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An Indolent Natural Killer Cell Leukemia Presenting with Bilateral Ankle Arthritis and Low Grade Fever

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Abstract

NK-cells are morphologically similar to other lymphocytes but immunologically different from them. They have variable expression of one or other T-cell markers but essentially not expressing surface or cytoplasmic CD3 except a minor population of cytoplasmic epsilon CD3.Clinically neoplasm of NK-cell presents as either aggressive or indolent lymphoma/leukemia behaving differently from neoplasm of T-cell and B-cell. Till now treatment protocol is not well-defined and effective for this resistant type lymphoma/leukemia. In this case, patient presented with low grade fever and bilateral ankle arthritis and NK-cell lymphocytosis in peripheral blood and bone marrow. Because NK-cell leukemia is rare and presentation of this case is not totally fitting in aggressive or indolent variant of NK-cell leukemia, thus I report this case.

Key Words: *Natural killer cell, Large Granular Lymphocyte, Immunophenotyping, Cell markers*

Introduction

Lymphocytes may be T-Lymphocytes, B-Lymphocytes or Natural Killer cells. Natural Killer cells make up approximately 10-15% of the peripheral blood lymphocytes that are characterized by lack of T-cell receptor complex, lack of gene rearrangement for T-cell receptor and immunoglobin genes. The features are also substantiated by NK cells leukemia/lymphoma. NK cells are somewhat larger than small lymphocytes & they contain abundant azurophilic granules. So, they are also called large granular lymphocytes.NK cells are empowered with an innate ability to lyse a variety of tumour cells & virally infected cells.

Although they share some immunophenotypic markers with T-cells (i.e. CD2, CD7), NK cells do not rearrange T-cells receptor genes & they are CD3 negative.[1] Two cell surface markers, CD56

& CD16 are widely used to identify NK cells.[2,3] NK cell leukemia / lymphoma are very rare.[4]

In this article we report a case of indolent Natural Cell Leukemia which primarily presented with low grade fever, bilateral ankle arthritis & peripheral lymphocytosis.

Case Summary

A 39 years female was asymptomatic before January 2006, and after that she gradually developed bilateral ankle arthritis and low grade fever and presented in the department of Immunology of Super-speciality health centre where she was treated with analgesic, local methylprednisolone injection & antibiotics. Her leg pain & swelling were decreased but fever persisted. Low grade fever continued without any systemic symptom & clinical deterioration. She had no lymphadenopathy or nasal mass.

At the time of presentation she had mild anemia, other hematological & biochemical parameters were normal. She was again evaluated for fever after four month & first time she was detected with abnormal hemogram i.e. HB: 10.5 gm/dl, TLC: 25100/dl & lymphocytes 80%. {Figure. 5, 6}The provisional diagnosis of CLL was made. During further follow up she had fluctuating abnormally high level of TLC & lymphocytosis associated with low grade fever. Bone marrow aspiration & biopsy were done, aspiration showed mild increase in lymphocytes & biopsy showed mild interstitial lymphocytosis. {Figure .7, 8))She underwent ultrasound abdomen but no lymphadenopathy & hepatosplenomegaly were seen. She had also skeletal nuclear scanning but no any bony primary or metastatic lesion seen. She had normal CT & MRI Head.

CSF showed not any abnormal cell. Peripheral blood smear examination was done to know morphology of lymphocytes, 75% lymphocytes were granular lymphocytes.{figure5,6)Bone marrow aspiration & bone marrow biopsy were done twice in this case, first to know involvement of bone marrow & showed mild lymphocytosis. Second time bone marrow aspiration was done to take sample for immunophenotyping. CLL panel was used to confirm diagnosis of CLL. Surprisingly all T-lymphoid & B-lymphoid markers were absent except CD2 & CD7. {Figure1,4}Both surface & cytoplasmic CD3 markers were absent. [1, 2]Provisional diagnosis of Natural Killer Cell expansion was made. Thus Further NK cell panel was used both on peripheral blood & bone marrow aspirate, 60 %of all lymphocytes were CD56+/CD3- cells but CD16 was negative on all lymphocytes. [2]

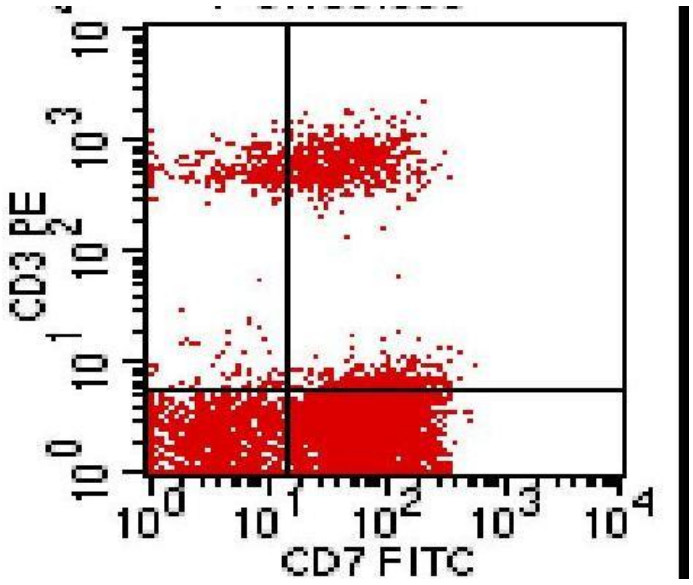


Figure 1. Dot plot presentation of gated population shows majority of cells is positive for CD7 and negative for CD3 suggestive of NK-cell

population. A minor population is positive for both CD3 and CD7 denoting population of T-lymphocytes.

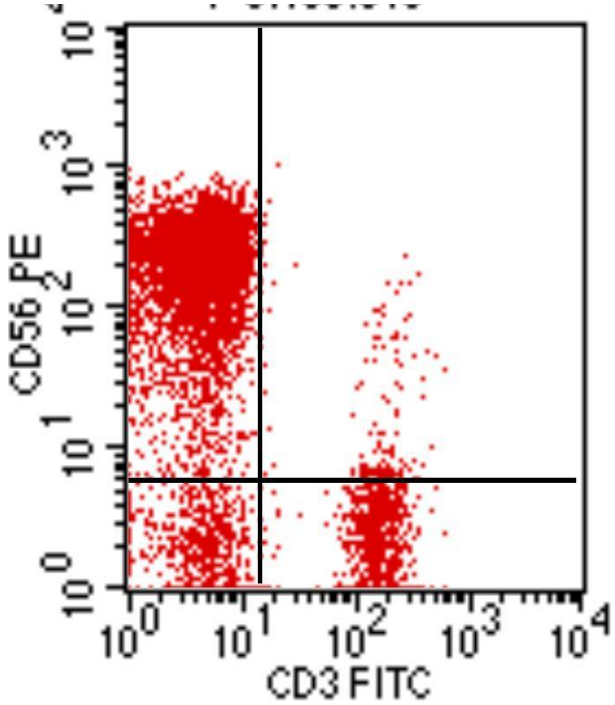


Figure 2. Gated population shows positivity for CD56 and negativity for CD3 confirming NK-cell nature of cells.

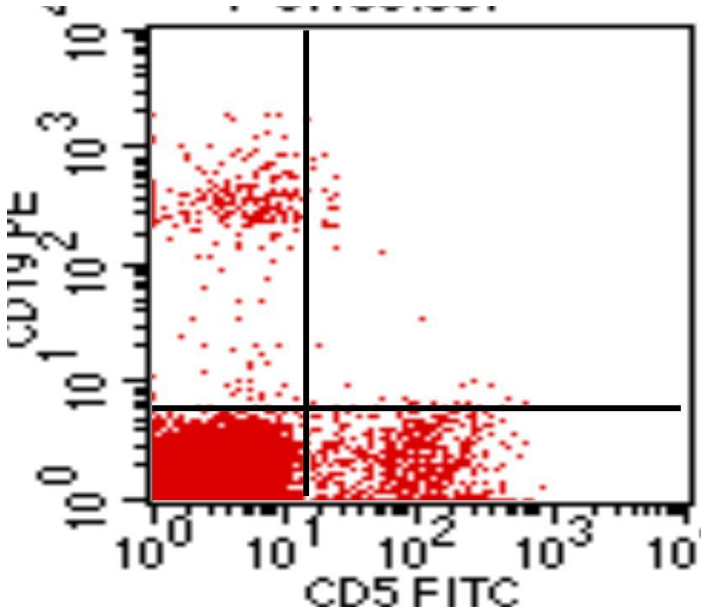


Figure 3. Almost all gated cells are negative for both CD19 and CD5.

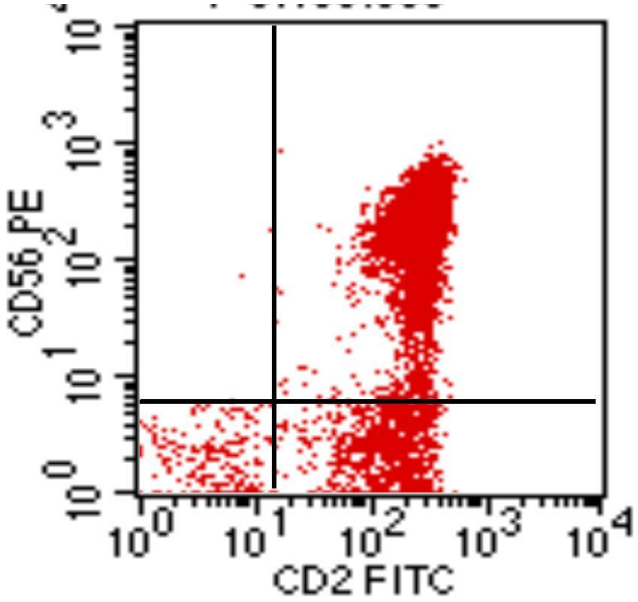
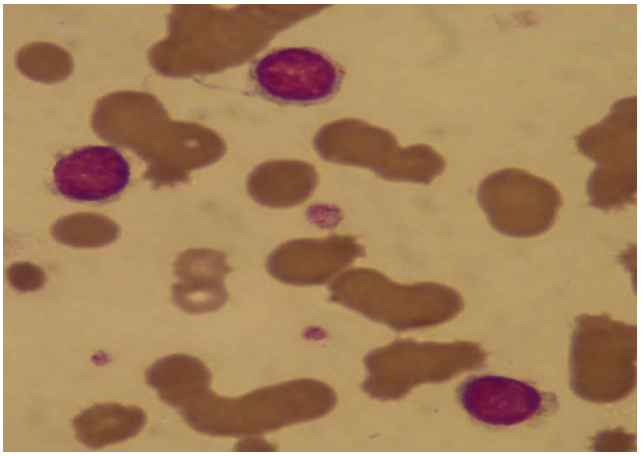


Figure 4. Majority of gated cells are positive for both CD56 and CD2 denoting NK-cell could be positive for T-cell markers.



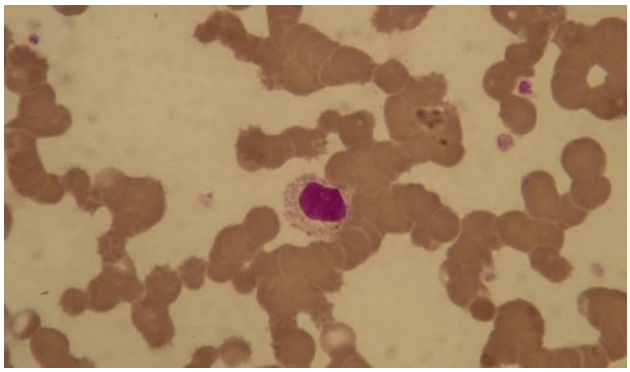
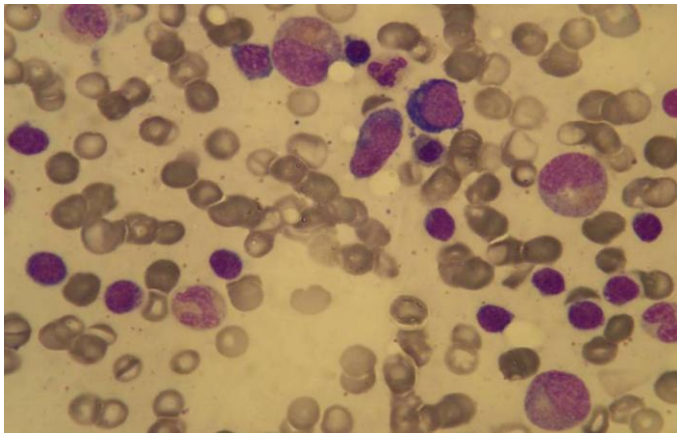


Figure 5 & 6. Peripheral blood smears show large granular lymphocytes.



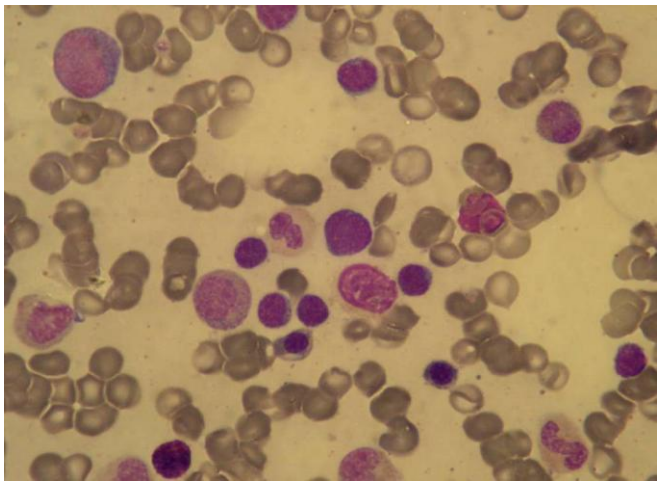


Figure 7 & 8. Bone marrow smears show atypical lymphoid cells and normoblasts.

Discussion

NK-cell neoplasms are aggressive and resistant type leukemia/lymphoma that are classified as aggressive NK-cell leukemia, extranodal NK/T-cell lymphoma, nasal and extra nasal type, and Blastic NK-cell lymphoma.{1} NK-cell disorder may present as NK- cell lymphoproliferative disorder, also known as chronic NK-cell lymphocytes or NK-cell large granular lymphocyte lymphocytosis with non-progressive course.{2} It occurs in adults. They are usually asymptomatic but occasionally have vasculitis. {3}There is no fever, hepatosplenomegaly or lymphadenopathy. {4}

In this case, course of patient was between aggressive and Indolent NK-cell lymphoproli-feration. {5}Patient presented with bilateral ankle arthritis that could be manifestation of vasculitis, however this was not proved by biopsy or other investigations in this case. Presentation and follow-up of this patient was not aggressive i.e. without multi-organ failure and rapid clinical deterioration but only low grade fever and mild arthritis. Low grade fever is not mentioned in non-neoplastic proliferation of NK-cell. Thus this case did not fit either in aggressive NK-cell leukemia or indolent NK-cell lymphoproliferative disorder. It denotes NK-cell expansion with possible progression of disease in aggressive NK-cell leukemia.{5}

NK- cells are large granular lymphocytes indistinguishable morphologically with large granular T-cell lymphocytes but they are typically positive for CD56 and negative for surface and cytoplasmic CD3.{1,3}Thus Immunophenot-yping of peripheral blood or bone marrow is must for recognition of NK-cell.

Conclusion

In Natural Killer Cell Leukemia NK cells may show positivity for CD56 and negativity for CD16 but consistently negative for CD3 & also may present with atypical features i.e. bilateral ankle arthritis & low grade fever denoting progressive nature of disease that could culminate in aggressive NK-cell leukemia.

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