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Short Communication

Relapsed EBV-negative aggressive NK cell Lymphoma of the orbit and scalp - A Case Report with review of literature

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ABSTRACT

Introduction: Nasal NK/T-cell lymphoma is a rare extranodal large cell lymphoma that involves the nasal cavity. In majority of cases, Epstein Barr virus is present and Immunophenotype shows CD3 and CD56 positivity. Loco-regional relapse is very common with poor prognosis.
Case Report: We report a case of Relapsed NK cell Lymphoma of the orbit and scalp region in a young boy with EBV negativity, CD3 negativity and clinically aggressive disease. Despite aggressive treatment, our case relapsed early and was complicated by prolonged pancytopenia, CNS involvement and patient died less than one year following diagnosis.
Conclusion: NK cell lymphoma is an aggressive cancer with high mortality. Multidisciplinary modalities are essential to treat the NK cell lymphoma with radiotherapy, chemotherapy, newer agents, and hematopoietic stem cell transplantation.

1. Introduction

Epidemiologically, Natural killer/T-cell lymphomas tend to affect mainly Asian and South American patients (3% to 10%) and are associated with Epstein-Barr virus seropositivity.[1] They are extremely aggressive and carry high mortality rates.Common presentation of nasal type are midline mass with obstruction, nasal bleeding, and perforation of the hard palate.[2] Microscopically it is marked by aggressive angioinvasion in a background of CD3+ and CD56+ atypical lymphocytes and inflammatory cells.[3] The prognosis is relatively poor with a 5-year cumulative survival rate of approximately 40%.[4] Concurrent chemotherapy with radiotherapy for early stage while chemotherapy alone is the mainstay of treatment for advanced stages.[5] Autologous or allogeneic hematopoietic stem cell transplantation has been considered in advanced disease with unclear prognostic benefits. Relapse is very common in local site along with invasion of orbit however metastasis to scalp region is not so common.

2. Case Report

A 22 years old male presented with history of fatigue, left nasal obstruction and swelling over the left side of neck for 2 months. There was no history of fever, nightsweats, itching, weightloss. Patient underwent FNAC at local hospital which was suggestive of NHL-Large cell lymphoma. He was then referred to our hospital for further evaluation and management. PET CT scan revealed metabolically active enhancing soft tissue involving the left ethmoid sinus and left upper nasal cavity with erosion of medial wall of left maxillary sinus. It also showed metabolically active cervical (L>R), left axillary, left deep pectoral and left superior mediastinal Lymphadenopathy along with metabolically active focal skeletal lesions suggestive of bone marrow deposits. Usg guided biopsy of the cervical lymphnode revealed neoplastic cells positive for CD56 and negative for CD20, CD3, CK20, CK7, EBER, CD30 and ALK suggesting NK lymphoma. Bone marrow aspiration, biopsy

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revealed in favor of a lymphomatous involvement of the marrow with NK cell.

Patient was diagnosed as Nasal type NK lymphoma stage 4A with IPI high score .He was planned for SMILE based systemic chemotherapy +/_ radiotherapy as per the standard protocol. He received 4 cycles chemotherapy with SMILE protocol. Post chemotherapy reassessment with PET CT scan showed near total interval resolution of previously noted heterogeneously enhancing soft tissue mass lesion involving the left ethmoid air cells, adjacent left superior – posterior nasal cavity, and superomedial left maxilla. It also showed significant interval regression of metabolically active cervical (L>R), left axillary, left deep pectoral and left superior mediastinal lymphadenopathy along with partial interval regression of previously noted focal skeletal hyper metabolism. BMA biopsy revealed hypercellular marrow with no definite evidence of lymphomatous involvement of marrow. Patient was planned for consolidation by stem cell transplantation.

One month later, patient presented with increased cervical Lymphadenopathy which on biopsy was proven as consistent with Relapsed NK Lymphoma. In view of aggressive status of the disease and early relapse, Patient was further planned for 2 cycles of 2^{nd} line chemotherapy with ICE regimen reduced dose with concurrent radiotherapy which will be followed by bone marrow transplantation. Post 1^{st} cycle of ICE chemotherapy, patient developed severe pancytopenias, bleeding and infection. Patient was started on radiation therapy but in view of low counts, nasal bleed, hematuria and malena, radiotherapy was with held.

After about 1 month of the 1^{st} cycle ICE, patient developed few lumps over the scalp of size about 2*3 cm as shown in FIG 1 of which biopsy was done which confirmed to be relapsed disease as shown in FIG 2. Patient further developed multiple new lesions over the scalp and sternum with proptosis of right eye as shown in FIG 3 along with complaints of thickening of tongue and slurred speech. On examination patient had reduced power in the bilateral lower limbs, proptosis of the right eye, multiple cranial nerve involvement by the tumor leading to multiple cranial nerve palsies. Patient developed bleeding symptoms and CBC showed pancytopenia. Patient was transfused with blood and blood products. Radiation Oncologist, Ophthalmologist and palliative opinion was sought and patient was started on palliative radiotherapy to scalp & extra cranial lesions using IMRT. Even on radiotherapy, patient started having new scalp lesions.

Patient developed a sudden loss of power in bilateral lower limbs and was not able to move both lower limbs. MRI spine showed cord compression at C4 & T5 – T8. Therefore patient was planned for urgent radiotherapy to the spine. MRI brain was done which showed progressive disease with gross lesions in the CNS. In view of relapse/ refractoriness of disease, we planned to go ahead with aggressive chemotherapy with mini BEAM regimen chemotherapy which may be followed by stem cell transplant if patient tolerates the treatment. Meanwhile, patient developed shock and succumbed to death.

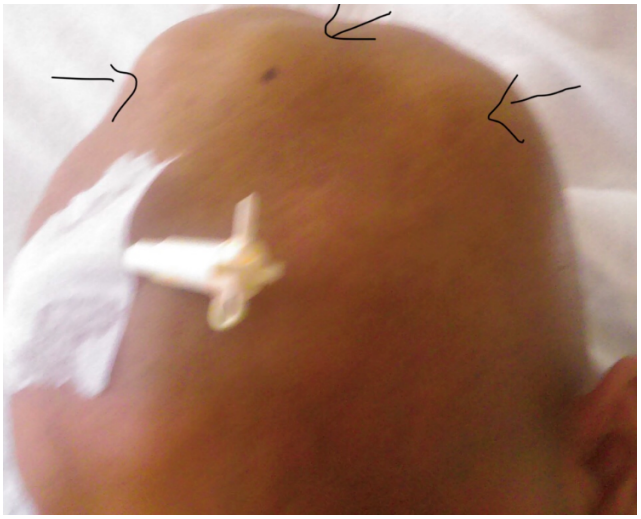

Fig. 1: Multiple scalp lesions

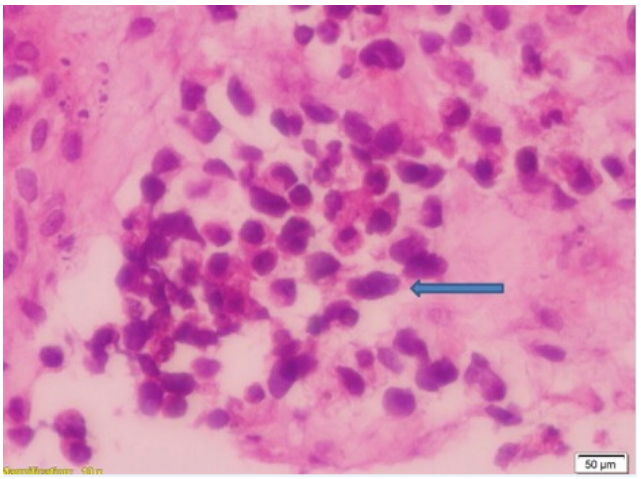

Fig. 2: Histopathology showing monomorphic tumor cells (NK cells).

3. Discussion

Aggressive natural killer (NK)-cell leukemia/lymphoma is a systemic NK-cell neoplasm that preferentially affects Asians with a fulminant clinical course and is almost always associated with Epstein-Barr virus (EBV).[6] The data on EBV-negative aggressive NK-cell lymphoma is limited. Our case also featured lack of blood lymphocytosis, EBER negativity, and atypical phenotype including CD3 negativity by immunohistochemistry. NK/T cells lymphoma

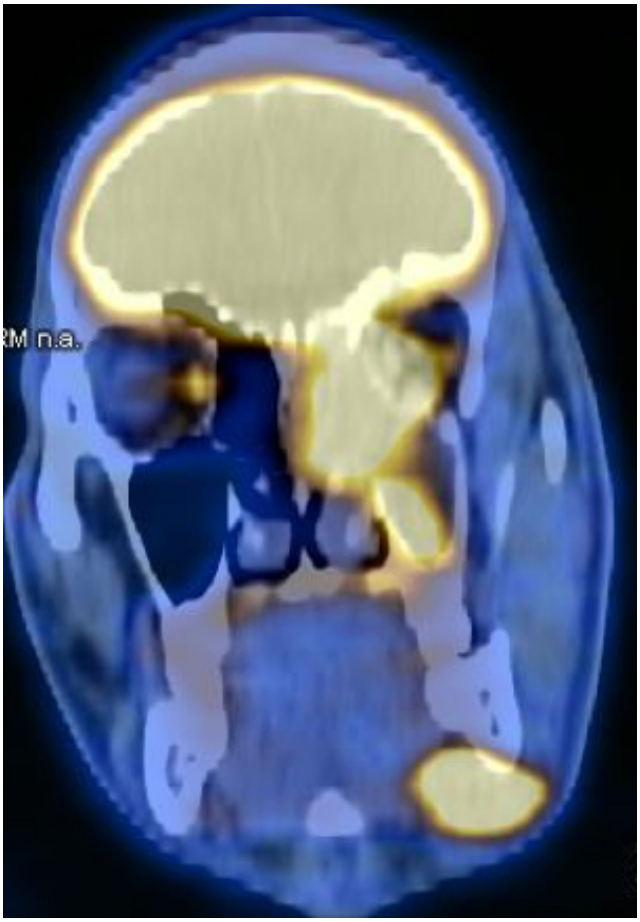

Fig. 3: PET CT Scan showing Orbital Involvement

are associated with JAK-STAT pathway for molecular pathogenesis which is usually negative in EBV negative NK lymphoma suggesting alternative molecular pathogenic mechanisms.[6]

Relapse of NK cell lymphoma of scalp lesion is a very rare presentation. Metastasis to scalp maybe due to locoregional spread or maybe due to microscopic systemic spread. Expression of a number of cell adhesion and homing receptors need to be examined. These molecules regulate normal leukocyte trafficking and are thought to determine the tissue- specific dissemination patterns of lymphoma subtypes.[7] For example, CLA mediates homing to skin via interaction with its ligand E-selectin, which is present on skin endothelium.CD54 or intercellular adhesion molecule-1 is involved with lymphocyte migration through high endothelial venules. Its expression is correlated with an angiodestructive phenotype in NK/T-cell lymphomas involving the skin.[8] In our case we haven't done these specific receptors examinations due to technical issues.

While early stage, localized disease is highly curable, metastatic disease and refractory cases carry a 5-year survival rate of <10%. In light of the high relapse rate with radiotherapy alone, combination of chemotherapy and radiotherapy is the current standard of care in patients who can tolerate systemic treatment. A commonly used anthracycline-containing regime is CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone). The expression of multidrug resistance (MDR) gene and high levels of P-glycoprotein in NK lymphoma cells underlies the resistance to anthracyclines and vinca alkaloids.[9] L-asparaginase-containing regimens like SMILE protocol have shown promise as L-asparaginase is not affected by P-glycoprotein. Since, tumor cells lack L-asparagine synthetase they are susceptible to L-asparaginase which depletes L-asparagines in NK lymphoma cells.[10]

We have also treated our case aggressively with SMILE protocol chemotherapy with plan of stem cell transplantation. Despite aggressive treatment, our case relapsed early and was complicated by prolonged pancytopenia, CNS involvement and patient died less than one year following diagnosis.

4. Conclusion

Relapsed NK cells lymphoma carries a very poor prognosis with resistant to conventional treatment. Multidisciplinary modalities are essential to treat the NK cell lymphoma with radiotherapy, chemotherapy, newer agents, and hematopoietic stem cell transplantation. Novel treatment Strategies targeting latent EBV, adoptive cellular therapy, Immune check points inhibitors are promising options in future.

5. Source of Funding

None.

6. Conflict of Interest

None.

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