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CASE REPORT | LIVER

Drug Reaction With Eosinophilia and Systemic Symptoms and Severe Drug-Induced Liver Injury After Off-Label Zonisamide Use for Weight Loss

Raha Sadjadi, MD[1,2], Elizabeth Cogdell, DO[3], Mohamed E. Mostafa, MD[4], Florencia Anatelli, MD[5], Lindsay Ackerman, MD[6], Karn Wijarnpreecha, MD, MPH[1,2], and Ma Ai Thanda Han, MD[1,2]

[1]*Division of Gastroenterology and Hepatology, Department of Medicine, University of Arizona College of Medicine—Phoenix, Phoenix, AZ*
[2]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Banner University Medical Center, Phoenix, AZ*
[3]*Department of Medicine, University of Arizona College of Medicine—Phoenix, Phoenix, AZ*
[4]*Department of Pathology, Banner University Medical Center—Phoenix, Phoenix, AZ*
[5]*Division of Dermatopathology, Southwest Skin Specialists, US Dermatology Partners, Scottsdale, AZ*
[6]*Medical Dermatology Specialists, Phoenix, AZ*

ABSTRACT

Drug-related eosinophilia with systemic symptoms (DRESS) is a drug-induced hypersensitivity reaction causing rash and systemic symptoms. Associated liver injury ranges from abnormal laboratory results to liver failure. We report a case of zonisamide-induced DRESS with severe liver injury, characterized by vanishing bile duct syndrome. Despite stopping zonisamide and initiating immunosuppressive therapy, the patient's hepatic function remained abnormal. After a prolonged course, the patient died from pneumonia and Hodgkin lymphoma. This case highlights the gravity of DRESS syndrome and drug-induced liver injury along with the risks of immunosuppressive therapies.

KEYWORDS: drug-induced liver injury; drug-related eosinophilia and systemic symptoms; zonisamide; severe cutaneous adverse reactions; vanishing bile duct syndrome

INTRODUCTION

Drug-related eosinophilia with systemic symptoms (DRESS) is a drug-induced hypersensitivity reaction yielding a rash and systemic symptoms 2–6 weeks after exposure,[1] even if the medication has been stopped. The most commonly impacted extracutaneous organ is the liver.[2] Injury includes abnormal liver chemistries to liver failure.[2] Zonisamide, a newer antiepileptic, is less commonly associated with DRESS compared with older antiepileptics.[2,3] We report a case of zonisamide-induced DRESS with drug-induced liver injury (DILI), characterized by vanishing bile duct syndrome (VBDS), in an adult taking zonisamide off-label for weight loss.

CASE REPORT

A 55-year-old woman with hypertension began taking zonisamide to lose weight. Three weeks later, she developed flu symptoms and stopped the medication. She then developed jaundice and a rash. Outside hospital evaluation revealed aspartate amino transferase 277 units per liter (U/L), alanine amino transferase 517 U/L, alkaline phosphatase (ALP) 514 U/L, total bilirubin (TBili) 13.6 mg/dL, international normalized ratio (INR) 1, and normal abdominal imaging. Liver biopsy showed ductopenia consistent with VBDS and lobular cholestasis suggestive of DILI from zonisamide (Figure 1). She was discharged after laboratory improvement. Subsequent rash biopsy suggested DRESS (Figure 2). A few weeks later, her liver chemistries worsened. She was admitted to our hospital with concerns for liver failure.

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Correspondence: Ma Ai Thanda Han, MD (maaithanda.han2@bannerhealth.com).

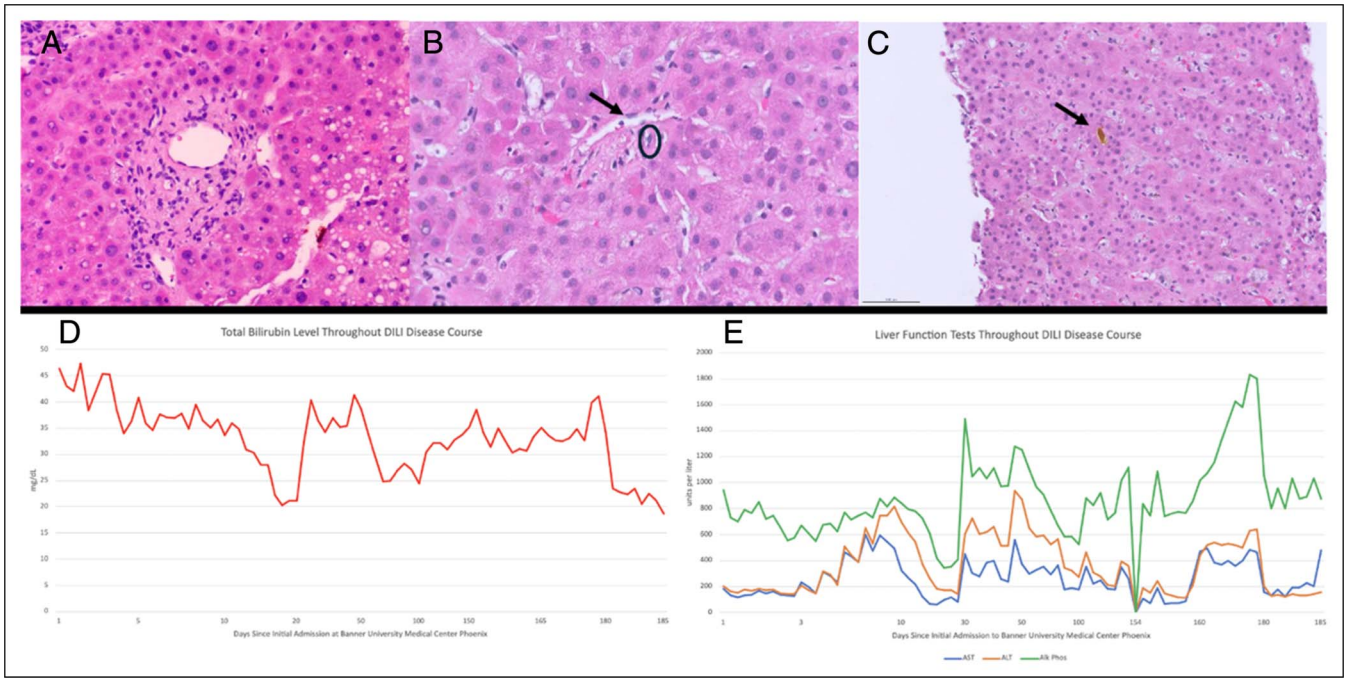

Figure 1. (A) First liver biopsy: portal tract without bile duct. (B) Second liver biopsy: portal tract without bile duct (arrow: portal vein, circle: hepatic artery). (C) Third liver biopsy: lobular cholestasis (arrow). (A–C) H&E stain, 20× magnification. (D) Bilirubin over clinical course. (E) Liver chemistries over clinical course.

Admission laboratory results showed aspartate amino transferase 182, alanine amino transferase 204, ALP 944, TBili 46.4, and INR 3.3. She was started on intravenous n-acetylcysteine and ursodiol. Her rash spread to her trunk and extremities with mucosal involvement, without lymphadenopathy. Human herpes virus (HHV) 6, HHV8, cytomegalovirus, and Epstein-Barr virus serologies were negative. She received 500 mg intravenous methylprednisolone daily for treatment of DRESS with hepatic injury. She completed 7 days of n-acetylcysteine and 3 days of methylprednisolone. Her liver chemistries improved after adding oral cyclosporine 150 mg twice daily for 10 days followed by 150 mg daily for 4 days. She was discharged on ursodiol and a prednisone taper starting at 50 mg daily.

While hospitalized, her chest radiograph showed a widened mediastinum. Chest computed tomography revealed a mediastinal mass with possible local invasion. Core biopsy, fine needle aspiration, and surgical biopsy showed benign inflammatory tissue.

Three weeks later, she was readmitted with elevated liver chemistries. Repeat liver biopsy showed lobular cholestasis and ductopenia without significant fibrosis (Figure 1). Her presentation was attributed to worsening of her DRESS and DILI from decreased immunosuppression. Her steroids were increased with plans for a slower taper. Cyclosporine was resumed, and later dupilumab was added to facilitate weaning off prednisone and cyclosporine.

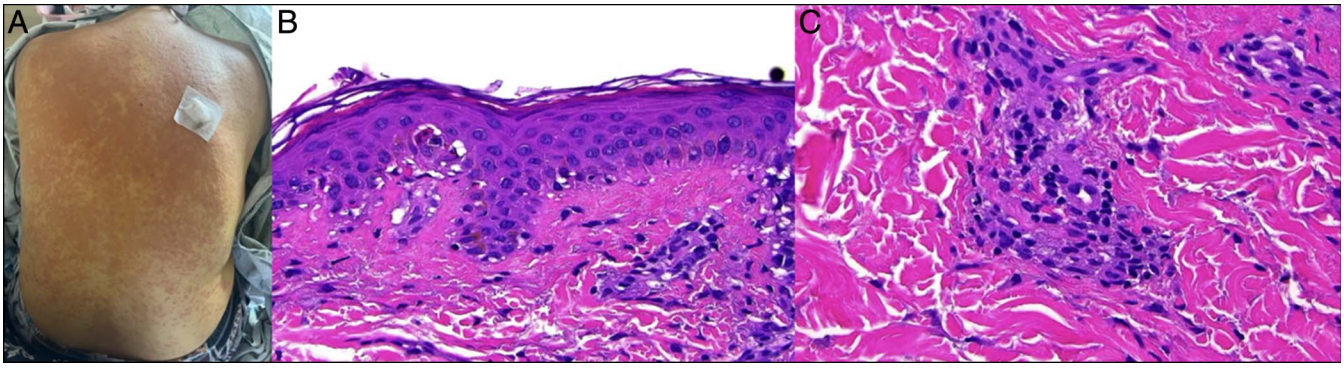

Figure 2. (A) Dress rash. (B) Cutaneous punch biopsy with interface dermatitis: basal vacuolar change and multiple scattered apoptotic keratinocytes in the epidermis. (C) Cutaneous punch biopsy with vascular damage: perivascular lymphocytic infiltrate, swollen endothelial cells, and red blood cell extravasation. (B) and (C) H&E stain, 400× magnification.

Three months later, she was readmitted with fever and worsening liver chemistries after undergoing a third liver biopsy (Figure 1). Imaging showed cavitary pneumonia. She tested positive for rhinovirus and received antimicrobials. Two weeks later, she represented with respiratory failure. Despite life supporting measures, she died. Autopsy confirmed DRESS, DILI, necrotizing pneumonia, and mediastinal Hodgkin lymphoma.

DISCUSSION

Our patient developed DRESS with DILI (DwD) from zonisamide. Immunosuppression facilitated some recovery, but she relapsed with de-escalation of therapy, highlighting the sometimes prolonged and nonlinear recovery from DRESS.[4] This is the seventh published case report of DwD from zonisamide (Table 1).

DRESS treatment includes discontinuing the causative drug, supportive care, and for severe cases, steroids.[10] Steroid-sparing therapies including cyclosporine have been studied; yet, randomized double-blind placebo controlled trials evaluating their efficacy are needed.[10] Interleukin (IL) 5 and 4 have been implicated in DRESS's pathophysiology.[11,12] One study found cyclosporine, through IL-5 inhibition, was effective in treating DRESS and shortened the time to cessation of DRESS progression after treatment initiation compared with corticosteroids.[11] In case reports of DRESS that rebounds with steroid reduction, dupilumab, through its anti-IL-4 activity, yielded clinical improvement and decreased steroid use.[12,13] It is impossible to know if DRESS treatment at our patient's index hospitalization might have changed her course. However, her prolonged illness and relapses with steroid reduction despite concurrent cyclosporine use suggest a treatment resistant disease that may not have been altered by earlier therapy. The median duration of DRESS is 52 days.[1] A prospective study found 22% of patients' disease lasted 90 days or greater.[1] Our patient falls into this subset.

The etiology, natural progression, and type of DILI seen in our patient are also unique. Zonisamide caused one of 1,711 cases of DILI from 2004 to 2020.[3] In a case report of a patient taking zonisamide for weight loss, the patient developed DILI with VBDS without DRESS.[14] Zonisamide withdrawal led to bile duct and laboratory recovery, unlike our patient. VBDS, a subcategory of cholestatic DILI, defined as fewer than 50% of bile ducts present on liver biopsy, is seen in 7% of patents with DILI.[15] Some hypothesize VBDS, like DRESS, is a T-cell vs toxin-mediated hypersensitivity reaction, with injury targeting

Table 1. Published case reports of DRESS with DILI from zonisamide

First author	Patient age (years)	Zonisamide indication	Latency from zonisamide initiation to DRESS onset (months)	Peak liver chemistries	Extrahepatic and extracutaneous manifestations	DRESS treatment	Viral serologies	Liver biopsy	Patient outcome	Latency to rash improvement/ resolution after DRESS treatment (days)	Latency to DILI improvement/ resolution after DRESS treatment (days)
Khan[5]	8	Epilepsy	19	AST 144, ALT 388 ALP 582	NA	Steroids	HHV6 + CMV−	NA	Rash improved	5	NA
Trivedi[6]	11	Epilepsy	2	AST 71 ALT 99 ALP > 250 GGT >300	NA	Steroids, IVIG	NA	NA	Rash resolved	<23	NA
Fujita[7]	29	Epilepsy	1.5	AST 561 ALT 881 ALP 661 TBili 0.4 GGT 153	AKI	Steroids	HHV6+	NA	Rash improved	At least 10	NA
Shibuya[4]	46	Hereditary hemorrhagic telangiectasias	8	AST 67 ALT 133 ALP 220	Eosinophilic pneumonia	Steroids	HHV6 + CMV, EBV−	NA	Improved pulmonary lesions	NA	NA
Takamiyagi[8]	66	Poststroke numbness	0.7	AST > 150 ALT >350	Graft vs host disease like enterocolitis	Steroids, ganciclovir	HHV6− CMV +	NA	Death from respiratory failure	<100	54
Murata[9]	72	Postop seizure prophylaxis	0.8	AST 481 ALT 648	NA	Steroids	HHV7 + HHV6, CMV, EBV−	NA	Rash resolved	16	6

(-), negative; (+), positive; AKI, acute kidney injury; ALP, alkaline phosphatase; ALT, alanine amino transferase; AST, aspartate amino transferase; CMV, cytomegalovirus; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; GGT, gamma-glutamyl transferase; HHV, human herpes virus; IVIG, intravenous immunoglobulin; NA, not available; TBili, total bilirubin.

bile ducts.[14,15] VBDS is predominantly seen in patients with prolonged cholestasis.[15] Our patient developed VBDS shortly after disease onset. Patients with VBDS are more likely to develop chronic liver injury.[15] VBDS is associated with a disproportionately larger mortality rate compared with overall DILI, 19% vs 6.2%, respectively.[15] DwD is regarded as its own subclass of DILI.[16] Globally, the prevalence of DwD ranges from 3.7% to 19%.[17] Hepatic injury is usually cholestatic or mixed hepatitis.[16,17] Jaundice and higher Tbili are poor prognostic markers.[16,17] Marked hepatitis can foreshadow a chronic relapsing remitting course.[18]

Our patient's Hodgkin lymphoma implores us to question whether her rash and VBDS were paraneoplastic processes rather than drug-related hypersensitivity reactions. Cutaneous paraneoplastic syndromes related to Hodgkin lymphoma have been described, although no specific association with DRESS has been suggested.[19] Still, it is recommended to evaluate for neoplasia when exanthems fail to respond to therapy.[19] Paraneoplastic VBDS from Hodgkin lymphoma has also been reported.[20] Studies emphasize performing an exhaustive search for the cause of VBDS including medication review and ruling out infection, malignancy, and autoimmune disease.[20] This case reminds us to remain vigilant when illness recovery does not progress as expected. One must reconsider their treatment strategy, weighing the risks and benefits of immunosuppression, and reevaluate every possible underlying cause of disease.

DISCLOSURES

Author contributions: R. Sadjadi: manuscript drafting, revising the manuscript critically for important intellectual content, and final approval to be published. E. Cogdell: data collection, manuscript drafting, and final approval to be published. ME Mostafa, F. Anatelli: pathology slides and interpretation, editing, and final approval to be published. L. Ackerman: revising the manuscript critically for important intellectual content, and final approval to be published. K. Wijarnpreecha: revising the manuscript critically for important intellectual content, and final approval to be published. MAT Han: revising the manuscript critically for important intellectual content, supervision, and final approval to be published. MAT Han is the article guarantor.

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