Extranodal NK/T-cell lymphoma primarily presenting as two adjacent slowly growing skin nodules with prominent epidermotropism and CD30 expression; a case report and review of literature

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Abstract

Extranodal NK/T-cell lymphoma (NKTCL) is a rarely occurring non-Hodgkin lymphoma with predilection for the nasal cavity. Cutaneous involvement, rarely occurring and often aggressive in behavior, may present as nodular mass-forming lesions with or without ulceration. Histologically, lesions are characterized by an atypical dermal lymphoid infiltrate with angioinvasion and associated necrosis. Fortuitously, Epstein-Barr virus (EBV) infection, implicated in the pathogenesis of this entity, serves as a useful diagnostic marker (i.e., Epstein Barr virus-encoded RNA in situ hybridization).

Keywords: brentuximab, CD30, EBV, epidermotropism, NK/T-cell lymphoma, TCR

Introduction

We present a 54-year-old-man who initially presented with two ulcerations on the right lower leg which progressed despite antibiotic therapy. Histologic examination demonstrated dense lymphoid infiltrates exhibiting epidermotropism, angiocentricity and angioinvasion extending into the deep dermis. Immunohistochemical staining demonstrated expression of CD2, CD3, CD8, TIA1, perforin, and granzyme B, consistent with a cytotoxic T cell phenotype. Additionally, CD56 was positive, confirming the presence of a coexistent NK cell phenotype. Testing also demonstrated significant CD30 expression, and molecular analysis was positive for TCR gene rearrangement. These findings, in conjunction with Epstein Barr virus-encoded RNA in situ hybridization positivity, confirmed a diagnosis of extranodal NKTCL. We aim to increase awareness of this rarely occurring lymphoma with cutaneous involvement. CD30 expression in NKTCL raises the possibility of targeted treatment with brentuximab.

Extranodal NK/T-cell lymphoma (ENKTCL) is a non-Hodgkin lymphoma that has a predilection for the upper aerodigestive tract but can initially present in extranasal sites such as the gastrointestinal tract, skin, soft tissue, and testis. It is invariably associated with EBV infection and is frequently of NK cell origin. It is most common in East Asia and Latin America but is rare in Europe and the United States with a median age at presentation between 50 and 60 years [1]. Cases with cutaneous presentation are characterized by multiple progressive plaques, nodules, and tumors. Histopathologically, there is a dermal angiocentric infiltrate of medium sized cells with or without necrosis, ulceration, and subcutaneous involvement. Epidermotropism and CD30 expression are relatively infrequent [2]. Herein, we report a case of ENKTCL primarily presenting as two slowly growing ulcerative nodules on the lower extremity of a 54-year-old male. We highlight several

unusual clinical and histopathologic features in this patient's presentation and review the most recent literature.

Case Synopsis

A 54-year-old otherwise healthy man presented with two adjacent asymptomatic sharply demarcated erythematous nodules on the right lower extremity that had been slowly growing over the past one year. Approximately 5 months prior to presentation, these 6cm tumors began to ulcerate (**Figure 1A**). More recently, the patient reported night sweats and unmeasured low-grade fevers. He otherwise did not have anemia, thrombocytopenia, or hepato-splenomegaly.

Punch biopsies of nonulcerated regions of both nodules revealed an epidermotropic, angiocentric, and angioinvasive infiltrate of atypical medium-sized mononuclear cells. Immunohistochemical studies showed diffuse expression of CD2, membranous and cytoplasmic CD3, CD5, CD8, and CD56 suggesting an NK-like T cell origin. Epstein Barr virus-encoded RNA in situ hybridization was positive in a subset of lesional cells. Additional studies showed strong expression of cytotoxic markers (perforin, TIA, and granzyme) and of CD30. T cell receptor (TCR) gamma chain gene rearrangement studies showed identical clones in both biopsies. These findings were consistent with a diagnosis of ENKTCL (**Figures 1-3**). Given that this neoplasm expressed CD3 and T cell receptor (detectable by next generation sequencing) it was determined to be an extranodal NK/T cell leukemia over an aggressive NK leukemia/lymphoma. Subsequently, the patient underwent a positron emission tomography–computed tomography (PET/CT) scan which showed ^{19}F-fluorodeoxyglucose-avid disease in soft tissues of the distal right leg (primary lesions), lower distal left thigh lymph node, penis, left testicle, left rectus muscle, and thoracic lymph node. He also underwent bone marrow biopsy, which revealed a small population of atypical CD8 lymphocytes consistent with involvement by the patient's NK/T cell lymphoma. Identical TCR clones were identified in the bone marrow and peripheral blood. Based on these findings, the patient was diagnosed with Stage IVB NK/T-cell lymphoma. As leg lesions were rapidly expanding and initial impression of the immunophenotype was similar, suggesting a peripheral T-cell lymphoma, we opted to begin treatment with a typical regimen active against aggressive lymphomas at our institution. The regimen chosen was etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin . Later, after CD30 positivity was determined, and in accordance with the findings from the ECHELON-2 trial, brentuximab, cyclophosphamide, doxorubicin, and prednisone multi-agent chemotherapy (BV-CHP) was used [3]. The patient responded well to BV-CHP and on his most recent follow-up four months after initial treatment, the patient had received four cycles of BV-CHP. He was clinically stable after hospital admission for febrile neutropenia and his tumors had nearly resolved and were without any further ulceration. CT scan of the abdomen and pelvis did not show any acute changes.

Case Discussion

Extranodal NK/T cell lymphoma (ENKTCL) is a rare subtype of non-Hodgkin lymphoma characterized

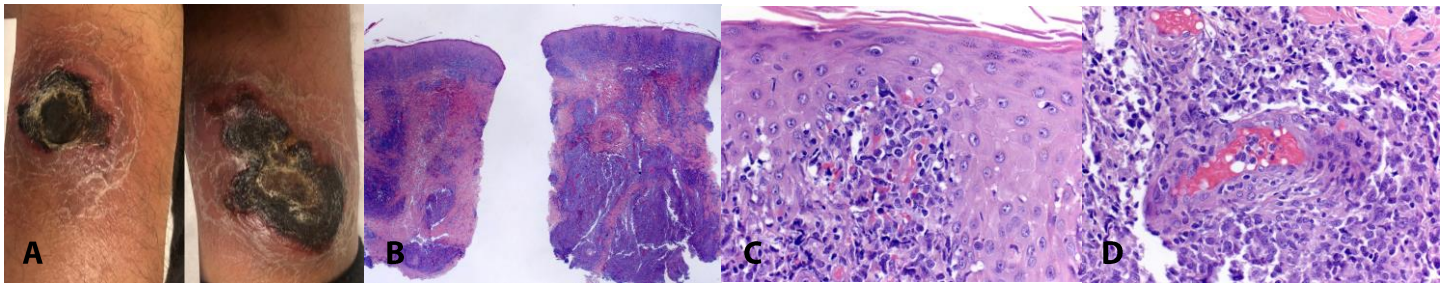

Figure 1. ***A)*** *Nodules with ulceration on right lower extremity.* ***B)*** *Angiocentric and epidermotropic lymphoid infiltrate, H&E, 20×.* ***C)*** *Areas of epidermotropism of lymphoid infiltrate, H&E, 200×.* ***D)*** *Angiocentricity and angioinvasion demonstrated by lymphoid infiltrate, H&E, 200×.*

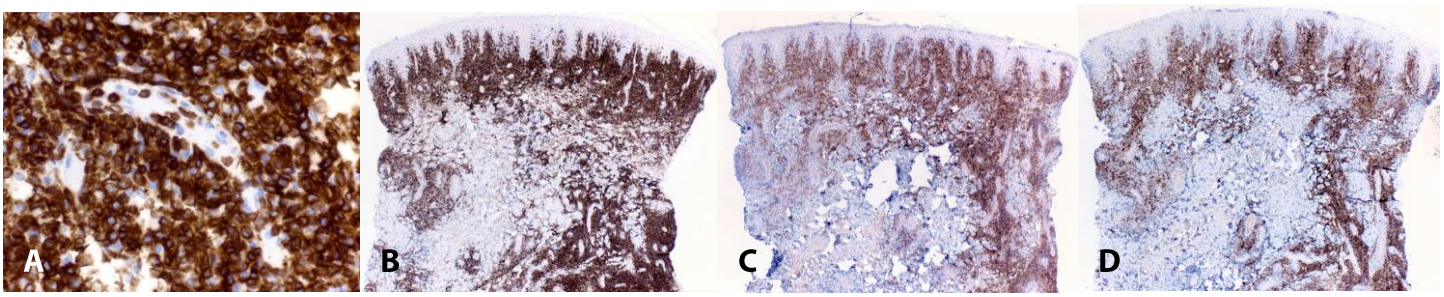

Figure 2. ***A)*** *Lymphoid cells are diffusely positive for CD3, angiocentricity and angioinvasion also demonstrated, 200×.* ***B)*** *Lymphoid cells showing strong positivity for CD8, 40×.* ***C)*** *Lymphoid cells are diffusely positive for CD56, 40×.* ***D)*** *Lymphoid cells expressing positivity for CD30, 40×.*

by a universal association with Epstein-Barr virus (EBV) and prominent angiocentricity [4]. Although the skin is the most common site of extranasal involvement in ENKTCL, skin-only involvement at the time of initial staging, termed primary cutaneous NKTCL, is exceedingly rare. Cutaneous presentation of NKTCL involves the extremities most commonly, followed by head and neck, or trunk. Presentations vary as papules, nodules, erythema, subcutaneous nodules, or ulceration may be exhibited. In addition, bone marrow involvement occurs in less than 10% of patients with ENKTCL [5].

The phenotype of the majority of ENKTCL, especially those with cutaneous presentation, features expression of cytoplasmic-only CD3, CD56, and germline TCR consistent with NK cell origin. Less frequently, cases with NK-like T cell origin are encountered; this is similar to our patient's tumors with, expression of surface CD3 and clonally rearranged TCR [6]. In previous reports, there was no significant association between cellular lineage and clinical outcomes. Notably, Hong et al. reported high false negative results with gene arrangement analysis alone and recommended the integration of immunohistochemistry to characterize the cell of origin.

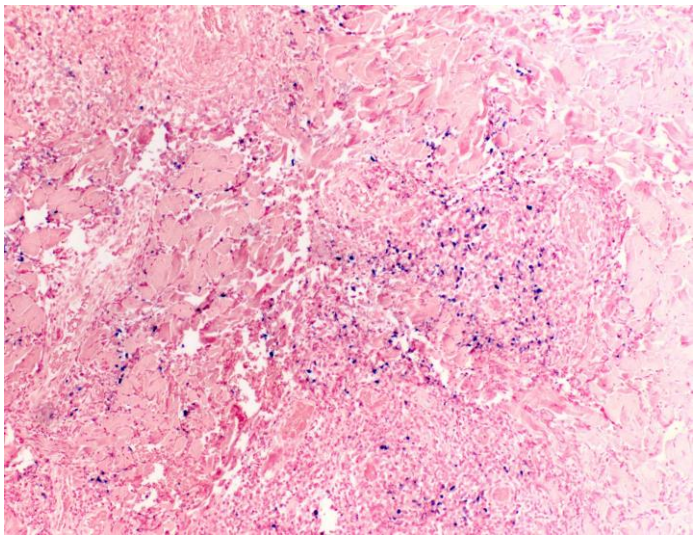

Figure 3. *Epstein Barr virus-encoded RNA in situ hybridization, 100×. Lymphoid cells demonstrating positivity for Epstein Barr virus-encoded RNA.*

CD30 positivity in ENKTCL is reported to be around 20-40% [7]. The importance of that is multifaceted. First, in cases with limited skin presentation, the histopathological differential diagnosis includes primary cutaneous anaplastic large cell lymphoma (PCALCL), as large cell cytomorphology can be seen in some cases of ENKTCL [8]. The distinction between ENKTCL and PCALCL is of clinical significance as the former is associated with a worse prognosis [9]. Second, CD30 expression can be of prognostic significance although reports in the literature show conflicting results. Some studies showed no difference in survival in patients with or without CD30 expression whereas others suggested a better prognosis in CD30 positive cases [10,11]. It is noteworthy that the latter report included cases with no detectable EBV in neoplastic cells. Finally, brentuximab vedotin has shown promise in refractory CD30 positive lymphoma and may complicate comparison of prognosis with the older literature in which this monoclonal antibody was not available as targeted treatment.

In addition to PCALCL, the histopathologic differential diagnosis in our patient included primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma. This is due to the presence of prominent epidermotropism of CD8 positive

lymphocytes, a feature not commonly encountered in this entity [12]. This is especially true as occasional cases of primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma can express CD30 in lesional cells. However, in these circumstances, EBV testing is critical to differentiate the two entities.

Although overlap between NK-cell leukemia and advanced (leukemic stage) ENKTCL may exist, the following features strongly support a diagnosis of advanced ENKTCL: initial presentation as cutaneous lesions, lack of an extensive leukemic blood picture (no anemia, leukopenia, or thrombocytopenia), NK-like T cell phenotype rather than NK cell phenotype (negative for CD3 and TCR), and lack of hepatosplenomegaly [2].

Given the rarity of extranasal and ENKTCL and its heterogeneity, there is currently no consensus on ideal treatment strategy. Unlike nasal ENKTCL, patients with extranasal disease have a higher incidence of advanced stage at presentation, poorer performance profile, and worse prognosis [4]. Median survival time for these patients ranges between two to 15 months. Our patient was treated with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin for his first cycle and switched to brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone for his subsequent cycles given CD30 positivity. At his last follow up, the patient was clinically stable with nearly resolved lesions after repeated hospital admissions as a result of febrile neutropenia.

Although novel therapeutic strategies such as L-aspariginase containing regimens, radiotherapy, sequential chemotherapy and radiotherapy, and concurrent chemoradiotherapy have improved outcomes, the overall survival of patients with advanced stage disease in ENKTCL is poor [13]. Immunotherapy targeting antigens such as CD30, CD38, PD1, NFκB, and JAK1/2/3 may offer more effective treatment, but further clinical trials are needed to guide treatment given poor outcomes and small patient sizes, especially for novel targets such as EBV antigen and chimeric antigen receptor T-cell therapy.

Conclusion

This report highlights a rare case of NK/T-cell lymphoma, underscoring the spectrum of clinical presentation, histopathologic findings, and immunophenotype. It is our aim to increase awareness of this rarely occurring lymphoma and avoid misdiagnosis with closely mimicking differential diagnoses.

Potential conflicts of interest

The authors declare no conflicts of interest.

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