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Case Report

Hepatic Infiltration with Malignant T-cells Manifesting as Impending Acute Liver Failure in Sezary Syndrome

Yumeng Zhang[1], Jinming Song[2], David Rutenberg[1] and Lubomir Sokol[2].

[1] University of South Florida, Tampa, FL 33612
[2] Moffitt Cancer Center, Tampa, FL 33612

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Abstract. We describe a case of impending acute liver failure in a patient with Sézary syndrome (SS). The three-phase computed tomography (CT) of the liver showed neither mass nor hepatomegaly. Liver biopsy confirmed infiltration with malignant CD4+ clonal T-cells. Prompt administration of combination chemotherapy, consisting of gemcitabine, dexamethasone, and cisplatin (GDP), resulted in full recovery of liver function. To the best of our knowledge, this is the first report of liver failure from SS. Commercial next-generation sequencing panel identified 11 clinically relevant mutations. Interestingly, the identified ARID2 mutation, frequently observed in hepatocellular carcinoma, rarely occurs in hematologic malignancies. Further studies are necessary to elucidate the role of ARID2 mutations in the biological behavior of Sezary cells, such as a propensity to infiltrate liver parenchyma.

Keywords: Sezary Syndrome; Cutaneous T cell Lymphoma; Acute Liver Failure; ARID2 mutation.

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Correspondence to: Dr. Lubomir Sokol. Department of Malignant Hematology, Moffitt Cancer Center, 12902 USF Magnolia Dr, Tampa FL 33612. E-mail: Lubomir.Sokol@moffitt.org

Introduction. Cutaneous T cell lymphoma (CTCL) is characterized by skin infiltration with malignant monoclonal CD4+ T cells, or rarely CD8+ T cells. CTCL is rare and mostly affects older patients with a median age of 60 years at diagnosis. Early-stage mycosis fungoides (MF), manifesting with patch/plague disease, has an indolent clinical course in contrast to patients with skin tumors or leukemic disease. Sézary syndrome (SS) is an aggressive leukemic form of CTCL. It presents with circulating Sézary cells in peripheral blood, generalized erythroderma, and frequently lymphadenopathy.[1]

Patients with hematologic malignancies infrequently develop acute liver failure (ALF). The main mechanisms for ALF include tumor infiltration, drug-induced hepatotoxicity, and reactivation of viral hepatitis. ALF has not been reported in SS. Here, we report a case of impending ALF secondary to hepatic involvement of SS. The patient had full recovery of the liver function after initiation of chemotherapy.

Case Presentation. A 70-year-old white man with MF on external beam radiation therapy presented with uncontrolled pruritus, erythroderma, skin desquamation, and rapidly enlarging lymphadenopathy of the neck, axilla, and groin for three weeks. He also had fatigue and a 15 lb weight loss over one month. Forty years ago, he was diagnosed with diffuse large B cell lymphoma (DLBCL) of the right testis. The patient was successfully treated with three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), followed by methotrexate, radiation therapy, and orchiectomy. He has not had recurrent disease since. Labs on admission showed a white blood cell count of $20x10^3/\mu L$ (normal range [NR] $4.6\text{-}10.2x10^3/\mu L$) with 39% atypical lymphocytes.

Liver function tests (LFT) showed an AST of 159 IU/L (NR 10-50 IU/L), ALT of 263 IU/L (NR 0-41 IU/L), and alkaline phosphatase (ALP) of 326 IU/L (NR 40-130 IU/L). Total bilirubin and INR were normal. Peripheral blood flow cytometry showed 26234 Sézary cells/μL. Skin biopsy revealed a large cell transformation of MF. Bone marrow biopsy showed mildly hypercellular marrow infiltrated with a monoclonal CD4+ T cell population. Left axillary lymph node biopsy showed an aberrant CD4+ T-cell population without large-cell transformation. A high Ki-67 proliferation index (50%) suggested an aggressive disease.

While being treated for his symptoms, he developed worsening of transaminitis and anasarca on hospital day (HD) 4. Despite stopping potentially hepatotoxic agents including allopurinol and gabapentin, his LFTs rose exponentially. On HD 6, his AST/ALT/ALP were 1570/1442/660 IU/L, respectively, total bilirubin was 6.7 mg/dL, and INR was 1.3. Work-up included negative infectious etiologies (hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, and herpes simplex virus); negative hemophagocytic lymphohistiocytosis markers; negative antinuclear antibody and anti-mitochondria antibody. Anti-smooth muscle antibody was mildly elevated (38 units, normal range 0-19 units), which was more consistent with liver injury than autoimmune hepatitis. Abdominal Doppler ultrasound and triple-phase CT scan of the liver were negative for liver pathology or hepatomegaly (**Figure 1**).

A trial of steroids was initiated. However, the AST/ALT continued to increase rapidly to the 2000s IU/ml by HD 7. His jaundice and mental status worsened. Despite the absence of liver abnormalities on imaging studies, ALF secondary to hepatic involvement of SS was suspected. He was referred for diagnostic core needle liver biopsy. The final pathology report of the liver biopsy confirmed malignant hepatic infiltration with Sézary cells. Cytomorphology showed dense portal infiltrate by mostly small mature atypical lymphocytes without large cell transformation; immunohistochemical staining revealed CD4+ T cells with loss of CD7 (**Figure 2**); flow cytometry and T-cell receptor gene rearrangement studies of the tissue confirmed monoclonal T cell population. Next-Generation Sequencing (NGS) of peripheral blood (Foundation One Inc. Cambridge, MA) showed a high mutation burden (25 mutations/Mb) and identified 31 genetic alternations. Seven clinically relevant mutations included CCND3 P203L, STAT3 D661Y, ARID2 G70Fs*20, ASXL1 T822fs*11, CBL C3965, CD58 Q32*, CDKN2a splice site 151-1G>A, CIITA Q909*, EP300 Q641*, MAPK1 E322K, and TNFAIP3 loss.

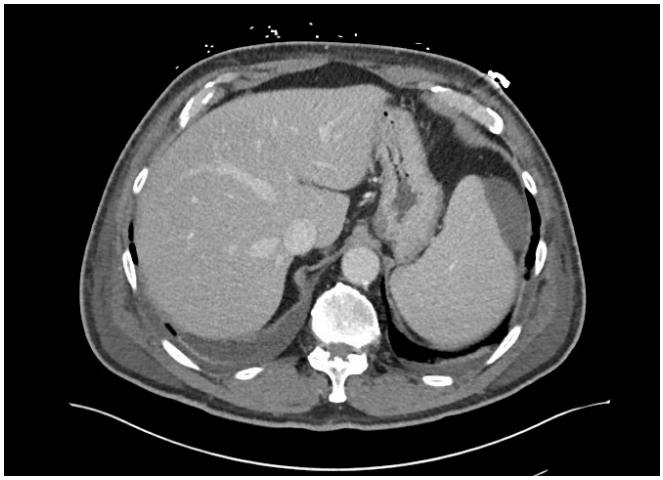

Figure 1. Triple-Phase CT scan of the liver. No focal lesions were present in the liver or spleen. Hepatosplenomegaly was absent. Generalized edema was seen diffusely.

He was treated with a chemotherapy regimen consisting of gemcitabine, dexamethasone, and cisplatin (GDP). The patient's LFTs and mental status started to improve on the second day of GDP.

His LFTs normalized and erythroderma resolved during the 1-month follow-up. He completed two additional cycles of GDP, followed by maintenance gemcitabine. Restaging PET/CT showed complete remission. Unfortunately, he passed away six months later due to myocardial infarction.

Discussion. SS comprises approximately 5% of all CTCL cases. SS carries a poor prognosis with a median overall survival rate of 2-3 years. SS can involve the bone marrow, liver, lung, and gastrointestinal tract in advanced stages.[2] Large cell transformation in patients with MF/SS is associated with more aggressive clinical behavior. Huberman et al. reported visceral involvement in 70-90% CTCL patients at the time of death.[3] In a small cohort, 16% of patients with CTCL had biopsy documented hepatic infiltrates. Clinical factors that are associated with hepatic infiltrate include peripheral blood involvement, leukocytosis, and generalized erythroderma. Interestingly, none of the patients had abnormal LFTs.[3] ALF is a very poor prognostic sign with a mortality rate of 83% and a mean survival rate of 10.7 days from the time of diagnosis in other non-Hodgkin's lymphomas. Remission from chemotherapy only occurs in less than 15% of cases.[4] In the case of acute liver failure in a Japanese patient with MF, the patient passed away within eight weeks of visceral involvement.[5]

To the best of our knowledge, the present case is the first report of liver injury from malignant hepatic infiltration of SS. This case showed that the prompt administration of chemotherapy could result in the complete recovery of liver function and prevent progression into ALF. The diagnostic dilemma included the lack of abnormalities in multiple imaging modalities and concerns for recurrent disease of the

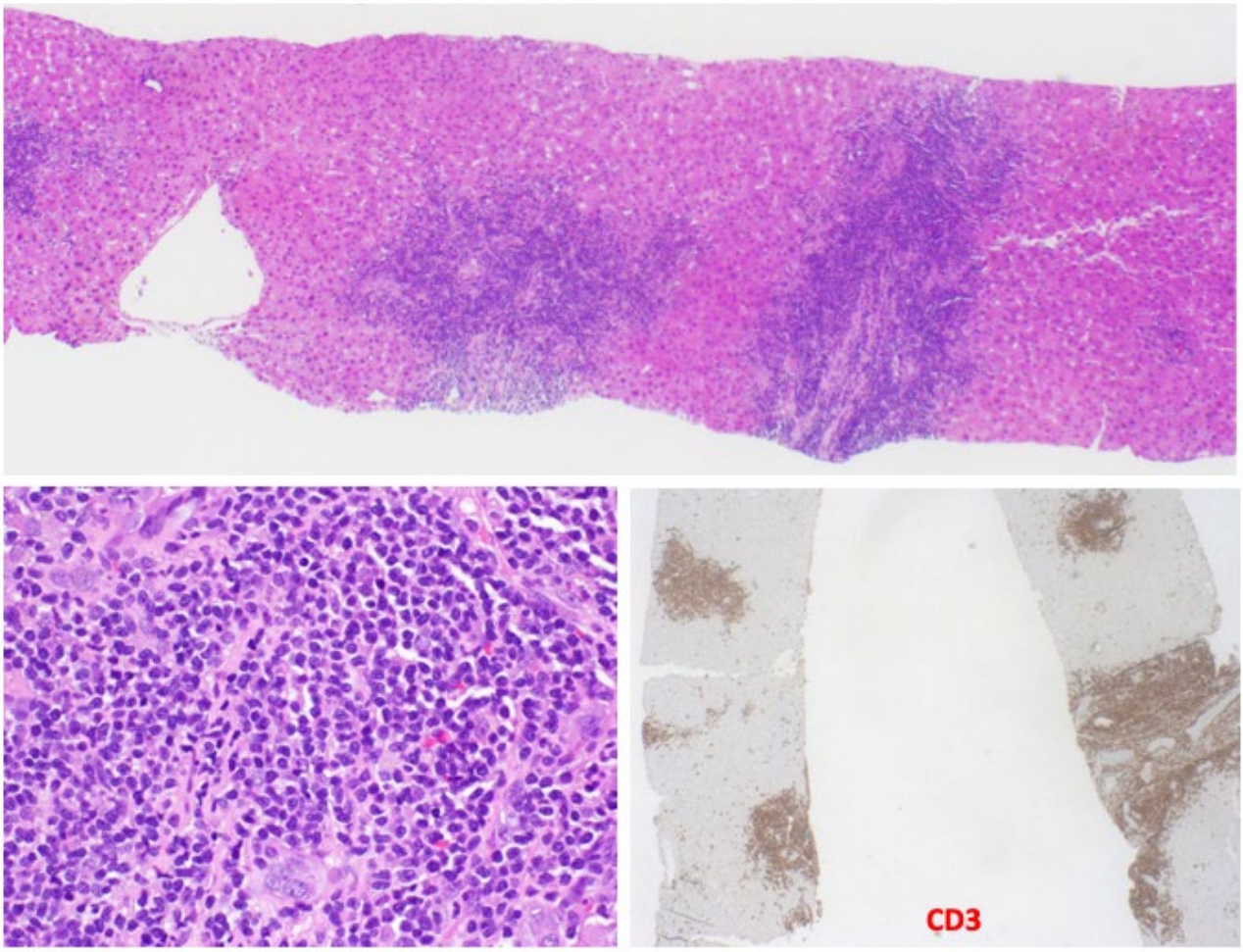

Figure 2. The core needle biopsy of the liver. There were diffuse and dense peri-portal infiltrates by small mature atypical lymphocytes with irregular nuclear contours. The lymphoid infiltrate consisted of mostly T cells by CD3 immunohistochemical stain.

previously treated DLBCL. Homogeneous infiltration of malignant cells in the liver occasionally makes it difficult to detect with imaging studies and can result in a delay in diagnosis. High clinical suspicion should trigger liver biopsy and molecular studies.

A high mutation burden in NGS may potentially explain the aggressiveness of the disease. Among the identified mutations, TNFAIP3 mutations have been reported in CTCL previously.[6] CCND3, STAT3, ASXL1, CBL, CDKN2A, EP300, and MAPK1 have been reported in adult T cell lymphoma/leukemia and other types of mature T cell lymphomas (COSMIC 2017).

ARID2 mutation has rarely been reported in hematologic malignancy (prevalence: 0.5%), but frequently described in hepatocellular carcinoma (prevalence: 5-20%).[5,7] ARID2 encodes a subunit of the SWI/SNF-B (PBAF) chromatin remodeling complex, which assists in mediating gene expression[8] and double-strand DNA gene repair.[9] ARID2 functions as a tumor suppressor gene and is associated with loss-of-function mutations in most cases. In the absence of ARID2, cells are sensitized to DNA damage secondary to ultraviolet light and other carcinogens. In the present case, ARID2 mutation was a frameshift mutation of G70fs*20 in the splice site, likely resulting in loss of function. The ARID2 mutation possibly predisposes Sezary cells to acquire more mutations and aggressive features. Further studies are necessary to elucidate the role of ARID2 mutations in the biological behavior of Sezary cells, such as a propensity to infiltrate liver parenchyma.

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