INTRODUCTION
Urticaria is a common vascular reaction of the skin involving pruritus and transient wheals surrounded by erythema.\(^1\) It results in plasma extravasation into the dermis, because mast cell degranulation and its byproducts, such as histamine, leukotrienes, cytokines, and chemokines, alter vasopermeability.\(^1\) Urticaria appear abruptly, induced by factors that include allergens, infections, autoimmunity, and autoreactivity, and they usually vanish within 24 hours.\(^1\) Yellow urticaria, however, is an uncommon, rarely reported variant characterized by yellow eruptions.\(^2\)

Clarke\(^3\) first described yellow urticaria in 1969 in a patient with cold urticaria who had jaundice during infectious hepatitis. Urticaria manifested during the jaundice period, remitting after the hepatitis resolved. Interestingly, despite mild degrees of jaundice detected at more than 2 mg/dL of bilirubin levels,\(^4\) other cases of yellow urticaria\(^2\) did not report an association with jaundice, even in the presence of total bilirubin values ranging from 2.8 to 8.4 mg/dL.\(^2\)

Here we report a case of yellow urticaria associated with biliary pancreatitis. The pancreatitis was accompanied by yellow urticaria secondary to dermal bilirubin deposits.

CASE REPORT
An 82-year-old woman with chronic cholelithiasis presented to the emergency room with acute abdominal pain secondary to biliary pancreatitis and acute cholecystitis. She was referred to our department because of a 24-hour history of generalized hives and pruritus. During a comprehensive history taking, the patient denied a history of atopia, allergies, previous urticaria episodes, new dietary changes, and recent herbal supplements or drug consumption.

A physical examination found large, disseminated urticarial plaques with erythematous borders and inner yellow areas. The plaques were distributed across the trunk, abdomen, and upper and lower extremities (Fig 1). She also presented with mild and generalized jaundice, and there was no angioedema or dermatographism.

Blood tests found increased bilirubin levels: total bilirubin was 5.3 mg/dL (0.2-1.2 mg/dL), direct bilirubin was 4.0 mg/dL (0-0.5 mg/dL), and indirect bilirubin was 1.3 mg/dL (0-0.8 mg/dL). Liver enzyme readings showed an increase in aspartate aminotransferase of 169 U/L (5-34 U/L), alanine transaminase of 102 U/L (0-55 U/L), and alkaline phosphatase of 244 U/L (40-150 U/L). The pancreatitis diagnosis was supported by a higher-than-normal concentration of blood serum amylase (1178 U/L [13-53 U/L]). Results of other tests, including hematric biometry, blood chemistry, and urinalysis, were normal.

A hematoxylin and eosin-stain skin biopsy found dermal edema, which supported the urticaria diagnosis. A Hall stain was performed for bilirubin\(^5\) and found olive-green, polyhedral interstitial crystals that were confined to the reticular dermis and subcutaneous tissue (Fig 2).

The patient was given 10 mg of loratadine every 12 hours, resulting in total resolution of the lesions within the ensuing 18 hours. The loratadine was continued for 30 days, and there was no recurrence. The biliary pancreatitis and acute cholecystitis were treated successfully with open cholecystectomy 2 days after the acute urticaria disappeared. Intraoperative cholangiography confirmed the absence of remaining calculi, and the patient was discharged 2 days later.
DISCUSSION

Cases in the literature indicate that patients with yellow urticaria had an underlying predisposition to hives that was not secondary to deposits of bilirubin in the skin. The yellowness of the wheals was attributed to underlying hyperbilirubinemia with skin deposits. In this case, the patient denied previous urticarial history, and, at physical inspection, she presented with slight jaundice that was considerably lighter than the urticarial lesions. We hypothesized that increased vasopermeability and subsequent plasma extravasation led to increased skin deposits, resulting in distinctly yellow lesions that appeared dissimilar to the surrounding skin. Additionally, because blood flow is diminished secondary to dermal edema, a fainter red hue was produced, as was a yellowing because of the bilirubin.

Bile salts can stimulate mast cells to release histamine. Thus, increased bile salts can stimulate wheals in patients with previous urticaria. Because our patient had no urticaria antecedent, it is possible that the elevated bilirubin level contributed to the urticaria, as there was no other identifiable cause. In addition, the patient did not experience a recurrence after the cholecystectomy. However, other possible mechanisms of urticaria development in our case may be related to the pathogenesis of pancreatitis.

Key factors implicated in the onset of biliary pancreatitis include ampullary obstruction by gallstones and activation of trypsinogen by enteric peptidases to trypsin. Trypsin is able to activate proteinase-activated receptors expressed in primary sensory neurons of the pancreas and mast cells. Protease-activated receptor 2 sensitizes transient receptor potential vanilloid 1. Primary sensory neurons in the pancreas express transient receptor potential vanilloid 1 channels, activation of which induces pancreatic inflammation. In addition, transient receptor potential proteins have been implicated in the regulation of mast cell activation,
promoting inflammatory mediator release. Thus, an increase in trypsin concentration during pancreatitis might have contributed to the development of urticaria in this patient.

On the other hand, however, the mechanisms that triggered urticaria and angioedema may have been involved in the pathogenesis of pancreatitis in this case. The literature described this association in a woman in her sixth postpartum week; she experienced urticaria and 24 hours later manifested an episode of acute pancreatitis. Moreover, skin swellings like hereditary angioedema are able to induce acute pancreatitis secondary to C1 inhibitor deficiency leading to unregulated generation of bradykinin. This increases vascular permeability into pancreatic tissue.

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