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Case Report:
Blastic NK Cell Leukemia/Lymphoma

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ABSTRACT

Blastic natural killer (NK) cell lymphoma/leukemia is a rare NK cell malignancy of unknown etiology. It occurs in multiple sites and with a propensity for skin involvement. We report a 56-year-old male presented with nasopharyngeal mass, hepatosplenomegaly, lymphadenopathy and multiple skin lesions. Laboratory data revealed pancytopenia with, peripheral blood and bone marrow involvement with blast cells. These cells showed negative cytochemical staining for myeloperoxidase, α naphthyl butyrate esterase and positive cytochemical staining for acid phosphatase. By immunophenotyping, these cells were positive for CD4, CD56, CD7, CD38, cCD3 and HLA-DR. The patient was treated with adult ALL protocol; after 2 cycles of induction chemotherapy there was complete resolution of all masses but with persistent blast cells in bone marrow.

Key Words: *Blastic NK cell lymphoma/leukemia – CD4+/CD56+cells – Bone marrow.*

INTRODUCTION

Natural killer (NK) cells are lymphoid cells that mediate lysis of tumor cells and bacteria- or virus-infected cells and the production of immunomodulatory cytokines **[1,2]**. Natural killer (NK) cells are believed to arise in the bone marrow, thymus, and fetal liver from "common lymphocyte precursors," which are derived from pluripotent hematopoietic stem cells **[3,4]**. Mature NK cells constitute 10% to 20% of lymphocytes in normal blood **[5]**.

Morphologically, mature NK cells are large granular lymphoid cells, which are characterized by the presence of pale cytoplasm containing azurophilic granules. Unlike T cell large granular lymphocytes, they are negative for surface CD3 but characteristically express cytoplasmic CD3 epsilon (ε), CD56, and cytotoxic molecules. Furthermore, clonal rearrangement of the T-cell receptor (TCR) genes is also absent in NK cells **[6,7]**.

Blastic natural killer (NK) cell neoplasms are rare, highly aggressive malignancies with a poor prognosis. They have a predilection for the skin, and disseminate rapidly into the blood, bone marrow, lymph nodes, and extranodal organs **[1]**. This type of aggressive T-cell neoplasm is more common in Asia and Latin America but very rare in Middle East **[8,9]**. Epstein-Barr virus (EBV) is found in most cases of NK-cell leukemia/lymphoma, suggesting an oncogenic role **[10]**.

CASE PRESENTATION

A 56-year-old Egyptian male was admitted to Oncology Department of Cairo University Hospital on 6/9/2012 with bilateral diminution of hearing for 3 months with progressive dysphagia and dyspnea with no particular family or past history of medical illness. On admission, clinical examination revealed the presence of large nasopharyngeal mass, enlarged submandibular and right posterior cervical lymph nodes, hepatosplenomegaly and multiple cutaneous lesions (Fig. 1) of long duration.

A complete blood count showed mild leucopenia with white blood cell count of 3,600/μL and 30% peripheral blasts, mild anemia with hemoglobin concentration of 11g/dL, and marked thrombocytopenia with platelet count of 48,000/μL. Biochemical results revealed (aspartate aminotransferase, 55U/L (RR: 0-37);

alanine aminotransferase, 70U/L (RR: 10-40), lactate dehydrogenase; LDH, 485U/L (RR: 230-460) and uric acid, 6.1mg/dl (RR: 3-5.7). Hepatitis C virus (HCV) was screened by 3rd generation ELIZA and the result was negative.

Morphologic study of bone marrow aspirates on the patient's first admission demonstrated hypercellular marrow with dyserythropoiesis and high count of abnormal cells (90% blast cells). The cells were with almost eccentric nuclei, fine nucleolated nuclear chromatin and bluish occasionally vacuolated cytoplasm (Fig. 2); they were encroaching on all other hemopoietic elements which were depressed. Cytochemical tests revealed that the abnormal cells were negative for myeloperoxidase (Fig. 3-A) and α naphthyl butyrate esterase but positive for acid phosphatase reactions (Fig. 3-B). Bone marrow biopsy revealed hypercellular bone marrow with nodular collection of atypical lymphocytes.

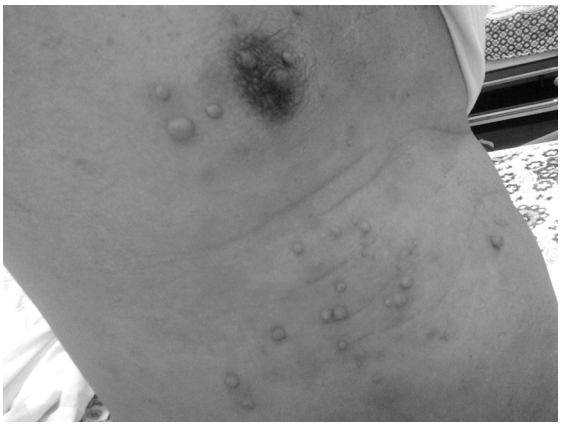

Fig. (1): Multiple well defined cutaneous lesions.

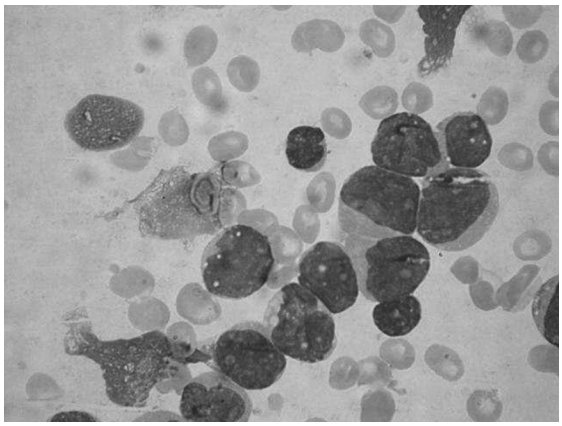

Fig. (2): Bone marrow aspirate showing mononuclear cells with eccentric nucleus and occasionally vacuolated cytoplasm (100 x).

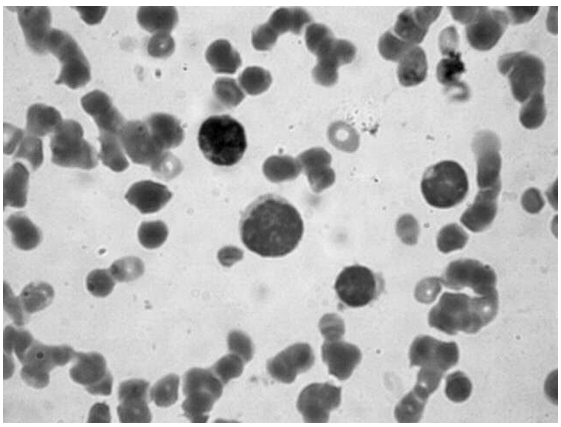

Fig. (3A): Blast cells were negative for myeloperoxidase (100 x).

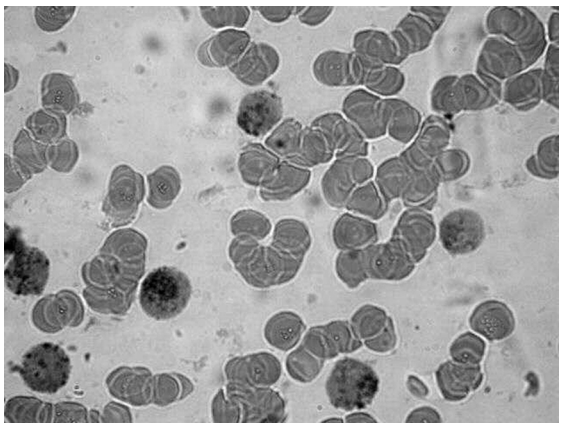

Fig. (3B): Blast cells were positive for acid phosphatase (100 x).

Flow cytometric analysis on bone marrow aspirate clearly highlighted an immunophenotypic feature: Positive for CD4 (51.7%), CD56 (71.8%), CD38 (58%), CD7 (48%), cCD3 (56.2%) and HLA-DR (69%), but negative for CD13, CD33, CD2, CD3, CD5, CD10, CD19, CD20, cCD22 and CD34.

Rhinoscpoic biopsy of the nasopharyngeal mass showed pieces of tissue lined by focally hyperplastic, focally keratinized stratified squamous epithelium and pseudo stratified columnar epithelium of respiratory type. The sub epithelial layer was expanded and densely infiltrated by atypical lymphoid tissue with diffuse and vague

nodularities. They were formed of atypical lymphocytes. Immunohistochemistry revealed that these atypical cells were positive for CD56, CD4 and CD3. Excision of one of skin nodule revealed diffuse infiltration by mononuclear cells in the dermis and subcutis. Immunohistochemistry revealed that the mononuclear cells were CD56 and CD45 positive.

The diagnosis of blastic NK-cell lymphoma/ leukemia stage IV was made with involvement of nasopharynx, lymph nodes, skin, liver, spleen and the bone marrow.

The patient started treatment with adult ALL protocol according to The International ALL trial (MRC UKALL XII/ECOG E2993). He received two induction cycles. After 2 months, reevaluation before starting maintenance phase revealed complete resolution of nasopharyngeal mass, cervical nodes, HSM and almost all cutaneous nodules. BM examination revealed residual blast cells (9%) compared with 90% at initial presentation. Then the patient achieved hematological remission at 5 months from presentation and remained in remission till relapse after 1 year and appearance of Liver metastasis.

The publication was approved by the IRB of the Clinical Oncology Department, Cairo University and an informed consent was taken from the patient.

DISCUSSION

Blastic natural killer (NK) cell lymphoma, a relatively rare NK-cell malignancy was first described by Suchi and Mori in 1994 **[11]**. It can occur at any age, but most commonly in the middle and older-aged males. This disease tends to involve multiple sites, with a tendency for the skin showing erythematous and purpuric indurated plaques or nodules. Moreover, lymph nodes, soft tissue, peripheral blood or bone marrow can be simultaneously involved. A majority of patients show widespread disease at the initial presentation **[12]**.

A special immunophentypic feature of blastic NK cell lymphoma is the positivity of CD56 antigen; it is expressed very early on committed NK precursor and on more than 95% of mature NK cells **[4,5]**. CD7 also is expressed early in NK cell development **[4]**. Markers found on developing and mature NK cells include variable expression of CD2, CD8, CD11b, CD25, CD16, CD57, TIA-1, perforin, and granzyme. Differentiation of "true NK cells" from CD56+ cytotoxic "NK-like T cells" can be difficult because they may express similar surface antigens **[5]**. NK cells are currently best distinguished from T cells by lack of TCR gene rearrangement and lack of CD3 expression on the cell surface **[13]**.

Blastic NK-cell lymphoma is a disease with poor prognosis, particularly when bone marrow involvement is seen at onset **[14]**. With the exception of few case reports **[15-17]**, chemotherapy alone seems to be inadequate to attain long-term complete remission in patients with disseminated blastic NK-cell lymphoma. Our patient reached partial response with treatment that is usually used for induction of remission in ALL. As reported previously, regimens for ALL could be effective for this disease. Even if complete remission is achieved by chemotherapy alone, the period of CR is usually short and most patients relapse within several months. Local irradiation to bulky diseases requires doses in the range of 50Gy **[14]**.

The median survival time when treated with chemotherapy alone is 12-20 months **[18]**; therefore, bone marrow transplantation is the only option for long-term remission **[19]**. A retrospective analysis by Suzuki and colleagues comparing stem cell transplantation to chemotherapy alone in patients with a variety of NK neoplasms revealed a significant increase in long-term survival in the transplant arm versus the chemotherapy alone arm (40% at median follow-up of 51 months vs. 25% at median follow-up 32 months) **[18]**. Patients who underwent an allogeneic transplant had higher transplant-related mortality (TRM), but a lower relapse rate compared to autologous transplant patients, suggesting a graft-versus-leukemia effect. For patients without a suitable matched donor, umbilical cord blood (UCB) has emerged as a viable alternative source of hematopoietic progenitor cells. In comparison to matched unrelated donor (MUD) bone marrow allografts, UCB demonstrates a greater degree of tolerance to human leukocyte antigen (HLA) mismatches with similar rates of severe acute GVHD. Additionally, cord blood has a high concentration of donor-derived NK cells that exhibit functional cytotoxic properties, which may confer protection through a graft-versus-leukemia effect **[20]**.

In conclusion, we present a typical case of blastic NK-cell lymphoma/leukemia. This disease is highly malignant and until now, has no definite curative treatment. Appropriate therapeutic approaches to this disease should be explored.

Conflicts of interest:

None

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