A rare case of NK cell lymphoma, associated with Epstein - Barr virus

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Citation

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Abstract

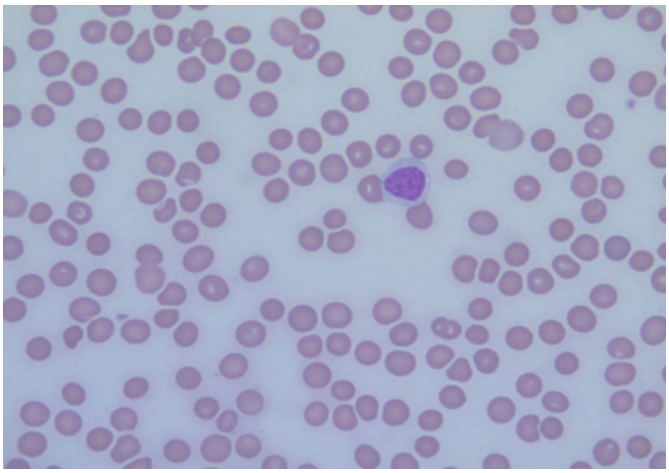
Natural Killer (NK) cells represent a distinctive lineage of lymphocytes that aremorphologically large granular lymphocytes (LGL) and express CD 56 surface antigen. NK cell neoplasms are highly aggressive, rare and demonstrate an association with Epstein - Barr virus (EBV). We report a case of a 68 year old white male who presented with fever and drenching night sweats of four weeks duration. His clinical status deteriorated despite aggressive supportive treatment; finally patient succumbed to multisystem organ failure (MSOF).

CASE REPORT

68 year old Caucasian male presented with fever and drenching night sweats of four weeks duration. Upon admission, he was acutely ill, hemodynamically unstable, required pressor and respiratory support. He had no significant medical history other than hypertension. Physical examination revealed scleral icterus and splenomegaly. Admission labs revealed anemia (8.7gm/dL), thrombocytopenia (39,000 /mm3), Microangiopathic hemolytic anemia and coagulopathy (INR 1.43 sec, APTT 39 sec, LDH 3234 U/L, fibrinogen 89mg/dl) consistent with disseminated intravascular coagulation (DIC), elevated creatinine (3.9mg/dL) and liver enzyme abnormalities (AST 33U/L, ALT 230U/L, ALP 531 U/L and serum total bilirubin 10.7mg/l.) Peripheral blood examination revealed large granular lymphocytes (Figure-1).

Figure 1

Figure 1: Peripheral bloods smear showing large granular lymphocytes (LGL).



EBV panel showed elevated IgG early antigen (1:5800 titres) signifying past infection. Serial blood cultures were negative and transesophageal echocardiogram showed no vegetation. Bone
marrow biopsy revealed predominant malignant lymphoid cells (Figure-2) and peripheral
blood flow cytometry showed 76% cells in the lymphocyte region that were CD 56
positive and CD3 negative consistent with Aggressive Natural Killer cell leukemia
(ANKL). His hospital course was further complicated by ischemic colitis and
GI bleeding confirmed by colonoscopy and diagnostic laparoscopy. Biopsy of the

mesentery and small bowel demonstrated atypical lymphoid aggregates consistent with
ANKL (Figure-3). His clinical status deteriorated despite aggressive supportive
treatment. The patient succumbed to multisystem organ failure (MSOF) 10 days after
admission.

Figure 2

Figure 2: Bone marrow smear shows atypical lymphoid cells

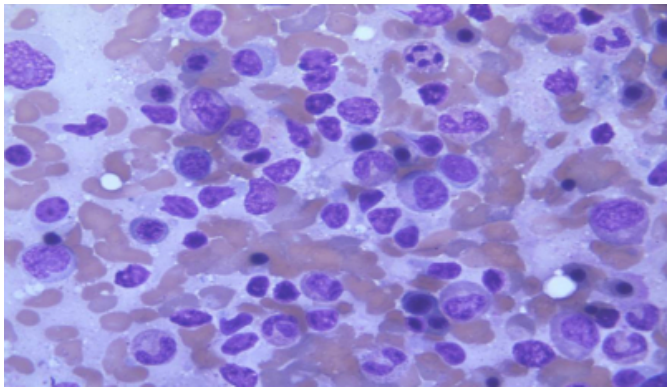
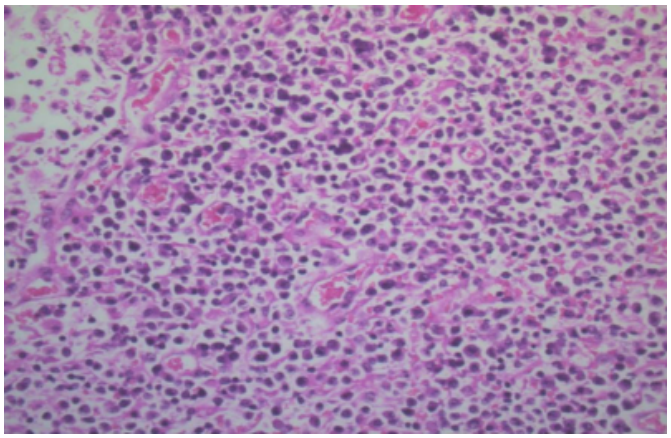


Figure 3

Figure 3: High power view of the biopsy of small intestine showing lymphoid aggregates.



DISCUSSION

Aggressive natural killer cell leukemia (ANKL) as its name implies is a highly
malignant, relatively uncommon EBV associated disease that is widely disseminated at
the time of diagnosis. WHO classified NK cell malignancies into 3 broad categories1,
(1)Extranodal NK cell lymphoma involving the nasal cavity, GI tract, skin and testis. (2)
Aggressive Natural killer cell leukemia involving the blood and bone marrow (3) Blastic
NK cell lymphoma arising from the precursor NK cell. Immamura et al in 19902 coined
the term Aggressive Natural Killer Cell Leukemia (ANKL). Aggressive NK-cell
leukemia/lymphoma and extra nasal NK-cell lymphoma were arbitrarily defined by the
presence or absence of 30% or more of large granular lymphocytes in the bone marrow
or peripheral blood 2. ANKL represents the leukemic variant of NK cell neoplasms and
has the following feature: (1) Higher incidence in Asian population (2) slight male
predominance (3) more common in young to middle aged adults (4) strong EBV
association (5) prominent systemic B symptoms (6) presence of peripheral blood
involvement (7) widespread tissue involvement with marrow infiltration (8) highly fulminant clinical course.

Aggressive NK cell leukemia typically affects young to middle aged adults and is
more prevalent in Asia, Central and South America. ANKL may mimic a reactive
process because of its typical extranodal presentation, varying degrees of NK cell
involvement and bone marrow pathology. Clinically patients are very ill and present with
fever, B symptoms, hepatosplenomegaly and lymphadenopathy. Anemia, neutropenia,
thrombocytopenia, DIC and multi-system organ failure complicate the hospital course.
Persistent lymphocytosis with LGLs is found in peripheral blood and an association with
EBV is seen in more than 50% cases. Circulating leukemic NK cells can range from few percent
to more than 80% of all leukocytes. Morphologically they are large granular lymphocytes with
round or irregular nuclei with basophilic cytoplasm containing fine or coarse azurophilic
granules. These cells typically are CD2+, CD56+, surface CD3- , however germline T
cell receptor genes are not rearranged. EBV encoded small nuclear RNA (EBER) is
positive in most cases on in-situ hybridization. Histologically apoptosis3, areas of
necrosis and hemo-phagocytosis are common features of NK cell malignancies.
Haemophagocytic syndrome (HPS) 4, 5 is a

clinicopathologic syndrome characterized by systemic activation of benign macrophages showing phagocytosis of hemopoetic cells and resulting in fever, organomegaly and cytopenias. Some authors6 believe that Interferon–gamma released from abnormal NK cells activates macrophages and eventually give rise to HPS. Expression of proteins such as granzyme B, perforin and Fas ligand (FasL) by NK cells have been proposed as contributory factors for necrosis and apoptosis. Hematophagocytosis, dyserythropoiesis and stromal degeneration are the most frequent findings in the bone marrow. Neoplastic cells in the bone marrow were consistently CD2 (+), CD56 (+), CD45 (+), CD34 (-), CD117 (-) and surface CD3 (-).Loss of chromosomes 6q, 11q, 13q and 17p are the recurrent aberrations.

Aggressive Natural Killer cell leukemia has a fulminant course with a median survival of 2 months. Patients respond poorly to CHOP chemotherapy and most will succumb to coagulopathy and MSOF. ANKL being an EBV associated lymphoid malignancy, tumor cells express P-glycoprotein leading to multidrug resistance. Thus far, no treatment has been found to be effective for this disorder. A recent phase I trial has shown promising results with a new chemotherapeutic regimen, SMILE, a combination of steroids, dexamethasone, methotrexate, ifosfamide, L-asparaginase and etopside7. The components of SMILE are agents which are effective in multidrug resistance state of the disease. Etopside has shown both in vivo and in vitro efficacy against EBV associated lymphoproliferative disorders 7. There are reports in the literature which has suggested a possible role for allogenic hematopoietic cell transplantation, which might be a promising therapy with curative potential 8. There is a phase II trial approved by Cancer Therapy Evaluation Program (CTEP)-which is expected to open shortly looking into the efficacy of the farnesyl transferase inhibitor tipifarnib (Zarnestra) for both T-cell and NK-cell LGL leukemia 9. There are reports of high serum FasL in NK cell malignancies prompting some authors to suggest the possible use of Herbimycin A 6 or Cyclosporine in combination with chemotherapy, as these agents are known to inhibit induction of FasL expression. Campath-1H 10, a humanized antibody against CD 52 antigen, has been shown to inhibit NK cell mediated cytotoxicity in-vitro. However its role in ANKL still needs to be determined.

CONCLUSIONS

Aggressive Natural Killer cell leukemia is a very rare lymphoid neoplasm with distinguishing features such as racial predilection, strong association with EBV and poor clinical outcome. Clinicians should be aware of this disease entity and should include in the differential in patients presenting with fever, MSOF, DIC and atypical lymphoid cells in the peripheral blood. Rarity of these neoplasms has made large clinical trials difficult to carry out and therefore the optimal treatment modality remains undefined. Pooling data from available case reports on ANKL should throw more light in to the ongoing researches on this rare highly malignant neoplasm.

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