflammatory cell infiltration in the lamina propria (original magnification 40×, scale bar = 500 μm). **b** High-power view of the hard palate lesion demonstrating perivascular dense inflammatory infiltrates without obvious cytological atypia (original magnification 200×, scale bar = 25 μm). **c**-**d** High-power views of the labial lesion showing perivascular dense lymphocytic infiltration with occasional cells displaying cytological atypia (original magnification 200×, scale bar = 25 μm)

rigorous differential diagnostic process in the absence of EBV infection evidence.

Atypical symptoms such as isolated lip swelling and mucosal ulcers may mimic benign conditions including infections, allergies, or granulomatous cheilitis [15]. This similarity often leads to misdiagnosis, delaying treatment and affecting patient prognosis [19]. Although lip swelling as the initial presentation of ENKTL is rare, several case reports have been published [20, 21]. These cases share similarities with the present report, all presenting with atypical oral or facial symptoms. However, most cited case reports focus primarily on symptom description with limited relevance.

In this case, there was a discrepancy in atypia between hard palate and lip biopsy specimens: the hard palate sample showed no significant atypia, while the lip sample contained atypical lymphocytes. The core reasons are uneven distribution of necrosis and tumor cell heterogeneity in ENKTL. The hard palate sample was obtained from the central necrotic area of the lesion, where tumor cells were obscured by necrotic tissue and inflammatory cells; the lip sample was taken from the lesion margin with milder necrosis and highly proliferative tumor cells (Ki-67 70%), making atypia more readily identifiable [22]. Although the dual-site biopsy sampling strategy successfully captured the positive sample, there is room for optimization: prioritizing deep tissue sampling from more swollen areas while avoiding superficial necrotic layers of ulcers could further improve tumor cell detection rates. Necrosis is a major interfering factor in the pathological diagnosis of ENKTL, as illustrated by the initial potential misdiagnosis of the hard palate sample as an infectious ulcer in this case [23].

It is important to reflect that evidence regarding genetic variations in ENKTL-NT remains limited and inconsistent. In single-case reports, mNGS is unlikely to provide clear diagnostic or therapeutic guidance through genetic testing, and its core value remains focused on microbial-based differential diagnosis rather than genetic analysis [24]. In clinical practice, primary institutions can complete diagnosis using pathology, IHC and EBER-ISH, while mNGS is recommended for differential triage of

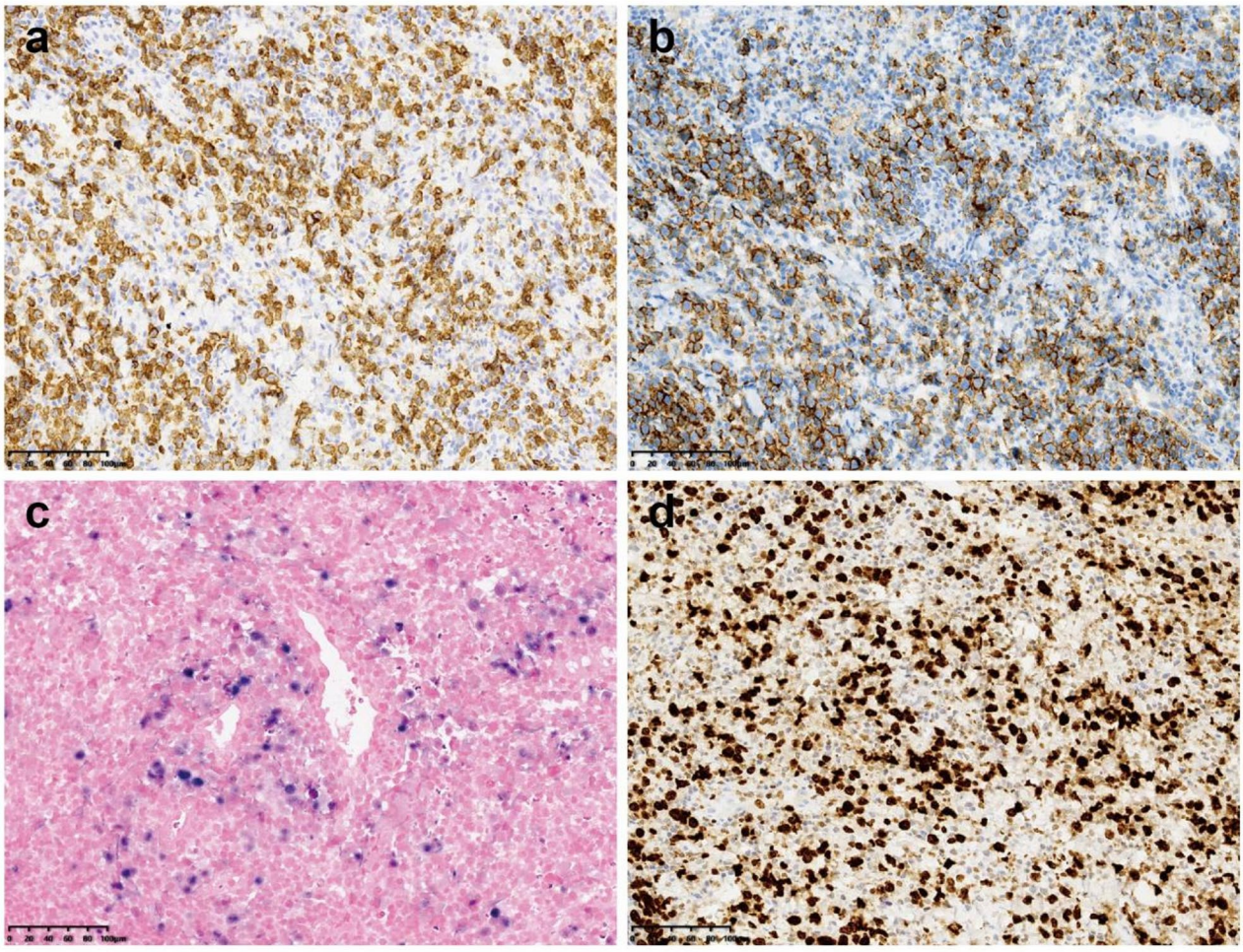

Fig. 4 Immunohistochemical and in situ hybridization findings in the labial lesion. **a** CD3 immunohistochemistry (original magnification 200×, scale bar = 100 μm). **b** CD56 immunohistochemistry (original magnification 200×, scale bar = 100 μm). **c** Scattered Epstein–Barr virus–encoded RNA (EBER) positivity detected by in situ hybridization (original magnification 200×, scale bar = 100 μm). **d** Ki-67 immunohistochemistry showing a high proliferation index (original magnification 200×, scale bar = 100 μm)

complex cases to guide downstream immunophenotypic analysis and genetic research.

When ENKTL presents as an oral lesion, it requires accurate differentiation from EBV-associated mucosal ulcers, granulomatous cheilitis, and other lymphomas, primarily relying on pathological morphology and EBV detection. EBV-associated mucosal ulcers lack angiocentric infiltration and have a favorable prognosis; granulomatous cheilitis has no evidence of EBV infection and responds well to steroid therapy [25, 26].

Furthermore, multidisciplinary team collaboration remains crucial for diagnosis and treatment: stomatologists are responsible for precise sampling, pathologists confirm diagnosis using gold standard techniques, hematologists develop chemotherapy regimens, and radiation oncologists optimize dosages. Especially in resource-limited regions, multidisciplinary team collaboration can maximize the use of existing technologies to improve diagnostic accuracy and treatment outcomes [27]. Early diagnosis (Ann Arbor stage IE) is key to improving prognosis—patients with early diagnosis have significantly higher 5-year survival rates compared to those with late diagnosis [28, 29], and diagnostic delays adversely affect survival outcomes [30, 31]. The combination of the universality of gold standard techniques and the auxiliary role of mNGS represents the optimal approach to balancing diagnostic accuracy and accessibility [21, 32].

Beyond assisting in the diagnosis of malignancies such as ENKTL, mNGS also demonstrates utility in the early diagnosis of infectious diseases [33, 34], particularly when conventional methods fail [35, 36]. This capability is especially valuable in distinguishing infectious from non-infectious etiologies in complex clinical presentations. Diagnostic delays adversely affect survival outcomes [37, 38], and the combination of the universality of gold standard techniques and the auxiliary role of mNGS represents the optimal approach to balancing diagnostic accuracy and accessibility [39].

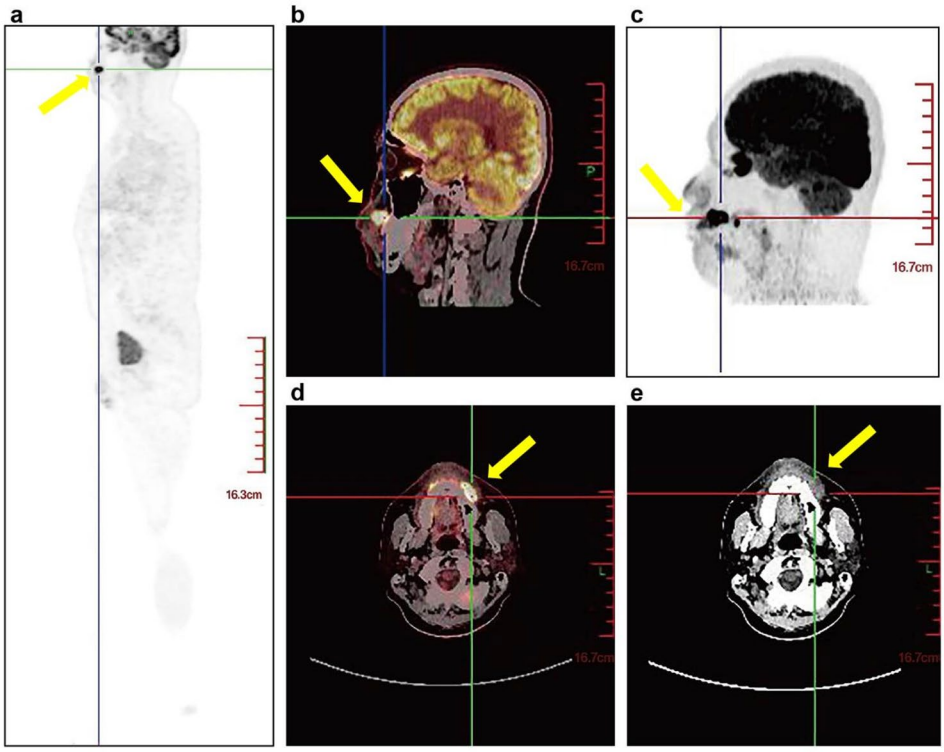

Fig. 5 PET/CT of the hypermetabolic soft tissue lesion in the left upper lip. **a** Whole-body sagittal PET image showing a focal area of increased FDG uptake in the left upper lip (yellow arrow). **b** Sagittal PET/CT fusion image demonstrating the hypermetabolic soft-tissue mass in the left upper lip, measuring approximately 2.7 cm ×1.5 cm (SUVmax = 19.8). **c** Sagittal PET image of the head and face showing localized abnormal glucose metabolism in the left upper lip region. **d** Axial PET/CT fusion image showing the left upper lip lesion with markedly increased FDG uptake. **e** Corresponding axial CT image of panel (**d**), revealing a soft-tissue mass with heterogeneous density (yellow arrow)

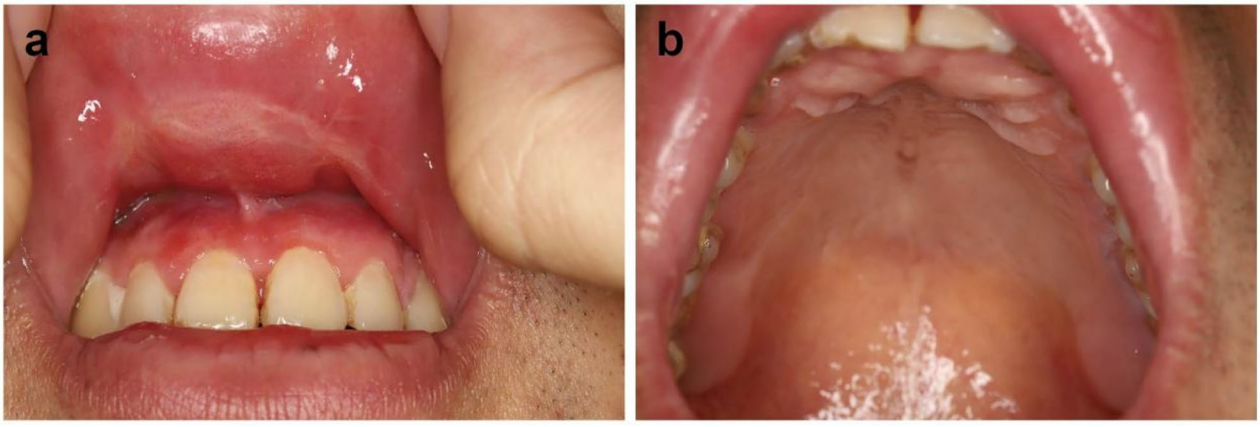

Fig. 6 Follow-up clinical photographs taken four months after diagnosis. **a** Complete healing of the mucosal ulcer on the upper labial mucosa. **b** Complete healing of the ulcer on the right hard palate

Consistency Analysis of Diagnostic Methods in Other Reports. Numerous other clinical reports on ENKTL have adopted the same core diagnostic system as this study, namely pathological biopsy combined with immunohistochemistry and EBER in situ hybridization as the gold standard for confirmation, supplemented by imaging examinations (^{18}F-FDG PET/CT) for staging assessment [40]. Clinical practice guidelines further confirm that pathological biopsy, IHC (targeting markers such as CD3 and CD56) and EBER detection is the universal standard for ENKTL diagnosis, applicable to cases involving different sites including the nasal cavity, oral cavity, and orbit [31]. In contrast, mNGS has only been used in this study and a few complex case reports to rule out infectious etiologies and shorten the differential diagnosis cycle, and has not become a core diagnostic technology in other

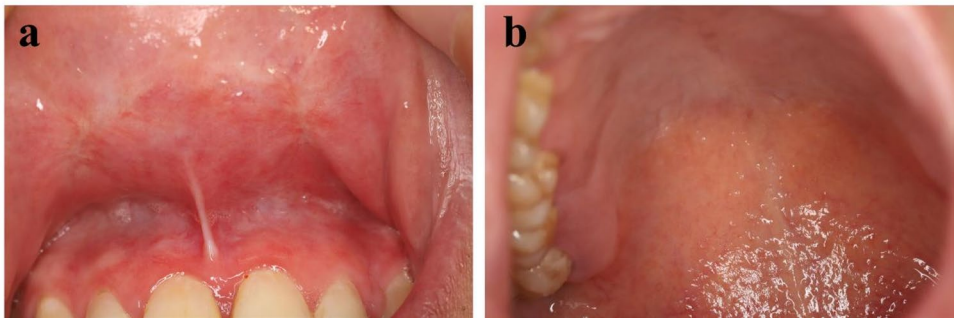

Fig. 7 Clinical follow-up photograph at eight months. **a** Persistent complete healing of the upper labial mucosal ulcer without evidence of recurrence. **b** Persistent complete healing of the ulcer on the right hard palate without evidence of recurrence

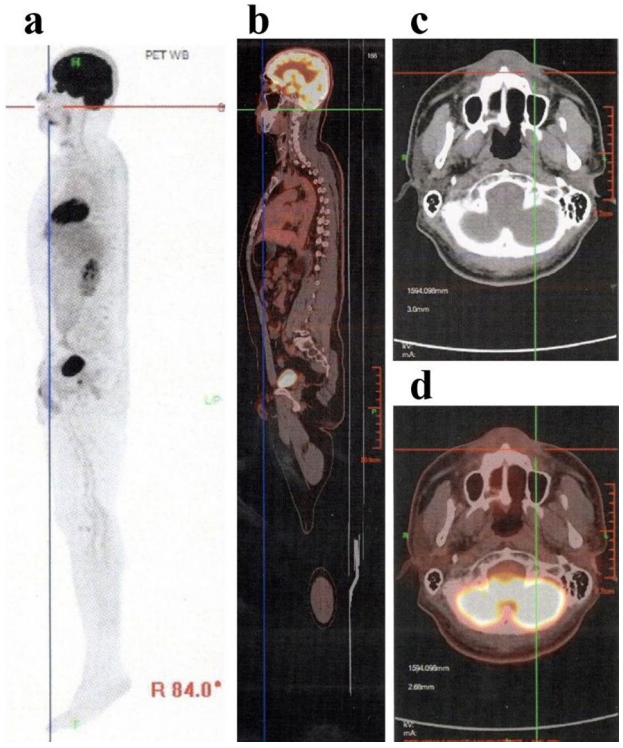

Fig. 8 PET/CT findings at eight-month follow-up. **a** Whole-body sagittal PET image showing no hypermetabolic activity in the left upper lip region compared with the initial PET/CT. **b** Sagittal PET/CT fusion image confirming the absence of abnormal FDG uptake in the left upper lip. **c** Axial CT image of the upper lip showing no residual soft-tissue mass. **d** Axial PET/CT fusion image demonstrating no abnormal FDG uptake at the site of the original left upper lip lesion

routine reports—consistent with mNGS auxiliary nature in terms of resource accessibility and diagnostic positioning [17].

Conclusion

This case report describes the application of mNGS in a patient presenting with unusual lip swelling and multiple mucosal ulcers. Through mNGS analysis of tissue samples, a high load of EBV DNA was detected, guiding further immunohistochemical testing and confirming the diagnosis of ENKTL. This approach can reduce the need for repeated invasive biopsies and minimize diagnostic delays, ultimately enhancing patient outcomes. In summary, this case demonstrates the significant clinical impact of mNGS in diagnosing rare presentations of ENKTL, advocating for its broader adoption in medical practice to enhance early detection and optimize patient care.

Abbreviations

ENKTL	Extranodal NK/T-cell lymphoma
EBV	Epstein-Barr virus
mNGS	metagenomic next-generation sequencing
T-SPOT	tuberculosis infection T-cell test
LCA	leukocyte common antigen
CK	cytokeratin
EBER	Epstein–Barr virus–encoded RNA

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Authors' contributions

Zhenlai Zhu, Jingrui Kang and Qianyun Guo contributed to manuscript preparation. Zhenlai Zhu, Mengmeng Song, Yang Liu, Lei Wang, Hongjuan Dong, Meng Fu and Qing Liu were responsible for oral examination and treatment of the patient. Zhenlai Zhu, Jingrui Kang, Hongjuan Dong, Chufan Ma, Qianyun Guo and Qing Liu contributed to collect clinical and laboratory data. All authors have read and approved the final manuscript.

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Data availability

The datasets generated and analysed during the current study are available in the China National Center for Bioinformation (https://ngdc.cncb.ac.cn/) repository, https://ngdc.cncb.ac.cn/gsa/s/OX8h38i1.

Declarations

Ethics approval and consent to participate

Informed consent about clinical management was obtained from the patient in this case.

Consent for publication

Written informed consent for publication was obtained from the patient to publish all clinical date and any accompanying images.

Competing interests
The authors declare no competing interests.

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