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Treatment of Refractory Pruritic Dermatitis in the Setting of Primary Biliary Cholangitis and CREST Syndrome With Upadacitinib

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ABSTRACT

Primary biliary cholangitis (PBC) can present with overlapping features of limited systemic sclerosis, commonly known as calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST). Here, we discuss the case of a PBC patient with CREST who experienced treatment-resistant and progressively worsening pruritic dermatitis that responded to upadacitinib with associated improvement of her liver enzymes and symptoms. This is the first documented report of a Janus kinase (JAK) inhibitor used to treat cutaneous symptoms in the setting of an autoimmune liver disease.

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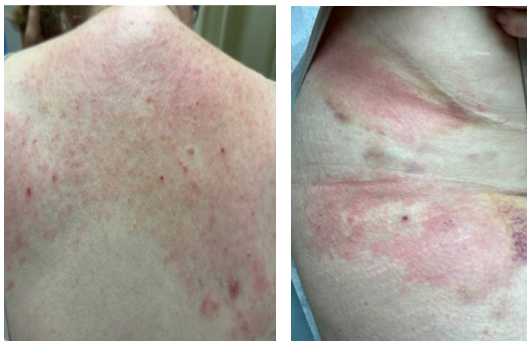
CASE REPORT

A 66-year-old woman with vulvar lichen sclerosis, Raynaud's phenomenon, and biliary colic status-post cholecystectomy presented for an intensely pruritic rash ongoing for several months. The eruption affected her right ankle, upper back, extensor elbows, and suprapubic area (Figure 1). She also reported mild gastrointestinal reflux. Prior to dermatology evaluation, she completed 3 prednisone courses, with persistent or recurrent symptoms. Topical steroids, antihistamines, and empiric scabies treatments were also ineffective. Family history included renal cell carcinoma (father) and bullous pemphigoid (mother).

FIGURE 1. Scaly erythematous patches and plaques with overlying hemorrhagic crust on the upper back in a butterfly distribution (A), and on the right lateral hip (B).

(A) (B)

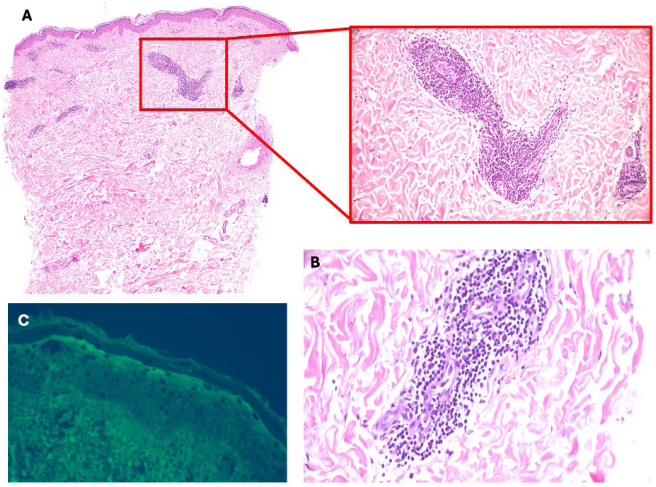


Punch biopsies of the back and thigh showed superficial and mid-dermal perivascular lymphocytic infiltrate with rare eosinophils (Figure 2A, 2B). Periodic Acid-Schiff (PAS) stain was negative for fungi or basement membrane thickening, and Alcian blue showed no significant mucin. Direct immunofluorescence revealed speckled dust-like IgG in the epidermis, suggesting circulating autoantibodies (Figure 2C).

A rheumatology workup for chronic fatigue revealed positive ANA (1:320, nuclear pattern) and anti-centromere antibodies (>8.0 units). Further serologic testing was negative for deamidated gliadin peptide, tissue transglutaminase antibodies, C3/C4, BP180/BP230, ANCAs, RF, CCP, dsDNA, SPEP, Ro, La, Sm, RNP, and TPO, but positive for smooth muscle antibodies (1:80) and antimitochondrial antibodies (AMA; 122.2).

She was diagnosed with primary biliary cholangitis (PBC) with limited systemic sclerosis (CREST syndrome) and referred to gastroenterology for an endoscopy and liver biopsy. The liver ultrasound showed hyperechogenicity and mild hepatomegaly. Despite starting ursodeoxycholic acid (50 mg/kg/day) and cholestyramine, the pruritus continued to persist even in setting of adjunct and maximally titrated topical steroids, gabapentin, and antihistamines. Eventually, monotherapy with upadacitinib 30 mg daily led to significant pruritus reduction. Within 3 weeks, she reported 95% reduction in itch severity via POEM scores. Liver markers normalized after 3 months (Table 1).

FIGURE 2. (A) 10x and 50x (inset). (B) 100x magnification. H&E histopathology reveals superficial and mid-dermal, tight, perivascular lymphocytic infiltrate with rare eosinophils. PAS was negative for fungal elements or basement membrane thickening. Alcian blue stain did not reveal significant dermal mucin deposition. (C) Direct Immunofluorescence demonstrating intrakeratinocytic particulate, speckled IgG deposition and positive ANA/intranuclear antibodies.



DISCUSSION

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by T-cell mediated progressive destruction of the small intrahepatic bile ducts, causing fibrosis and cirrhosis.[1] The disease typically presents in the fourth to sixth decade of life, with a higher prevalence among women, with a female-to-male ratio of approximately 9:1.[2] The incidence of PBC is estimated to range from 2 to 40 cases per 100,000 people,[2] making it a relatively rare condition. A diagnosis is established when 2 of 3 criteria are met: biochemical evidence of cholestasis, AMA positivity, and/or histologic confirmation of destructive cholangitis.

Sixty percent of patients with PBC have at least one concurrent autoimmune condition.[2] Overlap with the limited cutaneous form (CREST) is most notable,[1] where the coexistence of both conditions is reported in 10% to 15% of cases of PBC.[1] The pathogenesis of PBC-CREST is multifactorial;[3] the overexpression of a T-cell receptor beta chain variable region TCRBV3 has been associated with the condition.[4] One syndrome usually precedes the diagnosis of the other, often with a 4 to 5 year interval between the two presentations.[3,5]

Without treatment, PBC can progress to cirrhosis and an increased risk of hepatocellular carcinoma.[6] The chronic cholestasis drives pruritus and xanthoma development, which significantly impacts quality of life.[3] Furthermore, the manifestations of CREST syndrome increases the risk of systemic complications, such as pulmonary arterial hypertension, interstitial lung disease, and esophageal dysmotility.[3,5] It is unclear why the presence of PBC-CREST yields a better prognosis than PBC alone.[5,7]

In cholestasis, bile acids are poorly excreted, leading to their retention in the skin and circulation. As such, treatment of PBC centers on the use of ursodeoxycholic acid, which is the first-line therapy and slows the progression of liver disease and improves survival.[8] Accumulation of bile acids also activates sensory neurons in the skin, including the μ-opioid receptor, which exacerbates pruritus.

This case highlights an important distinction between classic cholestatic pruritus and inflammatory dermatitis pruritis in autoimmune overlap syndromes. In classic cholestatic pruritus, the skin is typically devoid of primary findings and biopsies either lack specific diagnostic features or reflect secondary changes from chronic scratching such as prurigo nodularis.9 While the patient's biopsy did demonstrate a perivascular lymphocytic infiltrate with rare eosinophils, suggesting the presence of an active inflammatory dermatitis, her elevated

TABLE 1.

Relevant Laboratory Values					
Test	**Reference Range**	**11/22/2024**	**9/16/2024**	**8/8/2024 (Upadacitinib started)**	**7/23/2024**
AST	17-35 U/L	20	21	13	13
ALT (SGPT)	8-39 U/L	21	25	63 (↑)	26
GGT	9-64 U/L	56	65 (↑)	67 (↑)	96 (↑)
Total Bilirubin	0.1-1.2 mg/dL	1.2	1.1	1	0.7
Bilirubin, Direct	0 – 0.5 mg/dL	0.4	0.3	0.2	--
Bile Acids, Total	0 – 10 mmol/L	6	4	18 (↑)	--
Cholesterol, Total	<200 mg/dL	262	--	256	--
Triglycerides	<150 mg/dL	179	--	329	--

AST; Aspartate aminotransferase, ALT; Alanine Transaminase, GGT; Gamma-Glutamyl Transferase

serum bile acids – a known correlate of cholestasis – indicate that this pruritus was likely driven by both impaired bile acid clearance and autoimmune inflammation. The coexistence of these mechanisms may explain the progressive severity and treatment-resistant nature of her symptoms.

Options in managing cholestatic pruritus remain limited, but includes sertraline, rifampicin, and naltrexone.[10] Difelikefalin, a k-opioid receptor agonist that demonstrated effectiveness in uremic pruritus, could also hold promise.[11] In this case, systemic corticosteroids, antihistamines, gabapentin, ursodeoxycholic acid, and cholestyramine all failed to provide durable relief. These therapies target downstream symptoms of pruritus but do not directly address the underlying autoimmune inflammation driving both the dermatitis and hepatic dysfunction.

In atopic dermatitis, upadacitinib has proven highly effective for its dual-action mechanism – targeting both the underlying T-cell-mediated inflammation and providing relief from the debilitating itch.[12] This case marks the first documented use of upadactinib, a selective JAK1 inhibitor, to concomitantly treat pruritus in the setting of cholestasis and autoimmune dermatitis, with associated improvement in liver function markers and itch scores.[13,16] Upadactinib reduces the expression of other pro-inflammatory cytokines and diminishes the activity of pathogenic T-cells (eg, Th1 and Th17), which may play a role in PBC, and the action of key cytokines like IL-4, IL-13, and IL-31 that drive pruritus.[14] While dupiliumab and nemolizumab have been shown to be effective in cholestatic pruritus, it may not address the underlying autoimmune liver pathogenesis.[12,15,17] Since upadacitinib was instrumental in achieving symptom resolution along with normalization of liver biomarkers, JAK inhibition may be modulating the inflammatory pathways in PBC-CREST overlap syndrome, making this a promising therapeutic strategy.

Given the progressive nature of PBC and its impact on long-term survival, early intervention with targeted immunomodulatory therapies could prevent disease progression, mitigate systemic inflammatory damage, and enhance quality of life. Future research into this complex overlap syndrome is needed to understand the underlying pathogenesis and design of novel therapies.

DISCLOSURES

The authors have no relevant financial relationships or conflicts to disclose.

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