

Non-Metastatic Cholestatic Liver Injury as a Presenting Sign of a Rare Hematologic Malignancy: First Reported Case

Abstract

Paraneoplastic syndromes are disorders that are triggered due to the presence of a neoplasm, leading to different signs and symptoms resulting from damage to tissues or organs occurring remotely from the tumor. These syndromes are thought to be mediated from altered immune response to the cancer and not as a result of direct spread and are therefore classified as non-metastatic systemic diseases. Knowledge of these syndromes is crucial especially as these may occasionally be the first presenting symptom of a malignancy in an individual. While most paraneoplastic syndromes are documented in the literature and well recognized by the medical society, there remain a few rare outliers whose presence still baffle healthcare providers and may delay diagnosis. Stauffer's syndrome is one such paraneoplastic manifestation. We present a case of a patient who presented with this uncommon syndrome and was subsequently diagnosed with a rare hematologic cancer.

Keywords: Stauffer's syndrome; Paraneoplastic syndrome; Angioimmunoblastic T cell lymphoma; Cholestatic liver injury

Case Report

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Fahad Zubair¹, Jad Bou-Abdallah² and Sidra Anwar^{3*}

¹Department of Internal Medicine, University at Buffalo Catholic Health System, USA

²Department of Internal Medicine, Division of Gastroenterology, University at Buffalo, USA

³Department of Internal Medicine, Division of Geriatrics and Palliative Care, University at Buffalo, USA

***Corresponding author:** Sidra Anwar, Department of Internal Medicine, Division of Geriatrics and Palliative Care, University at Buffalo, USA, Email: sidra.anwar@hotmail.com

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A 55 year old Caucasian male was referred to the hospital for evaluation of abdominal pain, increasing abdominal girth and general malaise since the past few months. During his interview he endorsed poor appetite but denied any nausea or vomiting. He had not noted any change in his bowels. He had maintained a clear sensorium throughout. He admitted to drinking 7-8 beers daily and had been doing so since the past 8 years. He stated his generalized abdominal pain had greatly worsened the past week, he was increasingly lethargic and he had noticed his urine was darker. On physical examination he had a low-grade temperature and was slightly tachycardic. He appeared to be of thin-build overall. His abdomen was protuberant, non-tender on palpation and dull to percussion. Mild lower extremity edema was found. No other stigmata of chronic liver disease were present.

Lab work was sent, revealing pancytopenia, hyponatremia, hypoalbuminemia, mild transaminitis and cholestatic liver disease with elevated alkaline phosphatase levels, total and direct bilirubin as well as gamma-glutamyl transferase. Additional studies showed elevated inflammatory markers, positive Anti-nuclear and Anti smooth muscle antibody levels with normal Anti mitochondrial and Anti Liver Kidney microsomal antibody levels. CT scan of the abdomen with IV contrast revealed mild hepatosplenomegaly, accompanying ascites and nonspecific abdominal, inguinal and retroperitoneal lymphadenopathy.

Despite the initial impression that the patient was probably suffering from liver disease due to prolonged alcohol intake,

Gastrointestinal consult team services were still requested for further management. Viral testing for CMV, EBV, Hepatitis viruses and HIV were all negative. Paracentesis was performed which revealed spontaneous bacterial peritonitis and he was started on Ceftriaxone. The Serum-Ascitic Albumin was less than 1.1 and subsequent cultures of the ascitic fluid were all negative. MRI of the abdomen with and without contrast showed mild hepatosplenomegaly with no architectural abnormality of the liver, no dilatation of intra or extra hepatic biliary ducts, normal gallbladder and pancreas and nonspecific mild periportal, gastrohepatic, perisplenic, and para-aortic adenopathy.

During his inpatient stay he began to develop hypotension and his blood counts dropped further, necessitating multiple blood and platelet transfusions. The GI service remained unconvinced that all the clinical findings could be attributed to alcoholic liver disease. Given his extensive lymphadenopathy and systemic symptoms the possibility of malignancy was considered and the oncology service was consulted. Review of multiple peripheral blood smears revealed acanthocytes, rouleaux formation and few atypical lymphocytes. Multiple other imaging studies were performed. CT of the chest revealed additional axillary and mediastinal lymphadenopathy after which PET imaging was done. This showed increased metabolic activity in all the enlarged lymph nodes, most marked in the axillary lymph nodes. Bone marrow biopsy as well as biopsy of the axillary lymph nodes was performed and ultimately the patient was diagnosed with Angioimmunoblastic T-cell lymphoma. Chemotherapy was begun without further delay with normalization of the liver function within a few days after the first cycle.

Discussion

The patient had presented with the icteric variant of Stauffer's syndrome, a rare paraneoplastic manifestation, characterized by non-metastatic hepatic dysfunction. This is a separate entity from cholestasis caused by hepatic metastatic infiltration or mechanical bile duct obstruction. This syndrome was originally described in 1961 in the context of renal cell carcinoma by Dr. Maurice H Stauffer [1], in which the presence of Stauffer's syndrome along with other paraneoplastic syndromes portrayed worse oncologic outcomes for such patients than those with incidentally found tumors [2].

Since that time, this syndrome has been defined in other cancers such as gastrointestinal malignancies, sarcomas, bronchogenic cancer [3], prostate cancer [4,5] and less often in hematologic malignancies such as Hodgkin's disease [6], T-cell lymphoma [7] and chronic lymphocytic leukemia [8].

For this diagnosis, common causes for cholestatic liver injury must first be excluded such as drugs, alcohol or other toxins, viral illness, autoimmune diseases or malignant infiltration of the liver or bile ducts. As in the case of our patient this must be a diagnosis of exclusion after thorough investigations. Liver biopsy is not needed to make the diagnosis as typically only nonspecific findings are seen such as sinusoidal dilatation and infiltration with neutrophils, lymphocytes and monocytes [9]. Rarely granulomas may be present.

The underlying mechanisms for this syndrome remain unclear. Prior research suggests a role of elevated Interleukin-6 (IL-6) in the pathogenesis of this paraneoplastic syndrome [10,11], driving the biologic inflammatory response in the body often seen in paraneoplastic cholestasis [12] and leading to the systemic symptoms suffered by patients. Treatment with Anti IL-6 monoclonal antibody was seen to reverse some of the biochemical abnormalities [10].

Angioimmunoblastic T-cell lymphoma (AITL) is a rare and aggressive lymphoma that comprises less than 2% of the Non-Hodgkin lymphomas diagnosed in the United States [13]. It is characterized by sudden onset of constitutional symptoms, lymphadenopathy and frequent autoimmune phenomena, particularly hemolytic anemia and thrombocytopenia [14]. Other usual characteristics that might be found in such patients include a cutaneous rash and arthralgias [15].

In a recent study of clinicopathologic characteristics of 243 patients with AITL at the time of presentation, generalized lymphadenopathy was noted in 76% of patients, skin rash was observed in 21% of patients, hemolytic anemia and hypergammaglobulinemia occurred in 13% and 30% of patients, respectively [16]. While hepatosplenomegaly is also associated with this cancer [17-19], to our knowledge this is the first reported case of Stauffer's syndrome associated with this particular kind of malignancy. This case further indicates the complexity of the possible presenting symptoms of this cancer that typically carries a dismal prognosis.

Conclusion

Awareness of cholestatic hepatic injury as a possible paraneoplastic syndrome ensures an underlying malignancy is not missed.

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