A Unique Presentation of an Epstein-Barr Virus–Associated Natural Killer/T-Cell Lymphoproliferative Disorder in a White Male Adolescent

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**Background:** Extranasal natural killer (NK)/T-cell lymphoma and aggressive NK-cell leukemia are strongly associated with Epstein-Barr virus (EBV) and most often occur in middle-aged individuals. Overlap between these 2 diagnoses is rare. In addition, pathologic findings for these 2 diagnoses are typically notable for necrosis, apoptosis, angioinvasion, and angiodestruction.

**Observations:** We describe a 15-year-old male adolescent who had painful subcutaneous nodules and plaques over his anterior thighs, shins, and lower abdomen while receiving anti–tumor necrosis factor therapy with infliximab. He also was noted to have pulmonary nodules, liver nodules, hepatosplenomegaly, thrombocytopenia, and transaminitis. A skin biopsy revealed atypical small to intermediate-sized EBV-positive lymphoid cells of NK-cell origin infiltrating the subcutaneous adipose tissue, mimicking subcutaneous T-cell lymphoma. Similar atypical EBV-positive lymphocytes were noted in the bone marrow, liver, stomach, and colon. This patient had a rapidly fatal disease course.

**Conclusions:** We report a unique clinical and histological presentation most consistent with an extranasal NK/T-cell lymphoma and aggressive NK-cell leukemia overlap, although our case may represent a disease entity completely new to the literature. In addition, we report the first case to our knowledge of EBV-positive NK/T-cell lymphoma developing in the setting of tumor necrosis factor inhibitor therapy.

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**Extranodal Natural Killer (NK)/T-Cell Lymphoma, Nasal Type (EN-NK/T-NT)** is very strongly associated with Epstein-Barr virus (EBV) and most frequently occurs in the upper aerodigestive tract. Extranodal NK/T-cell lymphomas presenting in other locations are referred to as extranasal NK/T-cell lymphomas (ENKTLs), which tend to be highly aggressive and may overlap with aggressive NK-cell leukemia (ANKL) when the peripheral blood or bone marrow becomes involved.

EN-NK/T-NT is most frequently noted in Asia, Central America, South America, and Mexico. Men are more affected than women, and the disease occurs most often in adults in the fifth decade of life. ANKL is also more prevalent in Asia, but men and women are affected equally. The age of presentation for ANKL is younger than EN-NK/T-NT, with a median age of presentation of 42 years.

We report herein the clinical presentation and hospital course of an adolescent white male receiving anti–tumor necrosis factor (TNF) therapy with infliximab, whose disease may be best described as an ENKTL and ANKL overlap. However, this patient’s disease manifestations and pathologic characteristics are not completely consistent with either ENKTL or ANKL, and therefore his illness could potentially represent a distinct entity. We also report the first case to our knowledge of the development of an EBV-positive NK/T-cell lymphoma in the setting of anti-TNF therapy. In addition, we have reviewed the literature on ENKTL and ANKL with particular attention to the skin manifestations of these tumors.

**Report of a Case**

A 15-year-old boy was admitted to the pediatric inpatient service in June of 2009 with a 1-month history of daily cyclic fevers up to 40.6°C, new pulmonary and liver nodules noted on computed tomographic (CT) scan, and crampy abdominal pain. The patient also had a 1-month history of new-onset tender lesions over his legs and lower abdomen. The pa...

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The patient's medical history was notable for atypical inflammatory bowel disease, PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and adenitis), and non–biopsy-proven hydroa vacciniforme. Of note, he had been treated with infliximab every 6 weeks from April of 2007 until June of 2009 for inflammatory bowel disease, at which time the infliximab was discontinued owing to the development of the aforementioned complex of symptoms. A monospot screening result had been negative in June of 2006, which was prior to the initiation of infliximab. In April of 2007, immediately prior to the initiation of infliximab, IgM antibody to the EBV viral capsid antigen was negative. IgG antibody to the EBV viral capsid antigen was positive. IgG antibody to the EBV early antigen was in the equivocal range, and IgG antibody to the EBV nuclear antigen was positive. These serologic findings are consistent with a previous EBV infection.

On physical examination, the patient had scattered discrete pink to violaceous subcutaneous nodules and erythematous patches, predominantly over his anterior thighs and shins but also over his lower abdomen (Figure 1). He also had hepatosplenomegaly. Magnetic resonance imaging of the abdomen and a CT scan of the chest prior to admission revealed numerous nonspecific poorly enhancing liver lesions, bilateral pulmonary nodules, and splenomegaly. Results from admission laboratory analysis were notable for elevated levels of alkaline phosphatase, 2087 U/L (reference range, <525 U/L); lactate dehydrogenase, 3337 U/L (reference range, <645 U/L), alanine aminotransferase, 214 U/L (reference range, <40 U/L), and aspartate aminotransferase, 173 U/L (reference range, <60 U/L) (to convert to microkatal per liter, multiply by 0.0167). The platelet level and hemoglobin level were pathologically low at 104 × 10^9/µL (reference range, >150 × 10^9/µL) (to convert to ×10^9/µL, multiply by 1.0) and 11.4 g/dL (reference range, 13.0-16.0 g/dL) (to calculate as grams per liter, multiply by 10), respectively. His white blood cell count was within the reference range (4500 µL; reference range, 4500/µL-13 000/µL).

Biopsy specimens taken from the lesions on the patient's left anterior thigh revealed a dense lobular atypical lymphoid infiltrate in the subcutaneous adipose tissue with small to intermediate-sized lymphoid cells, scattered macrophages showing hemophagocytosis, relative sparing of the dermis, and areas of necrosis. T-cell receptor (TCR) gene rearrangement by polymerase chain reaction was negative. Immunohistochemical staining revealed that the atypical lymphoid infiltrate was CD4−, CD8−, CD30−, CD56−, and cytoplasmic CD3+. The Ki-67 proliferative index was markedley elevated at 50%. Most importantly, these atypical lymphoid cells were EBV positive by in situ hybridization for EBV messenger RNA transcripts (Figure 2). Liver, stomach, and colonic biopsies revealed EBV positive atypical lymphoid infiltrates. A bone marrow biopsy revealed medium atypical lymphoid cells more consistent with NK cells, given that they were CD2+, CD7+, and CD16+. By flow cytometry, the cells were CD56+ and cytoplasmic CD3+, but the negative CD3 staining result was believed to be due to technical difficulties. As in the skin, hemophagocytosis was noted.

The patient's hospital course continued to deteriorate with the development of ascites, worsening coagulopathy, pulmonary effusions, and hematochezia. During the admission, the patient's white blood cell count dropped to 3500/µL (reference range, 4500/µL-13 000/µL), platelet level dropped to 81 000/µL (>150 000/µL), and hemoglobin level dropped to 7.9 (reference range, 10.0-18.0 g/dL). Total bilirubin level rose to 1.8 mg/dL (reference range, <1.3 mg/dL) (to convert to micromoles per liter, multiply by 17.104), and international normalized ratio rose to 2.3. Quantitative EBV polymerase chain reaction returned a positive result at 645 000 copies/mL (detectable at >390 copies/mL). His interleukin 2 receptor level was notably elevated at 9493 U/mL (reference range, 223-710 U/mL). Findings from laboratory evaluations for familial hemophagocytic lymphohistiocytosis by syntaxin 11, perforin 1, and RAB 27 mutations were negative. In addition, the result from SH2D1A gene mutation analysis for X-linked lymphoproliferative disorder was negative. Despite 2 weeks of treatment with etoposide, ifosfamide, cyclosporine, and dexamethasone, the patient died after a cardiopulmonary arrest.

The spectrum of EBV-related malignant neoplasms is undergoing rapid expansion. Originally isolated from Burkitt lymphoma, EBV has also been identified in Hodgkin lymphoma, nasopharyngeal carcinoma, posttransplant B-cell lymphoma, EBV-positive T-cell lymphoproliferative disorder of childhood, EBV-positive large B-cell lymphoma of the elderly, hydroa vacciniforme-like T-cell lymphoma, and, pertinent to this case, NK-cell lymphomas.5-7

The evidence of EBV malignant potential stems from molecular analysis of EBV virus in cancer cells.8 Epstein-Barr virus has been found in tumor cells that the virus normally does not reside within. Immune status is strongly associated with its malignant behavior. In addition, EBV oncoproteins activate key nuclear receptors, including nuclear factor-κB, thus promoting cell survival and bypassing normal receptor-mediated signaling pathways.9-12 Pathways that are activated by known EBV oncoproteins are also activated by non-EBV alternative mechanisms in the same types of cancers, thus demonstrating the importance of EBV in oncogenesis.

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Classification of EBV-associated NK/T-cell lymphomas originated with typical cases of EN-NK/T-NT that
have a strong EBV association, and demonstrate significant vascular damage, tissue necrosis, and NK/T-cell phenotype on histological evaluation. ENKTL and ANKL are related to EN-NK/T-NT by their etiology and demographics. However, ENKTL and EN-NK/T-NT have different clinical presentations and prognoses (Table). ENKTL skin lesions are generally described as smooth-surfaced, violaceous nodules and plaques that can ulcerate. The lesions have a predilection for the trunk but also can involve the extremities, head, and neck. Patients with ENKTL are more likely to have a higher lactate dehydrogenase level, lower hemoglobin level, lower platelet level, more advanced stage of disease, shorter survival time, more aggressive clinical course, and poorer response to therapy than patients with EN-NK/T-NT. Like patients with EN-NK/T-NT, bone marrow involvement and hemophagocytic syndrome may be rare complications. When peripheral blood and bone marrow involvement occur, such cases may overlap with ANKL.

ANKL is a rare form of a rapidly progressive leukemia, strongly associated with EBV. Interestingly, unlike most other leukemias, the number of circulating neoplastic cells in the bone marrow or peripheral blood can be limited. Unlike EN-NK/T-NT and ENKTL, skin is only rarely involved. These patients generally present with fever, high lactate dehydrogenase levels, hepatosplenomegaly, transaminitis, and lymphadenopathy. Coagulopathy, thrombocytopenia, neutropenia, anemia, hemophagocytic syndrome, and multiorgan failure are common. ANKL is uniformly fatal, irrespective of treatment.

EN-NK/T-NT and ENKTL pathologic characteristics are essentially identical (Table). Both have an angiocentric and angiodestructive growth pattern, with cells varying from small to large and anaplastic. Like patients with EN-NK/T-NT, bone marrow involvement and hemophagocytic syndrome may be rare complications. When peripheral blood and bone marrow involvement occur, such cases may overlap with ANKL. ANKL also shares a similar immunophenotype with EN-NK/T-NT and ENKTL, but the neoplastic cells in ANKL are CD16+.

Prognosis is variable for EN-NK/T-NT. Radiotherapy is fundamental to treatment in early stage disease. Some patients with early stage disease are cured by radiation alone, while others experience early local or systemic recurrence. Patients with stage III/IV disease are generally treated with non–anthracycline-based chemotherapy. Unfortunately, advanced disease is frequently chemotherapy resistant. A recent study by Yong et al showed potential promise in the treatment of refractory or relapsed EN-NK/T-NT with an L-asparaginase-based salvage regimen, with a 66.9% over-
stage, relapsed, or refractory disease is still unknown. Therapy and stem cell transplantation in advanced-stage disease has been noted at approximately 12 months of diagnosis, and the long-term remission rate is less than 10%. The proper sequencing of chemotherapy and stem cell transplantation in advanced-stage, relapsed, or refractory disease is still unknown. ANKL prognosis is dismal. Survival is measured in days to weeks, with only transient response to chemotherapy or hematopoietic stem cell transplantation.

Based on the current NK-cell malignancy classifications, we would best classify our patient as having an EN-NK/T-NT overlap, although his presentation does not completely conform to either disease. The skin involvement in our patient favors ENKTL, while the patient’s age, bone marrow infiltration, peripheral blood involvement, diffuse systemic involvement, and rapid decline favor ANKL. Our patient is unique, as he is considerably younger than the usual age of onset for both ENKTL and ANKL. His white ethnicity is also rare in both of these diagnoses, since most cases of ENKTL and ANKL are of Asian descent. In addition, the patient’s biopsy findings mimicked the histologic patterns seen in subcutaneous T-cell lymphoma, as opposed to having the usual angiocentric and angioinvasive pattern of ANKL and ENKTL. However, unlike our case, subcutaneous T-cell lymphoma is a cytotoxic T-cell lymphoma with a mature αβ T-cell phenotype and EBV-negative cells. Our case is also very similar to primary cutaneous γδ T-cell lymphoma based on systemic symptoms, cutaneous manifestations, and the CD4+, CD8+, CD56+, cytotoxic protein positive immunophenotype. Unlike our case, primary cutaneous γδ T-cell lymphoma is EBV negative and CD30 positive and demonstrates clonal rearrangement of TCRβ and TCRγ.

Systematic review of available cases of EN-NK/T-NT demonstrates that there may be a bimodal distribution in the age of onset of ENKTL, pointing toward the presence of a distinct subcategory of the disease. Recently, it has been speculated that this subcategory might overlap with another pathological entity described as a spectrum of EBV-associated NK/T-cell lymphoproliferative disorders of children and young adults. Thus, our patient may later be categorized into this more heterogeneous group of disorders once these disorders are better characterized.

Of particular interest, our patient had been treated with infliximab for 2 years prior to his presentation, which raises the question as to whether his EBV infection or malignant lesions may have been related to his prior TNF inhibitor treatment. Recent studies have shown an increased risk of hepatosplenic T-cell lymphoma in young patients with Crohn disease being treated with infliximab in combination with another immunosuppressant, such as azathioprine or prednisone. A recent review of the literature by Dommasch and Gelfand revealed that the current data are not sufficient to either rule out an increased risk of lymphoma associated with biological agents or establish a firm causal relationship between biological agents and lymphoma. However, the study concluded that up to 4 years of treatment with a biological agent was safe with respect to lymphoma risk. As of yet, there have been no case reports of ENKTL, EN-NK/T-NT, or ANKL developing after treatment with a TNF inhibitor. In addition, a small study by McKeown et al

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Table. Summary of EN-NK/T-NT, ENKTL, and ANKL

<table>
<thead>
<tr>
<th>Variable</th>
<th>EN-NK/T-NT</th>
<th>ENKTL</th>
<th>ANKL</th>
</tr>
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<tbody>
<tr>
<td>Epidemiology</td>
<td>Asia, Central America, South America, and Mexico; men are affected more than women; occurs most often in the fifth decade of life</td>
<td>Similar to EN-NK/T-NT</td>
<td>Asia; men and women affected equally; median age of onset of 42 y</td>
</tr>
<tr>
<td>Sites of involvement</td>
<td>Starts in upper aerodigestive tract and can disseminate to skin, soft tissue, gastrointestinal tract, testes, and rarely bone marrow</td>
<td>Skin (primarily trunk but can also involve extremities, head, and neck), gastrointestinal tract, salivary glands, spleen, and testis. Overlaps with ANKL when peripheral blood and bone marrow is involved</td>
<td>Primarily bone marrow, peripheral blood, spleen, and liver, but any organ can be involved; skin is only rarely involved</td>
</tr>
<tr>
<td>World Health Organization Classification</td>
<td>Predominantly an extranodal lymphoma; angiocentric and angioinvasive; associated with EBV and a cytotoxic phenotype</td>
<td>Classified under EN-NK/T-NT</td>
<td>Systemic neoplastic NK cells almost always associated with EBV</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>CD2+, CD56+, cytoplasmic CD3ε−; CD16−, CD7−, surface CD3; CD4 and CD8 usually negative; cytotoxic proteins are positive; no clonal TCR gene rearrangement</td>
<td>Similar immunophenotype as EN-NK/T-NT</td>
<td>Similar immunophenotype as EN-NK/T-NT except CD16−</td>
</tr>
</tbody>
</table>

Abbreviations: ANKL, aggressive natural killer (NK) cell leukemia; EBV, Epstein-Barr virus; ENKTL, extranasal NK/T-cell lymphoma; EN-NK/T-NT, extranodal NK/T-cell lymphoma, nasal type.
found no EBV reactivation in 122 patients with inflammatory arthritis after 18 months of treatment with an anti-TNF agent. Similarly, Miceli-Richard et al demonstrated that patients with rheumatoid arthritis or spondyloarthropathy treated with a TNF inhibitor for 3 months had no increase in EBV-specific T cells or EBV viral load.

Several questions still remain unanswered in our case. We wonder whether a unique genetic composition made our patient susceptible to an EBV-mediated carcinogenesis and if the anti-TNF agent the patient received for inflammatory bowel disease played a key role in the rapid development of this fatal disease. Finally, the true nature and classification of our patient’s disease remains debatable, given our patient’s unique clinical and pathologic presentation.

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REFERENCES