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CASE REPORT

Nasal-type extranodal NK/T cell lymphoma in association with hemophagocytic syndrome: a case report and literature review*

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Abstract

We present a rare case of nasal-type CD56-negative NK/T-cell lymphoma. The patient developed hemophagocytic syndrome during diagnosis and treatment. The patient presented to our hospital (Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China) with "nasal congestion for 3 months and scattered erythema, nodules, and ulcers all over the body for 1 month." We analyzed clinical manifestations, skin histopathology, immunohistochemistry, and *in situ* hybridization results. Histopathology of the skin revealed a moderate amount of atypical lymphocyte infiltration between the entire dermis and collagen bundles. Immunohistochemistry showed the following: CD30 (+), TIA-1 (+), CD3(2GV6) (+), CD5 part (+), CD8 part (+), CD43 (+), CD56 (–), CD4 (–), CD20 (–), PAX5 (–), PCK (–), P63 (–), P40 (–), EGFR (–), Ki-67 (the hot spot LI is approximately 80%), and *in situ* hybridization EBER-ROCH (+). The diagnosis made was "NK/T cell lymphoma nasal type". This type of lymphoma is aggressive, progresses quickly, and has a poor prognosis. Early clinical manifestations are extremely atypical, especially in the absence of rash. Analysis of the skin manifestations of the disease has a positive effect on its early diagnosis, early treatment, and prognosis.

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Extranodal NK/T cell lymphoma (ENKTCL) is overwhelmingly an Epstein-Barr virus (EBV) associated lymphoma, showing CD56 positive, low survival and aggressive clinical behavior [1]. Nasal-type extranodal NK/T cell lymphoma (ENKTCL-NT) has atypical early clinical symptoms and is often delayed due to lack of early diagnosis and treatment. Most ENKTCL-NT cases were derived from NK cells expressing CD3ε and CD56, with positive expression of CD56. CD56-negative ENKTCL-NT has been suggested as a distinct lymphoma subtype with fewer clinical cases [2]. Hemophagocytic lymphohistiocytosis (HLH) is considered as a rare heterogeneous disease caused by excessive secretion of inflammatory cytokines, which seriously endangers the lives of patients. HLH is divided into primary HLH and secondary HLH, and the latter is associated with many diseases, such as infectious diseases, hematological malignancies and connective tissue disease, mainly non-Hodgkin's lymphoma. ENKTCL has been shown to be a major trigger of lymphoma-associated hematophagocytic syndrome (LAHS) [3], the 2-year survival rate of ENKTCL patients with HLH was 14.7%, and that of patients without HLH was 77.5% [4]. ENKTCL combined with HLH is rare, with rapid and explosive course and variable presentation, seriously threatening the lives of patients. We report a case of CD56-negative ENKTCL-NT complicated with HLH. Through the analysis of the diagnosis and treatment process of this case, it is expected to provide evidence for improving the diagnosis and treatment effect.

Clinical data

Medical history

A 56-year-old man visited our hospital's Otolaryngology Department (Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan,

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China) on September 14, 2020, due to nasal congestion for 3 months and scattered erythema, nodules, and ulcers all over the body for 1 month. Nasal congestion without an obvious cause occurred 3 months before the visit to our hospital, intermittent at first and then becoming continuous. Sinusitis was diagnosed and treated several times at another hospital; however, there was no obvious relief. Two months later, dark red infiltrating erythema, nodules, and ulcers repeatedly appeared on the patient's nose, trunk, and buttocks, with mild pain. During the illness, there were occasional headaches but no fever, cough, or other symptoms. The patient was transferred from the outpatient department to the Otolaryngology Department for inpatient treatment of a nasal mass. Nothing special was noted in the medical history of the patient. The patient reported no family history of similar diseases.

Skin histopathology, immunohistochemistry, bone marrow aspiration, and other related examinations were performed on the second day after admission. Anti-infectives were administered to treat symptoms. On September 18, 2020, the patient underwent sinuplasty under general anesthesia and sinus and nasal cavity lesion biopsy under nasal endoscopy. On September 21, 2020, he presented with acute fever. The highest body temperature reached 39.5 °C, and routine blood tests showed a white blood cell (WBC) count of 3.72×10^9/L, red blood cell (RBC) count 3.96×10^{12}/L, hemoglobin (Hb) level 128.0 g/L, platelet (PLT) count 111.0×10^9/L, and lymphocyte percentage 16.4%. After antipyretic treatment, the patient's body temperature did not decrease and the fever persisted. The pathological diagnosis of the bone marrow showed that the hyperplasia of the bone marrow was decreased, and hemophagocytosis was visible; combined with the results of skin histopathology, immunohistochemistry, and bone marrow aspiration, the patient was diagnosed with NK/T cell lymphoma on September 22, 2020 and transferred to the Oncology Department for treatment.

Routine blood tests on September 23, 2020 showed a WBC count of 3.18×10^9/L and PLT count 61.0×10^9/L. In view of the patient's continued decline in WBC and PLT counts, the treatments to increase WBC level (recombinant human granulocyte-macrophage stimulating factor), and PLT level (recombinant human interleukin-11), and an anti-infective treatment (moxifloxacin hydrochloride and cefoperazone natazobactam) were administered. However, the patient's condition was not relieved. On September 29, 2020, the patient developed persistent lower gastrointestinal bleeding. Routine blood tests on October 1, 2020, showed a WBC count of 3.17×10^9/L, lymphocyte count 0.52×10^9/L, lymphocyte percentage 16.4%, RBC count 2.26×10^{12}/L, Hb level 72.0 g/L, PLT count 53.0×10^9/L, fibrinogen level 1.32 g/L, triglyceride level 3.08 mmol/L, and ferritin level 3157.4 μg/L. The patient's RBC count, PLT count, Hb level, and fibrinogen level decreased rapidly, while triglyceride and ferritin levels increased significantly. The diagnosis was nasal-type NK/T-cell lymphoma (stage VI) with hemophagocytic syndrome. On October 1, 2020, the patient was treated with hormone plus VP-16. The patient still had a recurrent fever, and his condition rapidly deteriorated. The patient's family gave up treatment and patient was discharged on October 2, 2020. The patient died 2 days after discharge.

Physical examination

The following were noted upon examination: temperature of 37.2 °C, pulse rate 80 times/min, respiratory rate 20 times/min, and blood pressure 117/76 mmHg. The superficial lymph nodes throughout the body were not palpable or swollen. There were no obvious abnormalities on cardiopulmonary or abdominal examinations. Dermatological examination: infiltrating erythema with a diameter of approximately 1.5 cm × 3.0 cm was seen on the left side of the nose, with clear borders, ulceration in the center, thick brown scab overlying, and a small amount of purulent discharge (Fig. 1a). Infiltrating erythema and nodules with a diameter varying from 3.0 cm to 12.0 cm were scattered on the back, waist, and buttocks. Some skin lesions ruptured with scabs in the center (Fig. 1b). There were no obvious abnormalities in the oral mucosa or nails.

Auxiliary examination

9/15/2020 blood routine: WBC count 2.77×10^9/L, RBC count 3.88×10^{12}/L, Hb level 125.0 g/L, and PLT count 84.0×10^9/L. Activated partial thromboplastin time (APTT): 42.9 seconds (29.0–42.0 seconds).

9/17/2020 blood routine: Lymphocyte count 0.69×10^9/L, RBC count 3.65×10^{12}/L, Hb level 119.0 g/L, and PLT count 114.0×10^9/L.

9/29/2020: EBV nucleic acid in plasma and peripheral blood mononuclear cells were 1.14×10^4 and 1.54×10^4 copies/mL, respectively.

9/15/2020: Chest radiography showed no obvious abnormalities in the lungs, heart, and diaphragm.

9/16/2020: A facial computed tomography (CT) scan showed the density of the soft tissues of the left middle and lower nasal passages, which were not clearly demarcated from the turbinate. There was a possibility of tumor lesions being present in the newly identified parts.

9/20/2020: Pathological examination of the back skin tissue showed epidermal necrosis and scabs, and medium-density atypical lymphoid cell infiltration was observed around the whole layer of the dermis and between the collagen bundles (Fig. 2).

9/21/2020: A biopsy of the left nasal cavity and

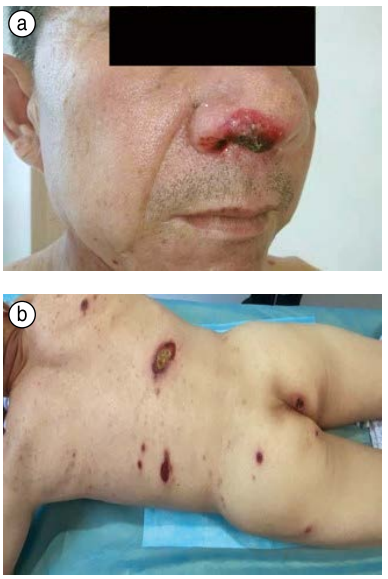

Fig. 1 (a) Erythema and ulcer on the left-wing of the nose; (b) Scattered erythema, nodules, and ulcers on the back, waist, and buttocks

middle nasal passage showed nasal extranodal NK/T-cell lymphoma. Immunohistochemistry revealed the following: CD30 (+), TIA-1 (+), CD3(2GV6) (+), CD5 part (+), CD8 part (+), CD43 (+), CD56 (–), CD4 (–), CD20 (–), PAX5 (–), PCK (–), P63 (–), P40 (–), EGFR (–), Ki-67 (the hot spot LI was approximately 80%), and *in situ* hybridization EBER-ROCH (+) (Fig. 3).

9/30/2020: CT of the small intestine and colon dual-phase enhancement + tomography showed thickening and edema of the ileocecal valve and the intestinal wall

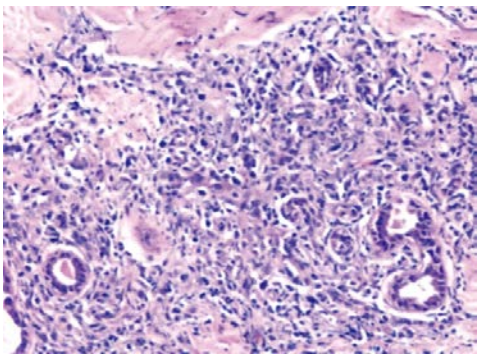

Fig. 2 Histopathology of the back skin (hematoxylin and eosin staining, × 100)

of the terminal ileum, increased and enlarged mesangial lymph nodes, thickening of the gastric wall of the gastric antrum, swelling of the Glisson sheath, and thickening and edema of the gallbladder wall. The spleen was slightly larger, bilateral inguinal lymph nodes were increased in number, peritoneum and mesangium were thickened and exuded, and abdominal and pelviceffusions were observed.

Discussion

ENKTCL is a rare type of non-Hodgkin lymphoma, which is considered to be closely related to EBV and usually affects the upper respiratory tract. Because it typically appears in the nasopharynx, the World Health Organization (WHO) classification includes both nasal and

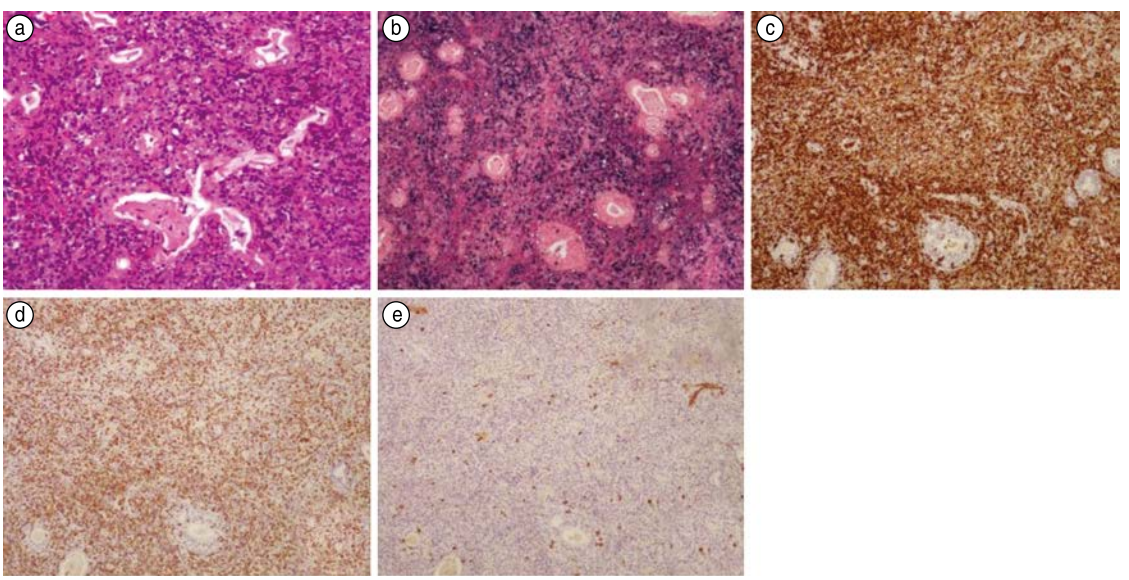

Fig. 3 Histopathology and immunohistochemistry of the left nasal cavity and middle nasal passage. (a) hematoxylin and eosin staining (x 200); (b) EBE-ROCH positive (× 200); (c) CD30 positive (× 200); (d) TIA-1 positive (× 200); (e) CD56 negative (× 200)

extranasal ENKTCLs in the same disease category. In light of its typical presentation in the nasopharynx, ENKTCL has also been classified as "nasal type" (ENKTCL-NT), and it has obvious regional and ethnic tendency. China is an area with a high incidence of ENKTCL-NT. The median age of onset for ENKTCL-NT is 45 years, with a reported incidence ratio of 4:1 (men : women) [5–6]. ENKTCL is characterized by prominent vascular destruction, tissue necrosis, and inflammatory cell infiltration [7]. Histologically, tumor cell infiltration usually manifests as vascular centrality and destruction, leading to band necrosis. Cytologically, the tumor cells were large, granular lymphocytes. Typical NK/T lymphomas mostly express T cell differentiation antigens (CD3 and CD45RO) or NK cell (CD56, CD2, and CD36) differentiation antigens, but not B cell differentiation antigens (CD20). In generalized cases, active hemophagocytic cells can be found in the liver, spleen, and bone marrow, leading to impaired liver function, hyperferritinemia, and pancytopenia [8–9].

HLH is a disease caused by the engulfing of blood cells by benign and reactive proliferating tissue cells in hematopoietic tissues, such as the bone marrow, spleen, and lymph nodes. It can be divided into primary and secondary cytophilia [secondary HLH (sHLH)] [10]. However, the pathogenesis of sHLH remains unclear. In sHLH, NK cells and cytotoxic T lymphocytes (CTL) are continuously abnormally activated, whereas cytotoxic effect defects or low function could result in antigens (pathogens, tumor cells, etc.) that cannot be effectively eliminated. These effects continue to stimulate and activate macrophages, leading to abnormal tissue cell proliferation and cytokine storms, which eventually cause high inflammation in multiple organs and immune damage to tissues and organs. Patients with NK/T-cell lymphoma are more prone to develop NK/T-cell lymphoma-associated hemophagocytic syndrome (LAHPS). Approximately 7.1% to 11.4% of ENKTCL cases were related to HLH. The prognosis of these patients is very poor, with a median survival of 30 days [11]. During the progression or treatment of lymphoma, 26.7%–47.8% of patients develop HLH. Disease progression or chemotherapeutic drugs may affect the clinical manifestations of LAHPS, leading to delays in diagnosis and treatment [12]. In addition, the following reasons may explain the occurrence of HLH. (1) NK/T-LAHPS is mostly associated with EBV infection. LAHPS related to EBV infection can express latent membrane protein (LMP-1), which activates the NF-κB pathway and upregulates cytokines (such as the expression of TNF-α and IFN-γ), consequently initiating a series of signal transduction pathways in cells and triggering a cytokine storm that finally leads to the occurrence of HLH. (2) NK/T cell lymphoma has obvious necrotizing lesions. Concurrent infections with focal necrosis can easily develop which may lead to increased cytokine levels and development of HLH [10–13].

In this case, the skin lesions showed erythema, nodules, and ulcers. The skin biopsy revealed epidermal necrosis, sparse medium-density atypical lymphocytes, and a small amount of tissue cell infiltration in the superficial and deep layers of the dermis. In addition, a biopsy of the sinus lesions revealed nasal-type extranodal NK/T-cell lymphoma. Based on the clinical manifestations, histopathology, immunohistochemistry, and *in situ* hybridization results, the patient was diagnosed with skin ENKTCL-NT. This was a rare case of CD56-negative ENKTCL. NK/T cell lymphomas are typically positive for CD3 (cytoplasm), CD56, cytotoxic markers (granzyme B, TIA1), and EBV. To the best of our knowledge, there are currently few reports of CD56-negative ENKTCL [14]. In a group of early ENKTCL patients, the survival rate of CD56-negative ENKTCL patients was significantly lower, indicating that CD56-negative ENKTCL can be regarded as a unique phenotype, and it is necessary to further optimize treatment strategies for this disease [15]. During the treatment of ENKTCL, the patient developed fever, progressive decline in blood cell counts, splenomegaly, hyperferritinemia, hypofibrinogenemia, and the presence of hematopoietic cells in the bone marrow, which met the five criteria in the HLH 2004 diagnostic guideline; thus, the patient was diagnosed with HLH. The prognosis of this disease in this patient was extremely poor, which is in line with previous reports in the literature [11]. The patient died within a short period. ENKTCL is a highly malignant, aggressive, and rapidly progressing tumor. Therefore, an early diagnosis is important. However, the early clinical manifestations of ENKTCL-NT are atypical, and they are easily misdiagnosed, especially when there is no rash. The patient's upper respiratory tract symptoms manifested as the first symptom, while skin erythema, nodules, and ulcers gradually appeared later. Unfortunately, he was misdiagnosed with sinusitis several times before being transferred to our hospital. Skin biopsy and other related examinations were performed promptly after admission, and the diagnosis was quickly confirmed. This case suggests that we should be vigilant about the possibility of ENKTCL-NT for persistent sinusitis, especially when it is accompanied by skin damage. Early nasal cavity, skin histopathology, immunohistochemistry or flow cytometry, and other related examinations are recommended for this type of disease to achieve early diagnosis and treatment.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

Author contributions

All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version of this manuscript.

Data availability statement

Not applicable.

Ethical approval

Not applicable.

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