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Case Report
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Extranodal NK/T-Cell Lymphoma with Cutaneous Presentation and Fever of Unknown Origin

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Abstract

Extranodal NK/T-cell lymphoma is a rare subtype of extranodal large cell lymphoma that typically involves the nasal cavity, nasopharynx, and the upper aerodigestive tract where as non-nasal NK-cell lymphoma involves any other locations of the body. Extranodal NK/T-cell lymphoma is exceeding rare in Western Countries, with most documented cases occurring in Asia. The disease often involves the skin, gastrointestinal tract, and testis. Involvement of lymph nodes, blood, and bone marrow can occur and typically overlaps with Aggressive NK-cell leukemia. Diagnosis is typically made with biopsy and immunostaining, however given the extensive necrosis seen in these tumors this often requires multiple biopsies. Typically Epstein Barr virus is present and immunophenotype shows CD56. Unfortunately this newly recognized distinctive lymphoma has not yet had a defined optimal therapy, however SMILE or CHOP and generally recommended. Prognosis is generally very poor, with the Korean Prognostic Index as the most widely used prognostic tool. Here we present a case of a 74-year-old female who presented with erythematous scalp raised patches and persistent fevers, chills, weight loss and night sweats found to have Extranodal NK/T-cell lymphoma.

Introduction

Extranodal NK/T-cell lymphoma is a rare subtype of extranodal large cell lymphoma that typically involves the nasal cavity where as non-nasal NK-cell lymphoma involves other parts of the body. The disease often involves the skin, gastrointestinal tract, and testis. Involvement of lymph nodes, blood, and bone marrow can occur and typically overlaps with Aggressive NK-cell leukemia. Our case is a 74-year-old female who presented with erythematous scalp raised patches and persistent fevers, chills, weight loss and night sweats.

Case Presentation

A 74-year-old female with a medical history significant for CVA and seizures presented with a two month history of progressively enlarging scalp masses, persistent fevers, chills, weight loss and drenching night sweats. Physical exam revealed non-tender violaceous indurated plaques from the left superior forehead extending to left frontal scalp and right temple extending to right lateral cheek inferiorly and right frontal/temporal scalp with overlying telangiectasias. On presentation, she was febrile and initial labs revealed pancytopenia. The patient was pan-cultured and started on broad spectrum antibiotics. She remained febrile on antibiotics without culture or serology evidence of infection. A fine needle aspirate (FNA) of the right temporal lesion showed atypical mononuclear cells and scattered mitotic figures suggestive of lymphoreticular neoplasm but no monoclonal B-cell

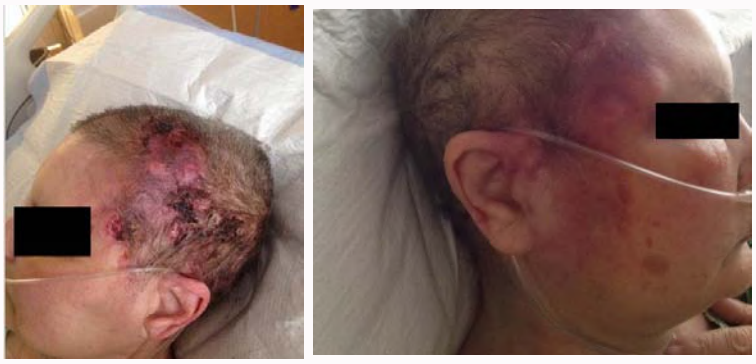

Figure 1: Pre Chemotherapy.

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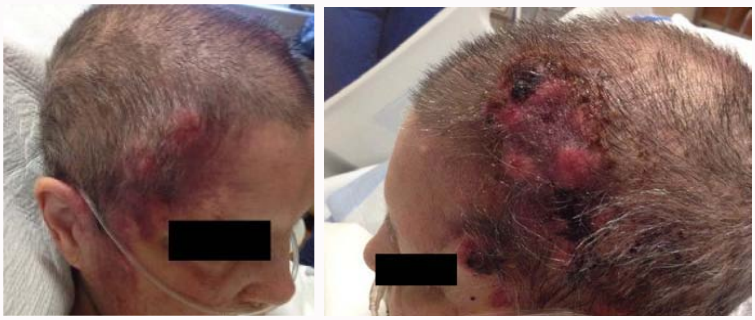

Figure 2: During Chemotherapy.

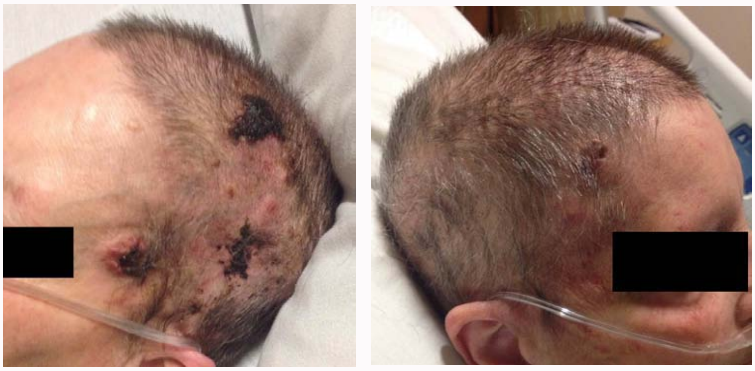

Figure 3: Post Chemotherapy.

or immunophenotypically aberrant T cell population were identified. She had a previous non-diagnositic FNA of the right temporal nodule re-examined at our facility which showed rare atypical cells of lymphoid origin. A bone marrow biopsy was performed which showed hypercellular marrow without evidence of malignancy. A punch biopsy of the left frontal scalp was performed by dermatology and showed suppurative neutrophilic dermatitis with PAS, GMS, and AFB stains negative for organisms. At this time the patient was administered intravenous prednisone with improvement of the skin lesions. Given the clinical suspicion of underlying malignancy the patient underwent a wider excisional biopsy of her left scalp prior to treatment (Figures 1-3). The infiltrate was composed of large and atypical T-cells which expressed CD3, CD8, granzyme B and weakly CD56. The malignant cells were negative for BetaF1 and TCR-gamma/delta (Figure 4). The malignant cells were positive for EBV by Epstein-Barr virus-encoded RNA in situ hybridization test and PCR for T-cell receptor gamma gene rearrangement was polyclonal. The findings were most consistent for EBV-associated extranodal NK/T cell lymphoma (Figure 5).

Following the diagnosis, a staging PET scan revealed widespread metastatic disease with multiple foci of uptake in soft tissues, muscles, and lymph nodes. There was no nasal involvement.

Patient was categorized as Risk Group 4 (elevation in LDH, stage >III, and B symptoms), which carries a 6.6% 5 year overall survival rate 6. The patient was treated with EPOCH (etoposide 89 mg, doxorubicin 17.8 mg, vincristine 0.5 mg, cyclophosphamide 750 mg/m^2, and prednisone 60 mg/m^2) with immediate clinical response of her skin lesions.

Discussion

NK/T–cell lymphoma is an aggressive hematological malignancy

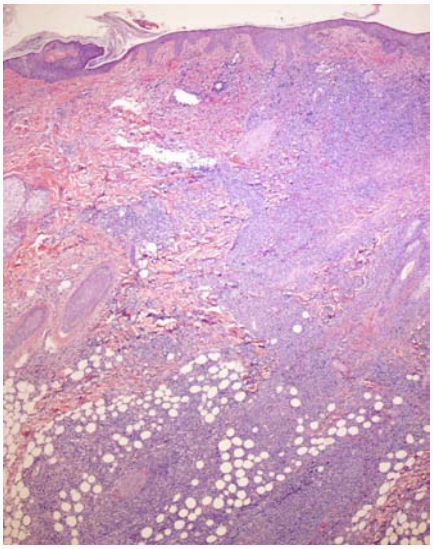

Figure 4: Malignant T-cells infiltrate the dermis, extending into the subcutaneous adipose tissue and focally surrounding eccrine glands and hair follicles, largely sparing the epidermis. (4x magnification).

rarely found in Western countries. EBV is frequently detected in these malignant cells and is theorized to have a role in the pathogenesis. Typically NK/T-cell lymphoma is extranodal and originates in the nasal area and upper airway, almost always presenting with lymphadenopathy and B-symptoms. Constitutional symptoms are more common in patients with the non-nasal type with presentations significant for weight loss, jaundice and high fever. Physical exam findings can include lymphadenopathy, hepatosplenomegaly and skin infiltration. Lab abnormalities in these patients include anemia and thrombocytopenia as well as elevated liver enzymes and evidence

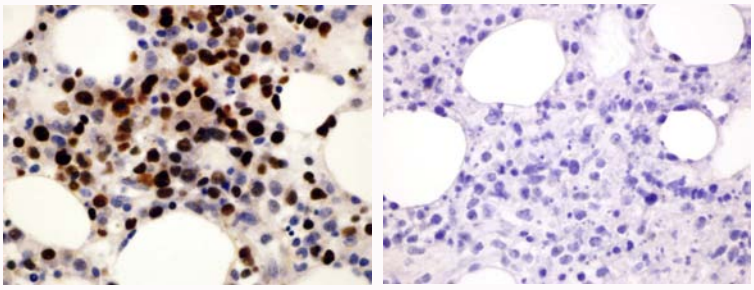

Figure 5: Extranodal natural killer/T-cell lymphoma tumor cells within subcutaneous adipose tissue, positive for Ebstein-Barr virus via in situ hybridization **(A)** and negative for CD20 immunohistochemistry **(B)**. (60x magnification).

of disseminated intravascular coagulopathy. In non-nasal and aggressive disease, the lymphoma typically involves the skin, GI tract, spleen, salivary gland, and bone marrow [1]. As with our patient, diagnosis often requires multiple biopsies due to the extensive necrosis in order to obtain significant tissue. Diagnosis can be made by immunostaining. The malignant cells are typically positive for $CD3^{\varepsilon+}$, CD56, and CD2 and negative for surface CD3. These cells do not show rearrangement of T-cell receptor (TCR) or immunuoglobulin genes. NK/T-cell lymphoma cells are almost always positive for Epstein–Barr virus (EBV) [2,3]. NK/T cell lymphoma is treated with conventional chemotherapy (CHOP) although an optimal therapy has not been established. Less than 10% of non-nasal NK/T cell lymphoma patients achieve remission and there have been no documented reports of remission in patients with aggressive NK/T cell lymphoma/leukemia treated with conventional chemotherapy [4]. The prognosis in both the non-nasal and aggressive disease is typically weeks to months [1,2,5,6].

Conclusion

T cell lymphoma is a difficult diagnosis to make as skin findings can be mistaken for infectious and rheumatologic process especially in the setting of inadequate tissue samples for a lymphoma diagnosis. Our patient's skin lesions responded to the EPOCH. The decision to use EPOCH rather than the SMILE regimen was made largely because of toxicity risk. The patient and family made an informed decision to use alternative choice of therapy. Unfortunately her case was complicated by prolonged neutropenia, healthcare associated pneumonia, and weakness. The family elected to take her home with hospice and she died less than 1 year following diagnosis.

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