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Case Report

Can targeted therapy improve outcome in Epstein–Barr virus-negative aggressive natural killer cell leukemia: A case report

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ABSTRACT

Aggressive natural killer cell leukemia (ANKL) is a rare hematological malignancy, with only a few cases reported in the literature. The overall median survival is estimated to be less than 2 months. Moreover, Epstein–Barr virus (EBV)-negative ANKL is a rarity, with only a few being EBV-negative. We present a 27-year-old male with pancytopenia, massive splenomegaly, and no lymphadenopathy. Bone marrow (BM) aspirate flow cytometry revealed abnormal lymphocytes showing moderate expression of CD56, CD16, CD38, CD2, and CD45, dim expression of CD7 and CD117, and variable cytoplasmic CD3 and were negative for immaturity markers and other T lymphocytic, myeloid, and plasmacytoid dendritic cell markers. The BM biopsy revealed negative terminal deoxynucleotidyl transferase, confirming the diagnosis of ANKL. EBV was negative; hence, the final diagnosis of EBV-negative ANKL was offered. The patient had a progressive course despite two cycles of modified SMILE regimen and CHOP. The addition of daratumumab (anti-CD38 monoclonal antibody) to CHOP resulted in disease remission. The patient has survived for more than 18 months after diagnosis and is presently on follow-up on maintenance daratumumab, awaiting an allogenic stem cell transplant. This article aims to report rare refractory EBV-negative ANKL patients successfully managed with an unconventional regimen; hence, further studies are warranted for targeted therapy in fulminant diseases like ANKL.

Keywords: Aggressive natural killer cell leukemia, Epstein-Barr virus, CD38, Daratumumab, Monoclonal antibodies, Flowcytometry.

INTRODUCTION

Aggressive natural killer cell leukemia (ANKL) is a rare hematological malignancy, with only a few cases reported in the literature.[1] The overall median survival is estimated to be less than 2 months.[2] Moreover, Epstein–Barr virus (EBV)-negative ANKL is a rarity, with only a few being EBV-negative.[3] The diagnosis of this disease poses difficulty, and treatment is challenging. This article aims to report a rare EBV-negative ANKL patient successfully managed with an unconventional regimen.

CASE REPORT

The patient is a 27-year-old male with no previously known comorbidities. He presented initially with a fever of 1-week duration, loss of appetite and 14 kg weight loss over 2 months. His physical

examination revealed mild pallor, icterus, hepatomegaly (4 cm), and massive splenomegaly (10 cm below the left subcostal margin). No skin lesions were seen, and no palpable lymph nodes were noted. His laboratory investigations are given in Table 1.

Bone marrow (BM) revealed the presence of few atypical lymphocytes. Flow cytometry (BM aspirate) showed abnormal lymphocytes, gated at 13% of all leucocytes, showing moderate expression of CD16, CD38, CD2, and CD45 and moderate to dim CD56. These lymphocytes showed dim expression of CD7 and CD117, variable cytoplasmic CD3, and were negative for surface CD3, T-cell receptor (TCR) alpha beta and TCR gamma delta, CD4, CD8, and CD5. Myeloid markers CD13, CD33, CD64, and markers for blastic plasmacytoid dendritic cell neoplasm CD123 were also negative. Immaturity markers, including HLA-DR, CD10, CD1a, CD34, and Tdt, were negative [Figure 1]. BM biopsy revealed interstitial infiltration of CD56 and CD2-positive atypical lymphocytes with no expression of Tdt.

Based on findings of BM biopsy, flow cytometry, negative Epstein–Barr encoding region – *in situ* hybridization, and EBV deoxyribonucleic acid, a diagnosis of EBV-negative natural killer (NK) cell leukemia/lymphoma was made. The modified SMILE (dexamethasone, methotrexate, ifosfamide, etoposide, and L-asparaginase) regimen was started as first-line therapy. A contrast-enhanced computed tomography (CECT) done after two cycles of the SMILE regimen showed disease progression. There was an increase in the size of the liver and spleen, with compression of the left kidney. The retroperitoneal lymph node enlargement was also evident. In view of the progressive disease, the CHOP treatment regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) was started. However, the disease response to this regimen was also not satisfactory, and disease progression was noted in CECT after the first cycle of the CHOP regimen. Due to the rapid progression of the disease with conventional treatment, it was decided to use daratumumab (anti-CD38 monoclonal antibody) along with CHOP regimen. The patient received eight cycles of the CHOP regimen and six cycles of daratumumab. The patient attained complete remission, with regression of hepatosplenomegaly, lymphadenopathy, and normal hematological and biochemical investigations at the end

Table 1: Laboratory investigation.

S. No.	Investigation	Result
1.	Hemoglobin	Hb 101 g/L
2.	Total leukocyte count	3.5×10^9/L
3.	Platelets	70×10^9/L
4.	Absolute neutrophil count	1.8×10^9/L
5.	Peripheral blood smear	Pancytopenia. Normocytic normochromic anemia. No abnormal lymphocytes
6.	Lactate dehydrogenase	729 U/L
7.	AST	203 U/L
8.	ALT	150 U/L
9.	Serum bilirubin	1.9 mg/uL
10.	Direct and indirect Globulin test	Negative
11.	Serum ferritin	290 ug/L
12.	Serum fibrinogen	1.8 g/L
13.	Serum triglyceride	210 mg/dL
14.	Quantitative EVB DNA	Negative
15.	Bone marrow EBER-ISH	Negative
16.	Cerebrospinal fluid	Not involved
17.	HIV, HBV, HAV, HCV, and HEV	Negative
18.	Whole body FDG PET CT	Hepatosplenomegaly, no FDG avid lesion in CNS or lymph nodes were noted.
19.	NCCT PNS	Normal study
20.	NGS	No clinically significant SNV, CNV, or fusions-negative JAK-STAT pathway-associated gene mutations

AST: Aspartate aminotransferase, ALT: Alanine transaminase, EVB: Epstein–Barr Virus, DNA: Deoxyribonucleic acid, EBER-ISH: Epstein–Barr encoding region-*in situ* hybridization, HIV: Human immunodeficiency virus, HBV: Hepatitis B virus, HAV: Hepatitis A virus, HCV: Hepatitis C virus, HEV: Hepatitis E virus, FDG: Fluro-deoxy glucose, PET: Positron emission tomography, CT: Computed tomography, NCCT: Non-contrast computed tomography, PNS: Peripheral nervous system, NGS: Next-generation sequencing, CNS: Central nervous system, SNV: Single nucleotide variant CNV: Copy number variation, JAK-STAT: Janus kinase-signal transducer and activator of transcription

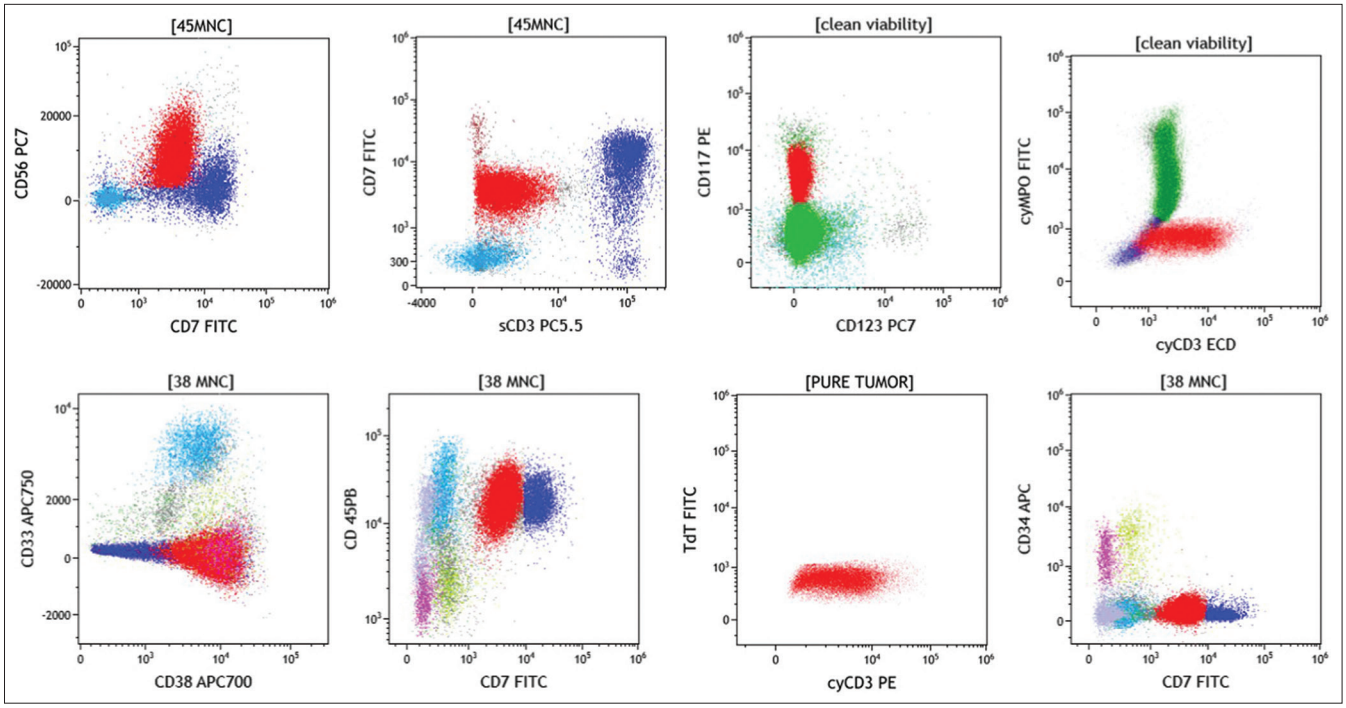

Figure 1: Representative flow cytometry plots showing moderate expression of CD45 and CD38; moderate to dim CD56, dim CD7 and CD117; positive for cytoplasmic CD3 and negative for surface CD3, TdT, CD34, CD33, CD123, and myeloperoxidase.

of the regimen. BM flow cytometry was negative for measurable residual disease. The patient has survived for more than 24 months after diagnosis and is presently on follow-up on maintenance daratumumab, awaiting allogenic hematopoietic stem cell transplant.

DISCUSSION

ANKL is a rare yet fulminant hematological malignancy of mature NK cells. It usually affects the younger age group; however, EBV-negative ANKL tends to occur in the elderly with a median age of 63 years.[3] The commonly involved sites are BM, peripheral blood, liver, and spleen. The usual clinical features are fever, hepatomegaly with hepatic dysfunction, hemophagocytosis, and disseminated intravascular coagulation. The disease has a rapidly progressive course spanning over weeks or sometimes months. The diagnosis of ANKL is challenging and sometimes delayed due to non-specific clinical features and the presence of fewer tumor cells in peripheral blood or BM.

Etiologically, ANKL has been associated with EBV. However, EBV-negative ANKL is also a well-recognized entity with a debatable prognosis.[3,4] The present case was also EBV negative but had immunophenotypic markers of mature NK cells such as CD56, CD7, and CD2. Other CD56-positive hematolymphoid neoplasms were excluded to confirm the diagnosis.

Due to the rarity and aggressive nature of the disease, there is no high degree of evidence to formulate a most effective chemotherapeutic regimen. L-asparaginase-based regimens are usually first-line therapy. Other regimen includes CHOP (with anthracycline and vincristine) and hemophagocytic lymphohistiocytosis-04 (containing dexamethasone and etoposide). Targeted therapy with a monoclonal antibody against CD38 (Daratumumab) has been utilized with gleaming prospect, but still is not standard of care.[5,6]

In the present case, daratumumab was utilized as a salvage therapy for progressive disease under the SMILE and CHOP regimen. The combination of daratumumab with the CHOP regimen resulted in excellent disease remission.

CONCLUSION

A rare case of EBV-negative ANKL is presented here. Despite the poor prognosis of the disease and the patient being refractory to two standard treatment regimens, the addition of daratumumab resulted in disease remission and increased survival of the patient. Hence, further studies are warranted for targeted therapy in fulminant diseases like ANKL.

Ethical approval

The research/study approved by the Institutional Review Board at Command Hospital Western Command Chandimandir, number 01//JAN/CHWC/2024, dated 08th January 2024.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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