Yellow Urticaria Secondary to Hyperbilirubinemia in a Patient With End-Stage Liver Disease

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GOAL

To describe a case of yellow urticaria in a patient with end-stage liver disease

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Review drugs that may induce skin discoloration.
2. List which metals, foods, and metabolic abnormalities are associated with changes in skin color.
3. Discuss the mechanism involved in the presentation of yellow urticaria secondary to elevated bilirubin.

CME Test on page 48.

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Acute urticaria is characterized by pruritic, erythematous, edematous plaques. We report the case of a 48-year-old man with acute urticaria, whose lesions appeared yellow secondary to an elevated bilirubin level.

Acute urticaria is a common condition that may be precipitated by a variety of stimuli, including medications, infectious agents, and physical factors.[1] The lesions are characterized by pruritic, evanescent, well-defined, edematous plaques that are pink to erythematous. We report the case of a patient with an unusual clinical manifestation of urticaria presenting as yellow plaques. The atypical color of our patient's lesions was attributed to an elevated bilirubin level secondary to alcohol-induced end-stage liver disease.

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Case Report

A 48-year-old white man with alcohol-induced end-stage liver disease presented with a 5-day history of an intensely pruritic, yellow eruption involving the trunk and thighs. Lesions appeared, enlarged, and resolved within several hours. There was no prior history of similar eruption, quinacrine use, or excessive ingestion of carotene-containing foods or supplements. His medical history included mild chronic renal insufficiency, anemia, ascites,

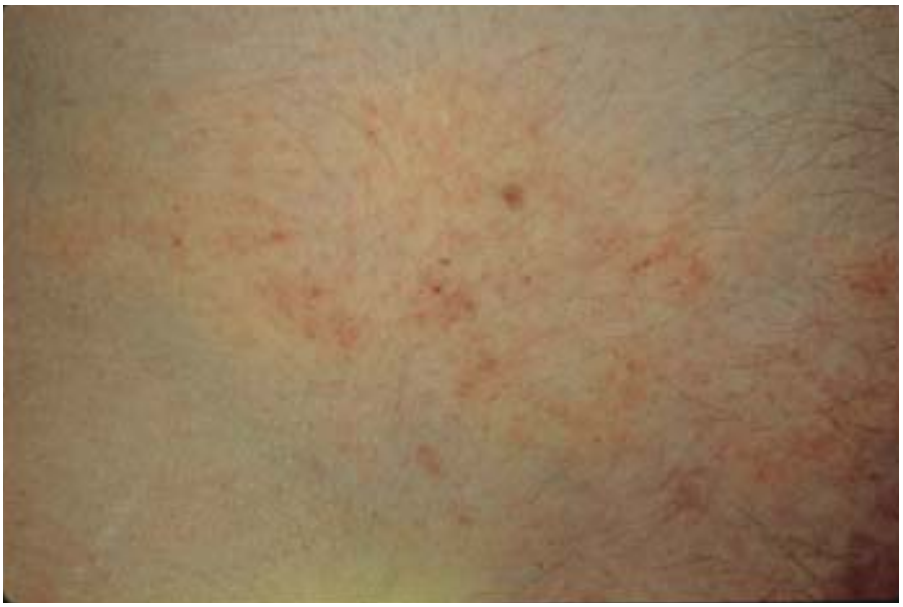

Figure 1. Yellow, smooth, edematous plaques.

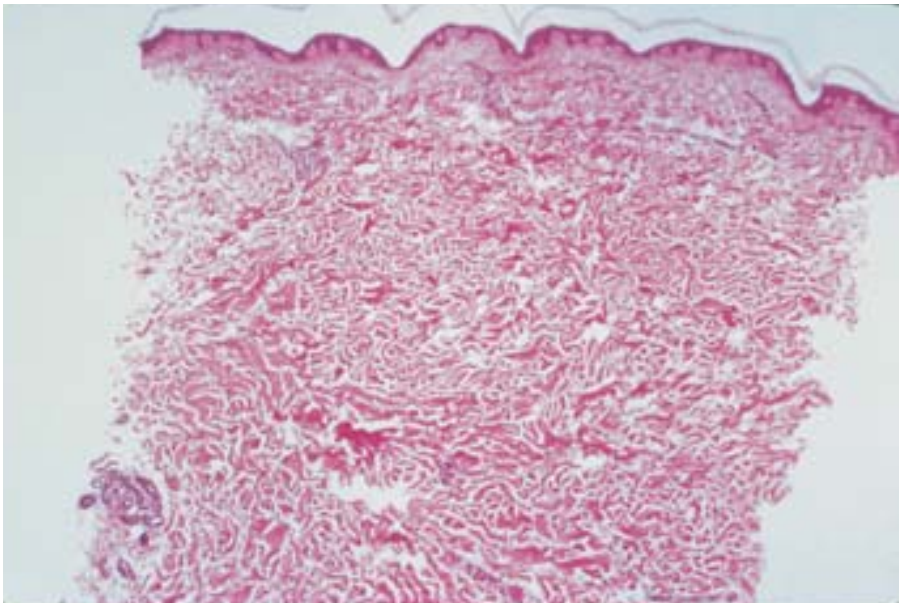

Figure 2. A mild superficial perivascular infiltrate and dermal edema (H&E, original magnification ×40).

and esophageal varices. The patient's medications included pantoprazole, fluoxetine, lactulose, and zinc sulfate. Results of a physical examination revealed multiple 2- to 4-cm well-defined, yellow, smooth, edematous, and variably annular plaques scattered on the trunk and thighs (Figure 1). Results of histopathologic examination revealed mild dermal edema and a mild superficial perivascular infiltrate consisting of lymphocytes, eosinophils, and neutrophils characteristic of urticaria (Figure 2). Special stains failed to reveal bilirubin. Laboratory studies yielded the following: total bilirubin, 5.4 mg/dL (reference range, 0.2–1.0 mg/dL); direct bilirubin, 1.5 mg/dL (reference range, 0.0–0.3 mg/dL); and aspartate aminotransferase, 47 U/L (reference range, 11–35 U/L). A complete blood count, renal profile, and alanine aminotransferase levels were unremarkable. Treatment with fexofenadine 60 mg twice daily was initiated, with prompt resolution of the eruption and symptoms within 24 hours. Seven days after initial presentation, physical examination results revealed only ill-defined, faintly yellow patches in locations where the lesions had resolved.

Comment

High levels of bilirubin caused the unusual color of our patient's lesions. Changes in skin color may

Causes of Skin Hyperpigmentation

Category	Etiology	Skin Color	Pigment
Drugs	Chlorpromazine	Slate gray	Melanin-drug complex[2,3]
	Amiodarone	Slate blue	Melanin and lipofuscin granules[4,5]
	Clofazimine	Pink to pink-brown	Lipofuscin and ceroid deposits[6]
	Quinacrine	Yellow	Drug[7,8]
	Minocycline	Blue-gray	Iron-drug metabolite complex[9]
		Muddy brown	Melanin[10]
	Hydroquinone	Blue-black	Drug or drug metabolites[11,12]
Metals	Argyria	Slate blue	Silver-melanin complexes[13]
	Chrysiasis	Slate blue	Gold[14]
	Mercury	Slate gray	Mercury-melanin granules[15,16]
Foods/ Supplements	Carotene	Yellow	Carotene[17]
	Lycopene	Deep yellow to orange	Lycopene[17]
Metabolic	Generalized melanosis (metastatic melanoma)	Dark brown to gray-black	Melanin[18]
	Alkaptonuria	Blue-black	Homogentisic acid[19]
	Jaundice	Yellow	Bilirubin

result from several etiologies (Table). Certain drugs may induce skin discoloration. For example, chlorpromazine produces slate-gray skin because of melanin-chlorpromazine complexes,[2,3] while amiodarone produces slate-blue skin because of melanin and lipofuscin granules.[4,5] Clofazimine causes a characteristic pink to pink-brown hue from deposits of lipofuscin and ceroid.[6] Quinacrine deposition induces yellow discoloration and concentrates in the epidermis at levels 100 to 200 times the plasma concentration.[7,8] Deposition of iron-drug metabolites with minocycline use causes a blue-gray pigmentation typically confined to the extremities.[9] Another form of minocycline pigmentation involves deposition of melanin in sun-exposed areas, resulting in a muddy brown discoloration.[10] Prolonged use of hydroquinone-containing preparations leads to exogenous ochronosis. Localized blue-black skin results from precipitation of drug or drug metabolites on degenerating collagen.[11,12]

Deposition of metals may lead to diffuse or localized discoloration. The diffuse slate-blue skin of argyria and chrysiasis results from the deposition of silver-melanin complexes and gold, respectively.[13,14] Long-term application of mercury-containing creams may result in localized slate-gray skin secondary to mercury-melanin granules.[15,16]

Several foods and supplements can alter skin color. The typical yellow discoloration of carotenemia results from excessive intake of carotene-containing foods, such as carrots, squash, spinach, mangoes, and red palm oil.[17] Lycopene, an isomer of carotene, tints the skin deep yellow to orange and is found in high concentration in rose hips, tomatoes, and bittersweet berries.[17] Carotene and lycopene exhibit special affinities for the epidermis.[17]

Metabolic abnormalities also may contribute to changes in skin color. Generalized melanosis and melanuria have been reported in association with excessive pigment deposition in metastatic melanoma. Patients exhibit a diffuse dark brown to gray-black discoloration.[18] Alkaptonuria results from deposition of homogentisic acid secondary to homogentisic acid oxidase deficiency and manifests as a generalized blue-black color and black urine.[19] Finally, jaundice, in the setting of hepatic disease, results from deposition of excess bilirubin.

Conclusion

End-stage liver disease is characterized by a decreased hepatic capacity to conjugate bilirubin, the breakdown product of heme. This impairs the normal process of excretion of bilirubin via the stool. As a result, the excess bilirubin deposits in tissues and associates with elastin, thereby yellowing the skin. Because of bilirubin's affinity for elastin, the jaundice may persist for several days, despite a normalized bilirubin.[20] Similar mechanisms were likely operative in our patient, with transport and deposition of bilirubin being enhanced because of the vasodilation and increased vascular permeability that is characteristic of urticaria. Elevated bilirubin and persistence of yellow skin despite resolution of the urticaria support deposition of bilirubin as a mechanism for the atypical color. Failure of special stains to reveal bilirubin possibly was secondary to inadequate tissue concentration. To our knowledge, this is the first reported case of yellow urticaria secondary to elevated bilirubin.

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