

Small Cell Variant of Anaplastic Large Cell Lymphoma Presenting As Leukaemia: A Case Report and Review of Literature

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Abstract

Background: Anaplastic large cell lymphoma with a small cell pattern is a rare T-cell lymphoma. This condition is frequently seen in young patients and should be considered in patients presenting with leucocytosis and constitutional symptoms. We report a case of small cell variant (SCV) of ALCL in a 68 year old man diagnosed by ALK immunohistochemistry (IHC) and cytogenetic analysis. The limitations of using only morphology in diagnosing this rare variant, has also been emphasised.

Keywords: Anaplastic large cell lymphoma; small cell variant; T-cell lymphoma; ALK immunohistochemistry

Introduction

Anaplastic Large Cell Lymphoma (ALCL) is a peripheral T-cell, non-Hodgkin lymphoma (NHL). ALCL represents 20% to 50% of the large cell lymphomas in children and 2% to 8% of NHLs in adults [1,2]. ALCL constitute a heterogeneous group of hematopoietic neoplasms that are characterized by the presence, of varying degrees, of large, pleomorphic "hallmark" cells [3]. ALCL consists of three major groups: primary systemic ALK (Anaplastic lymphoma kinase) positive ALCL, primary systemic ALK negative ALCL, and primary cutaneous ALCL. There are many morphological variants of ALCL of which the small cell pattern variant accounts for only 5–10% of cases. It is important that a detailed look into this rare small cell variant because, unlike other morphological variants, leukaemic manifestation is common [3-5]. Approximately 60% of ALCL cases are associated with chromosomal translocations involving ALK [6] on chromosome 2p23, with the most common translocation being t(2;5)(p23;q35), which is found in 70-80% of cases of ALK+ ALCL [7]. Clonal T-cell populations may be demonstrated in the peripheral blood in a variety of clinical conditions [8]. Lymphocyte morphology usually speaks out the diagnosis of ALCL. Nevertheless, presence of small cells in this variant reduces the index of suspicion. So phenotyping and cytogenetic analysis of the clonal population becomes valuable in establishing this diagnosis.

Case report

In October 2014, a 68 year-old man presented to Lady Hardinge Medical College, New Delhi; with high grade fever with night sweats and headache with momentary blurring of vision in left eye. He was diagnosed with temporal arteritis and was started on prednisolone 30mg daily. He responded well and was asymptomatic till July 2015, when again he developed high grade fever with generalised weakness, fatigue and cough for 2 weeks. On physical examination, he had no icterus, no lymphadenopathy, no hepatosplenomegaly, no sternal tenderness. CVS and RS examination were normal. The hemogram results were WBC count 2,95,000/ μ L ($295 \times 10^9/L$); hemoglobin 10.7 g/dL (106 g/L); platelet count $76 \times 10^3/\mu$ L ($76 \times 10^9/L$). Patient negative for viral markers – HTLV I & II, HIV, HCV & CMV.

Haematological findings

Peripheral blood film showed hyperleucocytosis with atypical lymphocytes, which were two times the size of small mature lymphocyte with high nuclear-cytoplasmic ratio and scant agranular cytoplasm. Many cells showed prominent nuclear clefting, indentation and slightly opened chromatin (Figure 1). Atypical lymphocytes:83%; Neutrophils:15%; Lymphocyte:2% Bone Marrow aspiration smear showed similar atypical lymphocytes with marked suppression of erythroid and myeloid series. Few megakaryocytes were seen.

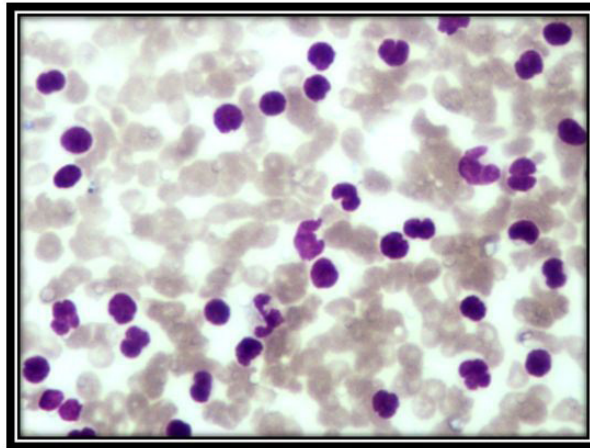


Figure 1: Peripheral smear shows atypical lymphocytes with scant agranular cytoplasm, prominent nuclear clefting and indentation [wright-giemsa stain, 400 xs]

Histopathology

Bone marrow biopsy smears showed bony trabeculae enclosing marrow spaces filled with atypical lymphocytes, few neutrophils and occasional megakaryocytes.

Flow cytometry: Flow cytometric analysis of bone marrow and peripheral blood samples showed that the Atypical lymphoid cells were positive for cCD3 (Figure 2), sCD3, CD4 (Figure 3), CD2, HLA DR, CD13, CD7 (Figure 4) & TCRαβ and negative for CD5, CD8, CD56, TCRγδ, myeloid markers, B cell markers & immaturity markers. Mature T cell neoplasm, possibly T-prolymphocytic Leukaemia was suggested.

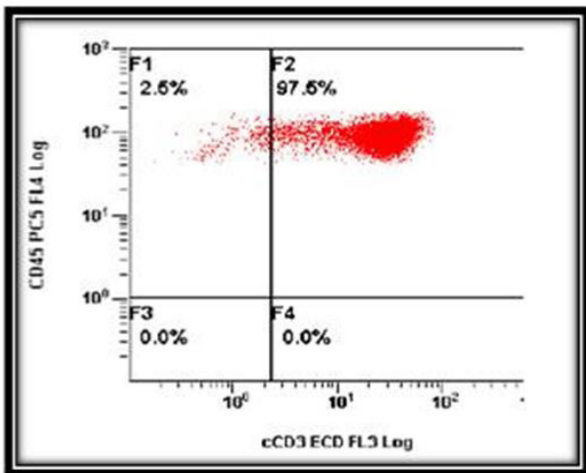


Figure 2: Flowcytometry of peripheral blood - atypical lymphocytes are showing CD3 expression

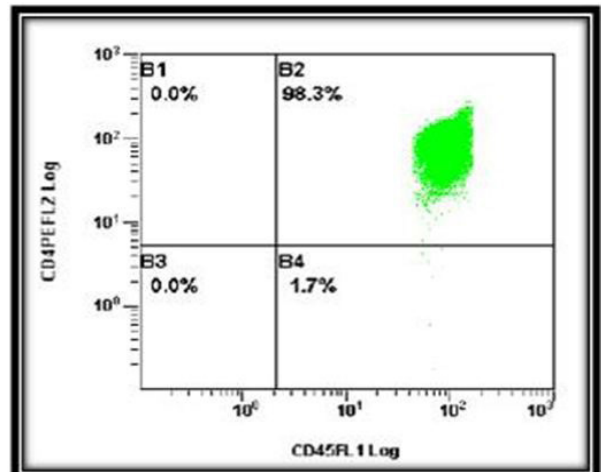


Figure3: Flowcytometry of peripheral blood - atypical lymphocytes are showing CD4 expression

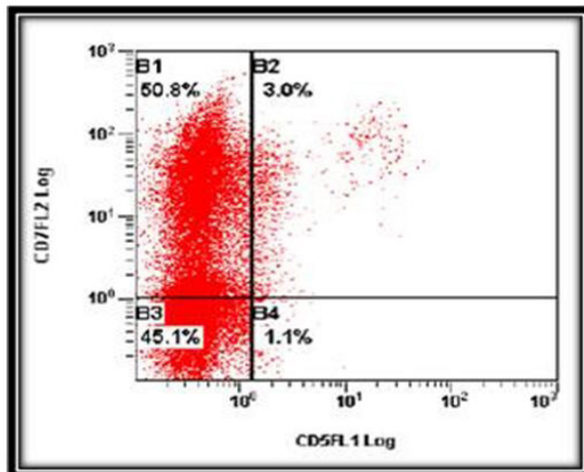


Figure4: Flowcytometry of peripheral blood -Decreasing intensity of CD 7 expression in atypical lymphocytes

Immunophenotyping: Immunohistochemical stains were performed on a peripheral blood cell block (Figure 5) preparation and on the bone marrow biopsy specimen. The tumor cells were positive for CD3, EMA (Figure 6) & ALK (strong nuclear & cytoplasmic positivity) (Figure 7), while negative for CD5, CD30 (Figure 8), CD20, CD19, CD23, MPO and glycoporin.

CT chest and Abdomen showed multiple non-necrotic mediastinal & retroperitoneal nodes and mild hepatosplenomegaly.

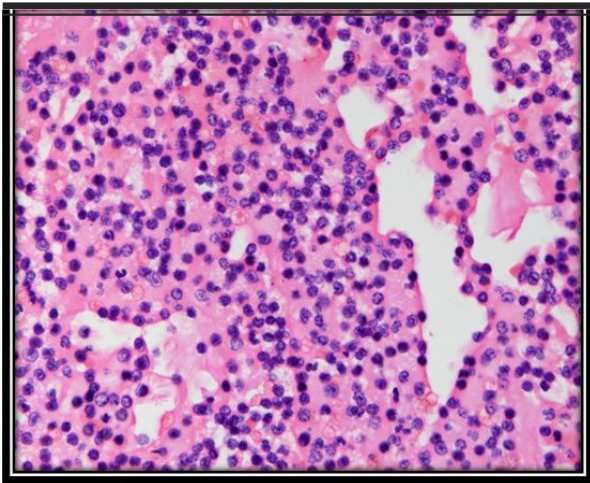


Figure 5: Cell block smears show atypical lymphocytes and few neutrophils [H&E stain,100x]

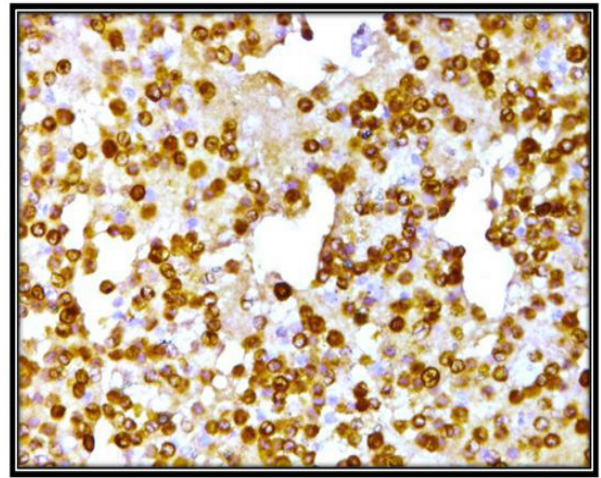


Figure 6: EMA immunostain positivity in atypical lymphocytes [Immunohistochemistry,400x]

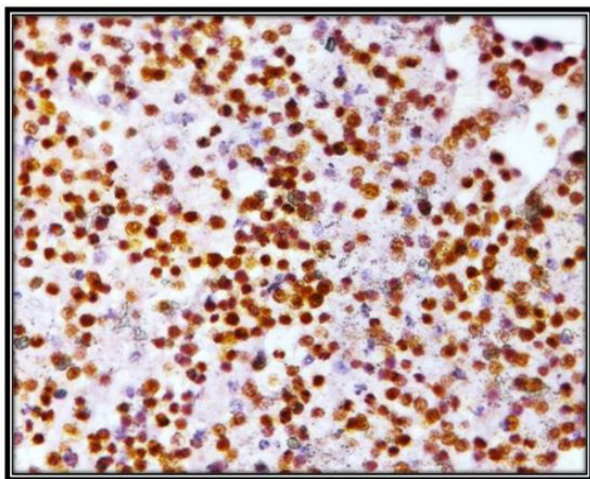


Figure 7: Atypical lymphocytes shows Anaplastic lymphoma kinase immunostain (ALK) nuclear positivity [Immunohistochemistry,100x]

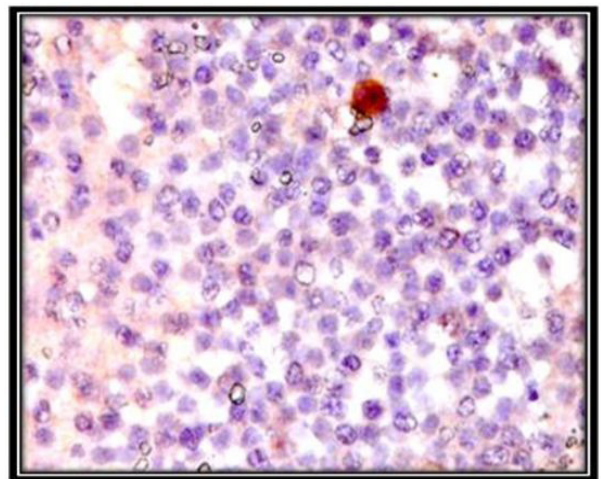


Figure 8: Atypical lymphocytes are CD30 immunostain negative [Immunohistochemistry,400x]

Cytogenetics: Cytogenetic analysis (GTG Banding) of a bone marrow sample showed the following karyotype: 46,XY,t(2;5)(p23;q35)[20]. There was a balanced reciprocal translocation between the short arm of chromosome 2 and the long arm of the chromosome 5, between the regions p23 and q35 respectively, found in all metaphases studied.

Diagnosis and treatment

The combined morphologic, immunophenotypic and cytogenetic findings were indicative of ALK positive Anaplastic large cell lymphoma- small cell variant. Patient was started on CVP regimen (cyclophosphamide, vincristine and prednisolone). He later passed away after a month despite treatment.

Discussion

Clinically, patients with ALK+ ALCL have a median age in the thirties and present with more extranodal involvement than ALK- patients [9]. However, our patient was 68 years old with ALK+ALCL. While leukemic peripheral blood involvement is rare in classic ALCL, it is common with the small cell variant which our patient had.

On the basis of the clinical presentation and examination of the peripheral blood smear, the diagnosis of this rare form of ALCL, may be difficult, because hyperlymphocytosis may suggest a viral infection [10]. In our patient a diagnosis of hyperlymphocytosis due to viral infection was considered as possibility and later ruled out.

Within the ALK+ ALCL group, there are morphological subgroups: the most common classic type, and less common lymphohistiocytic and small cell variants.

The classic type comprises about 70% of cases and is characterized histologically by sheets of “hallmark cells,” large cells with abundant cytoplasm and a horseshoe-shaped nucleus with multiple nucleoli surrounded by a prominent, pale Golgi region [2,11]. These cells can be found in all ALCL subtypes.

The lymphohistiocytic variant comprises 5-10% of cases and is characterized by tumor cells smaller than those in the common type that are often masked by a large number of histiocytes that do not proliferate despite monomorphic appearance. Immunostaining for CD-30 and Ki-67 is particularly important in this variant to identify tumor cells and to distinguish ALCL from malignant histiocytosis [2,11].

The small cell variant of ALK+ ALCL, was first described in 1993 by Kinney, et al.[12] This variant comprises 5-10% of cases, affects primarily younger patients (median age 14) [11], and is characterized morphologically by a mixture of small, medium, and large lymphoid cells with the nuclei of the small and medium cells often being irregular [2,10]. In our case, Large cell morphology was not clearly evident in the blood. Hence ALCL was not suspected initially. However, with 83% atypical lymphocytes in peripheral smear, acute leukemia was considered.

Flow cytometry for phenotyping, pointed towards mature T cell neoplasm possibly T-cell prolymphocytic leukemia. Interestingly, while the large cells are always CD30+, the small cells are often CD30 negative [13]. Absence of CD30 expression in our patient's neoplastic clones has reduced the index of suspicion. Hence, even now the possibility of ALCL was not enunciated.

IHC (AKL positivity) and cytogenetics (translocation) helped in arriving at the diagnosis.

Approximately 60% of ALCL cases are associated with chromosomal translocations involving ALK [on chromosome 2p23 [6]. Our patient also has this translocation. The fusion gene product, NPM [nucleophosmin]-ALK, is a functionally active tyrosine kinase that is associated with malignant transformation of the affected cells [14]. Leukaemic picture or even subcutaneous presentation [15] is common in small variant.

Conclusion

Leukaemic presentation, even if large hallmark cells are not seen in Peripheral smear or even if CD30 expression is negative, should raise suspicion about small cell variant of ALCL. ALK immunohistochemistry and cytogenetics for ALCL translocation has to be performed immediately to arrive at a definite diagnosis because unlike other variants, this rare small cell variant of ALCL has rapid progression and a very poor prognosis. Age-group restriction should not limit the suspicion.

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