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CASE REPORT | LIVER

Cholestatic Hepatitis as a Possible Paraneoplastic Syndrome of Endometrial Carcinoma

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ABSTRACT

Cholestatic hepatitis has not been reported as a paraneoplastic syndrome of endometrial adenocarcinoma to our knowledge. We present a patient who, shortly after endometrial adenocarcinoma diagnosis, presented with elevated liver chemistries in the setting of an acute, paraneoplastic sensorimotor polyneuropathy. Infectious, autoimmune, pharmacologic, malignant, metabolic, and structural causes of cholestatic hepatitis were screened for and ruled out. Our patient was diagnosed with simultaneous cholestatic hepatitis and acute sensorimotor polyneuropathy as possible paraneoplastic syndromes of endometrial adenocarcinoma. Clinicians should include paraneoplastic processes of cancer in the differential diagnosis for liver injury, especially when workup for alternative causes is unrevealing.

INTRODUCTION

Cholestatic hepatitis is a rare paraneoplastic manifestation of solid organ and hematologic malignancies.[1–9] Paraneoplastic liver injury most commonly occurs with renal cell carcinoma and lymphoma but also is linked to ovarian cancer, thyroid cancer, gastrointestinal carcinoid tumors, schwannomas, and soft-tissue sarcomas.[1,3–7,10,11] Endometrial adenocarcinoma can affect the endocrine, vascular, connective tissue, central nervous system, peripheral nervous system, and dermatologic organ systems.[12–14] It is not reported to cause paraneoplastic liver injury to our knowledge. We report a case of simultaneous paraneoplastic cholestatic hepatitis and acute sensorimotor polyneuropathy as possible paraneoplastic syndromes of endometrial adenocarcinoma.

CASE REPORT

A 66-year-old woman with newly diagnosed Stage IIIC endometrial adenocarcinoma and regional lymph node metastasis presented with ascending bilateral lower extremity weakness and numbness for 14 days. Diagnosis of endometrial adenocarcinoma was confirmed during the 2 weeks before hospitalization with endometrial biopsy, a transvaginal ultrasound, and abdominal, thoracic, and pelvic computed tomography with intravenous contrast. Laparotomy with mass removal was planned before chemotherapy, but the patient was hospitalized before intervention. Her medical and surgical history included cholecystectomy, hypertension, primary hyperthyroidism, and obesity. Home medications included amlodipine, hydrochlorothiazide, aspirin, atorvastatin, acetaminophen (not exceeding 4 g daily), and pantoprazole. She denied the use of herbal or over-the-counter supplements.

Physical examination showed bilateral foot drop, distal lower extremity numbness, and absent bilateral ankle reflexes. The patient had neither jaundice nor scleral icterus. Laboratory assessment showed alanine aminotransferase 172 U/L, aspartate aminotransferase 149 U/L, alkaline phosphatase (ALP) 243 U/L, and γ-glutamyl transferase 461 U/L. R factor was 0.1, suggesting a cholestatic pattern of liver injury. The patient had a 2-year history of ALP elevation between 150 and 200 U/L with normal transaminases as recently as 13 days before presentation. Neurologic workup, including lumbar puncture, electromyography, and magnetic resonance imaging of the spine, was consistent with an acute, symmetric paraneoplastic sensorimotor polyneuropathy, despite a negative paraneoplastic antibody panel. The patient was not treated for hypotension, sepsis, or infection. She never received chemotherapy nor other medications that cause cholestasis. Atorvastatin, which the patient had taken for years without complication, was stopped at presentation, and the liver enzymes continued to increase, suggesting it had no causative role.

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Alanine aminotransferase, aspartate aminotransferase, and ALP increased to peak values of 245, 202 and 659 U/L, respectively. Total serum bilirubin and prothrombin international normalized ratio remained within the normal limits. Platelet count ranged from 248 to 331 $\times 10^9$/L. Total serum protein and albumin were 7.8 and 3.7 g/dL, respectively. Creatinine kinase and thyroid-stimulating hormone were normal. Fractionated ALP mostly showed liver fraction. Serologies for hepatitis A, B, and C and human immunodeficiency virus were negative. Epstein-Barr virus serologies were consistent with past or convalescent infection. Cytomegalovirus qualitative polymerase chain reaction was positive, but complete blood count with differential was negative for atypical lymphocytes or lymphocytosis. Antinuclear, antimitochondrial, and antismooth muscle antibodies were negative. Ceruloplasmin, α-1-antitrypsin, and ferritin were within the normal limits.

Liver ultrasound with Doppler was negative for biliary or liver pathology. Computed tomography scan with intravenous contrast showed a normal liver. The patient respectfully declined liver biopsy because ascending paralysis progressed to paraplegia, and she opted for hospice care.

Infectious, autoimmune, metabolic, metastatic, drug-induced, and structural causes of cholestatic hepatitis were screened for and ruled out. The patient was diagnosed with a possible paraneoplastic, acute cholestatic hepatitis from endometrial adenocarcinoma. She was discharged to a nursing facility for hospice care.

DISCUSSION

We describe a patient with endometrial adenocarcinoma who presented with acute sensorimotor polyneuropathy and cholestatic hepatitis. Paraneoplastic syndromes typically present before a cancer diagnosis but sometimes are discovered after the diagnosis.[15] A diagnosis of possible paraneoplastic cholestatic hepatitis was supported by the temporal relationship of liver injury with endometrial adenocarcinoma diagnosis and negative workup for alternative causes.[16]

The most important facets of paraneoplastic syndrome diagnosis across all guidelines are temporality and the exclusion of alternative explanations for disease. The guidelines of Graus et al. designated paraneoplastic neurologic syndromes (PNSs) as either "definite" or "possible." "Definite PNS" diagnosis requires detection of antineuronal antibodies or symptomatic improvement after cancer-directed treatment. Without these features, our patient's polyneuropathy is categorized as a "possible PNS" because alternative causes were ruled out, and the "cancer [was] present within 2 years of diagnosis.[17]"

The proximity of our patient's cholestatic liver injury to a cancer diagnosis with a negative evaluation for alternative causes suggests possible paraneoplastic disease. Both liver biopsy and cancer-directed therapy were discordant with the patient's wishes so neither were pursued, precluding definite diagnosis of paraneoplastic liver disease. The negative evaluation of the patient's liver injury significantly diminishes the likelihood of an alternative cause. The shared temporality of liver injury and possible PNS to endometrial cancer diagnosis bolsters the likelihood of paraneoplastic liver disease and suggests the possibility of a shared pathophysiologic mechanism.

Mechanisms of autoimmunity and cancer-mediated inflammation can account for both PNS and paraneoplastic liver disease. An autoimmune response to endometrial tumor antigens may have resulted in antibody-mediated cross-reactivity to the identical nontumor liver and PNS antigens. Lysosomal enzyme release from tumor cells and upregulation of inflammatory cytokines are linked to paraneoplastic liver diseases such as the Stauffer syndrome.[18,19] This paraneoplastic syndrome of renal cell carcinoma leads to the upregulation of interleukin-6, which causes elevated ALP and γ-glutamyl transferase.[2,19] An early paraneoplastic proinflammatory state may have caused our patient's history of ALP elevation. Cancer progression may have worsened inflammation, causing sudden elevation of transaminases and ALP at the time of hospitalization.

Our patient's case is unique in that, to our knowledge, the simultaneous occurrence of sensorimotor polyneuropathy and cholestatic hepatitis as possible paraneoplastic manifestations of endometrial adenocarcinoma has never been reported. Our patient's liver injury may have occurred because of paraneoplastic proinflammatory state or tumor antigen-antibody cross-reactivity with liver cell antigens or a combination of both. In the setting of malignancy, physicians should include paraneoplastic processes of cancer in the differential diagnosis for liver injury, especially when workup of alternative causes is unrevealing.

DISCLOSURES

Author contributions: FG Wade wrote the manuscript and is the article guarantor. F-D Odufalu, C. Prather, and E. Marsicano revised the manuscript for intellectual content and approved the final manuscript.

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Informed consent could not be obtained from the family of the deceased. All identifying information has been removed from this case report to protect patient privacy.

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