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The Clinical Picture

Rash from hepatitis C treatment



FIGURE 1. Desquamation began on day 7 after the rash first appeared.



FIGURE 2. She developed vesiculobullae on her lower extremities, including the left medial thigh. No vesiculobullae were noted on the upper extremities.

A 54-YEAR-OLD WOMAN with hepatitis C virus infection presents with generalized rash, pruritus, and fever over the past week. The rash appeared on her left arm after she received her fifth weekly injection of pegylated interferon alfa 2b, in combination with daily oral ribavirin (Copegus, Rebetol). Over the course of 3 days, it spread to her face and the rest of her body.

She has no other known medical conditions, has no history of eczema or atopy, and is not taking any other drugs.

A diffuse erythematous macular rash now covers most of her body, with areas of desquamation (FIGURE 1). The rash spares her mucous membranes (oral cavity, genitalia, eyes). In addition, there are scattered vesiculobullae (FIGURES 2 AND 3) and nonblanching purpuric le-

sions on the front of her legs.

Her total white blood cell count is newly elevated at $18.5 \times 10^9/L$ (reference range 4.0–11.0), and the differential count is “shifted to the left,” with 83% neutrophils (reference range 50%–75%) but no eosinophils. The C-reactive protein level and erythrocyte sedimentation rate are elevated: the C-reactive protein is 1.1 mg/dL (reference range 0.0–1.0), and the sedimentation rate is 70 mm/hour (reference range for women 0–15). All other laboratory results, including aminotransferase and alkaline phosphatase levels, electrolyte levels, and coagulation studies, are normal. Additional tests for immunoglobulin A (IgA), IgM, IgG, complements C3 and C4, rheumatoid factor, antinuclear antibodies, and cryoglobulins are normal. Chest radiography is normal.

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Q: What is the most likely clinical diagnosis?

- ☐ Stevens-Johnson syndrome
- ☐ Mixed cryoglobulinemia
- ☐ Acute eczematous drug eruption
- ☐ Lichen planus

A: **Acute eczematous drug eruption** is the most likely diagnosis.

The clinical presentation and laboratory findings suggest (the latter by exclusion) that our patient had an allergic drug reaction to the interferon or to the ribavirin therapy, or to both. Although this combination is a standard treatment for chronic hepatitis C, some patients experience adverse reactions that lead to its discontinuation. Local injection-site reactions are the most prevalent, affecting up to 12% of patients, whereas eczematous dermatoses manifest less commonly, occurring in up to 5% of patients.¹

While awaiting the results of skin biopsy, a careful evaluation of the clinical features of the physical examination and an appropriate laboratory evaluation can rule out other important conditions in the differential diagnosis.

The absence of mucous membrane involvement steers the diagnosis away from **Stevens-Johnson syndrome**, a life-threatening hypersensitivity condition often triggered by drugs, malignant tumors, and viral infections, which may also affect internal organs. In this condition, skin biopsy specimens would be distinguished by subepidermal bullae and epidermal cell necrosis—neither of which was seen in our patient.

Mixed cryoglobulinemia should always be considered in hepatitis C patients because of the strong association between this infection and the development of cryoglobulins. The rash usually is purpuric, but it may be pleomorphic.^{2,3} This vasculitis often manifests with excess cryoglobulins, elevated rheumatoid factor, and low titers of complement in the blood due to consumption by immune complexes. Tissue biopsy would usually show typical vascular changes if performed on fresh lesions.^{4,5} The normal levels of these components in our patient coupled with the appearance of her skin makes cryoglobulinemia a less likely cause.

Furthermore, hepatitis C infection, whether or not treated with interferon and ribavirin,



FIGURE 3. Punch biopsy samples were taken from her left leg. The black patch on the right leg was from a prior skin graft, unrelated to the current presentation.

Treatment:
eliminate the
offending drug
and alleviate
the symptoms

can cause an onset or recurrence of other dermatologic conditions, notably lichen planus, psoriasis, vitiligo, and systemic lupus erythematosus.¹⁻⁴

In **lichen planus**, the rash is often described as flat-topped, pruritic, and violaceous. It may involve the extremities, the genitalia, and the oral cavity.^{4,5} The difference in quality of the rash compared with the rash in our patient makes lichen planus less likely.

Exclusion of the other conditions in the differential diagnosis, in addition to results from a definitive punch biopsy, solidified the diagnosis in our patient. Skin biopsy of the patient's lower-extremity lesions revealed spongiotic dermatitis with lymphocytes, neutrophils, and few eosinophils—a finding characteristic of an acute eczematous drug eruption. Improvement of her rash after discontinuation of interferon and ribavirin further supported this conclusion, although it was unclear whether one or both agents were responsible.

OUTCOME

Management of acute eczematous drug eruption entails stopping the offending drug and alleviating the symptoms. Our patient's non-life-threatening rash improved dramatically with cessation of interferon and ribavirin. She received a single dose of a systemic corticosteroid initially, out of concern for a severe medication-induced reaction (ie, Stevens-Johnson syndrome), but she was otherwise maintained with diphenhydramine (Benadryl) and a multivitamin ointment for the rash throughout her 9-day hospital stay. Her pruritus was well controlled with hydroxyzine (Atarax, Vistaril). At discharge, she was re-

ferred back to her hepatologist for further treatment of her hepatitis C, possibly with interferon and ribavirin again.

TAKE-HOME MESSAGE

Adverse reactions to interferon and ribavirin treatment in hepatitis C patients can manifest dermatologically, and the combination therapy should be discontinued to prevent further insult. A broad variety of conditions in the differential diagnosis should be taken into account, but dermatologic conditions that occur or recur specifically in hepatitis C patients should be considered as well. ■

REFERENCES

1. Dereure O, Raison-Peyron N, Larrey D, Blanc F, Guilhou JJ. Diffuse inflammatory lesions in patients treated with interferon alfa and ribavirin for hepatitis C: a series of 20 patients. *Br J Dermatol* 2002; 147:1142–1146.
2. Ferri C, Zignego AL, Pileri SA. Cryoglobulins. *J Clin Pathol* 2002; 55:4–13.
3. Faurie P, Broussolle C, Zoulim F, Trepo C, Sève P. Sarcoidosis and hepatitis C: clinical description of 11 cases. *Eur J Gastroenterol Hepatol* 2010; 22:967–972.
4. Shengyuan L, Songpo Y, Wen W, Wenjing T, Haitao Z, Binyou W. Hepatitis C virus and lichen planus: a reciprocal association determined by a meta-analysis. *Arch Dermatol* 2009; 145:1040–1047.
5. Aamir S, Ullah Z, Iqbal Z, Khan AA, Yaqub F, Malik K. Cutaneous manifestations of interferon alfa and ribavirin for hepatitis C. *J Pak Assoc Dermatol* 2008; 18:14–20.

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