THE NEW ARMENIAN MEDICAL JOURNAL
Vol.11 (2017), No 2, p. 10-15

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A PATIENT WITH EXTRANODAL NATURAL KILLER LYMPHOMA, NASAL TYPE, COMPLICATED BY BONE MARROW AND CENTRAL NERVOUS SYSTEM INVOLVEMENT

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Received 12/05/2016;accepted for printing 18/06/2017

Abstract

Natural killer cell neoplasms comprise a rare group of lymphoid malignancies, consisting of extranodal natural killer/T-cell lymphoma/leukemia, nasal type, aggressive natural killer cell leukemia, and natural killer cell lymphoproliferative disorder. Aggressive natural killer cell leukemia is considered as a separate entity from the lymphomas with CD16 and CD3 helping differentiate the diagnoses. Natural killer/T-cell lymphoma/leukemia fairs better given their sensitivity to chemotherapy and radiotherapy. Central nervous system and bone marrow involvement are quite uncommon in the nasal type with reports showing incidence of approximately 7%. Hemophagocytic lymphohistiocytosis is a known complication of aggressive natural killer cell leukemia, but is rarely reported in the nasal type.

We present the case of a 53 year old Asian male who presented with recurrent sinusitis and peripheral blood cytopenias. Further work-up revealed that he had a large retropharyngeal necrotic mass as well as bone marrow involvement of CD4/CD8- CD16/CD56+ atypical lymphoid cells consistent with natural killer cell origin. Natural killer cell function assay corroborated the diagnosis. There was evidence of hemophagocytic lymphohistiocytosis given elevated ferritin, soluble CD25 levels as well as active hemophagocytosis on bone marrow aspirates. After 2 cycles of therapy with steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase and etoposide he still had progressive disease, and died of sepsis.

While it is thought that these 3 diseases lay on a continuum, their clinical behavior as well as diagnostic signature are quite unique. As treatment options are quite limited for these patients, further researches will be necessary to offer therapeutic options.

Keywords: *hemophagocytic lymphohistiocytosis, extranodal natural killer lymphoma, nasal type.*

Introduction

Natural killer cell neoplasms are a rare group of malignancies of natural killer cells that span the spectrum from chronic lymphoproliferative disorder to extranodal natural killer cell lymphoma/leukemia (nasal and the controversial non-nasal type), aggressive natural killer cell leukemia and natural killer cell lymphoproliferative disorder [*Lima M, 2013*]. These Epstein-Barr driven malignancies are much more common in Asia and South America [*Parikh S et al., 2014*]. From these, aggressive natural killer cell Leukemia is the rarest with reported median survivals of 58 days [*Suzuki R et al., 2004*]. Due to its rarity, there are no randomized clinical trials comparing the supremacy of any one treatment to another [*Tse E, Kwong Y, 2013*]. While aggressive natural killer cell leukemia is considered a separate entity from the lymphoma, distinction is a moot point, with CD16 and cCD3 sometimes considered tiebreakers [*Kobayashi S, 2011*]. Considering its rarity, few randomized controlled trials are available demonstrating superiority of particular regimens [*Suzuki R et al., 2004; 2010; Jaffe E et al., 2013; Lima M, 2013; Tse E, Kwong Y, 2013*].

The extranodal natural killer/T-cell lymphomas

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tend to have better outcomes than the aggressive natural killer cell leukemia, especially if diagnosed at earlier stages [*Kobayashi, S, 2011*]. This is largely due to the effects of radiation therapy [*Cron R et al., 2015*] in locoregional disease control. L-asparaginase containing regimens have shown promise and allogeneic transplantation is seen as the only curative option for these patients [*Suzuki R et al. 2010*]. Central Nervous system involvement is not common in the nasal type [*Jaffe E et al., 2013*] with one reporting suggesting ~7% incidence across all 3 types. In the nasal type, bone marrow involvement is also uncommon at diagnosis, with one case series reporting only 2 out of 25 cases at diagnosis [*Ishida F et al., 2012*] and 7% in another [*Wong K et al., 2001; Ishida F, Kwong Y, 2010; Kobayashi S, 2011*; *Ishida F et al., 2012*].

Extranodal disease is a poor prognostic marker, but in particular with natural killer Cell leukemias, their propensity to be complicated by hemophagocytic syndrome [*Ishida F, Kwong Y, 2010*]. A well-established complication of extranodal natural killer/T cell leukemias is hemophagocytic lymphohistiocytosis [*Kim W et al., 2015*]. This is a hyperimmune response triggered by malignancy, infection, or an autoimmune crisis. Awaiting further deciphering of its pathophysiology, if left untreated, it is rapidly fatal, with progression to multi-organ failure. Diagnostic criteria were once hazy, but now a diagnostic score called the HScore has been developed [*Kwong Y, 2011*]. One large study from the Mayo clinic showed that roughly 50% of cases of secondary hemophagocytic lymphohistiocytosis were due to underlying malignancy, and of these 60% were due to T-cell lymphomas [*Arca M et al., 2015*]. In this report, we present the case of an Asian male with nasal type natural killer cell lymphoma involving both the central nervous system and bone marrow, whose course was further complicated by hemophagocytic syndrome [*Fardet L et al., 2014; Parikh S et al., 2014; Cron R et al., 2015; Schram A, Berliner N, 2015*].

Case Report

A healthy 53-year-old Vietnamese male presented to a community hospital after a syncopal episode at work. The patient's work-up at the time revealed pancytopenia with leukopenia with 1.4×10^3 *cells/mL* (ANC 600) Hemoglobin 6.1 *g/dL* and platelets of 14.000×10^9 *cells/mL*. The patient noted a one month history of fatigue, 15 pound weight loss, fevers, night sweats, epistaxis and a several month history of nasal congestion. The patient was transferred to our tertiary care center. Other notable diagnostic studies revealed Na^+ 130 *mEq/L*, alkaline phosphatase 121 *IU/L*, aspartate aminotransferase 92 *IU/L*, alanine aminotransferase 92 *IU/L*. By the fourth day of his hospitalization he showed progressive disease as evidenced by aspartate aminotransferase of 746 *IU/L*, alanine aminotransferase of 835 *IU/L* and alkaline phosphatase of 807 *IU/L*. Ferritin was reported as 4.498 *ng/mL* on admission and rose to >15.000 *ng/mL* by day 4. Lactate dehydrogenase increased from 467 *IU/L* to 1.357 *IU/L*. Fibrinogen level was 176 *mg/dL* on hospital day 5.

The clinical suspicion for hemophagocytic lymphohistiocytosis was high and the patient was started on a course of dexamethasone 10 mg/m^2 IV Q12H. IL-2R (sCD25) was elevated to 1.809 *pg/mL*. Iron panel showed 98% saturation with a serum Iron of 183 *mcg/dL* and total iron binding capacity of 187 *mcg/dL*. Erythrocyte sedimentation rate was elevated at 89 *mm/hr*. Triglycerides were elevated to 160 *mg/dL*. Serum Epstein-barr virus was log 6.0. Natural killer cell function assay showed 4 LU30 (normal >7.0). T-cell gene rearrangement studies were not sent because there was strong enough evidence to suggest that this was natural killer cell in origin.

Computed tomography scans of the head and large necrotic left sided nasopharyngeal mass and diffuse cervical and retropharyngeal lymphadenopathy adenopathy. There were no other enlarged visceral lymph nodes. The patient underwent a nasal endoscopy revealing inflamed, friable mucosa with fullness of the left lateral pharyngeal wall without ability to exclude a mass. There was high concern for extranodal natural killer cell leukemia/lymphoma given the nasal mass and cytopenias with active hemophagocytic syndrome. The patient underwent a bone marrow biopsy which revealed 70% involvement with natural killer cell lymphoma. Flow cytometry of the bone marrow aspirate revealed a CD4/CD8 negative and CD16/CD56 positive clonal population. Immunohistochemistry of the bone marrow sample corroborated these findings with positivity for CD16, CD56, cytoplasmic CD3, and EBER (Epstein-Barr virus-encoded small RNA) while negativity for CD4 and CD8.

Peripheral blood smear showed neoblastic natural killer cells. Cytogenetics showed no abnormalities. Lumbar puncture with cytology also showed the presence of malignant cells, confirmed by flow cytometry to be natural killer cells (Fig. 1). Core biopsy of a cervical lymph node also showed 1% involvement with natural killer leukemia/lymphoma cells (Fig. 2 and 3). The patient was started on a chemotherapy regimen of SMILE ifosfamide 1200 *mg/m²* days 1-3, mesna 300 *mg/m²* days 1-3, etoposide 60 *mg/m²* days 1-5, dexamethasone 15 *mg/m²* days 1-5, pegasparage 2000 *units/m²* D 8. The patient had an International Prognostic Index score of 3. He was also given twice weekly intrathecal injections of 10 *mg* methotrexate and 70 *mg* cytarabine and 30 *mg* hydrocortisone. The patient was given cycle 2, and a Day 35 bone marrow biopsy showed a markedly hypocellular marrow with 15% positivity with natural killer cells.

The patient's clinical course was complicated by subdural hematoma, recurrent seizures, methicillin-resistant Staphylococcus aureus/E. Coli ex-

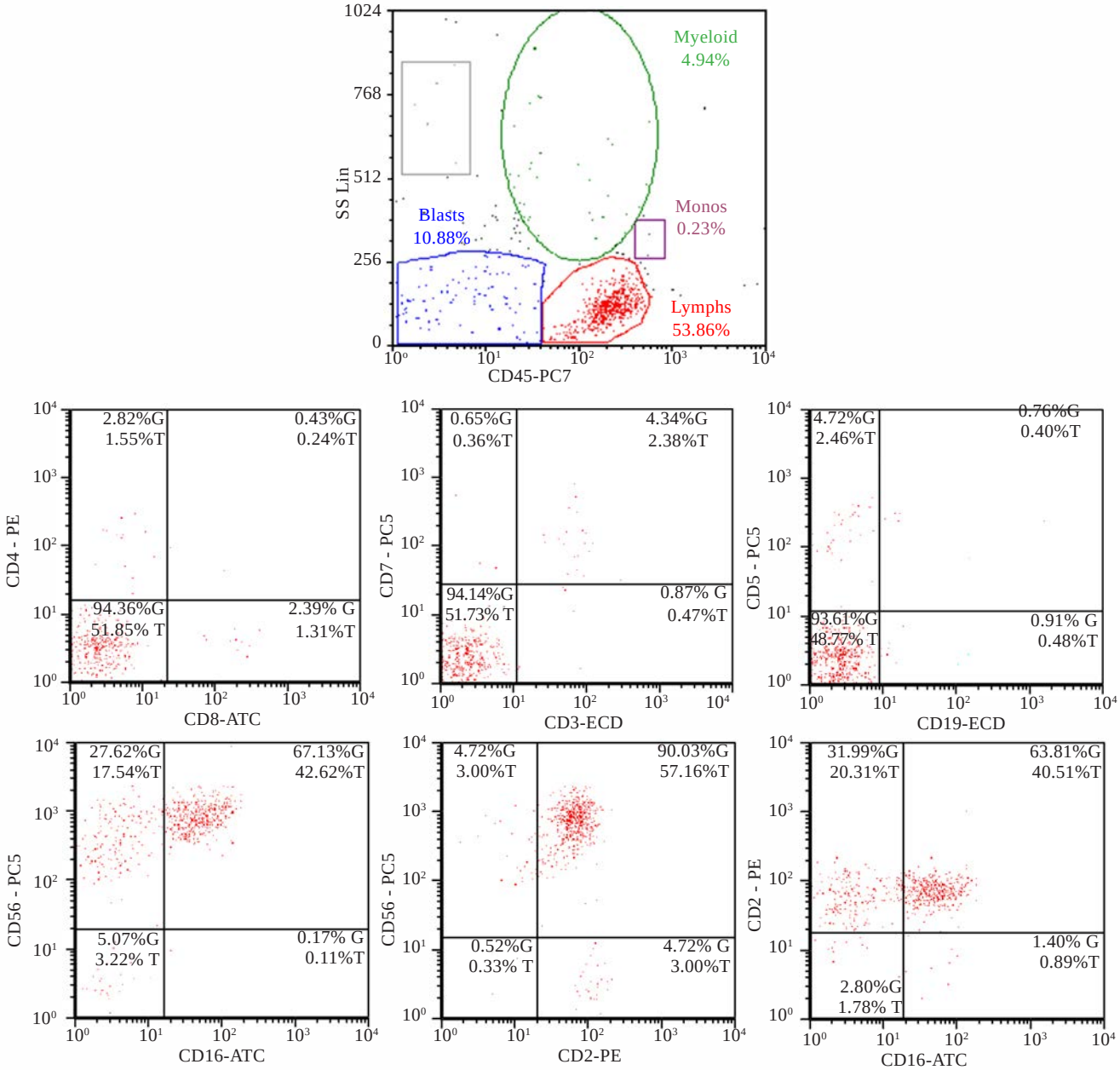

FIGURE 1: *The flow cytometry of the CSF sample showed a population of cells with low side scatter and bright CD45 expression, consistent with lymphocytes (54%). The lymphocyte gate showed approximately 95% of lymphocytes are NK cells with expression of CD2, CD16 and CD56 and lack of expression of CD3, CD4, CD7, CD8 and CD19.*

tended spectrum beta Lactamase secreting bacteria with Clostridium difficile colitis in the setting of neutropenia. He remained transfusion dependent for both red blood cells as well as platelets. After his second cycle of steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase and etoposide (SMILE), his clinical condition continued to deteriorate substantially and a decision to not pursue palliative and comfort measures.

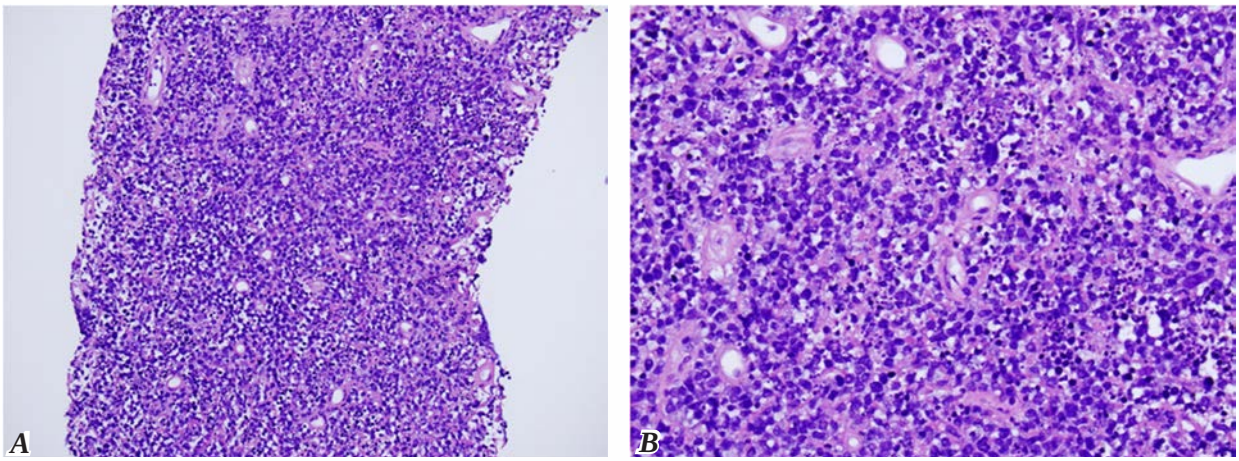

Figure 2: *A and B microscopic sections from lymph node biopsy showed complete effacement of nodal architecture due to diffuse infiltration of an abnormal atypical lymphoid cells with necrosis and karyorrhexis bodies. (H&E, (A)×200 and (B)×400)*

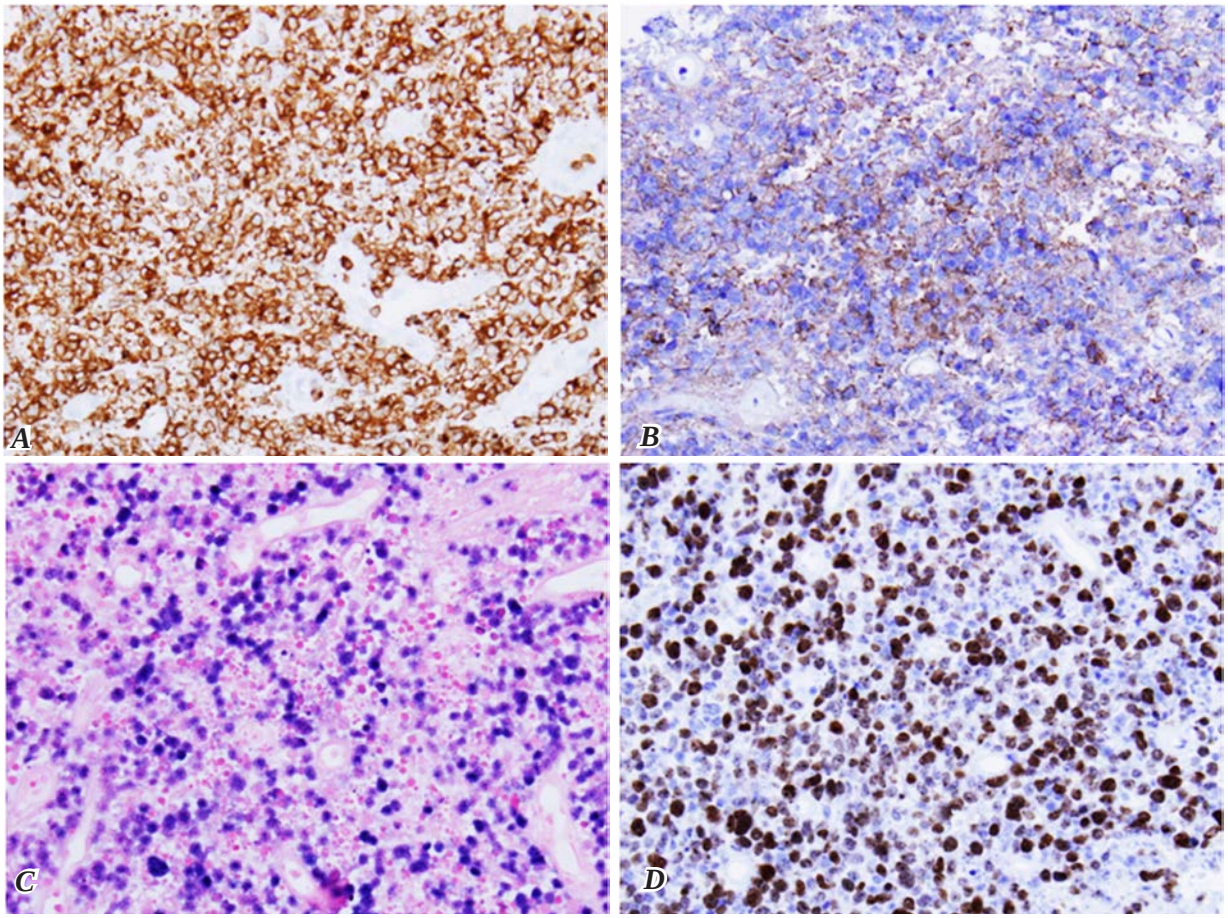

Figure 3: *The immunohistochemical staining of the lymph node biopsy showed those infiltrative atypical lymphocytes were mainly positive for (**A**) cytoplasmic CD3 (×400), (**B**)CD56 (×400) and (**C**) EBER-ISH. (**D**) Ki-67 proliferation index were about 70% (×400).*

Discussion

Natural killer cell neoplasms comprise a small niche of the leukemia/lymphoma disease space. It is only during the last 30 years that they have formally been recognized as unique entities versus their prior designation as large granulocytic leukemias. There are now three of these entities listed in the WHO catalog natural killer cell neoplasms as described above. The development of the T-cell receptor rearrangement assay as well as the natural killer cell functional assay has helped differentiate these diseases from other T-cell leukemias/lymphomas.

The distinction between the non-nasal natural killer/T-cell leukemia/lymphoma and the more aggressive natural killer/T-cell leukemia will remain challenging. The surface cluster of differentiation marker CD16 and cytoplasmic CD3 could potentially distinguish the aggressive leukemia from the stage IV nasal/extra-nasal types in the correct clinical context. Age of presentation and survival outcomes were another mode of deciphering for these diseases, with leukemias presenting in their 40's while their lymphoma counterparts were in their 50's. Immunohistochemically, the aggressive natural killer cell leukemias are primary bone marrow clonal neoplasms, defined as having a CD2+ CD3- CD16+ and CD56+ signature with near 100% positivity for Epstein-Barr virus. Extranodal natural killer cell lymphomas are also Epstein-Barr-virus-positive and can present with nasal and extra-nasal involvement with or without a detectable nasal primary.

Immunohistochemical staining criteria are a point of contention in the literature with some authorities advocating CD16+ as a tiebreaker between the extranodal natural killer/T-cell lymphoma and aggressive natural killer lymphoma. Oshimi K. (2007) showed that nearly 25% of cases of ENKL are CD16+ and this likely cannot be used to distinguish them. Hemophagocytic lymphohistiocytosis and central nervous system involvement are quite rare in these entities. While the largest prognostication model did not include the presence of hemophagocytic lymphohistiocytosis as a variable, it can be assumed that it is in and of itself a poor prognostic marker. One large retrospective study from the mayo clinic showed a median overall survival of 2 months for patients that had hemophagocytic lymphohistiocytosis secondary to a malignancy versus an autoimmune disease. A larger study showed that for lymphoma-associated hemophagocytic lymphohistiocytosis 81% of patients died of multi-organ failure. Another study showed a 20% mortality at 30 days for lymphoma associated hemophagocytic lymphohistiocytosis with an odds ratio of 11.9.

With that data in perspective, patients with extranodal disease have a median overall survival on the order of months while those with stage I/II natural killer cell lymphoma have a 5-year overall survival rate of 50%. Central nervous system involvement is also uncommon with <10% being reported in K. Oshimi's case series. Certain authorities do not advocate routine CNS screening as the yield tends to be low. Positivity is a poor prognostic marker, because it not only advances the stage, but drug delivery and efficacy are always limited in central nervous system metastases.

While SMILE has proven itself efficacious as a regimen, the response rates in the advanced stage are low. Allogeneic transplant remains the only curative option for these patients. The challenge lays in achieving a complete remission in these patients. Engaging the endogenous adaptive immune system may provide a therapeutic option for these patients in the future. PD-1/PD-L1 directed therapies, as well as bi-specific T-cell engagers and chimeric antigen receptor T-cells will need to be explored in these diseases.

This case highlights the importance of not only recognizing the rare natural killer cell neoplasm, but also understanding their clinical behavior. While there are only 3 diseases, and they are relatively rare, the practicing clinician must be cognizant of their potential diagnosis, as well as their natural history. Patients can decompensate quickly, and treatment may need to be initiated prior to the results of certain diagnostic tests or specialist hematopathology assessments are returned [*Takahashi N et al., 2001*; *Kwong Y, 2011; Arca M et al., 2015*; *Kim W et al., 2015*].

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