Case Report:
Blastic Natural Killer (NK) Cell Leukemia
(Agranular CD4+CD56+ Leukemia)

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Abstract. Blastic NK cell lymphoma is a rare hematolymphoid neoplasm. This report illustrates an unusual presentation of this entity, namely as a primary leukemia, but without skin lesions.

Keywords: NK leukemia, plasmacytoid monocytes, CD4/CD56

Introduction

Many types of leukemia and lymphoma are thought to originate from natural killer (NK) lineage cells, either from a precursor NK cell or mature NK cell [1]. The blastic NK cell lymphoma is considered as a hematolymphoid neoplasm and proposed to be derived from precursor NK cell. It is believed that it overlaps with, or may be identical to, the entity called primary cutaneous CD4+CD56+ hemato-lymphoid neoplasm [2-6]. This entity also has been termed “agranular CD4+CD56+ hematodermic neoplasm” [3]. Interestingly, recent studies suggest that this malignancy might possibly originate from plasmacytoid monocyte/interferon-producing cells (PM/IPCs) rather than precursor NK cells [3-6].

Case Report

The subject of this report is an 85-yr-old white male who presented to the outpatient clinic with chronic fatigue and was found to have leukocytosis, anemia, and thrombocytopenia. Hematologic parameters included: white blood count (WBC), 88,000/µl with 90% blast-like cells; hemoglobin (Hb), 10.2 g/dl with mean corpuscular volume (MCV), 89 fl; platelet count, 90,000/µl. Physical examination showed slight pallor and mild splenomegaly. There was no jaundice, nor skin lesions, nor palpable lymphadenopathy, nor hepatomegaly. Flow cytometric studies were performed on whole blood. Based on the flow cytometric data, morphologic features of the leukemic cells, and results of T- and B-gene rearrangement (Figs. 1-3) a diagnosis of “blastic NK-cell leukemia” was made.

Chromosomal analysis was performed on the bone marrow specimen at Genzyme Genetics (Fairfax, VA) and reported as follows: “an abnormal clone of the cells was identified and the cells showed multiple numerical and structural abnormalities in 9 cells and the abnormal results were: 42-45, XY, del(5)(q11.2q33), add (12)(p11.2), -13, add(14)(q32),-15, +mar[cp9]/46,XY{11}.”

The patient declined to have chemotherapy. Two months later, the patient returned with worsening anemia and thrombocytopenia, blood Hb, 6.2g/dl, RBC, 1.99 x 10⁶/µl, MCV, 106.5 fl, platelets, 21,000/µl, and WBC of 100,000/µl. Physical examination was essentially unchanged. No skin nodules or plaques were present. Bone marrow biopsy revealed sheets of leukemic cells replacing marrow. Repeat flow cytometry of the marrow aspirate specimen showed leukemic cells with immunophenotypic features identical to the leukemic cells from the blood.
Fig. 1. Panel A: In the blood smear, the leukemic cells show relatively dispersed nuclear chromatin and nucleoli and no cytoplasmic azurophilic granules. Panels B and C show the leukemic cells diffusely infiltrating the bone marrow.

Fig. 2. Immunophenotyping of the leukemic cells: CD45+ low, CD56+ bright, CD4+ bright, HLA-Dr+, CD43+, CD38+ CD68+; and CD3-, CD2-, CD5-, CD8-, CD7-, CD1a-, CD79a-, CD19-, CD20-, FMC-7-, CD24-, CD11c-, kappa-, lambda-, CD34-, TdT-, CD10-, CD30-, CD16-, and CD57-. CD13-, CD33-, CD11b-, CD15-, CD14-, and CD64- (data not shown).
This case illustrates an unusual presentation of an NK cell lymphoma. Leukemic cells were blast-like and agranular with strong expression of CD4 and CD56 antigens and absence of myeloid, pan-B, or pan-T lymphoid markers. IgH and TCR gene rearrangements by PCR were both negative. Cytogenetic study showed multiple complex chromosomal abnormalities. All of these features are consistent with a blastoid NK-cell leukemia/lymphoma, a distinctive entity in the updated World Health Organization (WHO) classification [1]. The primary leukemic presentation, but without skin lesions, has rarely been reported.

Cases with features of NK cell lymphoma have long been observed. Pretrella et al [2] first reported a series of cutaneous hematolymphoid tumor with similar immunophenotypic features of NK cell lymphoma (CD56+, CD4+) and the author named the disease as “CD4+CD56+ cutaneous neoplasm.” Subsequently, similar cases have been published [3-6]. Based on the accumulated data from these cases along with recent research findings, this hematolymphoid tumor has been tentatively assigned a designation of “agranular CD4+CD56+ hematodermic neoplasm” (blastic NK cell lymphoma).

“Aggranular CD4+CD56+ hematodermic neoplasm” is considered to be a variant of blastic NK cell lymphoma. This disease typically presents with a skin lesion (nodule or plaque), frequently with cytopenia, but with or without lymphadenopathy or splenomegaly. The tumor cells have blast-like/plasmacytoid morphology with characteristic CD4+ and CD56+ and lack of cytoplasmic granules. Most of the reported cases have shown CD123+. Parenthetically, immunohistochemistry performed on a bone marrow core biopsy of our patient also revealed the expression of CD123 on the leukemic cells. The tumor cells are also CD45+, CD43+, HLA-Dr+, and in some cases CD68+. There is absence of pan-T, pan-B, or myelomonocytic antigens.

Very rarely, CD4+ and CD56+ malignancies have been reported to variably express CD2, cytoplasmic CD3, CD33, and T cell receptor gamma gene rearrangement [7,8]. No recurrent cytogenetic abnormalities were identified so far [1]. Interestingly, all of these so-called “agranular CD4+CD56+ hematodermic neoplasms” end up with prominent blood and marrow involvement. It is conceivable that our case falls within the spectrum of “agranular CD4+CD56+ hematodermic neoplasm” with predominant blood and bone marrow involvement.

The concept of blastic NK cell lymphoma originating from precursor NK cells has been challenged in view of recent research [3,6]. It has been proposed that the cell of origin of blastic NK cell lymphoma/“agranular CD4+CD56+ hematodermic neoplasm” is related to plasmacytoid monocytes/interferon producing cells (PM/IPC) [6].

Fig 3. Panel A: the gel picture shows negative gene rearrangement of IgH gene. Lane 1-DNA ladder (50 bp), Lanes 2 and 3-no DNA; Lanes 4 and 5-DNA from benign tonsil; Lanes 6 and 7-DNA from positive control (expected PCR product of 180 bp); Lanes 8 and 9-DNA from the patient’s leukemic cells. Panel B: the gel picture shows negative gene rearrangement of TCR gamma subunit. Lane 1-DNA ladder (50 bp), Lanes 2 and 3-no DNA; Lanes 4 and 5-DNA from benign tonsil; Lanes 6 and 7-DNA from positive control (expected PCR product of 120 bp); Lanes 8 and 9-DNA from the patient’s leukemic cells.
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References


