

**PRIMARY CUTANEOUS NK/T CELL LYMPHOMA-NASAL TYPE WITH CUTANEOUS ASPERGILLOSIS. A CASE REPORT AND LITERATURE REVIEW**Geetha Krishnanand<sup>1</sup>, Vidya Monappa<sup>2</sup>, Anuradha C.K. Rao<sup>2</sup><sup>1</sup>Department of Pathology, American University of Antigua, St George, Antigua and Barbuda<sup>2</sup>Department of Pathology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India

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**Abstract**

We report a 66-year-old male who presented with a blackish discolored ulcerated nodule over the right flank of 2 months duration. Biopsy of the lesion revealed ulcerated epidermis with fungal hyphae of *Aspergillus* overlying dense, angiocentric atypical lymphoid infiltrate involving the dermis, and extending into sub cutis with geographic areas of necrosis. The patient had three episodes of cutaneous recurrence over a three year period. The cutaneous lymphoid infiltrates showed similar immunohistochemical profiles: LCA+, CD3ε+, CD20- and CD56-. CD30 was positive in a small percentage of cells. P53 proliferation marker was strongly positive. There was no evidence of systemic involvement by the neoplastic lymphoid and fungal infiltrates. This is one amongst the rare reports of cutaneous aspergillosis with primary cutaneous NK/T cell lymphoma nasal-type.

**Key words:** NK/T cell lymphoma; skin; aspergillosis**Cite this article:**

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**Introduction**

Nasal-type NK/T cell lymphoma presenting in the skin is a highly aggressive tumor with a mean survival of less than 12 months [1,2]. The WHO-EORTC classification for cutaneous lymphomas describes it as extranodal NK/T cell lymphoma-nasal type [1].

Cutaneous aspergillosis is infrequent and occurs as primary (direct inoculation) or secondary infections (direct extension from adjacent foci or hematogenous dissemination) [3,4]. Reports in literature have described cutaneous aspergillosis in more than 50 cancer patients with leukemia being the commonest underlying malignancy.

In this report, we describe a case of primary cutaneous NK/T cell lymphoma-nasal type with the unusual association of primary cutaneous aspergillosis.

**Case report**

A 66-year-old-male (farmer), presented with a blackish discolored ulcerated nodule over the right flank with a single enlarged left axillary lymph node. Laboratory investigations revealed peripheral blood eosinophilia (21%), ESR (36mm/1<sup>st</sup> hr), serum uric acid (5.3), LDH (47.5), alkaline phosphatase (59). Biopsy from skin lesion suggested lymphoma with aspergillosis.

Chest x-ray, computerized tomography scan of thorax and abdomen revealed a single 1x1 cm lymph node anterior to arch of aorta with no other abnormality. Excision biopsy of lymph node showed reactive changes. Patient was subjected to wide local excision of right flank lesion followed by local radiotherapy. He received weekly intra-muscular methotrexate 50mg for four weeks; later patient discontinued treatment.

Ten months later the patient developed another swelling on right middle thigh. One month afterwards he had another swelling over right frontal region. Wide excision biopsy of both lesions suggested tumor recurrence. Bone marrow aspiration and biopsy ruled out systemic involvement of the lymphoma.

He returned one year later with progressive swelling in left flank region. On local examination superficial erythematous swelling measuring 5x5 cms on left flank/lumbar region was seen. Another subcutaneous 1x1cm papular lesion was observed over sternal head of left clavicle. Bone marrow aspiration and biopsy revealed no involvement by tumor. Peripheral smear showed eosinophilia (25%). Serum LDH was 844 and ESR was 40mm/hr. The patient received local radiotherapy and has been advised weekly methotrexate injections. He has been on regular follow-up since then.

## Pathological Findings

Gross specimen of Rt. Flank lesion consisted of skin covered oval mass of tissue measuring 5x4.5x1cm, with a surface ulcer covered by necrotic skin. On cut section blackish discoloured area seen infiltrating into the subcutaneous tissue.

Hematoxylin and eosin stained sections of the initial skin biopsy revealed partly elevated ulcerated epidermis with fungal hyphae. Fungal stains revealed narrow based, septate hyphae showing acute angle branching (Fig. 1). Dermis showed nodular, angiocentric and angiodestructive and periadnexal, atypical lymphoid infiltrate of a mixed population of large cells with vesicular nucleus, prominent nucleolus and moderate amounts of cytoplasm along with cells with cerebriform nucleus, mature lymphocytes, histiocytes, eosinophils and epithelioid cells (Fig.

2, 3). Epidermotropism, brisk mitotic activity, extension into subcutaneous fat and geographic areas of necrosis were the other features observed. Immunohistochemical (IHC) analysis revealed a predominant population of LCA+, CD3 $\epsilon$ + T cells (Fig. 4) admixed with few CD30+ cells (Fig. 5) and CD20+ B cells in the background. CD56 however was negative in the tumor cells. p53 proliferation marker was strongly positive in the neoplastic lymphoid population (Fig. 6).

Excision biopsy of axillary lymph node showed reactive changes with sinus histiocytosis and vascular transformation of sinuses. Subsequent excision skin biopsies revealed similar histological and IHC features, with no evidence of aspergillosis.

Bone marrow aspiration and biopsy performed on all occasions showed no evidence of involvement.

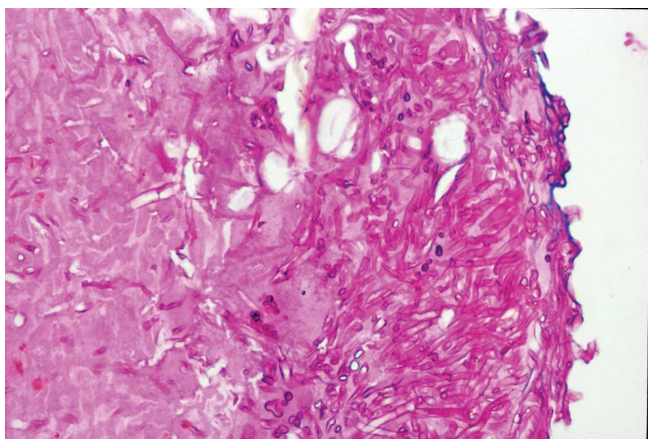


Figure 1. Ulcerated epidermis showing aspergillus hyphae. (PASD, 400x)

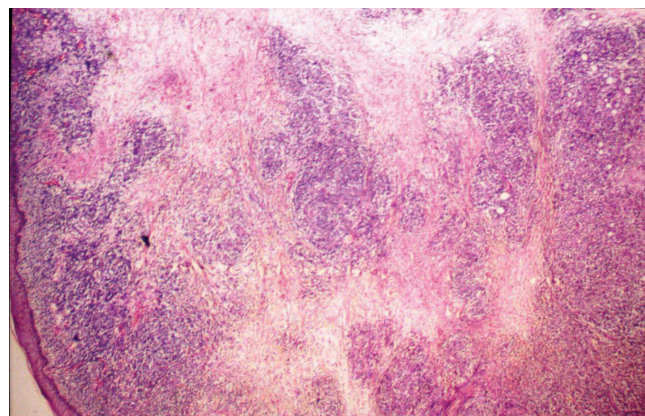


Figure 2. Dermis showing nodular perivascular neoplastic lymphoid aggregates with geographic areas of necrosis. (H&E, 40x)

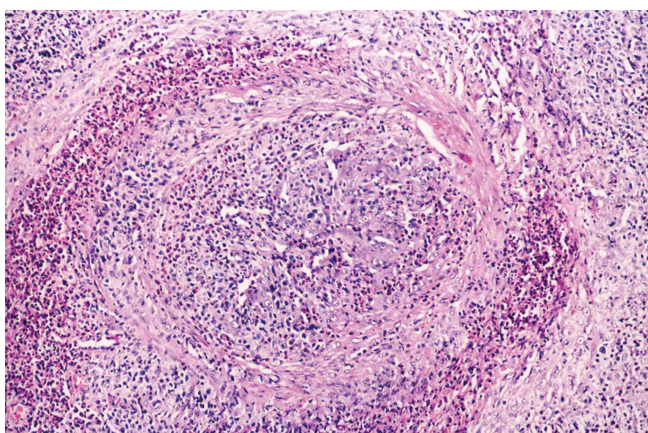


Figure 3. Angiocentric, angioinvasive proliferation of neoplastic lymphoid cells. Eosinophil aggregates seen. (H&E, 400x)

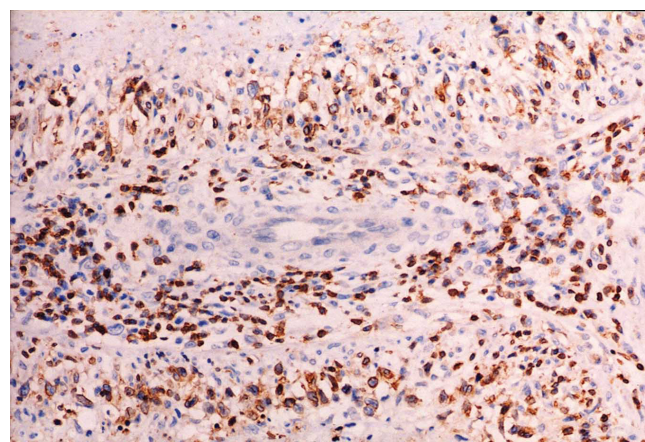


Figure 4.  $\epsilon$  CD3 cytoplasmic positivity in neoplastic cells. (400x)

## Discussion

Extranodal natural killer T (NK/T) -cell lymphoma, nasal-type, is a recently recognized distinct entity within the WHO classification of lymphoid tumors [8]. They show male predominance [6], have a higher frequency of T cell rather than NK cell phenotype and are less associated with EBV [7].

The skin is the most common extranodal site of involvement, and could be either primary or secondary manifestation of the disease. Other sites of involvement as reported in the literature include endometrium [9], breast following renal transplantation [10], skeletal muscle [11], testis [12] gastrointestinal tract, lung [13], soft tissue, spleen [5], kidney, upper respiratory tract and

rarely, the eye/orbit [7].

It is an aggressive neoplasm that often pursues a rapidly progressive course, with additional sites of disease appearing within weeks to months. The new sites of involvement are also mostly extranodal and similar to the predilection sites at presentation [5]. Extracutaneous involvement at the time of presentation is associated with a poorer prognosis. The present case had 3 cutaneous recurrences over a span of 3 years.

This lymphoma is more common in Asia, Central and South America. Patients are adults presenting with multiple plaques or tumors on the trunk or extremities. Ulceration and systemic symptoms are common.

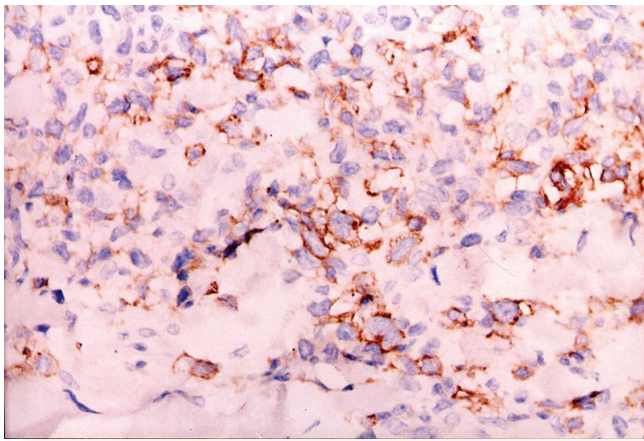


Figure 5. Large cells showing CD30 membrane and golgi zone positivity. (400x)

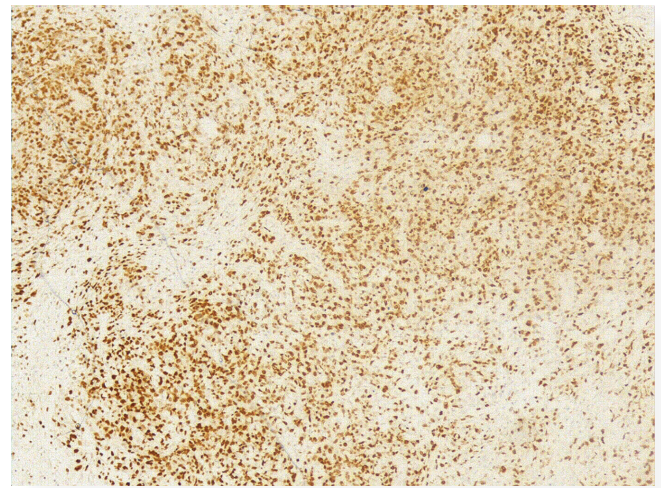


Figure 6. p53 diffusely positive in >90% cells. (100x)

Histologically NK/T cell lymphoma has broad cytologic spectrum with cells ranging from small, medium and large to pleomorphic cells [2] with irregular nuclei, dense chromatin and pale cytoplasm. The cells show prominent angiocentric, angiodestructive growth accompanied by extensive necrosis. Some cases are accompanied by heavy inflammatory infiltrate of small lymphocytes, histiocytes, plasma cells and eosinophils as was seen in this case.

Immunophenotypically the neoplastic cells express CD 3 $\epsilon$ , CD 56, cytotoxic proteins (TIA-1, granzyme B, perforin). Chan et al [8], observed that the atypical cells of all 11 cases exhibited T-cell markers [15]. Tseng-Tong Kuo reported 1 case which was CD 3 $\epsilon$  -ve. A few reports of CD 56 -ve cases have been reported in literature [2]. Patients with co-expression of CD 30 were observed to have a more favourable outcome [3,16]. Quintanilk-Martinez et al, observed a high prevalence of p53 over-expression in their series of 32 cases [17]; p53 was strongly positive in our case.

Several studies suggest association with EBV associated proteins – EBER-1, LMP-1, EBNA-1 [11,13]. Epstein-Barr virus RNA is present in the majority (80-100 %) of nasal NK/T-cell lymphomas and less often in nasal type NK/T-cell lymphomas (15-40 % or more in some series) [15].

The differential diagnosis includes lymphomatoid granulomatosis, blastic or monomorphic NK cell lymphoma/leukemia, CD56-positive peripheral T-cell lymphoma, and enteropathy-associated T-cell lymphoma [5]. CD 56+ lymphomas involving the skin are rare and extremely aggressive regardless of their histologic presentation and extent of skin involvement. The risk of death is particularly increased in older patients with CD 30- CD4- lymphomas [14].

NK/T cell lymphoma is associated with an increased risk of developing hemophagocytic syndrome; the systemic histiocytic activation presumably results from cytokines or other products released by the lymphoma cells [5].

Treatment modalities include chemotherapy, radiotherapy, surgery or a combination of the above [15]. Kuo T, observed that local irradiation was more effective than chemotherapy alone. They achieved an overall survival of 63.6% at 5 years as estimated by the Kaplan-Meier analysis, which was better than other series [2]. Mechanisms of drug resistance in T/NK lymphomas have included increased expression of the multidrug resistance proteins and p53 [16]. Multidrug chemotherapy

(CHOP regimen) followed by involved field radiotherapy appears to be the most effective treatment approach [19]. Our case was treated with surgery followed by radiotherapy.

A new prognostic model for extranodal NK/T –cell lymphoma, nasal type which included factors like presence of B symptoms, stage, LDH levels and regional lymph node invasion was proposed by Lee et al [20], from their retrospective multicentre study. They divided patients into four different risk groups: group 1, no adverse factor; group 2, one factor; group 3, two factors; group 4, three or four factors. The new model showed superior prognostic discrimination as compared with the International Prognostic Index (IPI).

Cutaneous aspergillosis occurs relatively less frequently and therefore remains poorly characterized. *A. fumigatus* and *A. flavus* are the most frequent causes of cutaneous aspergillosis [3]. Primary cutaneous aspergillosis usually involves sites of skin injury, namely, at or near intravenous access catheter sites, at sites of traumatic inoculation, and at sites associated with occlusive dressings, burns, or surgery. Secondary cutaneous lesions result either from contiguous extension to the skin from infected underlying structures or from widespread blood-borne seeding of the skin [4].

Reports in the literature have described cutaneous aspergillosis in more than 50 cancer patients most of whom had leukemia as the underlying oncologic diagnosis. In greater than 85% of cancer-related cases, primary cutaneous aspergillosis was associated with intravenous catheters, arm boards, or tape securing arm boards [4].

Julin et al [3], reported a case of cutaneous aspergillosis in a patient with cutaneous T-cell lymphoma. As in our case, underlying lymphoma was the major contributing factor which was facilitated by the poor local blood circulation and breach of overlying epithelium .

Review of the literature suggests that this is the very first case of primary cutaneous aspergillosis with extranodal NK/T cell lymphoma-nasal type.

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