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*Case Report*

# Extranodal Natural Killer/T-cell lymphoma, nasal type with bilateral breast involvement - A case report

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**ABSTRACT**

Extranodal natural killer/T cell (NK/T cell) lymphoma (ENKTL), nasal type, is a rare non-Hodgkin lymphoma originating in the nasal cavity or in the paranasal sinuses. It can involve the skin, gastrointestinal tract, soft tissue, and testis, but involvement of breast is rare. Herein we report a case of extranodal NK/T cell lymphoma with bilateral breast involvement in a middle aged female. The unusual presentation and difficulties in obtaining histological diagnosis created a diagnostic dilemma, but the progressive cavitating nasal lesion, repeat biopsies and immunohistochemistry study (IHC), eventually helped us to reach the rare diagnosis and plan the treatment accordingly.

**KEYWORDS:** Extranodal NK/T cell lymphoma , nasal type, breast, diagnostic dilemma

## INTRODUCTION

Extranodal natural killer/T cell (NK/T cell) lymphoma (ENKTL), nasal type, is a rare non-Hodgkin lymphoma originating in the nasal cavity or in the paranasal sinuses. It occurs in middle-aged persons and affects males more frequently than females [1,2]. Patients with this lymphoma mainly present with destructive lesions in the nasal cavity and other regions in the upper respiratory system [3]. This disease also originates primarily in the extra-upper aero digestive tract areas such as the skin, gastrointestinal tract, soft tissue, and testis [3,4], but involvement of breast is rare [5]. Herein we report a case of extranodal NK/T cell lymphoma with bilateral breast involvement, presenting as a diagnostic challenge. The progressive cavitating nasal lesion, repeat biopsies and immunohistochemistry study (IHC), helped us to reach the rare diagnosis and plan the treatment .

## CASE REPORT

A 39 years old Indian woman presented to our institute with complaints of nasal growth for three months and non-healing ulcer on the left breast for two months [Figure 1]. On examination, a polypoid growth was seen in left nasal cavity which almost obliterated the nasal space. An ulcer of size 2cm x 2cm was seen in upper periareolar region of left breast. A solitary ill defined lump of size 3cm x 3 cm was palpable beneath the ulcer. On the right side a lump of size 2 cm x 2 cm was palpable in upper inner quadrant and skin retraction was present. The axillae and the cervical regions were free of any lymphadenopathy. Routine blood tests were normal.

Ultrasonographic findings of abdomen and pelvis and chest X-ray findings were within normal limits. Nasal endoscopy revealed thick slough covered ulceroproliferative growth involving almost whole of left nasal cavity, ala of nose, left side of nasal septum, all the turbinates and meatii on the left side. Computed Tomography (CT) of the face and the skull showed irregular soft tissue mass within the vestibule of left nasal cavity abutting inferior turbinate and lateral wall of vestibule. Biopsy from the lesion showed wide area of necrosis and inflammation along with scattered islands of neoplastic cells [Figure 2]. IHC showed diffuse positivity for LCA, but the tissue was inadequate for further immunohistochemistry study and a rebiopsy was requested.

**Figure :1 Photograph showing nasal growth and left breast lesion**

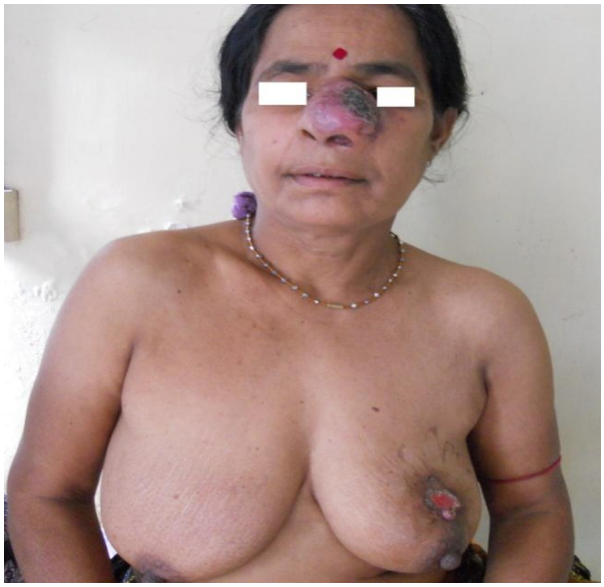
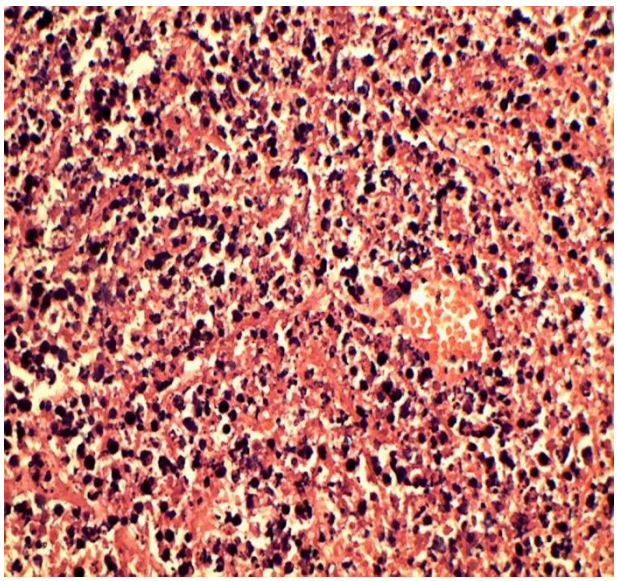


**Figure:2 Nasal growth histological sample (haematoxylin-eosin stain 40 x)**



Mammography identified oval shaped soft tissue opacity in the medial and retroareolar region of right breast extending up to the nipple. Skin thickening was present. Oval shaped large soft tissue opacity was seen in the retro areolar area of the left breast. Core needle biopsies were performed from both the breasts and the analysis revealed malignant cells but no clear diagnosis could be made, so incisional biopsy was done from the left breast lesion. It showed epidermis under which there was a mass composed of monomorphous population of round to oval cells predominantly centred in dermis.

Cells had vesicular chromatin, some with nucleoli and amphophilic cytoplasm. Mitotic figures were plenty [Figure 3]. IHC was negative for estrogen, progesterone and HER2 expression. CD45,CD3 [Figure 4a], CD5 and CD56 [Figure 4b] were diffusely positive in tumor cells, CD20 positive in few background lymphocytes and Ki-67 was positive (index >90%). In situ hybridization for Epstein-Barr virus-encoded mRNA (EBER) was diffusely positive. Depending on the histopathology and IHC study from the left breast lesion, the diagnosis of T cell lymphoma - high grade, favouring extranodal NK/ T cell lymphoma, nasal type was made. Bone marrow trephine biopsy was normal.

**Figure: 3 Left breast biopsy histological sample (haematoxylin-eosin stain 40 x)**

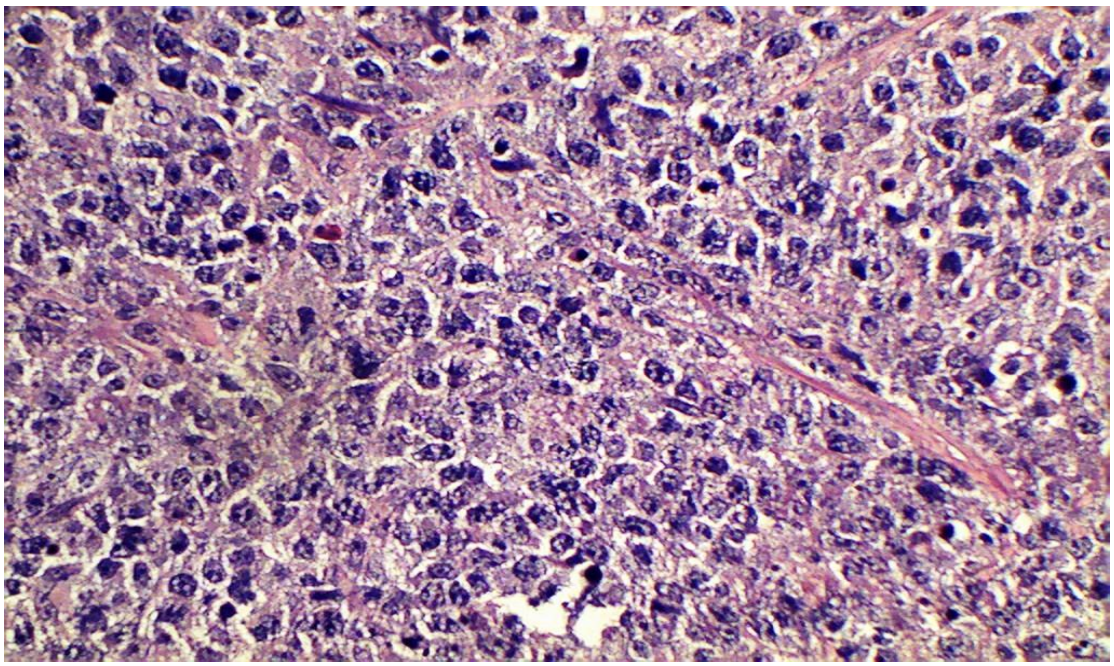


**Figure 4a.** Tumor cells positive for CD3.

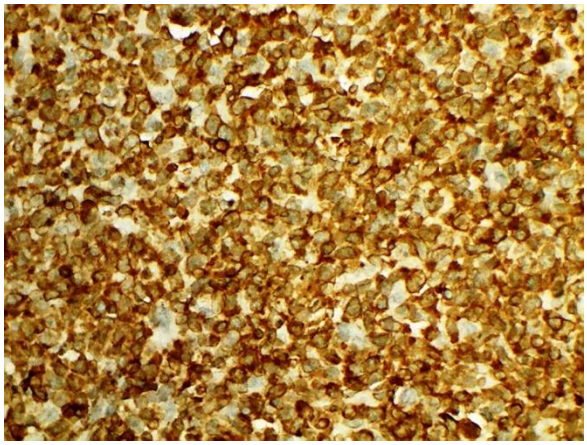
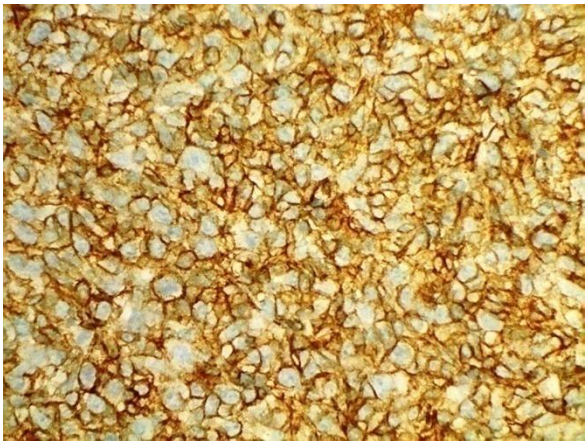


**Figure 4b.** Tumor cells positive for CD56.



In consideration of the poor general condition of the patient and need for early treatment, chemotherapy with Vincristine (2 mg), Cyclophosphamide (900 mg), Adriamycin (60 mg) and Prednisolone (100mg for five days) was started. The treatment was started on the basis of diagnosis of T-cell lymphoma but IHC diagnosis of NK cell lymphoma was pending at that time. After completion of first cycle of chemotherapy, she developed pancytopenia but the lesion in the midface and breast decreased in size. The patient received supportive management to combat pancytopenia. Meanwhile the final diagnosis of extranodal NK/ T cell lymphoma, nasal type was made depending on the IHC study, and it was planned to start "SMILE" regimen comprising of Dexamethasone, Methotrexate, Ifosfamide, L-asparaginase, and Etoposide, for further treatment of the patient. But the patient died after the first cycle of chemotherapy.

## DISCUSSION

Extranodal NK/T-cell lymphomas are a rare group of invasive and destructive lymphoproliferative disorders that are immunophenotypically distinct from B-cell and T-cell non-Hodgkin lymphomas. Because of their rarity, rapid clinical progression and inadequacy of biopsy specimen due to extensive necrosis, the diagnosis of ENKTL has always been a challenge. In this case the presentation with simultaneous bilateral breast lesion added to the diagnostic dilemma.They are derived from either activated NK cells or, rarely, cytotoxic T-cells. Now it has been classified as a distinct entity within the World Health Organization classification of hematopoietic and lymphoid neoplasms [6].

Its prevalence is higher in countries in South-East Asia and in Central and South America than in Europe and in North America. It occurs commonly in middle-aged persons and affects males more frequently than females [1,2].

These lymphomas are commonly extranodal and usually arise within the nasal cavity as midfacial destructive lesions and present with nasal obstruction, facial pain, or swelling. The nasal-type group however is more likely to have localized cutaneous manifestations and presents less aggressively compared to the extranasal and nonnasal groups which are more aggressive and disseminated [7]. The non nasal group symptoms could include cytopenia, B symptoms, early distant metastasis and hemophagocytic syndrome in approximately 3% of cases [7]. Hemophagocytic syndrome is often a fatal complication which may present with high fevers, maculopapular rash, central nervous system symptoms, multi organ failure, abnormal liver function tests, hepatosplenomegaly, cytopenias, and coagulopathy [8]. However, as such the patients with ENKTL usually do not have lymphadenopathy and bone marrow involvement [9,10].

The nonnasal group, as the name implies, has other sites of manifestation of NK/T-cell lymphomas that include the skin, gastrointestinal tract, salivary glands, spleen, and testis [3,4]. Breast is a rare site of involvement. Between 73 patients published recently by Li S et al [5], one patient had ENKTL involving the breast and the neoplasm was associated with a breast implant placed for cosmetic results. In this case report the patient is a middle aged female who presented with a nasal cavity mass and lesions in both the breasts without any lymphadenopathy and bone marrow involvement. In such cases it is important to explore the nasal cavity to confirm that the disease is really nasal-type lymphoma involving the breast and not primary breast carcinoma metastasing to nasal cavity.

Clinical course of ENKTL, nasal type is usually very rapid and disease is often in advanced stage at the time of diagnosis. In the majority of cases malignant cells are not found in blood smears or bone marrow aspiration studies [10]. Biopsy plays an important role in reaching the diagnosis. The interpretation of biopsy specimen, however, generally is not simple because of inadequate biopsy specimen size and masking of neoplastic cells by secondary inflammation and necrosis. In this case also, the unusual presentation with bilateral breast lesions and extensive necrosis of the nasal cavity lesion, made it very difficult to establish a diagnosis. But repeat biopsies and good pathological assistance helped us to think of ENKTL as a probable diagnosis, first detected in the breast specimen and then in the nasal lesion. The final diagnosis was however established by IHC of both the specimens.

Histologically, NK/T-cell lymphomas are often angiocentric with prominent necrosis and vascular destruction. Immunophenotypically, they typically express CD2 (T-cell marker), CD56 (NK cell marker), and intracellular cytoplasmic CD3 but lack surface CD3 expression. Other positive markers include cytotoxic granule proteins, Granzyme B, TIA-1, and Perforin [11]. Another distinguishing feature of NK/T-cell lymphomas is the strong association with EBV, with EBER positivity in greater than 80% of cases [12]. Our patient's tumour showed an angiocentric pattern of growth, EBV positivity and immunophenotypically, the tumour cells were CD56 and CD3 positive, confirming the histological diagnosis of extranodal NK/T cell lymphoma, nasal type. The high Ki-67 index(>90%), indicated that it was a high grade lesion [5].

The treatment of nasal NK cell lymphoma has been controversial. Initially, radiotherapy alone used to be the primary treatment in stage I/II disease and yielded a complete remission rate of between 40% and 80% [13]. Local relapses occurred at a rate of around 50% [13,14]. Contributing factors include dosages less than 45 Gy to 50 Gy and radiotherapy planning not assisted by radiological imaging [14]. Systemic relapses with radiotherapy alone occurred in 25–30% of patients, where more than a half were not associated with local recurrence, suggesting that subclinical dissemination of lymphoma has occurred in these apparently early staged patients who were "cured" [13,15].

The use of chemotherapy alone has been associated with a treatment failure of about 40%. Therefore combined chemotherapy and radiotherapy is the treatment of choice and can be expected to be curative in at least 70–80% of patients with stage I/II nasal NK cell lymphomas [15]. There are however documented relapses more than ten years and up to thirty years in early stage nasal NK cell lymphoma, and hence life-long follow-up is recommended [15].

Chemotherapy is the mainstay of treatment in advanced NK cell lymphomas [15]. A novel regimen "SMILE," comprising of Dexamethasone, Methotrexate, Ifosfamide, L-asparaginase, and Etoposide, has been shown to be promising in phase I and II studies. In patients with relapsed or refractory NK cell lymphoma, SMILE treatment resulted in an overall response rate of 74% and a complete remission rate of 35–50% [15]. The commonly used CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone) chemotherapy regime gives moderate response for stage I/II nasal NK/T-cell lymphomas but has a high rate of disease progression (30–40%) and a high rate of relapse (30–40%) after initial complete remission [14,17]. It has a poor outcome when used in advanced staged diseased with an overall response rate of below 20% [15,16].

The option of autologous and allogenic hematopoietic stem cell transplantation (HSCT) as a consolidation therapy following high-dose chemotherapy alone has been considered in patients with advanced stage, relapsed or refractory disease [15]. This is controversial as there are several issues to be considered. There are no prospective trials evaluating the role of autologous HSCT in patients. The largest retrospective trial of 47 patients only showed that HSCT had a survival benefit for patients with stage I/II disease and high risk patients who achieve complete remission [17].

However, patients in these lower stages are likely to have a complete remission with combined chemotherapy and radiotherapy, so it is doubtful that frontline autologous HSCT is beneficial [13]. As for the high risk patients in complete remission, the recommendation is to carefully consider autologous or allogenic HSCT for consolidation therapy [13,17]. In patients with advanced, relapsed or refractory diseases, the role of HSCT remains poor [17].

## CONCLUSION

We present a case of extranodal NK/T cell lymphoma, nasal type with bilateral breast involvement in a middle aged female. This tumour with breast involvement appears to be rare, as we could find only a few cases reported in the literature. The unusual presentation and difficulties of obtaining histological diagnosis can result in a delay in diagnosis. Clinical suspicion, immunohistochemistry and good interaction with the pathologist can help us in establishing the diagnosis of this rare disease. In conclusion, clinicians should consider extranodal nasal lymphoma as a differential diagnosis of destructive lesion of nasal cavity with breast involvement and plan the treatment accordingly because the disease has a rapid fatal course.

## DECLARATION

The patient has given her informed consent regarding publication of her case.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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