Acute Interstitial Nephritis Proteinuria and Herpes Simplex Virus Hepatitis in Pregnancy Mimic HELLP Syndrome (Hemolysis, Elevated Liver Enzymes, Low Platelets)

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ABSTRACT

Elevated transaminases, hemolysis, and thrombocytopenia in pregnancy are most often caused by a preeclampsia variant—HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). In atypical cases, it is important to consider other causes, such as herpes simplex virus (HSV) hepatitis. Acute interstitial nephritis (AIN)-induced proteinuria can make distinguishing HELLP from its mimics more difficult. A 43-year-old G4P3 gestational carrier at 28 weeks had abnormal laboratory findings consistent with HELLP, including proteinuria. However, she was normotensive and febrile, prompting an investigation into other possible causes of her signs and symptoms. She ultimately was diagnosed with disseminated HSV infection, started on definitive therapy, and allowed to continue her pregnancy to term. The proteinuria was attributed to AIN. AIN can cause proteinuria in the critically ill pregnant patient. When mimics of HELLP syndrome, such as disseminated HSV infection, are the cause of critical illness, the presence of AIN-induced proteinuria may falsely implicate a hypertensive disorder of pregnancy, resulting in iatrogenic premature delivery of the fetus and failure to initiate definitive potential lifesaving treatment.

KEYWORDS: Herpes simplex virus, hepatitis, proteinuria, acute interstitial nephritis, HELLP

The most common cause of hemolysis, elevated liver enzymes, and thrombocytopenia in pregnancy is HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). If the clinical picture is atypical, however, considering other causes of abnormal liver function tests may result in lifesaving treatment and pregnancy prolongation to term. We present a case where the presence of proteinuria obscured the true diagnosis of herpes simplex virus (HSV) hepatitis.

CASE REPORT

A 43-year-old woman, gravida 4, para 3-0-0-3 at $27^{6}/_{7}$ weeks by in vitro fertilization, acting as a gestational

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carrier, presented to an outside hospital with a 5-day history of general malaise, fever of 39°C, cough, and epigastric discomfort. Three days prior, she had visited a local emergency room where she was started on amoxicillin clavulanate for presumed cystitis, but a urine culture subsequently was negative. When her symptoms worsened, she returned to the hospital where she was noted to have elevated transaminases (aspartate aminotransferase peaked at 822 U/L and alanine aminotransferase at 413 U/L; normal 8 to 43 and 7 to 45, respectively). Mild proteinuria was present (329 mg/24 hours). Platelets were low normal, with a nadir 134×10^9/L (normal 150 to 450). Other laboratory abnormalities included lactate dehydrogenase 1323 U/L (normal 112 to 257), and a white blood cell (WBC) count of 3.8×10^9/L (normal 3.5 to 10.5). She had normal electrolytes, amylase, lipase, glucose, total bilirubin, haptoglobin, creatinine, prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen, and uric acid, and no schistocytes were present on the blood smear. She was normotensive.

A multispecialty evaluation for causes of abnormal liver function and fever in the setting of pregnancy was negative for hepatitis A/B/C, Epstein Barr virus (EBV), cytomegalovirus (CMV), *Babesia*, and *Anaplasma/Ehrlichiosis* infections. Prenatal laboratory results from early in pregnancy demonstrated that she was HIV-negative and hepatitis B surface antigen-negative, rapid plasma reagin nonreactive, and rubella-immune. A right upper-quadrant ultrasound, chest radiography, and fetal ultrasound were unrevealing. Amniocentesis revealed a negative Gram stain and culture. Blood and urine cultures were also negative. She was given ampicillin sodium/sulbactam sodium, azithromycin, intravenous (IV) magnesium for seizure prophylaxis and betamethasone for fetal lung maturity. She was transferred to our hospital for further evaluation at $28^4/_7$ weeks' gestation.

She denied the use of prescription, over the counter, or illicit drugs, tobacco, or alcohol and exposures to communicable diseases, recent travel, or ticks. She had a distant history of muscle and joint aches, with a reported negative workup for systemic lupus erythematous. She was sexually active with one new partner during this pregnancy. She denied any symptoms related to pregnancy, including regular uterine contractions, loss of fluid, or vaginal bleeding. Previous pregnancy complications included preeclampsia and postpartum hemorrhage during her first pregnancy, with subsequent normotensive pregnancies.

Upon arrival at our institution, her liver function tests had worsened; aspartate aminotransferase was 2301 U/L and alanine aminotransferase was 989 U/L. Platelets dropped to 72×10^9/L and WBC to 3.3×10^9/L. Her total bilirubin was mildly elevated to 1.1 mg/dL (upper limits of normal 1.0). Urinalysis showed 3 + protein and microscopy showed both red and white cells in the urine. She remained normotensive but febrile (38.5°C). She reported worsening respiratory symptoms of dyspnea, cough, and a persistent headache. HIV-1 and -2, varicella zoster, HSV, syphilis, hepatitis E, toxoplasmosis, CMV, H1N1 panel, anti–smooth muscle antibody, anti–nuclear antibody titers, ceruloplasmin, and serum protein electrophoresis were performed. Magnesium was discontinued upon admission. Oseltamivir was started for empiric treatment of influenza.

Preliminary HSV immunoglobulin M (IgM) was positive, so intravenous acyclovir was started and, within 18 hours, the patient was afebrile. Her transaminases immediately began to decline and were down to the 300 range by 72 hours Her proteinuria, however, worsened. Her first 24-hour collection at our institution had >2 g of protein.

Polymerase chain reaction (PCR) from blood confirmed primary disseminated HSV infection manifesting as clinical pneumonitis and hepatitis; all other infectious and autoimmune studies returned negative. The patient was treated with IV acyclovir for 14 days, and then oral acyclovir 400 mg three times a day until delivery. A 24-hour urine collection repeated 5 days after initiation of treatment finally showed a decline to 280 mg in 24 hours.

She was discharged home 8 days after transfer. Her transaminases returned to normal. A 24-hour protein measured 2 months postdiagnosis showed 84 mg of protein in 24 hours. Serial ultrasounds showed appropriate fetal growth and no obvious stigmata of congenital HSV infection.

The patient returned for an induction at term and had an uneventful vaginal delivery. The infant girl weighed 3720 g and had Apgar scores of 7 and 9. She received 14 days of IV acyclovir. Neonatal cultures from multiple sources (cerebrospinal fluid, blood, conjunctivae, nasopharyngeal, and rectal swabs) were negative for HSV.

DISCUSSION

When a pregnant patient presents with elevated liver enzymes, thrombocytopenia, and epigastric pain, the most common diagnosis is HELLP syndrome. Because hypertensive disorders of pregnancy are ultimately "cured" only by delivery, they often result in iatrogenic prematurity and its associated neonatal morbidities. It is important, therefore, to consider other causes for a "HELLP-like" illness that is not improved by delivery, especially in the presence of clinical features that make it atypical. In this case, the absence of hypertension and the presence of fever made the diagnosis of pregnancy-related disorders, such as HELLP and acute fatty liver of pregnancy, unlikely.

Finding a unifying diagnosis to explain all of her signs and symptoms remained elusive. Autoimmune disorders, such as lupus, could explain all of her findings, including proteinuria, but the evaluation was negative. Infectious processes that would cause hepatitis were actively investigated, but many of these also could not explain the proteinuria. The laboratory findings (positive HSV IgM), social history (a new sexual partner), and clinical picture of fever, general malaise, and anicteric hepatitis with associated right upper-quadrant pain prompted initiation of acyclovir treatment for acute disseminated HSV infection.

HSV hepatitis in pregnancy is known to mimic HELLP but is extremely rare, with only 28 reports since 1969.[1–5] When it does occur, it is most common in the third trimester and in otherwise healthy women.[1] It can be a result of both serotypes 1 and 2, and can occur in the setting of either primary infection or reactivation. Herpetic lesions of the mouth and genitals are only present in 50% of cases and generally infect those who are immunosuppressed, such as patients with inflammatory bowel disease, organ transplant, or autoimmune diseases.[1] Early recognition and treatment are essential, as maternal mortality can range from 20% in those treated to upward of 67% in cases where antiviral therapy was delayed or not administered.[1]

Shortly after starting treatment with acyclovir, the patient's symptoms improved and her transaminase levels began to decline, further supporting the diagnosis of HSV infection. Despite her overall clinical improvement, however, the patient's proteinuria worsened. Upon review of 28 reports in the literature involving HSV hepatitis in pregnancy, none reported proteinuria.[1–5] It also is not classically seen in disseminated HSV infection in the nonpregnant state. This progressive proteinuria resulted in continued consideration of both HELLP and autoimmune diseases, even after the initial positive HSV serologies. It was only after a positive PCR of HSV in blood that the diagnosis of HELLP was dismissed as a possible cause.

Intermittent proteinuria in the critically ill can be caused by acute interstitial nephritis. AIN is most commonly caused by medications, toxin exposures, or infections. Regardless of the insult, damage to the renal tubules is via a T cell–mediated/ delayed hypersensitivity reaction, and not a direct toxic effect of the drug and/or virus. Antibiotics, such as the β-lactams, are the most frequent culprits, but several viruses, such as CMV, EBV, HIV, and hepatitis A, B, and C, may cause AIN as well.[6] To date, HSV has rarely been recognized as a cause of AIN.[7]

The signs and symptoms of AIN manifest 3 days to weeks after exposure, often with fever, rash, and other nonspecific gastrointestinal symptoms. Eosinophiluria can be seen in a quarter of all cases and up to 67% of β-lactam related cases but was not present in this patient.[8] The urine sediment will often show white and red blood cells without bacteria; proteinuria is typically in the nonnephrotic range (i.e., <3.5 g/24 hours). With prolonged exposure to the offending agent, oliguria and a rising creatinine can develop, but mild cases do not necessarily display these features. The diagnosis can be confirmed by renal biopsy, which was not indicated in our patient due to resolving proteinuria. First-line treatment is discontinuation of the causative agent and supportive therapy.

Our patient likely had AIN as the result of exposure to amoxicillin/clavulanate, ampicillin/sulbactam, or azithromycin, all of which she received prior to transfer. Alternatively, the systemic HSV infection, similar to what has been described in other human herpes viruses, such as EBV and CMV, could have resulted in renal injury and AIN. Acyclovir was not considered as a possible offending agent, as her proteinuria abated, despite continued treatment with this drug.

If this patient's proteinuria was in fact due to antibiotic-induced AIN, in retrospect, the steroids given for hastening fetal lung maturity might have resulted in a quicker recovery.[8] Alternatively, adequate treatment of HSV infection with acyclovir might have led to resolution of the viremia and proteinuria, if the renal injury, indeed, was due to the viral infection.

AIN can cause proteinuria in the critically ill pregnant patient. When mimics of HELLP syndrome, such as disseminated HSV infection, are the cause of critical illness, the presence of AIN-induced proteinuria may falsely implicate a hypertensive disorder of pregnancy, resulting in iatrogenic premature delivery of the fetus and failure to initiate definitive potential lifesaving treatment. In the case of HSV infection, early recognition and prompt antiviral therapy are essential to reduce maternal and fetal mortality. In conclusion, in patients who present with an atypical HELLP-like picture, other causes should be considered even in the presence of proteinuria.

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