

Clinical Letter

Chronic spontaneous urticaria associated with primary biliary cirrhosis: a case report and literature review

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Dear Editors,

Chronic spontaneous urticaria (CSU) is a mast cell-driven disorder characterized by the appearance of wheals, angioedema, or both for a period of more than six weeks due to known or unknown causes [1]. The point prevalence of the disease is 0.5–1 % [2]. Significant circumstantial evidence indicates that CSU is an autoimmune disease, at least in a certain subgroup of patients [3]. CSU is frequently observed in patients with autoimmune thyroiditis [4], but we are aware of only three previously reported cases of CSU associated with primary biliary cirrhosis (PBC) [5, 6]. An autoimmune cholestatic disorder, PBC is characterized by the destruction of intrahepatic bile ducts and periportal inflammation resulting in liver failure. The prevalence of PBC is less than 1 in 2,000 [7]. Its close association with various autoimmune disorders (including scleroderma, thyroiditis, systemic lupus erythematosus) has been well established [8]. Herein, we report a rare case of PBC developing in a woman with a history of CSU, and review the relevant literature.

In 2013, a 30-year-old female patient presented to our department with a 2-year history of CSU. Clinical examination revealed numerous irregularly distributed confluent urticarial plaques, measuring 2 to 10 cm in diameter, which faded within 24 hours, leaving normal skin (Figure 1). Simple dermographism was observed after stroking the skin on the forearm.



Figure 1 Urticarial rash on the lower extremity of our PBC patient.

Symptoms were adequately controlled by antihistamines at standard daily doses. Quality of life was slightly impaired (The Dermatology Life Quality Index [DLQI]: 1, Chronic Urticaria Quality of Life Questionnaire [CU-Q₂oL]: 84.8 %). The patient had no history of allergies.

Laboratory tests revealed an elevated eosinophil count, accelerated ESR, elevated levels of total serum protein, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, tumor necrosis factor alpha, IgG, and IgA (Table 1). Vitamin D serum levels were decreased (10.4 pg/mL). Antinuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) tests were positive (1 : 640 and 1 : 20, respectively). The patient exhibited a 5-fold increase in serum levels of antimitochondrial antibodies (AMA) (52.9 U/mL). Given the aforementioned simple dermographism, skin testing with autologous serum was not performed. A liver biopsy showed moderate parenchymal bilirubin stasis (Figure 2). Small foci of hepatocyte necrosis (1–3 cells) as well as lymphocyte and macrophage infiltration were found in the parenchyma. Portal tracts were moderately enlarged, swollen, and infiltrated with macrophages and lymphocytes with an admixture of neutrophils and eosinophils. There were signs of cholangiopathy, nonsuppurative cholangitis, focal hyperplasia of biliary ducts, and mild sclerosis of portal tracts. The Knodell Histology Activity Index was 0–1–3–0 (4); fibrosis stage: 0. The histopathologic findings were compatible with stage 1 PBC. The patient was subsequently started on ursodeoxycholic acid therapy.

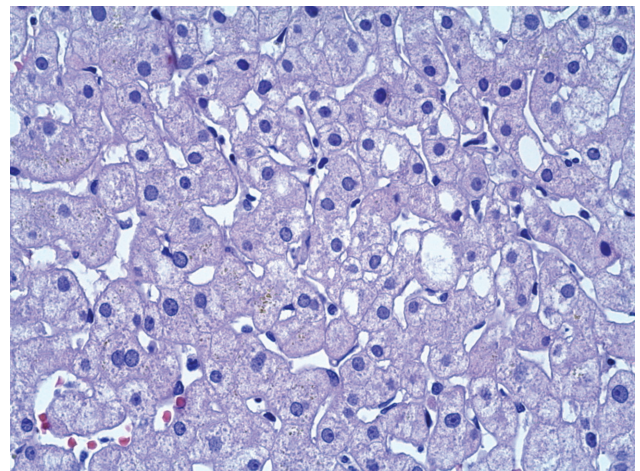


Figure 2 Liver histopathology revealed signs of low-grade nonsuppurative destructive cholangitis, involving small biliary ducts, moderate parenchymal bilirubin stasis; stage 0 fibrosis; compatible with stage 1 primary biliary cirrhosis (hematoxylin-eosin and picrofuchsin stain, original magnification x 100).

Table 1 Summary of CSU-associated PBC cases reported in the literature.

Study	Age	Gender	Onset of CSU prior to admission	Elevated laboratory parameters	Other symptoms and/or comorbidities	Treatment of CSU	Efficacy of CSU therapy
Our case, 2014	30	Female	2 years	Eosinophils (9 %), ESR (40 mm/h), ALT (48 U/L), AST (41 U/L), GGT (91 U/L), IgG (21.5 g/l), IgA (5.5 g/L), ANA (1 : 640), ASMA (1 : 20), AMA (52.9 U/mL)	None	AH	Good response
Covelli et al. 2006 [6]	49 (case #1)	Female	3 weeks	Eosinophils (9 %), ESR (48 mm/h), CRP (3.7 mg/dL), GGT (70 U/L), ANA (1 : 640), AMA (+)	Arthromyalgia, cough, fever	Prednisolone, clarithromycin	CSU resolved after 4-day course; relapsed within 10 days after treatment discontinuation
Covelli et al. 2006 [6]	50 (case #2)	Female	2 months	Eosinophils (9 %), ESR (40 mm/h), CRP (2.4 mg/dL), GGT (101 U/L), ALT (42 U/L), ALP (181 U/L), IgG (2.360 mg/dL), IgM (1.104 mg/dL), RF (30 U/L), ANA (+), cANCA (+), AMA (1 : 80)	Arthromyalgia	None	Skin rash absent upon admission
Bose et al. 2013 [5]	44	Female	6 weeks	Anti-TPO (306 U/mL), CRP (0.69 mg/dL), ANA (1 : 40), AMA (1 : 640)	Hashimoto's thyroiditis	AH Colchicine	Refractory CSU completely resolved

Abbr.: ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; AMA, antimitochondrial antibodies; CRP, C-reactive protein; RF, rheumatoid factor; cANCA, antineutrophil cytoplasmic antibodies; TPO, thyroid peroxidase; ALP, alkaline phosphatase; AH, antihistamines.

Primary biliary cirrhosis is associated with wide variety of skin conditions. Koulentaki et al. observed that 43 (88 %) of 49 PBC patients enrolled in their study had dermatological symptoms, and in 40 % of cases, skin involvement was the chief presenting complaint. The most common skin disorders observed in these patients were fungal skin infections (31.5 %), neoplastic lesions (18.4 %), and urticaria (18.4 %) [9]. As yet, there have been three reported cases of CSU as a possible manifestation of PBC (Table 1) [5, 6]. All three patients were women above the age of 30. Data from the literature suggests that both PBC [10] and CSU [2] predominantly occur in middle-aged women.

Our case demonstrates that early-stage PBC may be clinically asymptomatic, yet accompanied by CSU and marked elevation in liver enzymes and specific autoantibody levels. Symptoms of CSU were adequately controlled by antihistamines. In the two cases reported by Covelli et al. [6], CSU lesions either preceded or were accompanied by arthromyalgia. In one of the patients, the urticarial rash

promptly responded to corticosteroids but relapsed after treatment discontinuation. The other patient did not exhibit any skin lesions upon admission, two months after their initial onset. Bose et al. [5] described a patient with a 6-week history of CSU and elevated anti-TPO antibody and CRP levels who failed to respond to antihistamines. Symptoms recurred one week after discontinuation of corticosteroid therapy, and complete resolution of skin lesions and pruritus was only achieved following initiation of colchicine treatment.

Mast cell and/or basophil-activating autoreactive IgE and anti-FcεRI/IgE IgG autoantibodies have been found in CSU and in other autoimmune disorders like systemic lupus erythematosus [3, 11]. As yet, there has been no research aimed at detecting such histamine-releasing autoantibodies in PBC. One may nonetheless speculate that PBC – designated “a model autoimmune disorder” – may exhibit a similar phenomenon.

Both CSU and PBC are more likely to develop in middle-aged women. They are thought to be autoimmune in

nature and frequently associated with autoimmune thyroiditis. Although the coexistence of CSU and PBC in the same patient may be sheer coincidence, it may also suggest common pathomechanisms. Further research is required to shed light on this subject.

Conflict of interest

None.

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