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Vogt-Koyanagi-Harada Syndrome in a Pregnant Patient with Azathioprine-Induced Hepatitis and Cholestasis

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Keywords

Vogt-Koyanagi-Harada Syndrome, Azathioprine-Induced Hepatitis, Cholestasis, Pregnancy, Hepatotoxicity, Prednisolone, Fetal Death

Background

Vogt-Koyanagi-Harada disease (VKH) is a central nervous system condition that specifically affects vision and hearing. Descriptions of this disease date back to the 12th century, but the disease is named after three 20th-century physicians who described the collective manifestations of this disease. Alfred Vogt initially described bilateral iridocyclitis and eyebrow depigmentation in 1906, followed by Yoshizo Koyanagi's 1926 description of bilateral serous detachments in association with cerebrospinal fluid (CSF) pleocytosis. Einosuke Harada identified the integumentary symptoms of the condition shortly thereafter. The disease presents with signs and symptoms of a loss of immune tolerance to melanocytes within the meninges, eyes, skin, hair, and ears [1]. The exact etiology of VKH is not firmly established, but current theories posit that patients develop T cell-mediated immunity against melanocytes following recovery from an inciting viral environmental factor [2]. Recent genetic studies have implicated the presence of human leukocyte antigen (HLA) cell surface markers HLA-DRB4, HLA-DRB1-04*05, and HLA-DRB-04*01, as well as non-HLA genes involving lymphocyte regulations in IL-12 production and IL-17 production [3,4]. Downregulation of microRNA in the production of interleukins and changes in non-coding RNA may also play a role in this condition [5].

Azathioprine, a mercaptopurine prodrug that inhibits lymphocyte proliferation, was initially introduced in the 1960s as an anti-rejection medication and continues to be used in the management of many autoimmune conditions such as myasthenia gravis. Common reported adverse effects are nausea, rash, and bone marrow suppression, while less common side effects include hepatotoxicity, both acute and chronic [6]. US FDA pregnancy category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks [7].

Case Presentation

A 28-year-old female, G3P1+1, 28 weeks + 4 days, last delivery was five years ago by normal spontaneous

vaginal delivery, presented to the emergency department with complaints of itching and yellowish discoloration of her eyes and skin for the past two weeks. Additionally, she reported having dark urine and light loose stool, but denied experiencing any other symptoms. Her past medical history includes a diagnosis of Vogt-Koyanagi-Harada syndrome four years ago, when she experienced sudden vision loss that subsequently recovered with treatment. She was being treated with mycophenolic acid, but her ophthalmologist switched her to azathioprine 100mg orally twice daily and prednisolone 20mg orally once per day when she planned to become pregnant. The patient also had a history of cataract surgery one month prior to presentation.

Investigations

The laboratory evaluation was significant for elevated liver enzymes as follows: aspartate aminotransferase (AST) at 164 U/L, alanine aminotransferase (ALT) at 137 U/L, total bilirubin at 172.3 umol/L, and direct bilirubin at 122 umol/L. The patient had a negative viral hepatitis panel and autoimmune panel (including antinuclear antibody, antismooth muscle antibody, and antimitochondrial antibody). The peripheral CBC smear showed marked macrocytosis (MCV = 112) with normal WBC and PLT counts, and no evidence of hemolysis or megaloblastic anemia. The thyroid function test was normal. Abdominal ultrasound showed normal size and echo pattern of the liver, spleen, pancreas, and gallbladder, which was contracted with normal bile ducts. Obstetric ultrasound showed a single fetus with no gross anomalies, adequate liquor, and an estimated weight corresponding to a gestational age of 29 weeks.

Differential Diagnosis

The differential diagnoses in this case involve other causes of acute hepatitis and painless cholestasis, including viral hepatitis, autoimmune hepatitis, congestive hepatopathy, toxin-induced hepatitis, and common bile duct obstruction secondary to malignancy or stones.

Treatment

After excluding other causes of hepatotoxicity, the ophthalmologist discontinued Azathioprine and started the patient on Prednisolone 15mg orally daily. During the seven-day hospitalization, the patient's symptoms of urine and stool discoloration improved, and her laboratory evaluation showed modest improvements in AST/ALT (68 U/L/104 U/L), total bilirubin (81.6 umol/L), and direct bilirubin (75.3 umol/L). Four weeks later, liver function tests were repeated and showed normal levels.

Outcome and Follow up

The patient was followed up every one to two weeks and was asymptomatic with good fetal movement and a normally growing fetus as evidenced by twice-weekly ultrasounds. Unfortunately, she experienced sudden intrauterine fetal death at 36 weeks + 4 days. Labor was induced by prostaglandin and the patient had an uncomplicated normal vaginal delivery of a female fetus weighing 2750 grams with an unexplained fetal cause. The patient was referred back to her ophthalmologist to resume her pre-pregnancy medication.

Conclusion

Azathioprine is an immunosuppressant widely used for anti-organ rejection and in the treatment of numerous autoimmune diseases, such as myasthenia gravis, systemic lupus erythematosus, and inflammatory bowel disease [8-10]. The mean annual azathioprine-induced liver injury rate is estimated to be about 1.4% [6]. Hepatotoxicity from azathioprine occurs secondary to depletion of glutathione, resulting in mitochondrial injury, ATP depletion, and hepatocyte necrosis [8,10]. There may be an association between exposure to azathioprine during pregnancy and the onset of an unusual, early, and severe form of intrahepatic cholestasis of pregnancy, which can lead to adverse pregnancy outcomes.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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