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A Case Report of Primary Nasal Natural Killer (NK)/T-Cell Lymphoma in an African American Patient Presenting with Hemophagocytic Syndrome

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Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 55
Final Diagnosis: Primary NK-T cell lymphoma • nasal type
Symptoms: Fever • nasal bleeding • nasal mass • weight loss
Medication: —
Clinical Procedure: Chemotherapy×2 cycles • radiation therap
Specialty: Oncology

Objective: Rare disease

Background: Extranodal natural killer/T-cell lymphoma, nasal type (ENKTCL) is generally an aggressive and rare non-Hodgkin lymphoma. It is most common in East Asians, Native Americans, and South Americans, but is rarely reported in blacks.

Case Report: A 55-year-old African American male born in Grenada presented with a left nostril mass with facial swelling and biopsy subsequently confirmed a diagnosis of extranodal NK/T-cell lymphoma, nasal type (ENKTCL). Immunochemistry was positive for CD2, cytoplasmic CD3, CD7, CD 43, CD 56, granzyme B, and TIA-1. *In situ* hybridization was positive for Epstein-Barr virus encoded ribonucleic acid (EBERs). Bone marrow aspiration did not show lymphoma involvement. The patient had progressive neutropenia upon presentation, with further investigations showing hepatomegaly, hyperferritinemia, and hemophagocytosis in the bone marrow. We reached a diagnosis of hemophagocytic syndrome. He was treated with a high-dose combination chemotherapy and radiation therapy; the neutropenia improved significantly with steroids as treatment for immune activation in the setting of hemophagocytic syndrome.

Conclusions: To the best of our knowledge, this is the only second report of extranodal NK/T-cell lymphoma, nasal type in a black patient, and it raises the awareness of early recognition of rare manifestations of NK/T-cell lymphoma such as hemophagocytic syndrome.

MeSH Keywords: Epstein-Barr Virus Nuclear Antigens • Lymphohistiocytosis, Hemophagocytic • Lymphoma, Non-Hodgkin

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/900995

Background

Extranodal natural killer/T-cell lymphoma, nasal type (ENKTCL) is a very rare, aggressive peripheral T-cell lymphoma. Nasal cavity or paranasal sinus and other midline facial structures are the primary involvement sites [1]; less common sites include the gastrointestinal tract, skin, testis, and lung [2–5]. It is also well known as one of EBV infection-associated tumors, and incidence of the male to female ratio is about 1.8 [6]. ENKTCL is more prevalent in East Asians, Native Americans, and South Americans [7], and less common in non-Hispanic whites in the United States and much rarer in blacks [6]. To the best of our knowledge, this is only the second case of ENKTCL reported in a black patient [8]. Here, we report a case of ENKTCL presenting with nasal mass and progressive neutropenia, and later the patient was diagnosed with hemophagocytic syndrome. He responded well to chemotherapy and radiation therapy. Written consent for publication was obtained from the health care proxy.

Case Report

A 55-year-old African American male presented to the Emergency Department of Brookdale University and Medical Center (Brooklyn, NY) in February 2016 with facial swelling, persistent purulent discharge from the left nostril, and intermittent epistaxis for the previous 4 weeks. He had decreased appetite and had lost about 10 pounds during the previous 6 months. He denied any night sweats, headache, and any changes in vision, and also denied dyspnea, dysphagia, and odynophagia. He had intermittent fevers after hospitalization. He had schizophrenia diagnosed at age 21 and it had been controlled with risperidone for the past 10 years. He was born in Grenada and moved to the United States at age 18. On examination, there was a 1-cm exophytic mass attached to the lateral wall of the left nostril with surface ulceration in the left nasal cavity (Figure 1A); the left nasal cavity was almost totally obliterated. There was no palpable lymphadenopathy. Initial laboratory findings showed white blood cell count (WBC) was 3.3×10^9/L (normal range $4–11\times10^9$/L), absolute neutrophil count (ANC) was 1700/uL (normal range: 1900–8000/uL), hemoglobin 12.7 g/dL (normal range 13.5–17.5 g/dL), platelet 205×10^9/L (normal range $130–450\times10^9$/L), lactate dehydrogenase (LDH) was 828 IU/L (normal range 313–618 IU/L), and ferritin 974 ng/ml (normal range: 17.90–464.00 ng/mL). Liver enzymes and coagulation study were within normal range. Contrast computed tomography (CT) of the sinus showed an extensive soft tissue shadow in the left nasal cavity with mucosal thickening in the maxillary and ethmoid sinuses (Figure 2). Abdominal CT scan showed hepatomegaly (right lobe has a span of 19–20 cm) and splenomegaly (12–12.5 cm). Tissue biopsy performed under nasopharyngoscope showed a small to medium-sized atypical appearing neoplastic lymphoid cells proliferation with infiltration in the blood vessel walls (Figure 3). Immunophenotype analysis was positive for CD2, cytoplasmic CD3, granzyme B (Figure 4A–4C). CD7, CD 43, CD 56, and TIA-1 (T-cell intracellular antigen) were also positive. *In situ* hybridization was positive for Epstein-Barr virus encoded ribonucleic acid (EBERs) (Figure 4D). Ki 67 was 80–90%, which indicated high cell proliferation (Figure 4E). Serology was positive for EBV IgG antibody but negative for EBV IgM antibody. Human T-lymphotropic virus I/II (HTLV) and HIV antibodies both were negative. Tissue biopsy and immunophenotype confirmed the diagnosis of NK-T-cell lymphoma, nasal type. Pan-CT did not reveal any other involved lymph nodes or organs, bone marrow aspiration was negative for lymphoma involvement or leukemia but showed phagocytosis of nucleated cells by macrophages (Figure 5A, 5B). He had progressive neutropenia before and after diagnosis; the ANC decreased to 600/ul at 1 week before starting filgrastim. The ANC dropped to 0/ul after starting chemotherapy (Figure 6) and normalized quickly after treating the disease. His ENKTCL was defined as stage I-EB based on a solid mass in the nasal cavity without any other lymphadenopathy, no bone marrow

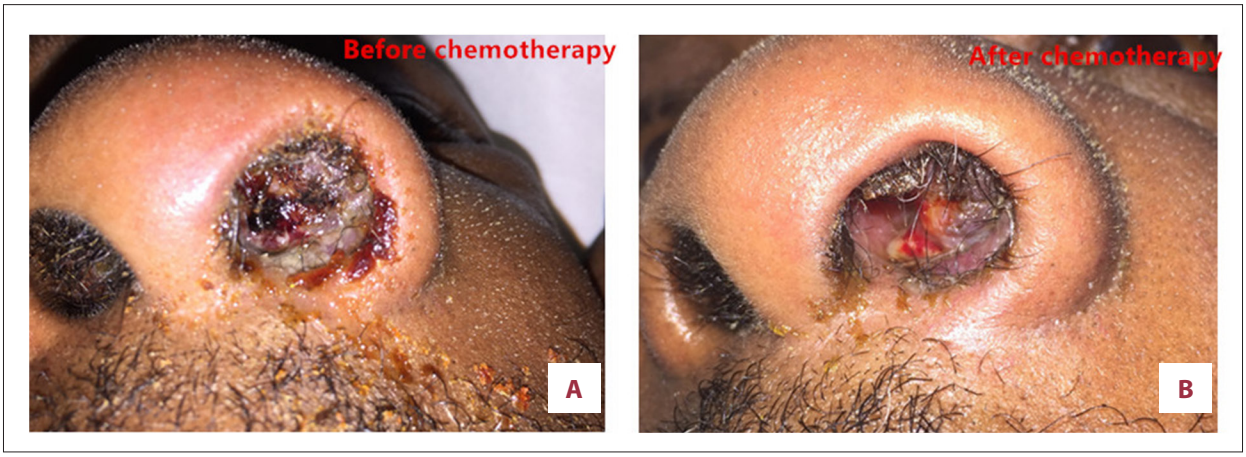

Figure 1. (**A**) Left nostril mass general appearance before any treatment. (**B**) Left nostril mass after first cycle chemotherapy.

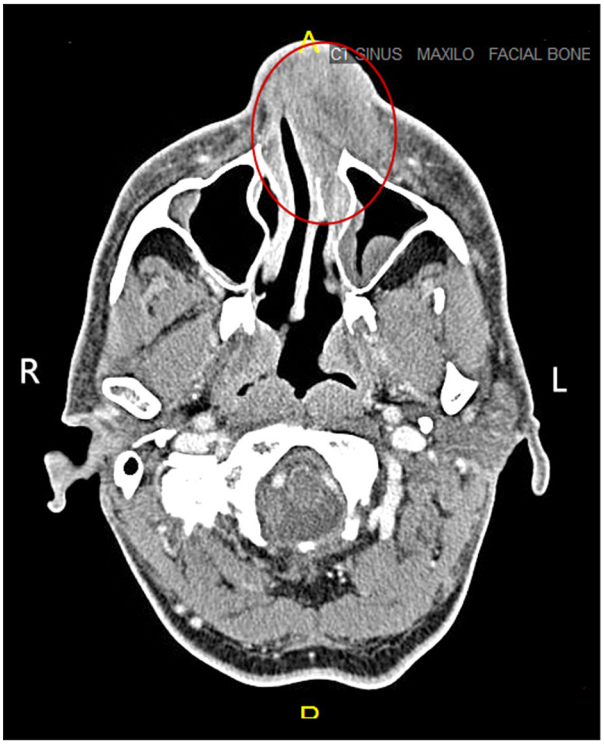

Figure 2. CT sinuses with IV contrast: a soft-tissue shadow in the left nasolabial fold with mucosal thickening in the maxillary and ethmoid sinuses.

involvement, and high grade as to Ki 67 was 80–90%. NK/T-cell lymphoma international prognostic index (NKIPI, risk factors include B symptoms, Ann Arbor stage, elevated LDH, regional lymphadenopathy) was 2, and the 5-year overall survival rate is about 34% [9]. Upon diagnosis, he was started on chemotherapy with SMILE protocol (Dexamethasone, Methotrexate, Ifosfamide, Peg-asparaginase, and Etoposide) for 2 cycles. During chemotherapy, the neutropenia continued to deteriorate and was complicated with spiking fever. Subsequently, he was treated with meropenem and vancomycin. The tumor in the left nostril became more ulcerated, had mild bleeding, and decreased in size significantly after the chemotherapy (Figure 1B). The WBC counts normalized and ANC recovered to 3600/ul after the first cycle of chemotherapy (Figure 6). He also finished localized radiation therapy (5580 cGy). Follow-up PET-CT was negative for any active lesions. He is currently in complete remission 8 months after initial diagnosis. Considering the high grade of the tumor and intermediate high NKIPI, he was referred to a bone marrow transplant center for evaluation for possible consolidation autologous hematopoietic stem cell transplantation (autologous-HSCT).

Discussion

Extranodal NK/T-cell lymphoma, nasal type was referred to as "midline lethal granuloma" or "angiocentric lymphoma" in the past, characterized with progressive destructive necrosis in the midface structures. Histopathologically, the tumor cells could be medium-sized or a mixture of small and large neoplastic lymphoid cells with diffuse proliferation; the blood vessel walls always are infiltrated with neoplastic cells and show an angiocentric or angiodestructive growth pattern [10]. The centered lymphoma flanked by areas of frank necrosis is also characteristic for ENKTCL. Our case presented with a localized nasal mass almost obstructing the whole nasal cavity, with tumor necrosis symptoms manifested with persistent purulent discharge and epistaxis. He also had concurrent B symptoms (fevers and weight loss). These clinical features raised the suspicion for lymphoma, and prompt tissue biopsy was performed to confirm the diagnosis.

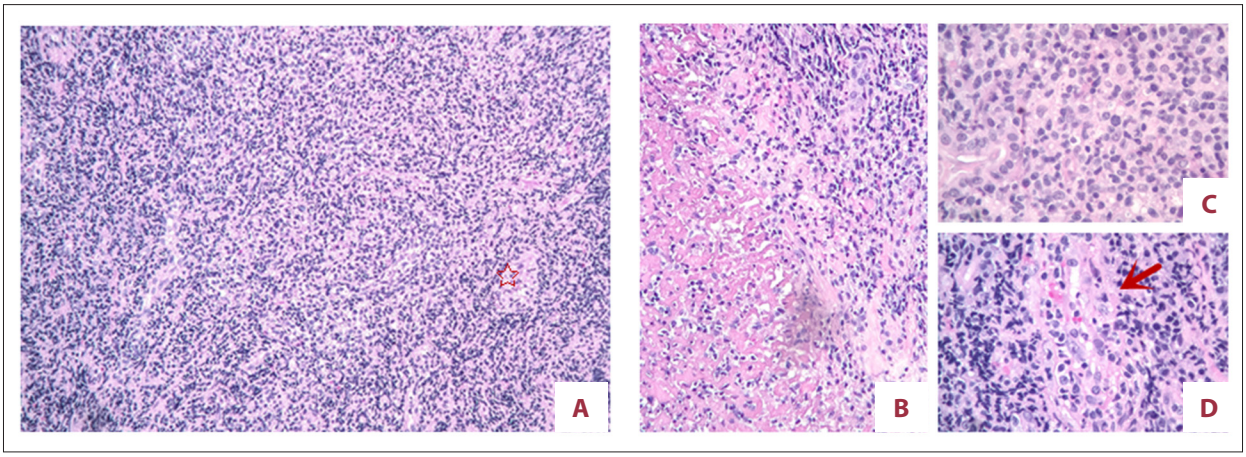

Figure 3. (**A**) Diffuse neoplastic proliferation of atypical lymphoid cells showing infiltration of blood vessel walls (star). (**B**) The lymphoma is flanked by areas of frank necrosis, typical for NK/T-cell lymphoma. (**C**) High-power view: medium-sized elongated and angulated cells admixed with larger cells showing distinct nucleoli. (D) High-power view: angiocentric/angiodestructive growth pattern (arrow).

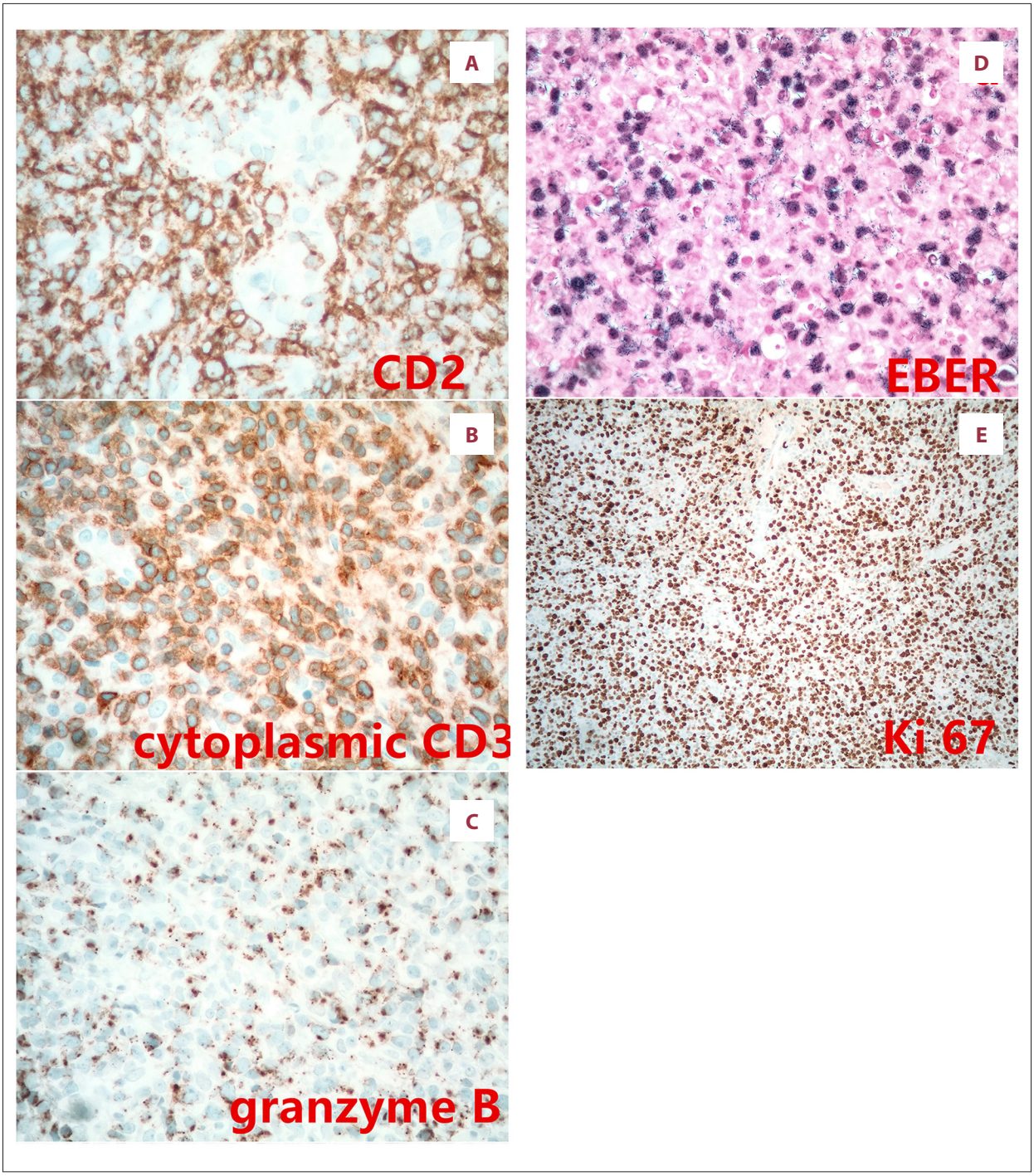

Figure 4. (**A**) Immunohistochemistry positive for CD2. (**B**) Cytoplasmic CD3. (**C**) Granzyme B. (**D**) *In situ* hybridization was positive for Epstein-Barr virus encoded ribonucleic acid (EBER). (**E**) Ki-67, high cell proliferation 80–90%.

Extranodal NK-T-cell lymphoma accounts for 5–10% of all non-Hodgkin lymphoma, with most cases reported in East Asia (China, Korea, Hong Kong, and Japan) [7]. The incidence of NK-T-cell lymphoma in the United States is around 0.036 per 10 000 people [6], and it has higher prevalence in Hispanic whites and Asian/Pacific Islanders and lowest among blacks. The patient we describe was born in the Caribbean and denied any Asian ancestry. So far, the epidemiology research data about the prevalence of ENKTCL in the Caribbean is lacking, but the EBV infection rate in Caribbean blacks is very high (92.2%) [11], which may contribute to the high prevalence of

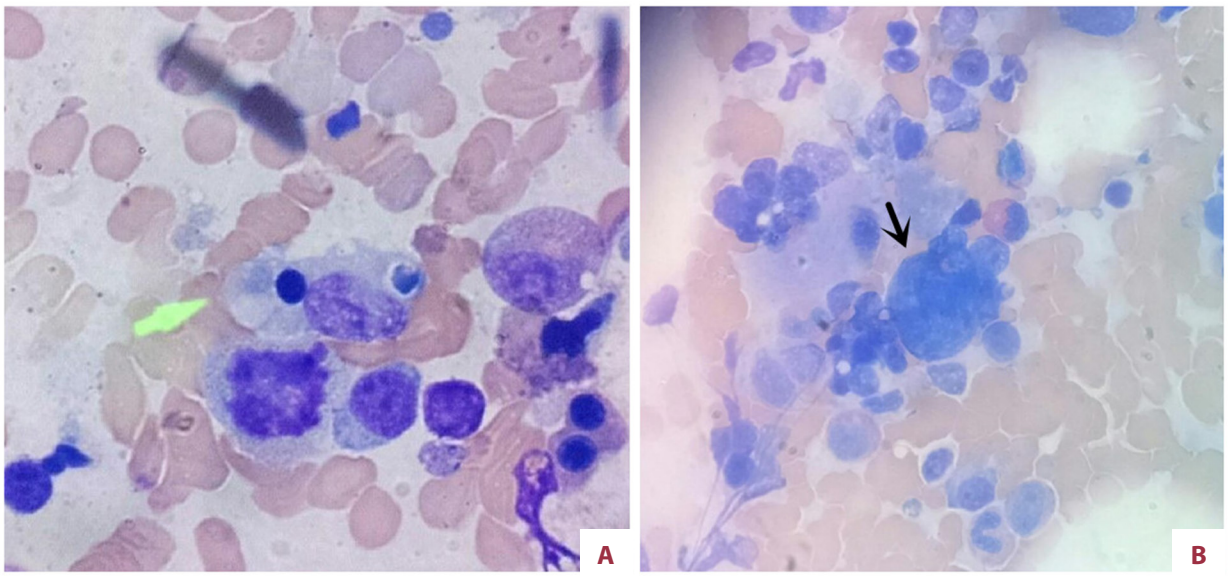

Figure 5. (**A, B**) Bone marrow aspiration showed phagocytosis of nucleated cells by macrophages (green arrow in **A** and black arrow in **B**).

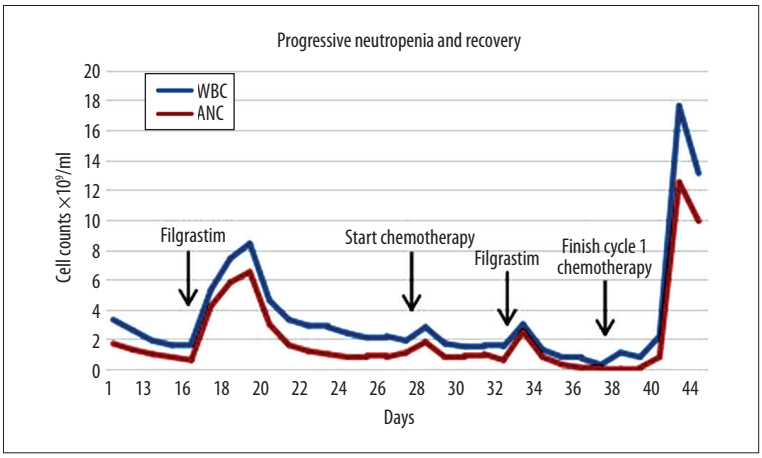

Figure 6. Progressive neutropenia and recovery.

NK/T-cell lymphoma in Caribbean people because EBV infection is a prerequisite for diagnosis of ENKTCL [12].

Our patient presented with progressive neutropenia before we reached the current diagnosis; he responded well to filgrastim but continued to deteriorate after medication withdrawal (Figure 6). Progressive neutropenia is an uncommon manifestation in ENKTCL, and usually warrants further investigation. After ruling out the medication adverse effects, the differential diagnosis includes lymphoma with bone marrow involvement, concurrent leukemia, and hemophagocytic syndrome. With hemophagocytosis in bone marrow, peripheral blood cytopenia (2 lines, neutropenia, and anemia, Hg 12.7 g/dL), hyperferritinemia, hepatosplenomegaly, and fever (5 out of 8 diagnostic criteria applied in the HLH-2004 trial [13]), the diagnosis of hemophagocytic syndrome was reached. About 3% of extranodal NK/T-cell lymphoma is associated with hemophagocytic syndrome [14], which may present with fever, hepatosplenomegaly, multi-organ failure, lymphadenopathy, cytopenia, and high serum ferritin levels. Hemophagocytic syndrome is a syndrome of pathologic immune activation and excessive inflammation caused by a lack of normal inhibition of activated macrophages and lymphocyte [15]. Hemophagocytosis in the bone marrow is characteristic for histopathological diagnosis for hemophagocytic syndrome, although sensitivity (about 70%) and specificity (about 66%) are not satisfactory [16]. For our patient, before he developed multi-organ failure or coagulopathy and other life-threatening conditions, we recognized it at an early stage and promptly started treatment for lymphoma. Steroids were part of the chemotherapy and were also an appropriate strategy to target the immune activation in the setting of hemophagocytic syndrome. The neutropenia significantly normalized after chemotherapy (Figure 6).

This patient's NK/T-cell lymphoma is defined as stage I-EB supported by no lymphadenopathy, no bone marrow, and other organ involvement. The patient started chemotherapy as soon as the diagnosis was established. Currently, SMILE protocol (dexamethasone, methotrexate, ifosfamide, L-asparaginase-substituted by Peg-Asparaginase in our patient, and etoposide) has been proposed as first-line chemotherapy. The overall response rate was 81% in newly diagnosed NK/T-cell lymphoma in a retrospective study of 87 patients [17], and common adverse effects include neutropenia, thrombocytopenia, and nephrotoxicity [17]. After the first cycle of chemotherapy, the tumor size significantly decreased, and the previous obliterated nasal cavity became patent (Figure 1B). Radiation therapy also plays an important role in the treatment of early-stage localized disease. Our patient responded well to radiation therapy and the localized tumor almost became invisible after radiation therapy. In a retrospective study of 105 patients, the complete response rate was about 87% after radiotherapy with or without chemotherapy [18]. It is controversial that autologous hematopoietic stem cell transplantation (Autologous-HSCT) should be proposed as consolidation therapy after chemotherapy and/or radiation therapy. The outcome of autologous-HSCT mostly depend on the pre-HSCT status [19], since the NK-T-cell lymphoma has a good prognosis in stage I/II disease [20]; the benefit of autologous-HSCT as consolidation therapy hasn't been established. So far, no clinical trial results are available for comparing therapy with *vs.* without autologous-HSCT in localized NK-T-cell lymphoma, due to the rarity of this disease. However, subgroups of patients who have high NKIPI risk scores had a significantly higher disease-specific survival at 5 years (100% *vs.* 51.2%) after receiving autologous HSCT when compared with a control group [21]. Our patient had an intermediate-high NKIPI risk score and high-grade lymphoma, with Ki-67 80–90%. It is reasonable to evaluate for probable autologous HSCT for consolidation therapy after complete remission with chemotherapy and radiation therapy.

Conclusions

We described a rare case of extranodal NK/T-cell lymphoma, nasal type in a black person. T the prevalence of this lymphoma in the black population, especially African-Caribbean, may be underestimated and should be further investigated. The rarer manifestations, such as hemophagocytic syndrome, in the setting of NK/T-cell lymphoma should be recognized early.

Competing interests

The authors have declared that no competing interests exist.

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