Jaundice and morbilliform eruption in a 20-year-old female

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INTRODUCTION

Drug rash with eosinophilia and systemic symptoms (DRESS) is a drug-induced systemic hypersensitivity reaction that classically presents with a rash, fever, hematological abnormalities, and internal organ involvement.[1] Various long-term sequelae have been described.[2] In this report, we discuss a case of a patient with vanishing bile duct syndrome (VBDS), an uncommon, acquired, but potentially serious form of chronic cholestatic liver disease.[3]

Abbreviations used:

ALT:	alanine transaminase
AST:	aspartate transaminase
DRESS:	Drug Rash with Eosinophilia and Systemic Symptoms
VBDS:	vanishing bile duct syndrome

CASE REPORT

A 20-year-old female with a past medical history of bipolar 2 disorder was admitted for a diffuse morbilliform eruption (Fig 1, *A*) and elevated aspartate transaminase (AST)/alanine transaminase (ALT) (AST/ALT, 128/270 U/L; ref: 9-32/7-33), secondary to lamotrigine. She was started on 25 mg lamotrigine 6 weeks prior to admission, which was uptitrated 2 weeks later (50 mg) and then again increased to 100 mg about 1.5 weeks prior to presentation. She was diagnosed with DRESS and initiated on systemic steroids (60 mg prednisone with transition to intravenous methylprednisolone 1.5 mg/kg daily, then to 80 mg prednisone). Despite this treatment, she developed scleral icterus on examination in addition to rising liver function tests (peak AST/ALT, 881/345 U/L; ref, 9-32/7-33), including total and direct bilirubin (7.7/6.0 mg/dL, ref: 0.0-1.0/0.0-0.4), consistent with drug-induced liver injury. Cyclosporine 3 mg/kg divided twice a day was added to treatment. By admission day 13, her rash resolved, and her transaminases had improved (AST/ALT of 92/288 U/L), but her bilirubin continued to uptrend (total and direct bilirubin of 17.5/15.0 mg/dL). Cyclosporine was discontinued, and she was discharged on 80 mg prednisone for 7 days, ursodiol 300 mg twice a day, and vitamin E 400 U twice a day. At outpatient follow-up 4 days after discharge, she reported worsening abdominal pain, new-onset pruritus, fatigue, positional dizziness, and multiple daily grey/clay-colored bowel movements.

Physical examination demonstrated worsening jaundice including scleral icterus (Fig 1, *B* and *C*), increased bruising, and no remaining morbilliform rash. Laboratory test results were remarkable for elevated total bilirubin (22.2 mg/dL; ref, 0.0-1.0), alkaline phosphatase (209 U/L; ref, 30-100), and gamma-glutamyl transferase (440 U/L; ref, 5-36). Workup for other causes of hepatitis and liver alteration were negative. Antinuclear antibodies and anti−smooth muscle antibodies were positive but were attributed to a drug-induced autoimmune response. Magnetic resonance cholangiopancreatography did not show any ductal dilation or structuring making obstructive causes unlikely.

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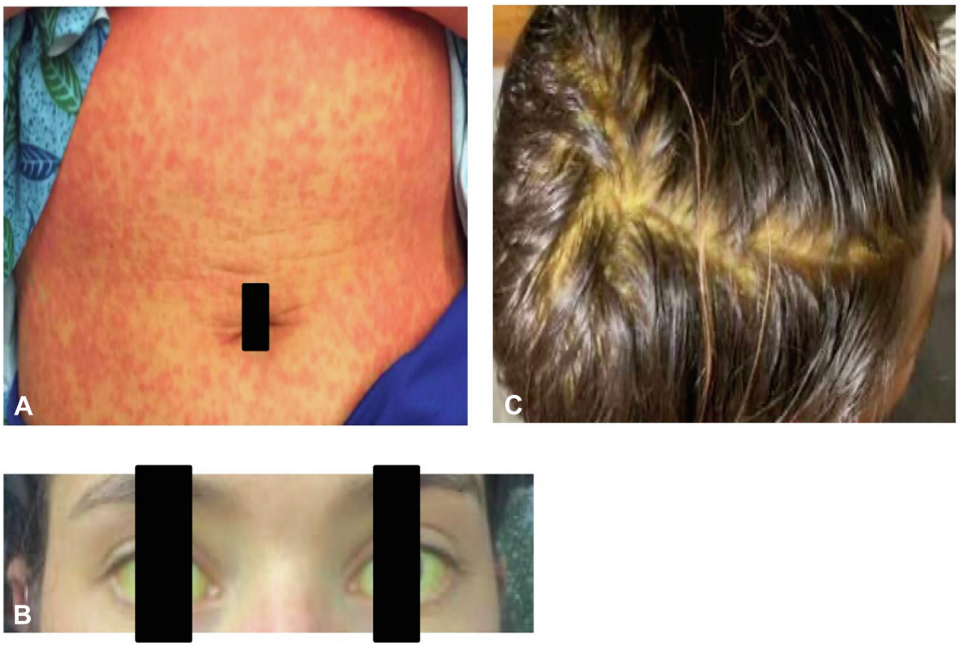

Fig 1. Physical examination findings in a 20-year-old female with DRESS-induced vanishing bile duct syndrome. **A**, Erythematous papules coalescing into thin plaques on the abdomen. **B**, Generalized jaundice including scleral icterus. **C**, Generalized jaundice including the scalp. *DRESS*, Drug rash with eosinophilia and systemic symptoms.

Liver biopsy revealed cholestatic liver with focal centrilobular degeneration, rare acidophil bodies, lobular ceroid macrophages, ductular reaction, and ductopenia, consistent with cholestatic drug-induced liver injury, with evolving VBDS.

The patient was treated with ursodiol 300 mg three times a day, cholestyramine 4 g twice a day, and vitamin supplementation, in addition to a 9-week-long oral 60 mg prednisone taper with a 37-week-long oral 1.5 mg twice a day tacrolimus cross-taper. This cross-tapering strategy was undertaken due to recrudescence of liver injury on initial oral prednisone taper. One year after discharge, the patient had resolution of pruritus and normalization of jaundice and liver function tests with the exception of minimally elevated indirect bilirubin (total and direct bilirubin, 1.8/0.3 mg/dL) and was off all medications.

DISCUSSION

This patient had a RegiSCAR score of 6 [eosinophilia (+2), atypical lymphocytes (+1), >50% body surface area (+1), rash suggesting DRESS (+1), liver involvement (+1)] consistent with 'definite' DRESS followed by VBDS. Lamotrigine is a well-known cause of clinically apparent liver injury, estimated to occur in 1 in 2000 to 10,000 treated patients, and often manifests as part of a systemic immunoallergic reaction like DRESS.[4] It is thought to be due to a hypersensitivity or an immunological response to a metabolically generated drug-protein complex with a dose-response relationship. A diffuse morbilliform rash is a common presenting symptom as seen in this patient. It may be followed by high fever, nausea, and vomiting. Likewise, eosinophilia is common, and facial edema, lymphadenopathy, and atypical lymphocytosis may occur. Liver injury typically exhibits a hepatocellular pattern and ranges from mild to moderate liver function test elevations, to icteric to severe hepatitis, and even to acute liver failure. Liver biopsy demonstrates portal inflammation, hepatocellular necrosis, and bile duct proliferation.

In contrast, VBDS is defined pathologically as hepatic ductopenia or bile duct paucity, which refers to a reduction in the number of intrahepatic bile ducts. It is manifested histologically by severe bile duct destruction, defined as a loss of the intralobular bile ducts in greater than 50 percent of portal areas.[5] VBDS typically arises in the setting of severe acute cholestatic hepatitis where there is an insufficient recovery evidenced by persistent elevations in alkaline phosphatase and bilirubin levels, despite a normalizing serum aminotransferase level.[6] The pathogenesis of VBDS is not well understood; Immune-mediated injury has been suggested in bile duct loss,

and T-cell-mediated immunologic reaction may lead to epithelial cell apoptosis. This process may ultimately lead to cholestatic liver disease and may progress to biliary cirrhosis, liver failure and transplantation, or death. Causes include idiopathic, immune-mediated disorders, infectious disease, malignancy, and drug-induced. Implicated drugs are amoxicillin/clavulanate, other penicillins, macrolide antibiotics, fluoroquinolones, sulfonamides, antifungal agents, nonsteroidal anti-inflammatory agents, phenothiazines, tricyclic antidepressants, and anticonvulsants.[5,7,8] Lamotrigine again has been implicated as a drug-induced cause with a pediatric case in the literature of a 12-year-old boy who developed a rash 2 weeks after initiating lamotrigine followed by jaundice [bilirubin, 14.8 mg/dL; ALT, 321 U/L; alkaline phosphatase, 123 U/L] and ductal paucity on liver biopsy; He demonstrated incomplete recovery on ursodiol and was referred for liver transplantation 2 years later.[8] Although cyclosporine may cause increased bilirubin, it has not been associated with VBDS and was not thought to be a contributing factor in this case. Treatment for VBDS includes discontinuing hepatotoxic drugs, administering ursodeoxycholic acid and immunosuppressants, and symptom control.

This case highlights a rare and possible DRESS-related hepatic and biliary system complication that may have a delayed clinical manifestation. Laboratory abnormalities reflecting cholestasis (elevations in alkaline phosphatase, total serum bilirubin, and gamma-glutamyl transpeptidase) should raise suspicion for this potential complication with a thorough assessment of symptoms such a jaundice, pruritus, change in stools, and fatigue. For patients who develop a rash and jaundice after ingesting implicated anticonvulsants, the drug should be stopped immediately and prompt treatment should be initiated.

Conflicts of interest

None disclosed.

REFERENCES

1. Cardones AR. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. *Clin Dermatol*. 2020;38(6):702-711. https://doi.org/10.1016/j.clindermatol.2020.06.008
2. Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY. Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. *J Am Acad Dermatol*. 2013;68(3):459-465. https://doi.org/10.1016/j.jaad.2012.08.009
3. Desmet VJ. Vanishing bile duct syndrome in drug-induced liver disease. *J Hepatol*. 1997;26(Suppl 1):31-35. https://doi.org/10.1016/s0168-8278(97)82330-6
4. Lamotrigine. In: LiverTox: clinical and research information on drug-induced liver injury. National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Accessed July 27, 2022. http://www.ncbi.nlm.nih.gov/books/NBK548562/
5. Bonkovsky HL, Kleiner DE, Gu J, et al. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. *Hepatol Baltim Md*. 2017;65(4):1267-1277. https://doi.org/10.1002/hep.28967
6. Vanishing bile duct syndrome. In: LiverTox: clinical and research information on drug-induced liver injury. National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Accessed July 27, 2022. http://www.ncbi.nlm.nih.gov/books/NBK548715/
7. Cotter C, Biswas M, Rao N, Selim A, Walsh S. Vanishing bile duct syndrome with eruptive xanthomas. *Clin Exp Dermatol*. 2020;45(3):364-366. https://doi.org/10.1111/ced.14043
8. Bhayana H, Appasani S, Thapa BR, Das A, Singh K. Lamotrigine-induced vanishing bile duct syndrome in a child. *J Pediatr Gastroenterol Nutr*. 2012;55(6):e147-e148. https://doi.org/10.1097/MPG.0b013e31823c2500