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Case Report

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A Case Diagnosed with Extranodal NK/T-Cell Lymphoma Nasal Type with HLH after over 20 Years of NPC and Literature Review

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Abstract

A 40-year-old male patient was admitted to our hospital on August 28, 2017, for nasopharyngeal carcinoma (NPC), which was diagnosed over 20 years ago and nasal bleeding over 1 year ago. He was diagnosed with NPC more than 20 years after undergoing biopsy of a nasal mass at Zhejiang Cancer Hospital and received radiotherapy and chemotherapy, after which the patient had stable disease. He came to our hospital for medical treatment because of suspecting hematologic cancer. After admission, there was a significant increase in the EBV DNA levels. Based on the symptoms of unexplained fever, splenomegaly, peripheral blood cytopenia, hypertriglyceridemia, hypofibrinogenemia and increased serum ferritin, the diagnosis of hemophagocytic lymphohistiocytosis (HLH) was confirmed. The biopsy of the nasal mass was performed again and pathology results confirmed Extranodal NK/T-cell lymphoma nasal type (ENKTL-NT). So the patient was finally diagnosed with ENKTL-NT with HLH after more than 20 years of NPC.

Keywords: Nasopharyngeal carcinoma; Hemophagocytic lymphohistiocytosis; Extranodal NK/T-cell lymphoma (nasal type); Epstein-Barr virus

Introduction

Nasopharyngeal Carcinoma (NPC) is a relatively common tumor in China, with the non-keratinizing pathological subtype accounting for more than 95% of cases in endemic areas, and this subtype is strongly linked to Epstein Barr virus (EBV) [1]. Extranodal NK/T cell lymphomas (ENKTL) is also strongly associated with EBV infection, especially in cases occurring in nasal locations, where EBV infection is present in 80-100%

[2]. However, it is extremely rare for a patient to have both NPC and ENKTL successively suffered. We first considered NPC recurrence when the patient was admitted to our hospital for nasal bleeding, which was very similar to the symptoms of NPC more than 20 years ago. However, the hospitalised patient was accompanied by Hemophagocytic Lymphohistiocytosis (HLH) and EBV DNA increased significantly. After a thorough examination by clinicians, he was diagnosed with extranodal NK/T cell lymphoma, nasal type. Therefore, we report a case of very rare NPC diagnosed more than 20 years later as ENKTL, nasal type with HLH, reminding clinicians to pay attention to the importance of re biopsy in tumor diagnosis in order to reduce the possibility of misdiagnosis.

Case Presentation

A 40-year-old male patient was admitted to our hospital on 28-aug-2017 because of confirmed NPC for 20 years and recurrent nasal bleeding for more than 1 year. He was diagnosed with NPC more than 20 years ago after experiencing nasal obstruction and haemorrhage following a biopsy of a nasal mass at Zhejiang cancer hospital. He received radiotherapy to the nasopharynx, both necks, as well as systemic chemotherapy, and his disease was stable. In May-2017, the patient had another nasal haemorrhage with swelling of the buccal region on both sides, difficulty breathing, at the beginning of August, self-measured body temperature more than 40 ℃, and the amount of nasal haemorrhage was more than before. A CT scan of the head and neck performed at a local hospital revealed a soft tissue mass in the nasal cavity. On August 25, 2017, He went to Zhejiang Cancer Hospital for a CT scan of his paranasal sinus, which revealed: no obvious space occupying in the nasopharyngeal wall, soft tissue shadow in the nasal cavity, and paranasal sinusitis on both sides. He also underwent nasal soft tissue biopsy, pathologic findings: in the nasopharynx, the lamina propria showed scattered lymphoid cells with more distorted and elongated nuclei and mild dysmorphic features, epithelioid mononuclear cells with presence of nuclear debris like tissue, Immunohistochemical findings: CD3 (+), CD45RO (+), CD14 (+ 20%), CD56 (+ 40%), CD30 (-). Special staining results: acid-fast staining (-), PAS (-), PAM (+ interstitium scattered few fine granular like material). Routine blood tests revealed the following data: 2.3×10^9 /L White Blood Cells (WBC) (normal range 4.0–10.0×10^9 /L), 0.45×10^9 /L neutrophils (normal range1.80–6.40×10^9 /L), 127 g/L Hemoglobin (HB) (normal range 120–170 g/L), and 36×10^9 /L blood platelets (PLT) (normal range 100–300×10^9 /L). Coagulation profile showed: 29.8 sec prothrombin time (PT) (normal range 10.5–14.5 seconds),35.9 sec activated Partial Thromboplastin Time (aPTT) (normal range 24–40 seconds) and 0.61 g/L fibrinogen level (normal range 1.7–5.0 g/L). The patient had nasal bleeding, accompanied by fever and cytopenia, consider the possibility of hematological malignant diseases, the patient came to our department of hematology for further diagnosis and treatment. After admission, physical examination of the patient showed: temperature was 38.2 °C, pulse 88 beats/min, respiratory rate 20 breaths/min, Blood Pressure (BP) 80/48 mmHg and the ECOG score was 1 point. The patient was conscious but depressed. There was no discernible yellow in the skin or sclera. There were no enlarged lymph nodes in the neck, bilateral axilla, or groyne. The lower sternum tenderness was negative, coarse breath sounds were heard in both lungs, no dry and wet rales. There were no additional sounds or murmurs to mask the heart sounds. The spleen was palpable and tenacious one finger below the subcostal margins, but the liver was not palpable. His abdomen was soft and no mass was felt, there was no tenderness and rebound tenderness on abdomen, shifting dullness negative. No edema of the both lower limbs. They are both Pap-negative. Blood tests revealed the following data: WBC 9.9×10^9 /L, neutrophils

0.9×10^9 /L, HB 118 g/L, and PLT 40×10^9 /L, triglycerides 3.13 mmol/L (reference range: 0.34–1.90 mmol/L), total bilirubin 24.9 μmol/L, Alanine Transaminase (ALT)183 U/L, Aspartate Transaminase (AST) 223 U/L, Lactate Dehydrogenase (LDH) 718 U/L, Procalcitonin (PCT) 0.26 ng/ml (reference range: 0.00–0.50 ng/ml) and the rapid whole blood CRP testing showed 45.15 mg/L (reference range: 0.00–3.30 mg/L). Blood cultures and TSPOT were negative. There were no obvious abnormalities found in the stool routine or urine tests. B-scan ultrasonography: splenomegaly. A CT scan revealed a small amount of infection in both lungs as well as a moderate volume pleural effusion on the right side. His gramme stain of nasal and pharyngeal secretions cultures revealed no bacteria and no anaerobes. After admission, the patient received 4.5 g intravenous drip of Piperacillin Sodium and Tazobactam Sodium for Injection Q8H anti infection treatment, and the temperature fluctuated at 38.2–39.1 ℃. Considering the possibility of HLH, he performed flow cytometry, the results showed that IL–6:11.8 pg/ml (reference range 1.7–16.6 pg/ml), IL–10: 336.2 pg/ml (reference range 2.6–4.9 pg /ml), IFN–γ:27 pg/ml (reference range 1.6–17.3 pg/ml). And his blood tests showed that ferritin 1584.1 μg/L (reference range 21.8–374.0 μg/L), EBV DNA was quantified by real-time PCR at 7.35×10^5 copies/ml soluble CD25 8927 pg/ml, suggesting a significant increase. NK cell activity (NKA) 28.14% (reference range ≥15.11%). On August 31st, the patient had bone marrow aspiration, which revealed a class of abnormal lymphocytes **(Figure 1)** and a normal bone marrow flow result. There were no morphological abnormalities in the chromosomes, the IgH/TCR gene rearrangement was normal, and a CT scan of the paranasal sinus revealed: both nasal soft tissue density shadow **(Figure 2).**

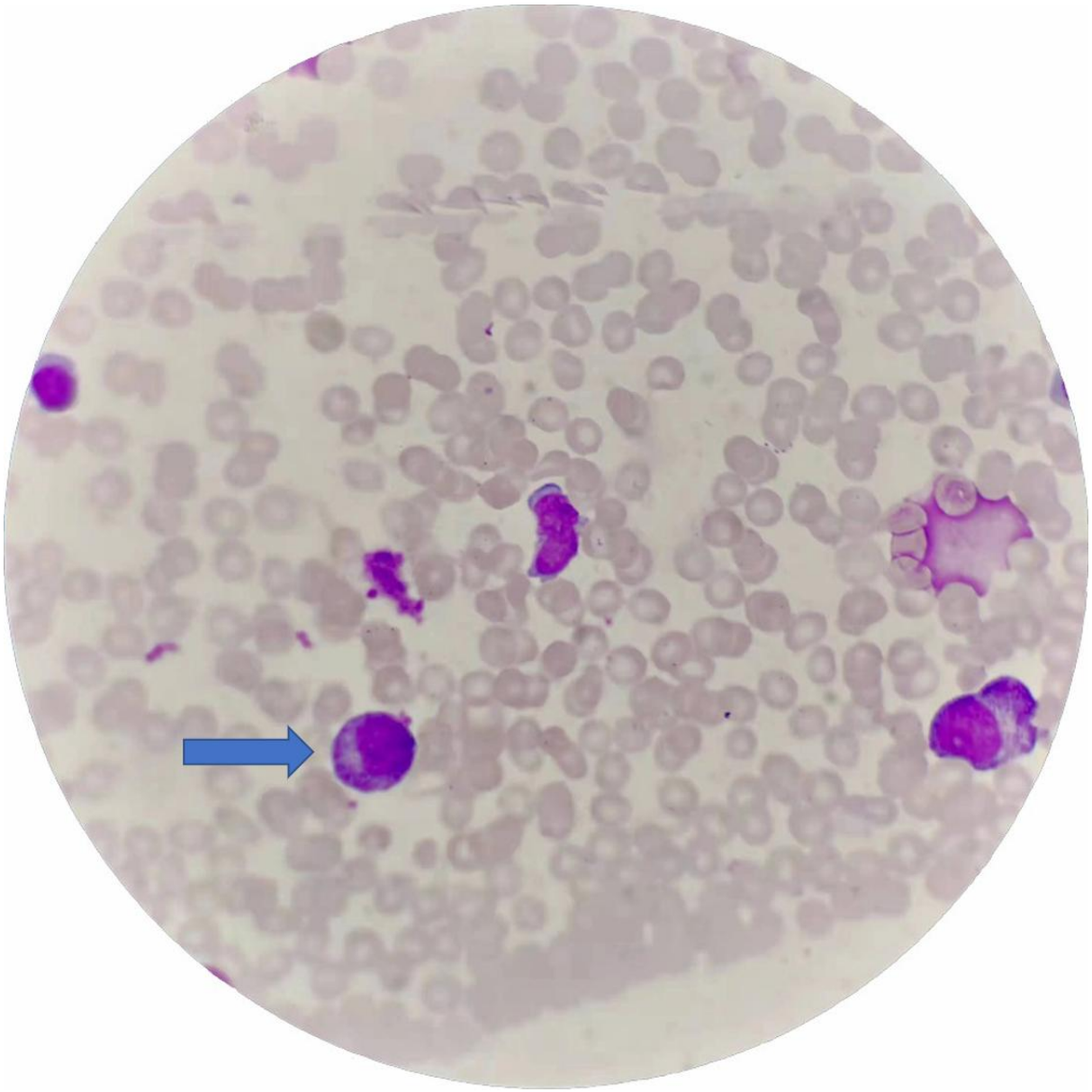

Figure 1: Results of conventional microscopy of bone marrow (Rayleigh staining; magnification, x1000). A class of abnormal lymphocytes.

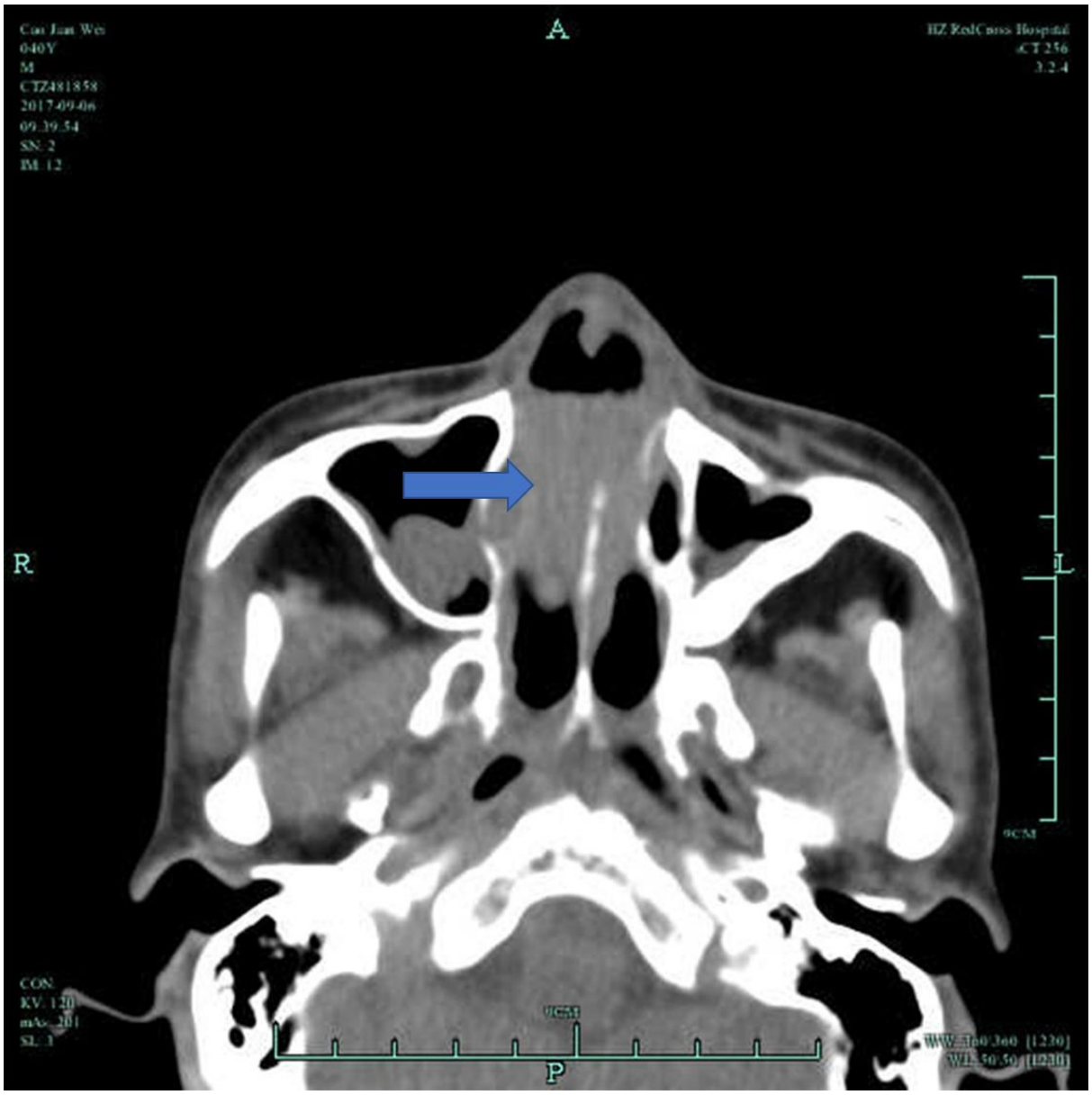

Figure 2: Computed tomography scan of paranasal sinus showed: both nasal soft tissue density shadow.

The patient has been suffering from high fever. On September 7th, he underwent nasal tumor biopsy again and blood routine examination again. The results showed that: WBC 5.0×10^9/L, neutrophils 4.10×10^9/L, HB 111 g/L, and PLT 85×10^9/L and fibrinogen 0.81g/L. The patient was admitted to the hospital with unexplained fever, splenomegaly, peripheral cytopenia, hypertriglyceridemia, and hypofibrinogenemia, serum ferritin was elevated, and soluble CD25 was significantly elevated; the above 6 points met 6 of 8 diagnostic criteria for Hemophagocytic lymphohistiocytosis: HLH-2004 **[3],** and the HLH diagnosis was established. Our doctor advised the patient to accept glucocorticoid combined with VP16 for HLH, but the patient's family refused, and the patient was discharged on September 10th. On September 12th, the pathological results of the patient's nasal tumor came out, and the results showed that: resembling round cell malignant tumor **(Figure 3A),** immunohistochemistry: CD138 (+ 1%), CD38 (+ + +), TIA-1 (+ + +), CD3 (+ + +), CD45RO (+ + +), CD56 (+ + +), CD57 (-), Ki67 (+ + +), EBER (+), CD2 (+ + +), CD43 (+ + +), granzyme-b (-), c-myc (+ 40**%) (Figure 3B-F).** The results were consistent with extranodal NK / T cell lymphoma (nasal type). Follow up the patient is

deceased. Therefore, the patient was diagnosed with ENKTL, nasal type with HLH.

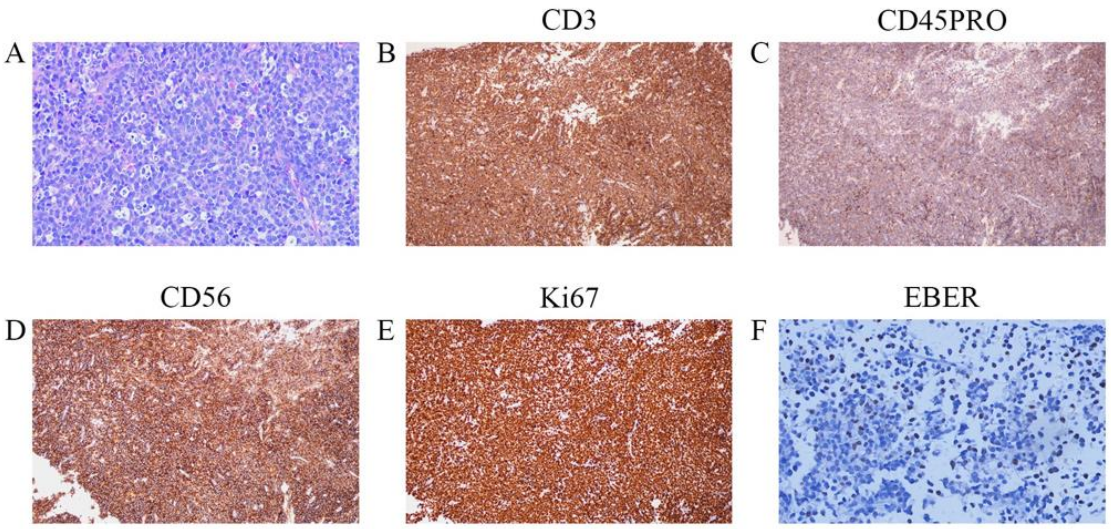

Figure 3: (A) Microscopic findings of nasal tumor: resembling round cell malignant tumor, Hematoxylin-eosin staining; magnification, x400. (B-E) Immunohistochemistry: CD3 (+ + +), CD45RO (+ + +), CD56 (+ + +), Ki67 (+ + +), Hematoxylin-eosin staining; magnification, x100. (F) Immunohistochemistry: EBER (+), Hematoxylin-eosin staining; magnification, x400.

Discussion

NPC and Nasopharyngeal Lymphoma (NPL) are two of the most common types of nasopharyngeal malignancies [4]. They often show similar clinical symptoms at early stages, such as chronic nasal obstruction, bloody nasal discharge, headache, and so on, which are extremely easy to misdiagnose and delay treatment. Histopathological examination is the gold standard for the diagnosis of NPC, considering patients with suspicious recurrence of NPC, the expert consensus [5] for the diagnosis of NPC recurrence and metastasis concluded that lesion tissue should be obtained for pathological examination whenever possible by choosing an appropriate method depending on the circumstances. Our patient was diagnosed as NPC by biopsy of a nasal mass 20 years ago, atypical symptoms such as nasal bleeding and fever recurred more than 20 years later, and a soft tissue mass in the nasal cavity was found, so the possibility of recurrence of NPC was greatest when first considered, but after re biopsy it was diagnosed as ENKTL, nasal type. Therefore, it illustrates that re biopsy is very important in tumor diagnosis. HLH is a kind of excessive inflammatory response syndrome caused by primary or secondary immune abnormalities. Adult HLH pathogenesis is mainly caused by the excessive secretion of cytokines after macrophages are stimulated by activated T lymphocytes, which have an imbalance of the Th1 cell to Th2 cell ratio and secrete a large number of cytokines such as IFN-γ, IL-6, and IL-10 activate cytotoxic T lymphocytes (CD8 + T lymphocytes) and macrophages, leading to a deregulated immune regulatory system in body cells [6]. IL-10, IFN- γ levels Significantly higher, with normal or mildly elevated IL-6 cytokine profiles are highly specific for HLH [7]. This patient had IL-10, IFN- γ significantly above the normal range,

while IL-6 was in the normal range, and in combination with the patient's clinical symptoms and histopathological examination of the nasopharynx soft tissue confirmed extranodal NK/T cell lymphoma with hemophagocytic syndrome, nasal type. Studies have reported **[8]** that EBV associated NK/T LPDs mainly occur in young patients and have a poor prognosis. The present patient was also an EBV positive young patient with NK/T cell lymphoma associated with HLH, and we considered that the high cytokine status such as IFN-γ and IL-10 in the patient is related to NK/T cell lymphoma secretion. NPC is an EBV-associated epithelial carcinoma, more than 97% of NPCs are EBV-positive **[9].** ENKTL has a close relationship with EBV infection, especially in cases that occur in the nasal site, and the infection of EBV is present in 80-100% **[2].** EBV is retained in the body in a latent form. In patients with impaired immunity, EBV infection is involved in multiple diseases. NPC and ENKTL both are associated with latency II, their common viral genes are expressed as EBNA1, LMP1, LMP2 **[10],** among which LMP1, LMP2 play an important role in the development of NPC, related studies are more thorough. LMP1 has been proposed to play an important role in NPC pathogenesis due to its ability to activate multiple cells signaling pathways which collectively promote cell proliferation and survival, angiogenesis, invasiveness, and aerobic glycolysis **[11].** The specific pathogenesis of NKTL is still unclear, but Monica **[12]** found that LMP1 may play an important role in the pathogenesis of NKTL, and Lu Sun et al**. [13]** found that LMP1 may act as an oncogene in NKTL by regulating eIF4E via activating the NF-κB pathway, functioning as an oncogene in NKTL. Radiotherapy is one of the main treatments for malignant tumors, when irradiated, the tissues in or around the irradiated field receive low doses of radiation, which activates related pathways (eg, ROS, MARK pathway, etc.) to induce side effects **[14-16],** and the activation of ROS pathways increases the levels of LMP1, which may change the type of EBV metabolism and leads to persistent infection of the virus **[9].** ENKTL incidence is low, especially rarer when complicated by NPC post-treatment. Whether the mechanism of occurrence of NPC and ENKTL is the same is not clear, but previous studies have shown that the occurrence and development of both are closely related to EBV. LMP1 can promote NPC cell migration and invasion, and LMP1 may be an oncogene in the progression of NKTL. The mechanism of both remains to be further clarified, so that it is expected to curb the occurrence and development of tumors from the aspect of the mechanism of occurrence.

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of Hangzhou Red Cross Hospital, and all participants provided written informed consent.

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