Case Report

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 bowel habits. 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 was slightly tachycardic. 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 hypergammoglobulinemia 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.

References

1. Morl D, Alacemi S, Lichtstein D (2006) Stauffer’s Syndrome Variant with Cholestatic Jaundice: A Case Report. J Gen Intern Med 21(7): C11-C13.
2. Moreira DM, Gershman B, Lohse CM, Boorjian SA, Cheville JC, et al. (2015) Mp44-14 Paraneoplastic Syndromes Are Associated With Adverse Prognosis Among Patients With Renal Cell Carcinoma Undergoing Nephrectomy. World J Urol 34(10): 1465-1472.
3. Saintigny P, Spamo JP, Tchemkian F, Pailler MC, Breaux J, et al. (2003) Non-metastatic intrahepatic cholestasis associated with bronchial adenocarcinoma. Ann Med Interne (Paris) 154(3): 171-175.
4. Reddy AN, Grosberg SJ, Wapnick S (1977) Intermittent cholestatic jaundice and nonmetastatic prostatic carcinoma. Archives of internal medicine 137(11): 1616-1618.
5. Kamikoski A, Kasapis C, Kallikidjis T, Kalpidis P, Grigoridis N (2003) Cholestatic jaundice as a paraneoplastic manifestation of prostate adenocarcinoma. Clin Gastroenterol Hepatol 1(6): 480-483.
6. Yalcin S, Kars A, Sökmenesser C, Atahan L (1999) Extrahepatic Hodgkin’s disease with intrahepatic cholestatic: report of two cases. Oncology 57(1): 83-85.
7. Wattersen J, Priest JR (1989) Jaundice as a paraneoplastic phenomenon in a T-cell lymphoma. Gastroenterology, 1989. 97(5): 1319-1322.
8. Pandey J, Bhowmik KT (1998) Chronic lymphocytic leukemia presenting as jaundice. Indian J Gastroenterol 17(1): 28.
9. Aoyagi T, Mori I, Ueyama Y, Tamaoki N (1989) Sinusoidal dilatation of the liver as a paraneoplastic manifestation of renal cell carcinoma. Human pathological 20(12): 1193-1197.
10. Blay JY,Rossi JF, Wijdenes J, Menetrier-Caux C, Schemmann S, et al. (1997) Role of interleukin-6 in the paraneoplastic inflammatory syndrome associated with renal cell carcinoma. International journal of cancer 72(3): 424-430.
11. Walther MM, Johnson B, Caldey D, Shah R, Weber J, et al. (1998) Serum interleukin-6 levels in metastatic renal cell carcinoma before treatment with interleukin-2 correlates with paraneoplastic syndromes but not patient survival. J Urol 159(3): 718-722.
12. Boer R, Waisman J, Lieber MM, Mampaso FM, Skinner DG, et al. (1978) Non-metastatic hepatic dysfunction associated with renal carcinoma. J Urol 119(4): 468-471.
13. Rüdiger T, Weizenburger DD, Anderson JR, Armitage JO, Diebold et al. (2002) Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin’s Lymphoma Classification Project. Ann Oncol 13(1): 140-149.
14. Innocenti E, FERRERI AI, MINARDI V, TRIPODO C, KREIPE HH (2008) Angioimmunoblastic T-cell lymphoma. Crit Rev Oncol Hematol 68(3): 264-271.
15. Lachenal F, Berger F, Chesquieres H, Binn P, Hot A, et al. (2007) Angioimmunoblastic T-Cell lymphoma: Clinical and Laboratory Features at Diagnosis in 77 Patients. Medicine 86(5): 282-292.
16. Federico M, Rudiger T, Bellei M, Nathwani BN, Luminari S, et al. (2013) Clinicopathologic Characteristics of Angioimmunoblastic T-Cell Lymphoma: Analysis of the International Peripheral T-Cell Lymphoma Project. J Clin Oncol 31(2): 240-246.

17. Dogan A, Ngu LS, Ng SH, Cervi PL. (2005) Pathology and clinical features of angioimmunoblastic T-cell lymphoma after successful treatment with thalidomide. Leukemia 19(5): 873-875.

18. Niino D, Komohara Y, Murayama T, Aoki R, Kimura Y, et al. (2010) Ratio of M2 macrophage expression is closely associated with poor prognosis for Angioimmunoblastic T-cell lymphoma (AITL). Pathol Int 60(4): 278-283.

19. Yoon GS, Chang SE, Kim HH, Choi JH, Sung KI, et al. (2003) Cutaneous relapse of angioimmunoblastic lymphadenopathy-type peripheral T-cell lymphoma mimicking an exanthematous drug eruption. Int J Dermatol 42(10): 816-818.