Crusted Scabies Presenting as Erythroderma in a Patient With Iatrogenic Immunosuppression for Treatment of Granulomatosis With Polyangiitis

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PRACTICE **POINTS**

- Crusted scabies is a highly contagious, severe cutaneous ectoparasitic infection that can present atypically in the form of erythroderma.
- Immunomodulatory drugs for the treatment of autoimmune disease can predispose patients to infection, including ectoparasitic infection.
- Dermatologists should be familiar with the full scope of the clinical presentations of scabies and should especially consider this condition in the differential diagnosis of patients who present in an immunosuppressed state.

The diagnosis of scabies can be difficult when the infection presents as erythroderma. Crusted scabies is a severe form of scabies caused by cutaneous ectoparasitic infection by the mite *Sarcoptes scabiei* var *hominis.* Crusted scabies most commonly occurs in patients with underlying immunosuppression from acquired infection or subsequent to solid organ or bone marrow transplantation. We present a rare case of a patient with granulomatosis with polyangiitis (GPA) who developed azathioprine-induced myelosuppression and subsequent erythrodermic crusted scabies. It is critical to maintain a broad differential when patients present with erythroderma, especially in the setting of medication-induced immunosuppression for the treatment of autoimmune disease.

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Scabies is caused by cutaneous ectoparasitic infection by the mite *Sarcoptes scabiei* var *hominis.* The infection is highly contagious via direct skin-to-skin contact or indirectly through infested bedding, clothing or fomites.[1,2] Scabies occurs at all ages, in all ethnic groups, and at all socioeconomic levels.[1] Analysis by the Global Burden of Disease estimates that 200 million individuals have been infected with scabies worldwide. The World Health Organization has declared scabies a neglected tropical disease.[3]

Crusted scabies is a severe and rare form of scabies, with hyperinfestation of thousands to millions of mites, and more commonly is associated with immunosuppressed states, including HIV and hematologic malignancies.[1,2,4] Crusted scabies has a high mortality rate due to sepsis when left untreated.[3,5]

Occasionally, iatrogenic immunosuppression contributes to the development of crusted scabies.[1,2] Iatrogenic immunosuppression leading to crusted scabies most commonly occurs secondary to immunosuppression after bone marrow or solid organ transplantation.[6] Less often, crusted scabies is caused by iatrogenic immunosuppression from other clinical scenarios.[1,2]

We describe a patient with iatrogenic immunosuppression due to azathioprine-induced myelosuppression for the treatment of granulomatosis with polyangiitis (GPA) who developed crusted scabies that clinically presented as erythroderma. Crusted scabies should be

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included in the differential diagnosis of erythroderma, especially in the setting of iatrogenic immunosuppression, for timely and appropriate management.

Case Report

An 84-year-old man presented with worsening pruritus, erythema, and thick yellow scale that progressed to erythroderma over the last 2 weeks. He was diagnosed with GPA 6 months prior to presentation and was treated with azathioprine 150 mg/d, prednisone 10 mg/d, and sulfamethoxazole 800 mg plus trimethoprim 160 mg twice weekly for prophylaxis against *Pneumocystis jirovecii* pneumonia.

Three weeks prior to presentation, the patient was hospitalized for pancytopenia attributed to azathioprine-induced myelosuppression (hemoglobin, 6.1 g/dL [reference range, 13.5–18.0 g/dL]; hematocrit, 17.5% [reference range, 42%–52%]; white blood cell count, 1.66×10^3/μL [reference range, $4.0–10.5\times10^3$/μL]; platelet count, 146×10^3/μL [reference range, $150–450\times10^3$/μL]; absolute neutrophil count, 1.29×10^3/μL [reference range, $1.4–6.5\times10^3$/μL]). He was transferred to a skilled nursing facility after discharge and referred to dermatology for evaluation of the worsening pruritic rash.

At the current presentation, the patient denied close contact with anyone who had a similar rash at home or at the skilled nursing facility. Physical examination revealed diffuse erythroderma with yellow scale on the scalp, trunk, arms, and legs (Figure 1). The palms showed scattered 2- to 3-mm pustules. The mucosal surfaces did not have lesions. A punch biopsy of a pustule from the right arm revealed focal spongiosis, parakeratosis, and acanthosis, as well as a perivascular and interstitial mixed inflammatory infiltrate with lymphocytes and eosinophils. Organisms morphologically compatible with scabies were found in the stratum corneum (Figure 2). Another punch biopsy of a pustule from the right arm was performed for direct immunofluorescence (DIF) and was negative for immunoglobulin deposition. Mineral oil preparation from pustules on the palm was positive for mites.

The patient was treated with permethrin cream 5% and oral ivermectin 200 μg/kg on day 1 and day 10. The prednisone dosage was increased from 10 mg/d to 50 mg/d and tapered over 2 weeks to treat the symptomatic rash and GPA. He remains on maintenance rituximab for GPA, without recurrence of scabies.

Comment

Pathogenesis—As an obligate parasite, *S scabiei* spends its entire life cycle within the host. Impregnated female mites burrow into the epidermis after mating and lay eggs daily for 1 to 2 months. Eggs hatch 2 or 3 days later. Larvae then migrate to the skin surface; burrow into the stratum corneum, where they mature into adults; and then mate on the skin surface.[1,4]

Clinical Presentation and Sequelae—Typically, scabies presents 2 to 6 weeks after initial exposure with generalized and intense itching and inflammatory pruritic papules on the finger webs, wrists, elbows, axillae, buttocks, umbilicus, genitalia, and areolae.[1] Burrows are specific for scabies but may not always be present. Often, there are nonspecific secondary lesions, including excoriations, dermatitis, and impetiginization.

Complications of scabies can be severe, with initial colonization and infection of the skin resulting in impetigo and cellulitis. Systematic sequelae from local skin infection include post-streptococcal glomerulonephritis, rheumatic fever, and sepsis. Mortality from sepsis in scabies can be high.[3,5]

Classic Crusted Scabies and Other Variants—Crusted scabies presents with psoriasiform hyperkeratotic plaques involving the hands and feet with potential nail involvement that can become more generalized.[1] Alterations in $CD4^+$ T-cell function have been implicated in the

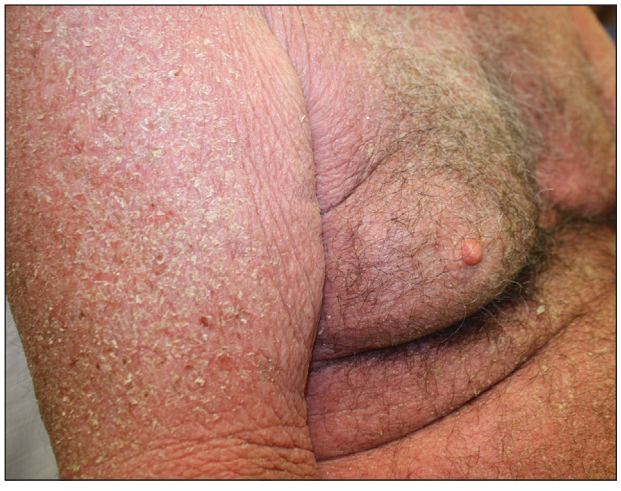

FIGURE 1. Diffuse erythema and thick yellow scale on the chest, abdomen, and arms.

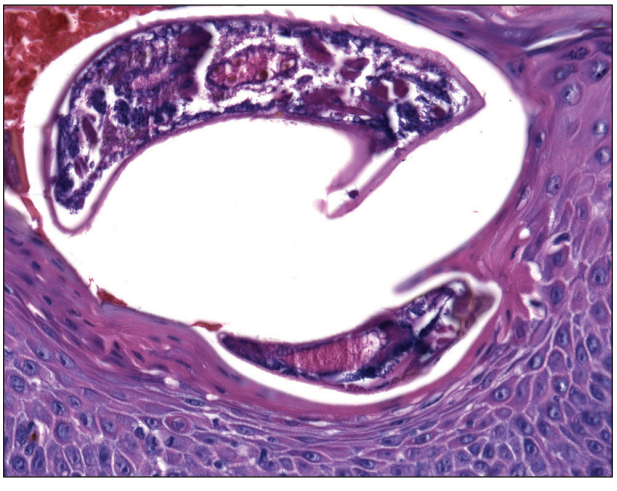

FIGURE 2. Organisms morphologically compatible with scabies were found in the stratum corneum (H&E, original magnification ×400).

development of crusted scabies, in which an excessive helper T cell (T_H2) response is elicited against the ectoparasite, which may help explain the intense pruritus of scabies.[6] Occasionally, iatrogenic immunosuppression contributes to development of crusted scabies,[1] as was the case with our patient. However, it is rare for crusted scabies to present with erythroderma.[7]

Other atypical presentations of scabies include a seborrheic dermatitis–like presentation in infants, nodular lesions in the groin and axillae in more chronic scabies, and vesicles or bullous lesions.[1]

Diagnosis—Identification of mites, eggs, or feces is necessary for definitive diagnosis of scabies.[8] These materials can be obtained through skin scrapings with mineral oil and observed under light microscopy or direct dermoscopy. Multiple scrapings on many lesions should be performed because failure to identify mites can be common and does not rule out scabies. Dermoscopic examination of active lesions under low power also can be helpful, given that identification of dark brown triangular structures can correspond to visualization of the pigmented anterior section of the mite.[9-11] A skin biopsy can help identify mites, but histopathology often shows a nonspecific hypersensitivity reaction.[12] Therefore, empiric treatment often is necessary.

Differential Diagnosis—The differential diagnosis of erythroderma is broad and includes a drug eruption; Sézary syndrome; and pre-existing skin diseases, including psoriasis, atopic dermatitis, pityriasis rubra pilaris, pemphigus foliaceus, and bullous pemphigoid. Histopathology is critical to differentiate these diagnoses. Bullous pemphigoid and pemphigus foliaceus are immunobullous diseases that typically are positive for immunoglobulin deposition on DIF. In rare cases, scabies also can present with bullae and positive DIF test results.[13]

Treatment—First-line treatment of crusted scabies in the United States is permethrin cream 5%, followed by oral ivermectin 200 µg/kg.[4,5,14,15] Other scabicides include topicals such as benzyl benzoate 10% to 25%; precipitated sulfur 2% to 10%; crotamiton 10%; malathion 0.5%; and lindane 1%.[5] The association of neurotoxicity with lindane has considerably reduced the drug's use.[1]

During treatment of scabies, it is important to isolate patients to mitigate the possibility of spread.[4] Pruritus can persist for a few weeks after completion of therapy.[5] Patients should be closely monitored to ensure that this symptom is secondary to skin inflammation and not incomplete treatment.

Treatment of crusted scabies may require repeated treatments to decrease the notable mite burden as well as the associated crusting and scale. Adding a keratolytic such as 5% to 10% salicylic acid in petrolatum to the treatment regimen may be useful for breaking up thick scale.[5]

Immunosuppression—With numerous immunomodulatory drugs for treating autoimmunity comes an increased risk for iatrogenic immunosuppression that may contribute to the development of crusted scabies.[16] In a number of autoimmune diseases such as rheumatoid arthritis,[17-19] psoriasis,[20,21] pemphigus vulgaris,[22] systemic lupus erythematosus,[23] systemic sclerosis,[22,24] bullous pemphigoid,[25,26] and dermatomyositis,[27] patients have developed crusted scabies secondary to treatment-related immunosuppression. These immunosuppressive therapies include systemic steroids,[22-24,26-31] methotrexate,[23] infliximab,[18] adalimumab,[21] toclizumab,[19] and etanercept.[20] In a case of drug-induced Stevens-Johnson syndrome, the patient developed crusted scabies during long-term use of oral steroids.[22]

Patients with a malignancy who are being treated with chemotherapy also can develop crusted scabies.[28] Crusted scabies has even been associated with long-term topical steroid[32-34] and topical calcineurin inhibitor use.[16]

Iatrogenic immunosuppression in our patient resulted from treatment of GPA with azathioprine, an immunosuppressive drug that acts as an antagonist of the breakdown of purines, leading to inhibition of DNA, RNA, and protein synthesis.[35] On occasion, azathioprine can induce immunosuppression in the form of myelosuppression and resulting pancytopenia, as was the case with our patient.

Conclusion

Although scabies is designated as a neglected tropical disease by the World Health Organization, it still causes a notable burden worldwide, regardless of the economics. Our case highlights an unusual presentation of scabies as erythroderma in the setting of iatrogenic immunosuppression from azathioprine use. Dermatologists should consider crusted scabies in the differential diagnosis of erythroderma, especially in immunocompromised patients, to avoid delays in diagnosis and treatment. Immunosuppressive therapy is an important mainstay in the treatment of many conditions, but it is important to consider that these medications can place patients at an increased risk for rare opportunistic infections. Therefore, patients receiving such treatment should be closely monitored.

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