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

Samir B. Patel, MD; Diya F. Mutasim, MD

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.

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. 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.

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,
Urticaria Secondary to Hyperbilirubinemia

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

Figure 1. Yellow, smooth, edematous plaques.

Figure 2. A mild superficial perivascular infiltrate and dermal edema (H&E, original magnification ×40).
result from several etiologies (Table). Certain drugs may induce skin discoloration. For example, chlorpromazine produces slate-gray skin because of melanin-chlorpromazine complexes, while amiodarone produces slate-blue skin because of melanin and lipofuscin granules. Clofazimine causes a characteristic pink to pink-brown hue from deposits of lipofuscin and ceroid. Quinacrine deposition induces yellow discoloration and concentrates in the epidermis at levels 100 to 200 times the plasma concentration. Deposition of iron-drug metabolites with minocycline use causes a blue-gray pigmentation typically confined to the extremities. Another form of minocycline pigmentation involves deposition of melanin in sun-exposed areas, resulting in a muddy brown discoloration. 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.

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. Long-term application of mercury-containing creams may result in localized slate-gray skin secondary to mercury-melanin granules.

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. 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. Carotene and lycopene exhibit special affinities for the epidermis.

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. Alkaptonuria results from deposition of homogentisic acid secondary to homogentisic acid oxidase deficiency and manifests as a generalized blue-black color and black urine. Finally, jaundice, in the setting of hepatic disease, results from deposition of excess bilirubin.

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

REFERENCES

DISCLAIMER
The opinions expressed herein are those of the authors and do not necessarily represent the views of the sponsor or its publisher. Please review complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

FACULTY DISCLOSURE
The Faculty Disclosure Policy of the College of Medicine requires that faculty participating in a CME activity disclose to the audience any relationship with a pharmaceutical or equipment company that might pose a potential, apparent, or real conflict of interest with regard to their contribution to the program. It is required by the Accreditation Council for Continuing Medical Education that each author of a CME article disclose to the participants any discussion of an unlabeled use of a commercial product or device or an investigational use not yet approved by the Food and Drug Administration. Drs. Patel and Mutasim report no conflict of interest. Dr. Fisher reports no conflict of interest.