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Case Report

Unusual presentation of an Epstein barr virus-negative extranodal natural killer/T cell lymphoma: A diagnostic dilemma

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ABSTRACT

Extra-nodal Natural killer/T cell lymphoma (ENKTL) is a well-defined and highly aggressive form of Non-Hodgkin's lymphoma with a scarcity of cases reported in literature. The most common primary site of involvement is the nasal cavity followed by skin and the gastrointestinal tract (GIT). Cutaneous involvement is a rarity. More than 95% of cases are usually in association with Epstein Barr Virus (EBV) infection. EBV negative ENKTL can be similar in clinical, pathological, and prognostic characteristics with EBV positive ENKTL. This malignancy is usually characterized by its poor prognosis irrespective of clinical stage and therapy. We describe here, a 58-year-old man presenting with multiple nodular lesions over legs and trunk, had an ileal perforation later, and was diagnosed as ENKTL on the ileal biopsy specimen. This case is being reported in view of the fulminant clinical course of the disease, simultaneous involvement of the GIT and skin without nasal or midline involvement, the usefulness of immunohistochemistry in arriving at a diagnosis, and EBV negativity which is quite rare in the Asian population.

Key words: Lymphoma, Extranodal, Natural killer/T cell lymphoma, Epstein Barr virus

INTRODUCTION

Extra-nodal Natural killer/T cell lymphoma (ENKTL) is a rare type of cytotoxic lymphoma which is usually associated with Epstein Barr Virus (EBV) infection. It is more common in the Eastern Asia and Latin America with only a few cases reported in the literature.[1] ENKTL is sub-categorized into two distinct types: "nasal" which are locally destructive tumors in the nasal cavity, maxillary sinuses or palate and "extra nasal-type" which occur in extra-nodal sites such as gastrointestinal tract (GIT), lung, skin, and testis without nasal involvement. Nasal-type ENKTL demonstrates many morphologic and immunophenotypic similarities to nasal ENKTL. ENKTL can have a very wide and vague clinical spectrum that might mimic a variety of reactive or non-reactive processes. We report a rare case of EBV negative ENKTL of the skin and ileum, where the patient had an aggressive and fulminant course.

CASE REPORT

A 58-year-old man presented with multiple nodular lesions on the trunk and bilateral lower extremities for 2 months. He had no B-symptoms. On examination, multiple well-defined tender

nodules of varying sizes were present over the legs and trunk. The surface of the lesions showed dryness, xerosis, occasional crusting, few of the lesions had pus discharge and some were bleeding [Figure 1].

There were no symptoms and signs related to the nasal region and no palpable peripheral lymph nodes. On investigation, hemoglobin was 8.9 g/dl; absolute neutrophil count of 3140 cells/cu.mm; platelet count of 2 lakhs/cu.mm; creatinine-1.28 mg/dl and lactate dehydrogenase-1591 U/L. Skin biopsy done from the right thigh showed diffuse T cell-Non-Hodgkin's lymphoma (NHL) with CD3+, CD 20+, and ki-67 index of 85%. 24 h after admission, patient had sudden onset abdominal pain, distension with tenderness, and sluggish bowel sounds. X-ray of the abdomen showed multiple air-fluid levels with dilated bowel loops. He was taken up for emergency surgery (exploratory laparotomy) for suspected hollow viscous perforation. An ileal perforation was identified and the perforated segment was resected. 36 h after the surgery, patient developed sudden onset breathlessness, tachycardia and hypotension, and cardiac arrest to which he succumbed. Gross examination of the ileal specimen was hemorrhagic and necrotic, with a 3.5 × 2.8 cm perforation. HPE of ileal mucosa showed small to intermediate atypical lymphoid cells having pleomorphic hyperchromatic nuclei, inconspicuous nucleoli, scanty to moderate cytoplasm arranged in diffuse sheets with an increase in mitotic activity [Figure 2]. On immunohistochemistry (IHC), the tumor cells were positive for CD 3, CD 2, CD 56; Ki 67:60% and negative for CD 20, PAX-5, Tdt, CD 30, CD 103, and EBV (EBER-ISH: EBV-encoded small RNAs- in situ hybridization). Based on IHC [Figure 3a-f] and staging workup, a final diagnosis of ENKTL-Nasal type, stage IV was made.

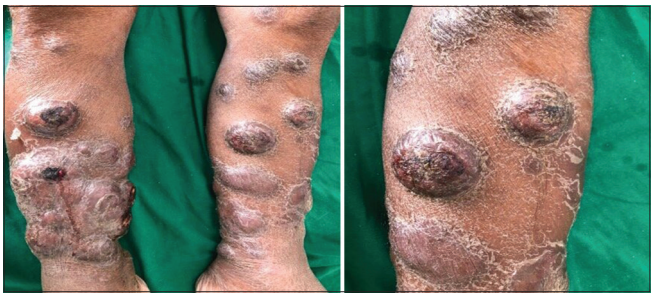

Figure 1: Multiple, tender nodular lesions with bleeding tendency on bilateral lower limbs.

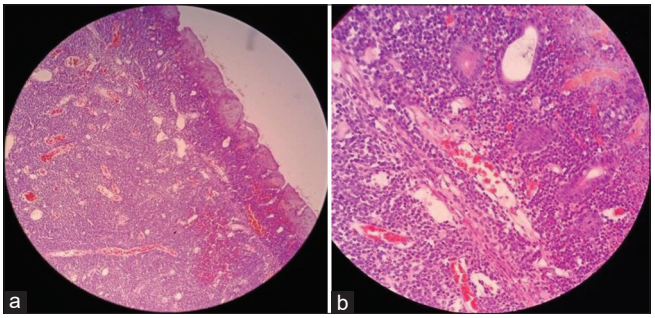

Figure 2: Hematoxylin and Eosin stained slides from ileal biopsy specimen showing atypical lymphoid cells with pleomorphic and hyperchromatic nuclei.

DISCUSSION

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of aggressive neoplasms that constitute <15% of all NHL in adults.[2,3] ENKTL or nasal NK/T lymphoma (formerly, angiocentric lymphoma), the most common cause of "lethal midline granuloma" syndrome is a class of PTCL representing <0.5% of all NHL.[4] The incidence of ENKTL is higher in Asia, Latin America, and South America. In endemic areas, it can account for 2–18% of all NHL.[5] The pathogenesis of ENKTL is poorly understood but is related in part to infection of the tumor cells with EBV. EBV positivity rate of EKNTL has been reported to the tune of 73–100%.[6] ENKTL can have a variable histopathological spectrum. In the early stages, polymorphonuclear leukocytes, eosinophils, and plasma cells accompany the lymphoma cells while in late stages there might be extensive inflammation and necrosis. Varying sizes and appearances of tumor cells are seen. The nucleus often has an irregular folding and crumpled chromatin. Angiocentricity, although a frequently noted feature of the ENKTL, is not pathognomonic.

Skin is the second most common site of involvement in ENKTL which can be in the form of cellulitis-like or abscess-like lesions, subcutaneous nodules, ulcerations, erythematous papules, and infiltrative plaques; commonly located on the trunk or extremities.[7] Other entities such as cutaneous large B-cell lymphomas of leg type, squamous cell carcinoma of the skin, cutaneous T cell lymphoma such as Mycosis fungoides which are relatively more common than ENKTL, have similar morphology leading to a diagnostic dilemma. Our patient also had a similar presentation with large multinodular and ulcerated lesions over legs and trunk.

Primary intestinal ENKTL is uncommon and accounts for 3.1% of all intestinal NHL cases. The small intestine is the most common site followed by the colon and ileocecal junction. The common presenting symptoms include abdominal pain and/or fever. Most intestinal ENKTLs present as ulcerative lesions rather than a polypoidal masses and these lesions are prone to perforation.[8]

Clinical, histopathological, and IHC findings must be carefully correlated to reach at a conclusive diagnosis. On H and E staining, a large amount of pleomorphic tumor

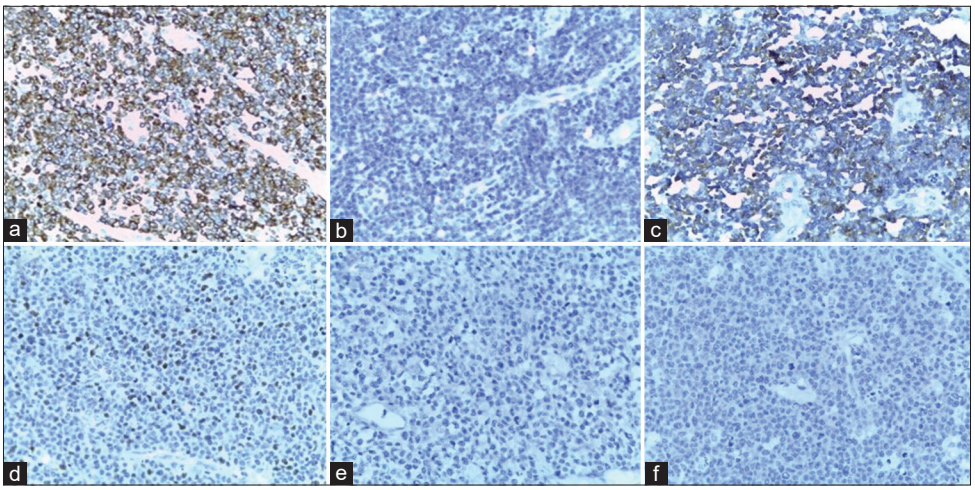

Figure 3: Immunohistochemical Staining (a) CD3 positive; (b) CD 2 positive; (c) CD 56 positive; (d) Ki 67-high proliferative index 60%; (e) CD 20 negative; (f) EBER-ISH Negative.

cell infiltration with significant vascular damage, apparent tissue necrosis, and cytotoxicity are highly suggestive. On IHC staining, the tumor cells are usually CD2+, cytoplasmic CD3+, and surface CD3-. As a marker of cell activation, CD 30 is frequently expressed in the tumor cells of extra nasal ENKTCL lesions than those of nasal ones.[9,10] The tumor cells show brisk proliferation with >50% of patients having high Ki 67 index, as was seen in our patient.

The pathogenesis of ENKTL almost invariably involves EBV infection, but few cases of EBV negativity have been reported in the literature. Nicolae *et al*. and Gao *et al*. reported a series of 7 cases and 3 cases of EBV negative aggressive ENKTL, respectively.[11,12] Both the series have noted that these lymphomas are clinically and pathologically indistinguishable from EBV-positive ENKTL. However, patients with EBV-negative disease tend to be older (median age 63 years) and have a rapidly progressive disease with high mortality within weeks of diagnosis.

The differential diagnosis considered in our case and the salient differences in IHC among them are summarised in [Table 1]. Generally, an L-asparginase based regimen, such as SMILE (dexamethasone, methotrexate, ifosfamide, L-asparginase, and etoposide) or P-GEMOX (peg-L-asparginase, gemcitabine, and oxaliplatin) are commonly used frontline chemotherapy regimens because ENKTCL cells lack asparagine synthetase activity. The complete remission rates ranged from 30% to 50% with these regimens.[13] Refractory disease and relapse are common, the outcome and survival rates of which remain poor irrespective of therapy with reported median progression-free survival of 8 months or less.[14] A study from China reported a 2-year survival rate of 33.3.%.[15] Recently, a case of EBV negative ENKTL treated with first-line pembrolizumab immunotherapy was described, suggesting that it could be employed in elderly patients with limited options and may be preferred over palliative therapy.[16]

Table 1: Salient features of the differential diagnosis considered in the index case.

Tumor IHC marker	NK/T	EATL	ALCL	PTCL-NOS
CD 20	–		–	–/+
CD 10	–	–	–	–/+
Cyclin D1	–		–	–
Bcl-6	–	–	+	–/+
CD 43	++		+	++
CD 3	++	++	+	++
CD 7	+	++	+/–	++
CD 2	++	+/–	++	+
CD 5	+/–	–/+	+/–	+
CD 4	–/+	–/+	+	++
CD 8	–/+	+/–	–/+	+/–
CD 30	+	+/–	++	+/–
CD 56	+	+/–	–/+	+/–
TIA-1	++	++	++	+
EBV	++	–/+	–/+	–

NK/T: Natural Killer/T-cell lymphoma, EATL: enteropathic T cell lymphoma, ALCL: anaplastic large cell lymphoma,
PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified

This case has been reported in view of the fulminant clinical course of the disease, simultaneous involvement of the GIT and skin without nasal or midline involvement, and also EBV negativity which is quite rare in the Asian population. This case highlights the extremely rare presentation of ENKTL nasal type, variability of cutaneous and gastrointestinal manifestations in the same patient, the advanced stage, and dismal prognosis at the time of diagnosis. We provide further evidence for the existence of EBV negative ENKTL

which is similar in clinical, pathological, and prognostic characteristics with EBV positive ENKTL.

CONCLUSION

EBV negative ENKTL can be similar in presentation to the EBV positive cases. Presentations can be variable with involvement of multiple organ systems in extra nasal ENKTL, and the tumor can be rapidly progressive.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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