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Case Presentation

Severe cutaneous adverse reaction to telaprevir

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Abstract

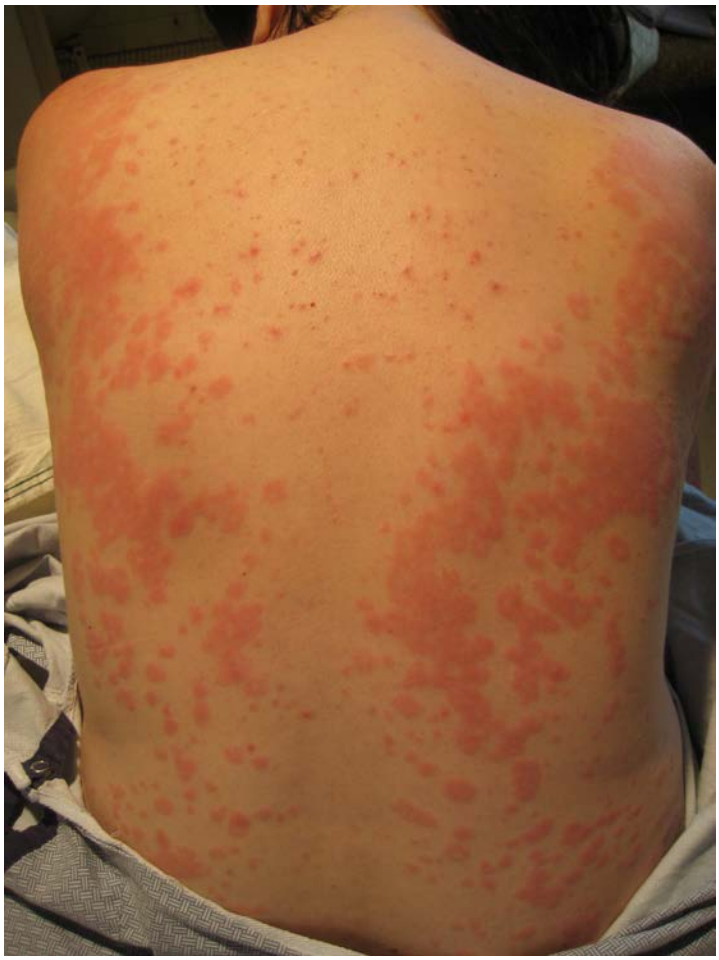
A 50-year-old woman presented with diffuse, intensely pruritic pink-red papules on her trunk and extremities three weeks after starting combination therapy with ribavirin, telaprevir, and interferon. She also had cervical lymphadenopathy, fever, eosinophilia, and transaminitis consistent with a severe drug reaction to telaprevir. She was started on high potency topical steroids under inpatient observation and recovered within two weeks. Severe cutaneous eruptions secondary to telaprevir have resulted in black-box warnings for potentially fatal skin reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN). Because these reactions carry acute mortality rates of 10%, prompt detection and treatment with steroids are important. As such, physicians should be aware of these potentially lethal side effects.

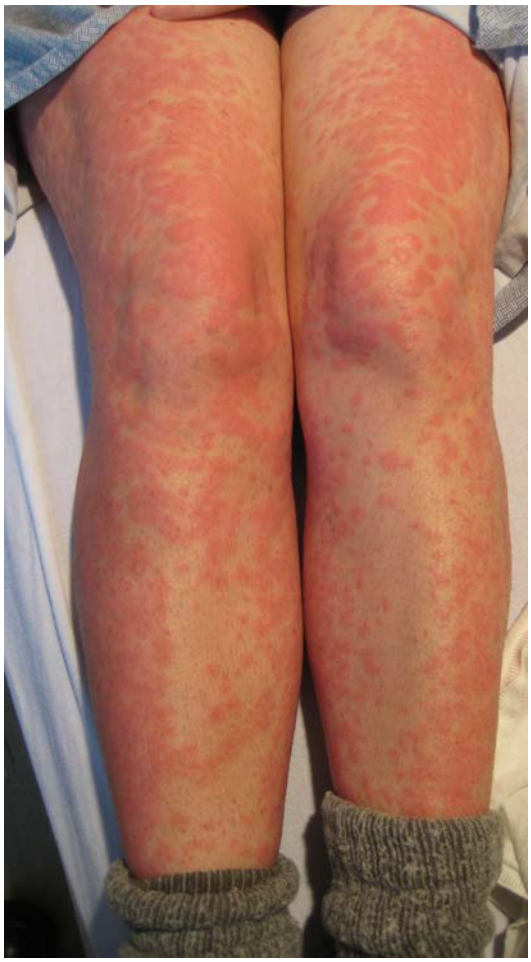
Keywords: telaprevir; drug eruption; DRESS; SJS

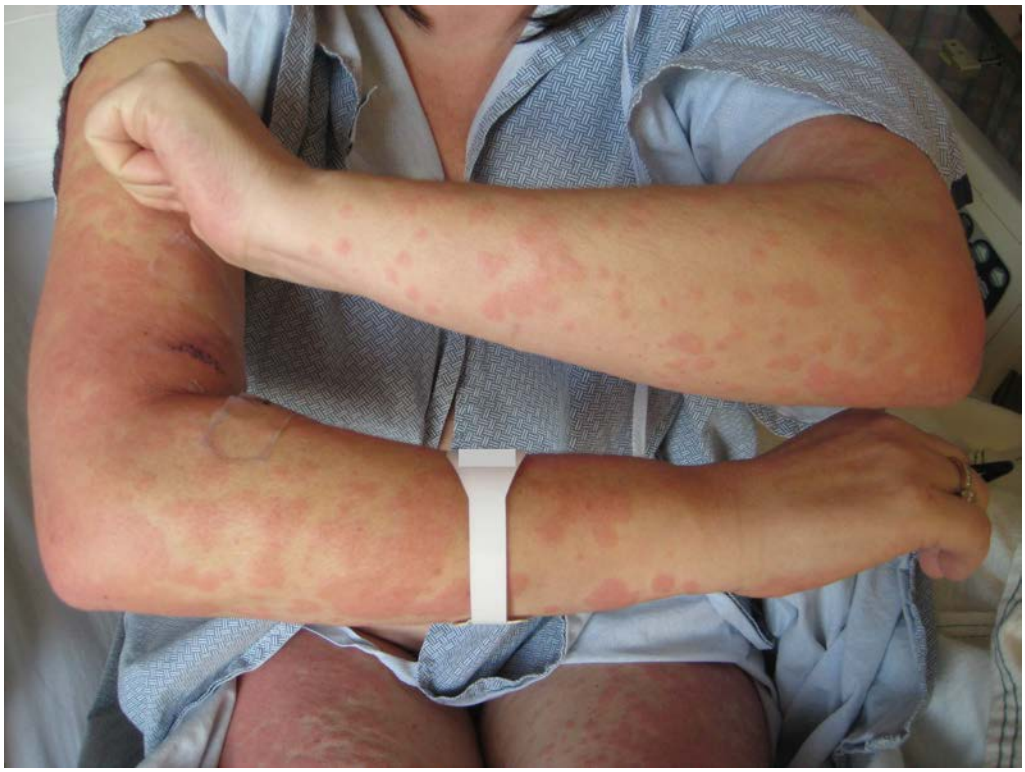
Case synopsis

A 50-year-old woman presented for evaluation of a new skin eruption. The patient had a history of remitting chronic hepatitis C, previously treated with ribavirin and interferon therapy. Three weeks after starting combination therapy with ribavirin, telaprevir, and interferon she abruptly developed several intensely pruritic papules on her buttocks that spread rapidly. Low potency topical steroids and oral hydroxyzine failed to alleviate her symptoms and she presented to the emergency department.

On presentation, she had diffuse pink-to-red papules coalescing into large plaques across her shoulders, arms, back, buttocks, and legs (Figures 1-3). They spared the face, palms, and soles. She also had cervical lymphadenopathy and fevers to 39.3^{o}C. The patient's hemoglobin concentration was decreased at 10.9 g/dL. Her platelet count was decreased at 112 K/uL. Additionally, her eosinophil count was elevated to 8.4%. Her ALT (180 IU/L) and AST (151 IU/L) were elevated to over twice their baseline values (ALT 67 IU/L, AST 61 IU/L).







Figures. Diffuse, well-circumscribed erythematous edematous plaques widely distributed on the back (Figure 1), lower extremities (Figure 2), and upper extremities (Figure 3) representing a severe cutaneous adverse reaction to telaprevir.

The patient was hospitalized and telaprevir, ribavirin, and interferon were discontinued. Skin biopsy was offered to confirm the suspected histopathological findings but the patient declined. The patient was treated empirically using twice daily clobetasol proprionate ointment with occlusion under inpatient observation. Her cutaneous eruption and eosinophilia resolved and her liver function tests returned to baseline over the next two weeks. Her viral load, which had decreased on combination therapy with telaprevir, rebounded to over 5 million IU/ml within months of discontinuation, and her transaminases rose concordantly. She was

subsequently treated successfully with interferon, ribavirin, and boceprevir for 6 months, with her viral load becoming and remaining undetectable. She tolerated the boceprevir-based treatment regimen without any cutaneous adverse reactions.

Discussion

Telaprevir was introduced in 2011 for treatment of chronic hepatitis C [1]. It is a serine-protease inhibitor, used in triple combination therapy with interferon and ribavirin [1,2]. In phase 3 trials of telaprevir plus interferon and ribavirin, 56% of subjects developed adverse cutaneous eruptions compared to 34% of control patients on placebo plus interferon and ribavirin [3]. Our patient had previously been on multiple cycles of interferon and ribavirin alone without any side effects, leading us to suspect that telaprevir was the etiology of her cutaneous and systemic manifestations; however, cutaneous reaction secondary to the combination of all three drugs cannot be excluded. Cutaneous reactions to interferon and ribavirin alone are typically pruritic, dermatitic, or eczematiform, and rarely necessitate treatment discontinuation [3].

In phase 3 trials comparing telaprevir plus interferon and ribavirin to placebo plus interferon and ribavirin, cutaneous events of special interest (ESI), defined as involving >50% of the body, epidermal detachment, or rash requiring medication discontinuation, were also more common in the study population receiving the drug (7.7%) versus controls (0.8%) [3]. 95% of ESIs were clinically identified as eczematous dermatitis, demonstrating epidermal spongiosis and superficial perivascular lymphocytic infiltrate on skin biopsy [3]. This cutaneous response has been termed ‘telaprevir related dermatitis’ and suggested treatments include emollients, topical steroids, or antihistamines for symptom alleviation [3,4].

Although the majority of cutaneous events in phase 3 trials were benign, severe reactions including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS) led to a black box warning [5]. Evidence of increased risk of severe cutaneous reactions was further supported by case series delineating probable or definite cases of DRESS secondary to telaprevir treatment [2].

Because these reactions carry acute mortality rates up to 10%, clinicians should monitor for signs of these reactions [6]. Markers of SJS include painful skin, involved mucous membranes (manifesting as mucosal sloughing as well as dysphagia, dysuria, or photophobia), vesicles, and the blistering of the skin with gentle rubbing or “Nikolsky’s sign” [4,7]. Confluent extensive rash, facial edema, fever, and lymphadenopathy should raise concern for DRESS [3]. Prescribers should monitor for elevations in eosinophil count and liver and renal function tests, commonly associated with DRESS [4]. If suspicion arises for SJS or DRESS, prompt discontinuation of telaprevir and dermatologic consultation is recommended in order to guide therapy.

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