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Clinical Dermatology and Surgery

Aggressive Extranodal NK/T-cell Lymphoma with Hemophagocytic Syndrome

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ABSTRACT

This report delineates a case of extranodal NK/T-cell lymphoma, nasal type, in a 30-year-old Caucasian male. Presenting symptoms encompassed fatigue, weight loss, and the emergence of cutaneous lesions evolving from asymptomatic red nodules to painful ulcerated plaques. Laboratory assessments revealed profound abnormalities. Despite a prior dermatologic evaluation, including a punch biopsy indicative of atypical lymphocytic infiltrate, therapeutic interventions, such as methotrexate and antibiotics, failed to impede disease progression.

Pathological scrutiny of skin biopsies confirmed an angiocentric infiltrate, with immunohistochemistry demonstrating positivity for CD3, CD56, and EBV-encoded RNA, supporting the diagnosis of NK/T-cell lymphoma. Subsequent imaging illustrated extensive systemic involvement, including cardiac tamponade, myocardial infiltration, and gastrointestinal complications. Treatment efforts, encompassing chemotherapy, were met with limited success, ultimately culminating in the patient's demise.

This case underscores the diagnostic challenges of cutaneous NK/T-cell lymphomas, particularly in non-endemic regions, emphasizing the necessity for heightened clinical vigilance and research efforts to optimize therapeutic strategies for this aggressive malignancy.

BACKGROUND

A 30 year old white male presented to the emergency department for fatigue, shortness of breath, weight loss (twenty-five pounds over two months), diarrhea, blurred vision, and widespread skin lesions involving his bilateral upper and lower extremities, groin, torso, and head. The eruption began two months prior as asymptomatic red and purple lesions in the groin, which then “turned black in the center.” The lesions were painful after ulceration.

He had been evaluated one month earlier by another dermatologist. At that time, labs were remarkable for thrombocytopenia (PLT 108) and hyponatremia (Na 128). Punch biopsy for hematoxylin and eosin staining demonstrated a superficial and deep, dense, perivascular and interstitial, atypical, lymphocytic infiltrate. There were scattered necrotic keratinocytes in the epidermis. CD30 was negative. Biopsy for direct immunofluorescence was negative. Culture showed moderate growth of Acinetobacter lwoffii. He was started on methotrexate 2.5mg daily (which he took once), light therapy, and he completed one week of trimethoprim/ sulfamethoxazole. He was advised to follow up at an academic center for further management.

He traveled to Mexico three years prior to this presentation, which was also when his symptoms began. Symptoms included intermittent fevers and chills, fatigue, and malaise. Symptoms would occur every three to six months and would last for one week. They were not associated with skin lesions at that time. The patient had no pertinent family history. He occasionally drank alcohol and smoked cigarettes daily. He last used cocaine, heroin, and marijuana three years ago. Not sexually active for three years. No other significant history, medications, or drug allergies.

On the bilateral upper and lower extremities, torso, and head, there were round, violaceous, and infiltrative nodules and plaques, many with central black eschars and peripheral violaceous rims. There were petechiae on the hard palate. There were erosions and ulcerations of the groin and testes. There was lymphadenopathy of the anterior and posterior neck and injection of the bilateral sclerae. T-cell receptor gene rearrangement by PCA and heteroduplex analysis did not show a clonal T-cell receptor gene rearrangement product. Tissue and urine cultures were positive for *pseudomonas aeruginosa.*

Transthoracic echocardiogram showed a moderate pericardial effusion and marked right ventricular chamber collapse consistent with tamponade physiology. Computed tomography of the chest demonstrated increased thickness associated with nodularity in the left ventricle consistent with an infiltrative disorder of the myocardium. Computed tomography of the abdomen and pelvis showed that the spleen was enlarged measuring 13.3 cm in length**,** perisplenic ascites, and patchy-appearing perfusion of the bilateral kidneys. There was also diffuse wall thickening of the entire colon and small bowel. Magnetic resonance imaging of the brain showed polypoid mucosal thickening in the maxillary and sphenoid sinuses. There was also mucosal thickening and patchy opacification of the ethmoidal and bilateral mastoid air cells. There were retained secretions in the nasopharynx and oropharynx. There was an enlarged and mildly enhancing right superior rectus muscle.

Punch biopsies from the right and left upper arm demonstrated a moderately dense perivascular and periadnexal infiltrate of highly atypical lymphoid cells with frequent mitotic figures. The angiocentric and adnexocentric atypical lymphoid infiltrate in the dermis stained positive for CD3, CD56, and EBV-encoded RNA (EBER in situ hybridization). Stain for CD10 highlighted the dendritic meshwork. Bone marrow biopsy showed a mildly hypercellular marrow with trilineage maturation and scattered EBV positive cells. Bone marrow flow cytometry did not show evidence of lymphoma or an increase in NK cells. Flow cytometry from the peripheral blood showed that NK cells comprised approximately 35% of the total leukocytes and 84% of the lymphocytes.

The above mentioned testing led to a diagnosis of Extranodal NK/T-cell lymphoma, nasal type. The patient became pancytopenic. His dyspnea did not improve after evacuation of his cardiac tamponade. Despite treatments with steroids, pressors, antibiotics, antifungals, and the initiation of chemotherapy with etoposide, the patient continued to decline and passed away. The autopsy revealed a gastric perforation, ascites, and candida albicans of the lung and serosal surfaces as well as disseminated lymphoma in the skin, heart, lungs, stomach, liver, spleen, testes, bone marrow, and lymph nodes.

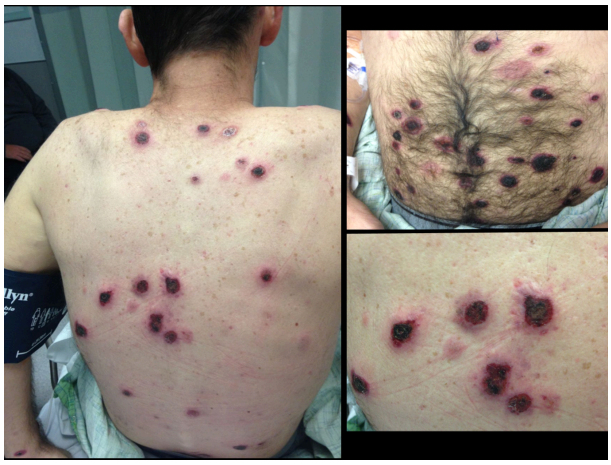

Figure 1: 30 year old male with widespread lesions over trunk and lower extremities

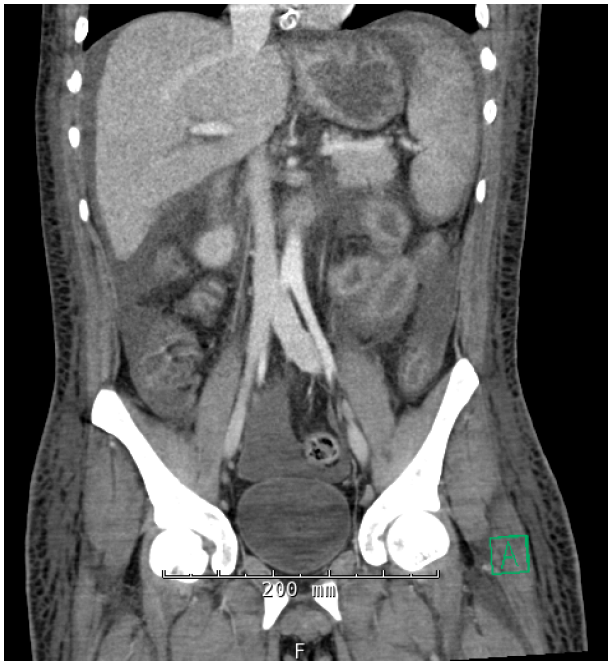

Figure 2: Computed tomography of the abdomen and pelvis showing splenomegaly, perisplenic ascites, and patchy perfusion of bilateral kidneys

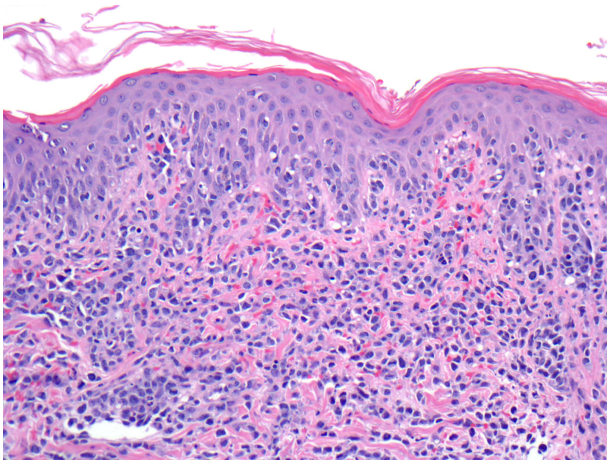

Figure 3: Punch biopsy of right upper arm showing dense perivascular lymphocytic infiltrate

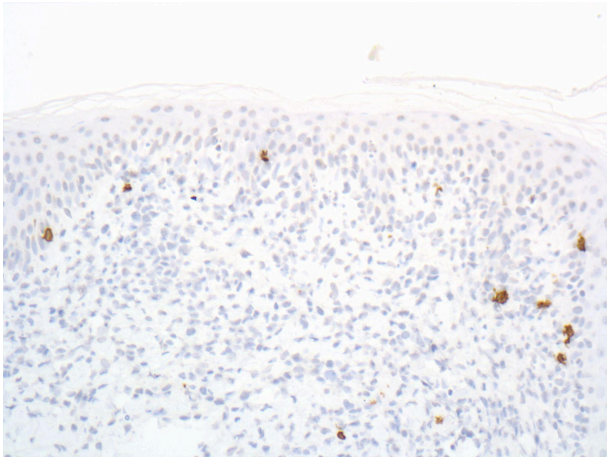

Figure 4: Positive dermis stain for CD20

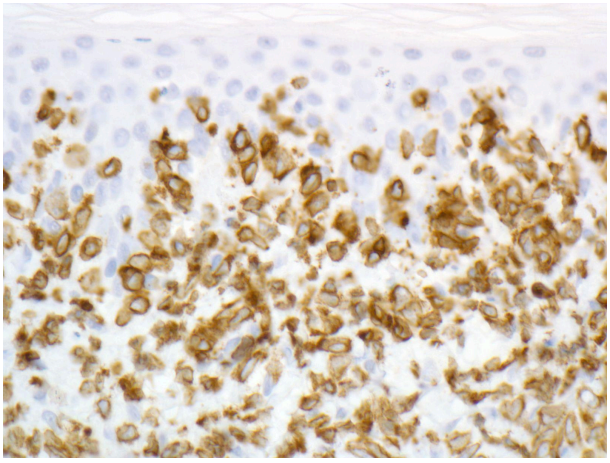

Figure 5: Positive dermis stain for CD3

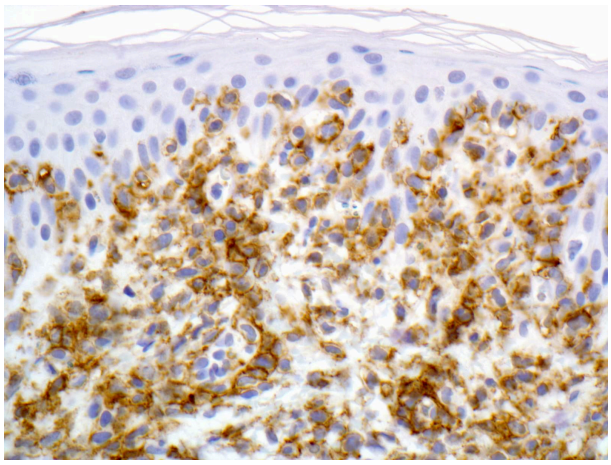

Figure 6: Positive dermis stain for CD56

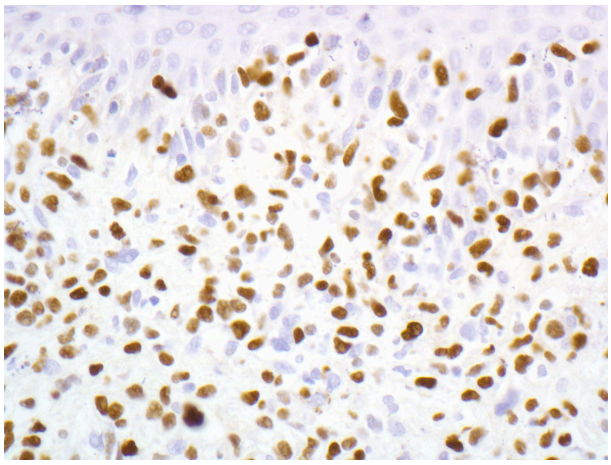

Figure 7: Positive dermis stain for EBER

DISCUSSION

In 1987, markers of natural killer (NK) cells were found in nasal and paranasal lymphomas. Further studies of similar tumors confirmed the presence of this marker—the neural crest adhesion molecule, (NCAM) or CD56. When NK lymphomas occur as nasal masses or destructive midline facial lesions, they are termed nasal NK/T-cell lymphomas. An identical tumor arising in an extranasal site is classified as an extranodal NK/T-cell lymphoma, nasal type. Some of the extranasal sites include the aerodigestive tract, skin, soft tissue, gastrointestinal tract, lungs, spleen, eye, brain, and testes. The skin is the second most common site of involvement after the nasopharynx. When the skin is involved, it is generally an aggressive neoplasm, and the patient may be unaware of extracutaneous disease.

It is a rare lymphoma, which is much more common in Asia, South America, and Central American than in Europe and North America. In a multination study of 129 cases of extranodal NK/T cell lymphomas, Asians accounted for 80% of the nasal cases and 84% of the extranasal cases, while Caucasians accounted for only 9% of the nasal and 13% of the extranasal cases. EBV is highly associated with the disease, although lower EBV infection rates have been described in the United States. It is also commonly associated with hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome, which usually follows a rapidly fatal course. To diagnose HLH, patients must have a molecular diagnosis consistent with HLH or fulfill five of eight diagnostic categories including fever, splenomegaly, ferritin ≥500 μg/L, soluble CD25 (IL-2 receptor) ≥2,400 U/ml, low or absent NK-cell activity, cytopenias (≥2 of 3 lineages in the peripheral blood), hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis in bone marrow, spleen, or lymph nodes.

Microscopically, there are inflammatory cells, atypical cells of varying sizes, and mitoses. The tumor cells are often angiocentric. They can infiltrate and destroy the blood vessel walls. Zonal necrosis is a consistent feature. There may be epidermotropism. Immunohistochemistry usually shows surface CD3–, cytoplasmic CD3e+, CD56+, TIA-1+, perforin+, and granzyme B+. Diagnosis often requires in situ hybridization of EBV using probes for EBV encoded RNA (EBER). Clonal T cell receptor (TCR) gene rearrangements can occur, but are usually negative.

CONCLUSION

This case illustrates a thirty-year old Caucasian male in the United States who presented with primarily cutaneous involvement of an extranodal NK/T-cell lymphoma, nasal type as well as hemophagocytic syndrome. Despite early evaluation and therapeutic intervention, the disease rapidly progressed, leading to multiorgan

dysfunction and a fatal outcome. The extensive systemic dissemination observed in imaging studies, coupled with the patient's deteriorating clinical course, underscores the complex nature of this rare lymphoma.

Concurrent presentation of extranodal NK/T-cell lymphoma with hemophagocytic syndrome is a contributing factor to the patient's rapid decline. The rarity of this type of lymphoma in a non-endemic region necessitates a heightened awareness among healthcare providers for timely diagnosis and intervention. This case emphasizes the need for ongoing research and clinical advancements to refine diagnostic approaches and enhance treatment modalities for extranodal NK/T-cell lymphomas.

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