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Case Report
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Cytophagic Histiocytic Panniculitis Masking as Primary Cutaneous T-Cell Lymphoma: A Spectrum of Disease

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Abstract

Primary Cutaneous Gamma-Delta T-Cell Lymphoma (PCGDTCL) comprises of less than 1% of primary Cutaneous T-Cell Lymphomas (CTCL). It is characterized by a highly aggressive clinical course with a median survival of 15 months. PCGDTCL involves the subcutaneous fat and can often mimic both clinically and histologically other more indolent conditions such as Cytophagic Histiocytic Phagocytosis (CHP) and Subcutaneous Panniculitic T-Cell Lymphomas (SPTCL). In addition, diagnosis of PCGDTCL can be challenging due to aberrant expression of surface markers in the neoplastic cells and varied histologic presentation and multiple biopsies are required to make a correct diagnosis. This is a case report that the initial histopathologic findings were most consistent with CHP but with a very aggressive and uncommon clinical course and with extreme subcutaneous ulcerations.

Introduction

Cytophagic Histiocytic Panniculitis (CHP) lesions show histiocytic infiltration of adipose tissue with hemophagocytosis and lymphocytic invasion [1,2]. The clinical course of CHP may be indolent with intermittent exacerbations or rapidly fatal heralded by fevers, hepatosplenomegaly, pancytopenia, coagulopathy, and transaminitis [2,3]. Non-fatal, indolent CHP is responsive to immunosuppressive therapy whereas fatal CHP often requires cytotoxic therapy [2,3]. The presentation of fatal CHP is similar to Subcutaneous Panniculitis-like T-Cell Lymphoma (SPTL) with differentiation made by the presence of malignant lymphocytes on histologic review of lesions [2]. However, initial biopsies of SPTL are often consistent with CHP suggesting that CHP represents an indolent lymphoid malignancy [3,4]. The following case illustrates an extreme clinical presentation of SPTL initially diagnosed as CHP.

Case Presentation

A 63-year-old Caucasian female presented with a month history of daily fevers up to 39.4C, night sweats, increasing fatigue, bilateral lower extremity edema and multiple erythematous lesions on her extremities and back. The patient reported she had similar symptoms of a milder nature one year prior, that had resolved spontaneously after six weeks without a diagnosis. At the time of presentation, the patient was a febrile and vitally stable. Multiple erythematous, patchy lesions with associated deep ulceration, necrosis, and subcutaneous nodular lesions were noted on the bilateral upper and lower extremities, left breast, and back (Figure 1-5). Cardiovascular, respiratory, and abdominal examinations were normal and without hepatosplenomegaly. Her course progressed rapidly over the next several months with aggressive, deep ulcerative lesions throughout her extremities, breast, and abdomen with ongoing intermittent fevers and progressive fatigue.

Initial blood work reported normal hemoglobin of 11.6 with giemsa smear showing microcytic hypochromic red blood cells and normal white blood cell and differential and platelet count. Iron studies were indicative of anemia of inflammation (Ferritin 1,188; Iron 44; TIBC 298 and Iron Saturation 15%). Markers of inflammation were elevated including CRP 7.9 and ESR 55. The patient had a mild transaminitis (AST 106, ALT 77) that spontaneously normalized on repeat laboratory work up.

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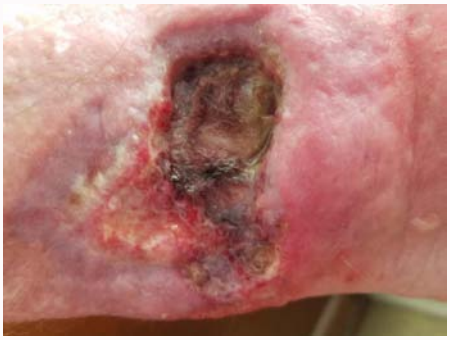

Figure 1: Ulcerative Panniculitis, left distal, medial leg.

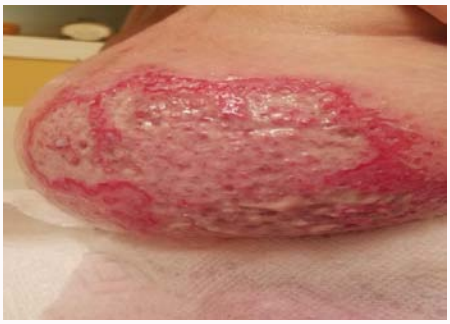

Figure 2: Left Breast.

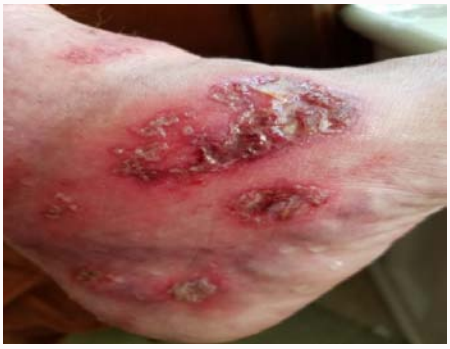

Figure 3: Left medial foot.

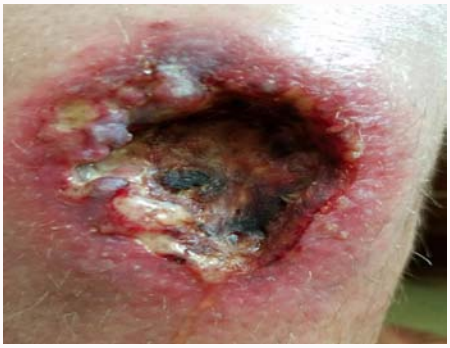

Figure 4: Left Leg.

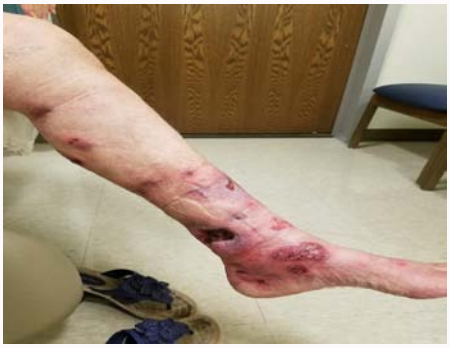

Figure 5: Left Leg.

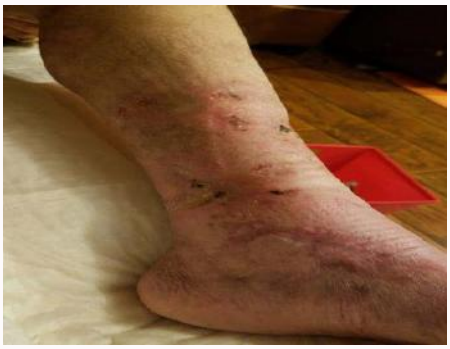

Figure 6: Healed Ulcerative panniculitic following chemotherapy.

Skin punch biopsy of lesions on upper and lower extremities were obtained from outside facility. Outside pathology of all three biopsies were read as squamous cell carcinoma with a co-existent lobular panniculitis. Second review of the original pathology was read as ulcer and atypical squamous proliferation with lobular panniculitis and interface dermatitis. Repeat biopsies were completed due to high suspicion of possible SPTL, but the pathology confirmed a lobular panniculitis composed predominantly of epithelioid histiocytes with phagocytosis of red blood cells. There were also small lymphocytes and karyorrhectic cells. Normal CD4:CD8 ratio with histiocytic predominance did not support a typical lymphoma diagnosis. Overall, these findings were reported suspicious for Cytophagic Histiocytic Panniculitis (CHP). No malignant or infectious processes were appreciated on complete pathologic stains.

Work-up for underlying causes of CHP was performed. Infectious etiologies including HIV, EBV, CMV, Hepatitis B, Hepatitis C, Syphilis, and Tuberculosis were excluded. Autoimmune and Vasculitis work-up was negative including Anti-Nuclear Antibodies (ANA), SS-A/Ro and SS-B/La antibodies, Beta-2-Glycoprotein, cardiolipin antibody, C-ANCA, P-ANCA, smooth muscle antibody, alpha-1-antitrypsin enzyme, angiotensin converting enzyme, and interleukin-2 receptor. However, mitochondrial antibodies were elevated at 1.31 with normal index value <0.91 and lipase was only mildly increased at 196. D-dimer was elevated at 1,214 ng/mL and fibrinogen was 556 ng/dL. Infectious disease and rheumatologic consults were obtained, both felt that an infectious or rheumatologic underlying process were unlikely.

Work-up for an underlying neoplastic process was performed. Computed Tomography (CT) of the chest, abdomen, and pelvis with contrast was obtained which noted mildly enlarged lymph nodes throughout the abdomen, pelvis, lower neck, mediastinum, and left axilla. Fat stranding of the subcutaneous soft tissues of the abdomen and pelvis and left breast were also reported. Mammography was reported as negative for malignancy.

While evaluating for underlying etiologies, the patient was actively being treated for aggressive CHP as she continued to have progressive

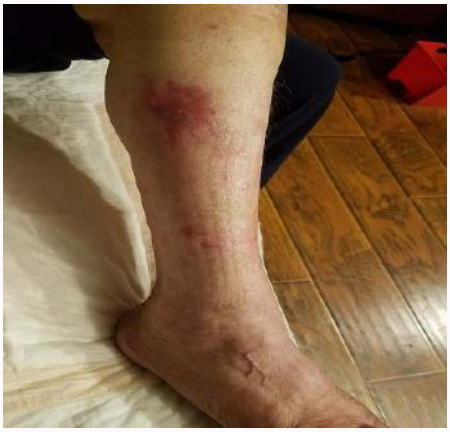

Figure 7: Healed lesions after chemotherapy.

deep cutaneous ulceration/panniculitis and systemic symptoms. She was started on prednisone 40 mg per day and hydroxychloroquine 200 mg twice daily for treatment of CHP. While this treatment course initially achieved mild improvement of skin lesions and edema, the patient developed progression of symptoms with visual disturbance, ptosis, and left eye discomfort. CT scan of the orbits showed an enlarged heterogeneous lacrimal gland without bony erosion or fat stranding. The patient was changed to prednisone 60 mg per day with cyclosporine 500 mg per day. The patient experienced disease progression on this regimen, and then she was initiated on Anakinra 100 mg subcutaneously daily.

Due to a worsening disease course despite immune suppression and concern that CHP may be masking and underlying SPTL, repeat multiple skin biopsies were obtained. The previous biopsies did not show abnormal T cells and PCR studies for TCR gene rearrangement were inconclusive. A final set of skin biopsies were then obtained. Pathology confirmed lymphocytes positive for CD3, TCR delta, CD56, and TIA positive, CD4, and CD8 negative. PCR identified a clonal TCR gamma gene rearrangement. These findings were consistent with Subcutaneous Panniculitis T-Cell Lymphoma (SPTL) gamma/delta type (Primary Cutaneous Gamma/Delta T-Cell Lymphoma (PCGDTCL)) presenting as cytophagic histiocytic panniculitis. Anakinra was discontinued and patient was referred to bone marrow transplant for further management. She received six cycles of EPOCH regimen with excellent response and healing of the large, deep cutaneous ulcers (Figure 6 and 7). She is currently receiving Pentostatin and being prepared for allogenic stem cell transplantation.

Discussion

Cytophagic Histiocytic Panniculitis (CHP) presents as ulcerating nodules or plaques based in the subcutaneous fat without antecedent infection [1,2]. CHP is defined histologically by infiltration of subcutaneous adipose tissue by benign appearing cytophagic macrophages and T-cell lymphocytes [1-3]. The course of CHP may be indolent or aggressive with a fatal hemophagocytic disorder [3,5]. As in this case, an initial benign course can progress to a fatal hemophagocytosis [2,3]. This progression is often heralded by systemic findings including recurrent pyrexia, pancytopenia, consumptive coagulopathy and hemodynamic instability [2,3,5]. This patient did not have any cytopenias, liver or spleen abnormalities or a consumptive coagulopathy. Her clinical course was unusual in that she had a mild form of the disease one year prior that became latent. Then, she developed progression of symptoms starting with cycling of fevers, fatigue, and multiple, large deep subcutaneous ulcers are not commonly seen to this extent in panniculitis. In addition, she developed orbital involvement that is also a rare finding in primary cutaneous gamma/delta T-cell lymphoma.

The systemic symptoms of aggressive CHP are also noted in SPTL [2]. Differentiation of CHP and SPTL is classically based on histologic findings, with SPTL displaying neoplastic T cell infiltrate into subcutaneous tissue involving fat septate and lobules [2,6]. However, a dominant benign inflammatory cell population accompanies neoplastic lymphocytes in SPTL, potentially obscuring them [5]. Furthermore, as documented in this case, initial biopsies of SPTL may be more consistent with CHP [3,6]. Thus, an indolent course of CHP with histology interpreted as benign cannot be assumed non-fatal, as neoplastic transformation or a missed diagnosis may occur [3]. In addition, the heterogeneity of the lymphoma can make this diagnosis more difficult to confirm.

T-cell gene rearrangements have been examined in an attempt to definitely differentiate CHP from SPTL. Though T-cell monoclonal rearrangements are more frequently associated with SPTL, they have also been noted in CHP [7]. Furthermore, T-cell clonality is sometimes observed in benign conditions, and therefore is a poor diagnostic marker [3]. EBV positivity has also been studied with latent infection noted in both CHP and SPTL [8].

Given the similarity of clinical presentation, the lack of definitive molecular tests, and the transition of presentation, CHP and SPTL may be better characterized as a clinical spectrum rather than separate entities. This case provides excellent illustration of such disease progression and heterogeneity in the pathologic specimens. Maintaining a high suspicion of the development or an underlying cutaneous lymphoma is warranted in these rare cases. In addition, this case provides a reminder that patients with initial diagnoses of indolent CHP should be carefully monitored for neoplastic disease. Patients with aggressive CHP or SPTL would benefit from early aggressive therapy to prevent a fatal course.

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