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Title: Yellow urticaria: report of two cases and review of the literature

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To the Editor:

Urticaria is a common skin disease characterized by transient appearance of itchy smooth and slightly elevated erythematous papules or plaques (wheals). It results from transient extravasation of plasma into the dermis that leads to dermal edema. By definition, individual lesions resolve without scarring in less than 24 hours. The diagnosis is based on detailed patient history and physical examination and skin biopsy is rarely required to confirm the diagnosis. Yellow urticaria is an unusual variant of urticaria, which has been rarely reported since the initial description by Clarke in 1969¹. We came across two patients with yellow urticaria in our department, which prompted us to report this interesting clinical situation.

Case 1. A 62-year-old man with hemochromatosis-related liver cirrhosis was admitted because of hepatic encephalopathy during an episode of urinary tract infection. He began treatment with amoxicillin/clavulanate and one week later developed itching migratory papulo-edematous skin lesions affecting his limbs. On examination, several erythematous, raised bordered polycyclic plaques that exhibited an inner area of deep-yellow dyspigmentation were observed (**Fig. 1a**). The rest of the skin did not show abnormalities. There was conjunctival jaundice; bilirubin levels in blood were elevated: total bilirubin 7.4 mg/dl (N 0.2-1.2mg/dl), direct bilirubin 2.4mg/dl (N 0.1-0.6mg/dl), indirect bilirubin 5.0mg/dl (N 0.1-0.02mg/dl) and liver enzymes showed mild liver dysfunction (GOT 101U/L, GPT 119U/L, GGT 31U/L). A skin biopsy confirmed the diagnosis of urticaria. Amoxicillin/clavulanate was withdrawn and the patient was administered dexchlorpheniramine maleate 2mg/12h therapy. The rash completely disappeared over the next 10 days.

Case 2. A 58-year-old man with alcohol-related liver cirrhosis was remitted to our outpatient department because of the sudden development of itchy edematous yellow papules and plaques on his arms and abdomen three weeks previously. The patient reported that individual lesions were evanescent and healed without scarring. On examination, there were several 2-3cm diameter yellowish edematous plaques on his trunk and upper extremities (**Fig. 1b**). Conjunctival icterus was detected by examining the sclerae. Blood tests revealed hyperbilirubinemia (total bilirubin 7.5mg/dl, direct 2.8mg/dl, indirect 4.7mg/dl) and hypertransaminasemia (GOT 100U/L, GPT 56 U/L, GGT 157 U/L). Patient was receiving propranolol 40mg/24h, norfloxacin 400mg/24h, furosemide 40mg/24h, spironolactone 100mg/24h, and had started omeprazole 20mg/24h one month previously. He was diagnosed with yellow acute urticaria induced by drugs, and omeprazole was discontinued. He was given ebastine 10mg/8h and topical methylprednisolone aceponate and the rash completely disappeared in two days without recurrences.

Yellow urticaria is an unusual variant of urticaria with only seven cases reported in the literature¹⁻⁷. All of them are associated with high bilirubin levels in blood due to diverse liver diseases (**Table 1**). In the setting of liver disease, the hepatic capacity to conjugate bilirubin

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can be decreased, and, as a result, the excess of bilirubin can deposit in tissues, particularly the skin (jaundice). Yellow hives appear to be a result of the accumulation of the excess of bilirubin in the surrounding dermis. The increased permeability of the blood vessels in urticaria and the exudation of plasma loaded with great amounts of bilirubin into the coalescent wheals cause the unusual color of the patient's lesions. This hypothesis has been recently confirmed by Narváez-Moreno et al, who described the presence of olive-green crystals on the skin biopsy using Hall's staining for bilirubin⁵.

In the same way as occurs in common acute urticaria, lesions resolve in less than 24 hours without scarring. However, because of bilirubin's affinity for elastin, the jaundice may persist for several days, despite the disappearance of the hives². The diagnosis is made by clinical examination and treatment does not differ from that of common acute urticaria.

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Figure 1a. Erythematous, raised bordered polycyclic plaques that exhibit an inner area of deep-yellow dyspigmentation.

Figure 1b. Yellowish edematous hives on the arm of the patient.

Table 1. All the cases reported in the literature are associated with high bilirubin levels in blood due to diverse liver diseases.

Title	Authors	Year of publication	Nº of cases	Age	Sex	Skin biopsy	Total bilirubin (mg/dl)	Direct bilirubin (mg/dl)	Indirect bilirubin (mg/dl)	Associated disease	Treatment
<i>Cold urticaria</i>	<i>Clarke GH.</i>	1969	1	Puberty	F	no	.	.	.	Infective hepatitis	Steroid therapy
<i>"Yellow urticaria secondary to hyperbilirubinemia in a patient with end-stage liver disease"</i>	<i>Patel S.B et al.</i>	2002	1	48	M	yes	5.4	1.5	3.9	Alcohol-induced end-stage liver disease	Fexofenadine 60 mg twice daily
<i>"Yellow urticaria associated with hepatitis type-C liver cirrhosis"</i>	<i>Imanishi H et al.</i>	2006	1	58	M	yes	4.1	3.1	1.0	VHC induced liver cirrhosis	Chlorpheniramine maleate
<i>"Urticaria amarilla por acumulación de bilirrubina" (article in spanish)</i>	<i>Cabanillas González M et al</i>	2008	1	68	M	yes	2.8	1.8	1.0	Liver cirrhosis	Hidroxicine 25 mg three times daily
<i>"Yellow urticaria"</i>	<i>Narváez-Moreno B et al</i>	2012	1	43	F	yes	8.4	7.5	0.9	Metastatic disease to the liver (breast)	Antihistamines (not specified)
<i>"Yellow urticaria in a patient with hepatic cirrhosis"</i>	<i>Chiba T et al.</i>	2014	1	56	M	no	8.1	5.2	2.9	VHC and alcohol-related liver cirrhosis	Not specified
<i>"Un cas d'urticaire jaune" (article in french)</i>	<i>Benamara-Lévy M et al.</i>	2015	1	65	F	no	4.8	2.7	2.2	Acute liver failure	Dexchlorpheniramine maleate 10mg once
<i>Present report</i>	<i>Combalia et al.</i>	2016	2	62	M	yes	7.4	2.4	5.0	Hemochromatosis-related liver cirrhosis	Dexchlorpheniramine maleate 2mg/12h
				58	M	no	7.5	2.8	4.7	Alcohol-related liver cirrhosis	Ebastine 10mg/8h and topical methylprednisolone aceponate

