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Case Report
Persistent Thrombocytopenia

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Persistent Thrombocytopenia Post Autologous Transplant In A Case Of Extra Nodal Nk Cell Lymphoma

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Natural killer (NK)-cell lymphomas are a rare type of lymphoid malignancy with predominantly extranodal nasal involvement leading to destruction of midline head and neck structures. This article presents a case of extranodal nasal type NK cell lymphoma which even after aggressive treatment relapsed in leukemic form with no evidence of lesion at the primary site or any solid organ. This case report aims to highlight the importance of careful peripheral smear examination, knowledge of flow cytometry in early and accurate diagnosis of leukemic spillover of this rare entity and the need for aggressive treatment.

Keywords: NK/T-cell non-Hodgkin lymphoma, Aggressive NK cell Leukemia

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Introduction

Natural killer (NK)/T-cell lymphomas (NKTCLs) fall under non-Hodgkin lymphomas which are mostly extra nodal, frequently of NK or (rare) T-cell origin, being closely related to the Epstein-Barr virus (EBV) [1].

The World Health Organization (WHO) classifies NKTCL into Extra nodal(nasal or non-nasal), aggressive NK cell leukemia and Chronic lymphoproliferative disorder of NK cells or NK-large granular lymphocytic leukaemia (NK-LGLL) as per WHO 5th edition[2].

Nasal type NKTCL, previously referred to as lethal midline granuloma or angiocentric T-cell lymphoma, involves the upper aero-digestive tract with the nasal cavity, nasopharynx, paranasal sinuses, tonsils or palate. Non-nasal NKTCLs frequently involve the skin, testis or gastrointestinal tract, but they can affect many other sites [3]. The disseminated type, as the name implies, can involve many organs, along with a concomitant leukemic phase [4].

We hereby present a case report of the relapsed case of extranodal NK-T cell lymphoma which had a rare presentation at relapse as a disseminated disease without any evidence at the primary site of origin or any solid organ confirmed by PET-Scan of the patient.

Case report

A 55-year-old gentleman presented with nasal stuffiness and blockage in the ENT department in November 2022 for which he underwent functional endoscopic sinus surgery and septoplasty. The tissue was sent for histopathological examination (Fig 1) which revealed **Extra nodal NK T Cell Lymphoma**. (CD2, CD3 and CD56 positive).

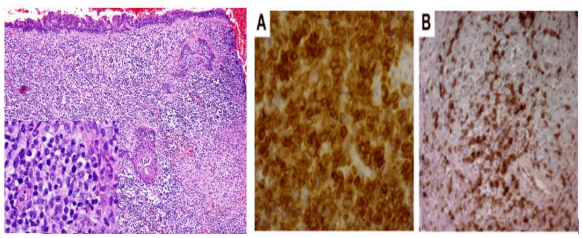


Fig -1. HPE – 10X(Dense infiltration of sino nasal mucosa by lymphocytes. Inset -40x. IHC (40X) A – CD3 B- CD56

A staging bone marrow study was done at that time which did not show signs of involvement by the lymphoma. EBV testing by PCR was positive and revealed 1,75000 copies. He fell under Lugano Stage III and CNS IPI -3. He was started on chemotherapy as per the P-GemOx protocol. He completed four cycles of chemotherapy on Jan 23. Post chemotherapy he also underwent Radiotherapy and received 44 Gy external beam radiotherapy by IGRT in 22 fractions in March 2023. He underwent an Autologous bone marrow transplant in June 2023. The protocol used was the BEAM protocol. (Carmustine, Cytarabine, Etoposide, Mephalan). Total peripheral blood stem cell dose 2.5*10 6 /kg. Post-transplant hospital stay was relatively uneventful with no major complications/infections with counts started improving on Day +10.

However, only two months after autologous stem cell bone marrow transplantation, he developed fever, vomiting, and abdominal pain in August. CBC revealed isolated thrombocytopenia which when reviewed by peripheral smear examination showed 70% abnormal lymphoid cells that were moderate to large, moderate N: C ratio, hyperchromatic nucleus, and prominent nucleoli with the majority of them showing azurophilic granules (LGLs) (Fig -2). Many of them have blastoid morphology along with marked thrombocytopenia. Bone marrow done a day later showed infiltration by abnormal lymphoid cells with similar cytomorphology. Sections from bone marrow biopsy variably cellular marrow spaces with an show cellularity of ~50-55% with diffuse infiltration of the marrow by abnormal lymphoid cells seen interstitially as well as in sheets and clusters. There was Grade 1 fibrosis.

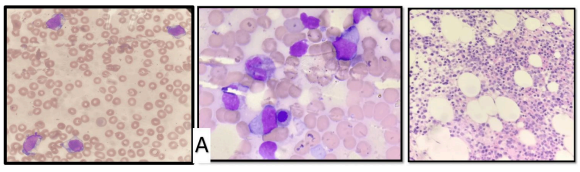
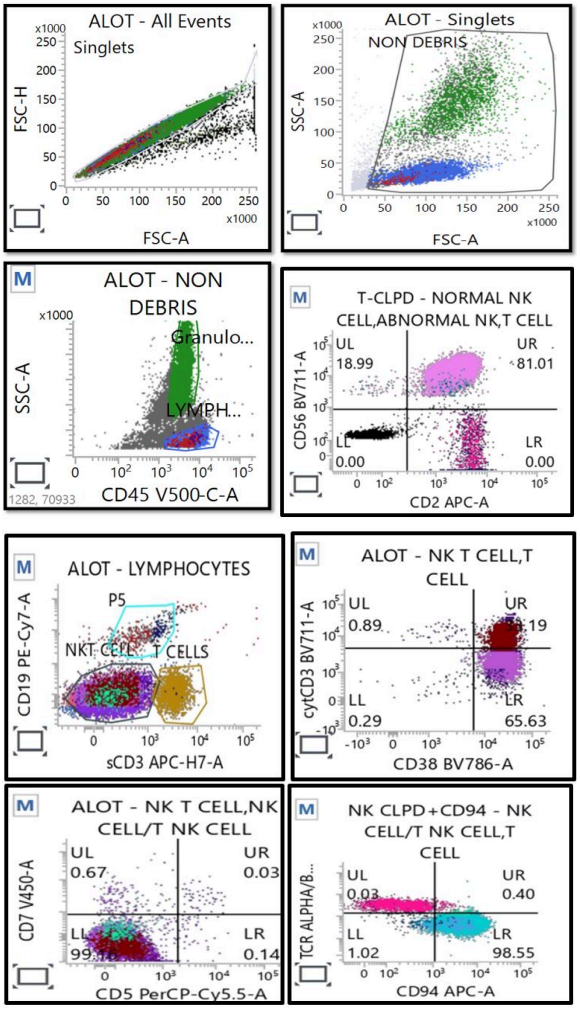


Fig -2 (a Peripheral smear, b- Bone marrow)– Large granular lymphocytes with blastoid morphology. (c) Bone marrow biopsy - diffuse infiltration of the marrow by abnormal lymphoid cells

Flow cytometry was done from peripheral blood which showed a cluster of abnormal lymphoid cells which had bright CD45 and low to intermediate Side scatter.

On further gating and analysis of the suspected population, these cells were found to be positive for CD56, CD2, cyt CD3 and negative for sCD3, CD7, CD5, CD4, CD8, CD16 and CD57 suggestive of NK cells. These cells showed bright tight clustering on CD94, CD38 and HLA-DR (Fig-3) and hence a diagnosis of relapse of extranodal N K cell lymphoma in disseminated form was given. A PET Scan was repeated at this stage which did not reveal any nasal or non-nasal solid organ involvement, which was a relatively rare presentation of a rare lymphoma (Fig 4)

He was started with one cycle of the Msmile regimen (modification of the SMILE regimen with dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide incorporating pegylated asparaginase). Post that he had developed cytopenias and soon succumbed to infections.



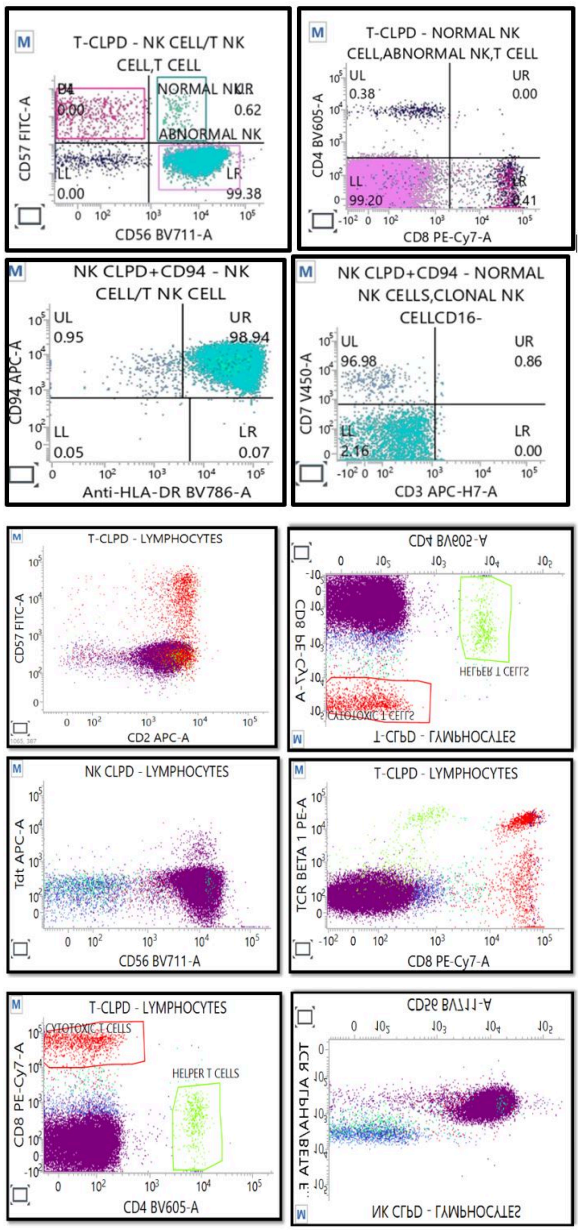


Fig -3: Flowcytometric plots of extranodal NK/T cell lymphoma/leukemia.

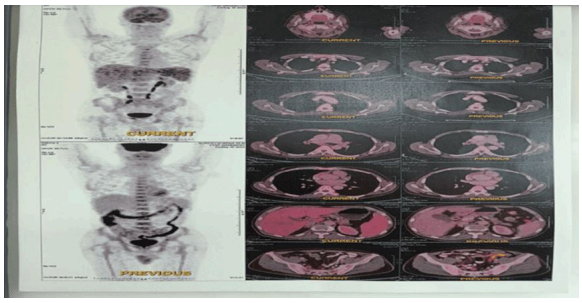


Figure -4. PET Scan – Comparison between at diagnosis and at relapse.

Discussion and Review of Literature

Natural killer (NK)/T-cell lymphomas (NKTCLs) come under the category of non-Hodgkin lymphoma which are frequently extranodal, most of them of the nasal type. As for its epidemiology, a higher incidence has been observed in Asia as compared with Europe (22 vs. 5%) with an average life expectancy of less than a year. NKTCL appears most frequently in patients over the age of 60 years. They are identified in 12% of lymphoma patients, 68% of them having the nasal type, 26% extra nasal type, and 6% aggressive or unclassifiable type [5].

Nasal-type lymphoma is frequently located in the upper aero-digestive tract: nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx and larynx, being invariably associated with the Epstein-Barr virus (EBV). The immunohistochemistry profile features include CD3+, CD43+, CD45RO+, CD56+, EBV+, CD8+, Epstein-Barr virus-encoded small RNA-positive (EBER+), with positivity for cytotoxic granular proteins [6,7]. The extranodal pattern of involvement seems to be connected with the CD56 marker, which is the neural cell adhesion molecule (NCAM) possessing hemophilic connection properties. The neoplastic cells are thus redistributed to other sites and evolve as new malignancy sites [8]. The skin is the most common site for NKTCL dissemination [9]

The general manifestations of NKTCLs include signs and symptoms located mainly in the face and neck regions: facial pain, diplopia, visual impairment, eyeball protrusion, eyelid ptosis, pupil anomalies, nasal obstruction, refractory sinusitis, velo-palatal motor disturbances, cranial nerve neuropathies, intra-orbital and intrasinus masses. Other associations consist of respiratory failure and liver and spleen enlargement.

FOXP3+ regulatory T cell expression of tumour-infiltrating lymphocytes is related to the early stage and predicts a better prognosis. Negative prognostic markers include age > 60, extranasal disease, B symptoms, elevated beta 2 microglobulin, soluble IL2 > 600 U/ml, C reactive protein > 1 mg/dl, high levels of serum or plasma cell-free EBV DNA by quantitative PCR and Stage III / IV[9,10].

Patients with aggressive NK-cell leukaemia have more prominent hepatosplenomegaly and lack the skin lesions occasionally found with extranodal NK/T-cell lymphoma. Expression of CD16 also is helpful, because this marker is negative in extranodal NK/T-cell lymphoma[11].

The therapeutic approach to extranodal NK/T-cell lymphoma is based on several factors, such as the age of patients, the extent of the disease, potential toxicities, and survivorship.

Patients with nasal disease (stage I–II) may be treated with concurrent chemoradiotherapy (CRT) regimens such as DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) with radiation therapy (RT),or VIPD (etoposide, ifosfamide, cisplatin, dexamethasone) with RT. Other regimens that may be considered include sequential CRT with modified SMILE [dexamethasone (steroid), methotrexate, ifosfamide, pegaspargase, and etoposide] with RT,and sandwich CRT with P-GEMOX (pegaspargase, gemcitabine, and oxaliplatin) with RT[12].

At the end of induction therapy, patients should undergo an evaluation with PET/CT scans,ear, nose, and throat examination, and EBV viral loadto establish remission status as we have done in our case. Results from PET/CT scans are interpreted using the Deauville criteria [13]

Patients with nasal disease (stage I–II) with complete remission (disappearance of all disease) may be observed without further treatment. In contrast, those with partial remission are treated as refractory diseases. In patients with nasal disease (stage IV) or extra nasal disease (stage I–IV) and relapsed/refractory disease hematopoietic stem cell transplant may be considered.

Conclusion

Our case is unique in a presentation at relapse because it presented as cytopenias (anaemia and marked thrombocytopenia) with the presence of abnormal aggressive-looking large granular lymphocytes present in both peripheral blood and bone marrow, suggestive of spillover or disseminated form of extranodal NK cell lymphoma, however, PET Scan did not reveal increased FDG uptake in any solid organ even at

The primary site. Also, our case highlights the aggressive nature of the tumour as it relapsed in 4 months after standard chemotherapy followed by autogenic stem cell transplantation. Hence, our case underlines the importance of not only early morphological and flow cytometric diagnosis of this rare lymphoma but also the need for the development of newer drugs/immunotherapy to cure it.

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