JAMA Dermatology Clinicopathological Challenge

Diffuse Vesicular Eruption

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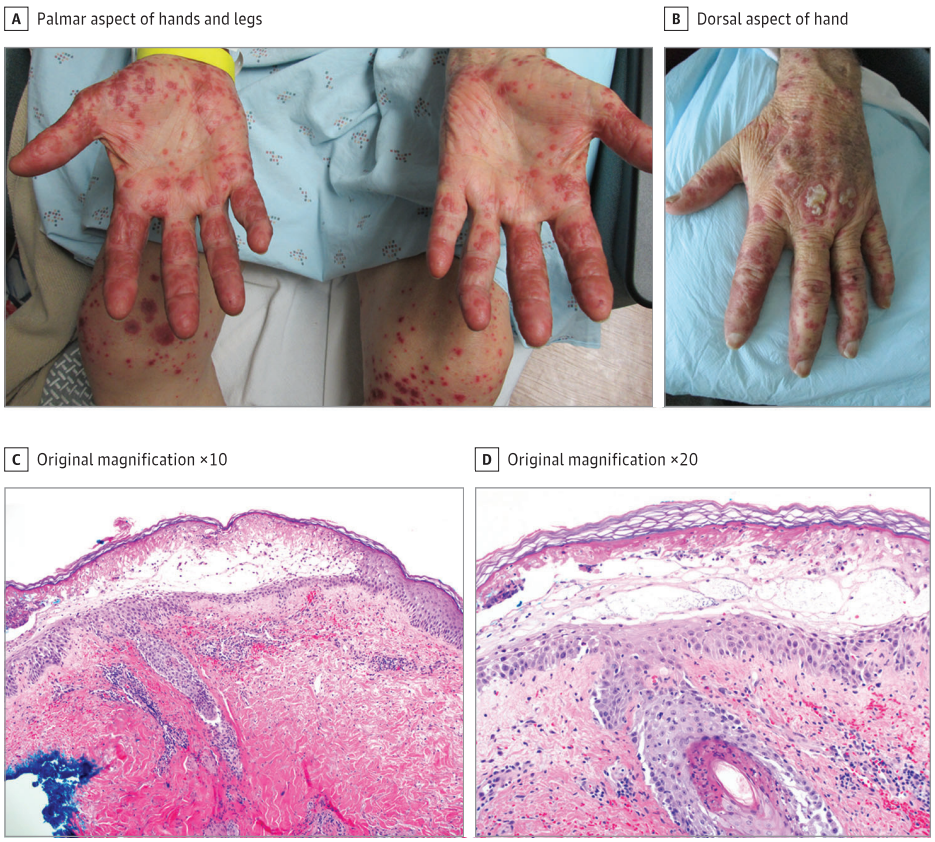

Figure. A and B, Patient with numerous erythematous macules, vesicles, and bullae. C and D, Punch biopsy specimen of bulla with superficial spongiotic dermatitis, superficial epidermal dyskeratotic necrosis, and mixed acute and chronic inflammation with associated erythrocyte extravasation. Hematoxylin-eosin.

A man in his 70s with a history of chronic lymphocytic leukemia (CLL) and prescribed cyclosporine, 100 mg twice daily, for pure red cell aplasia was admitted for spreading painful blisters on the hands and feet. He had initially developed rhinorrhea, cough, and low-grade fever 2 weeks prior. The patient was treated with azithromycin and subsequently developed few small, pruritic blisters on the hands and feet. He went to an urgent care facility and was diagnosed as having bronchitis and prescribed doxycycline and diphenhydramine. Over the next several days, he developed worsening fever, chills, and blisters and bullae on the arms, legs, and face. He was admitted to the hospital, and the dermatology service was consulted. Physical examination revealed numerous pink to violaceous macules, papules, and patches on the palms, dorsal hands, forearms, elbows, feet, and distal lower extremities (**Figure**, A and B). Fewer, scattered macules were on the face, neck, trunk, upper legs, upper arms, and scrotum. Dusky bullae were seen on the bilateral dorsal aspect of the hands, fingers, toes, and heels. In the oral cavity, there was 1 violaceous macule on the right buccal mucosa and a few linear, horizontal, white lines on the left buccal mucosa. Laboratory findings revealed a white blood cell count of 25 600/μL (reference range, 3700-10 500/μL) and a platelet count of 12 400/μL (reference range, 15 000-40 000/μL). Results from a Tzanck smear from the initial lesion on the right dorsal aspects of the third finger were negative for multinucleated giant cells. A punch biopsy was performed on the anterior side of the thigh (Figure, C and D).

WHAT IS YOUR DIAGNOSIS?

A. Atypical hand-foot-mouth disease

B. Disseminated zoster

C. Erythema multiforme

D. Leukocytoclastic vasculitis

Diagnosis

A. Atypical hand-foot-mouth disease

Microscopic Findings and Clinical Course

A 4-mm punch biopsy specimen of the left thigh demonstrated superficial spongiotic dermatitis featuring superficial epidermal dyskeratotic necrosis, follicular epithelial necrosis, and mixed acute and chronic inflammation with associated erythrocyte extravasation. Direct immunofluorescence studies revealed no marking for IgG, IgA, IgM, C3, or fibrinogen within the epidermis, along the dermoepidermal junction, or around dermal vessels. The patient was started on intravenous acyclovir, ceftriaxone, and vancomycin while in the emergency department. Over the next 2 days, he continued to develop new vesicles and bullae on the extremities and trunk, but at a decreasing rate. By hospital day 4, he was no longer developing new lesions and was soon thereafter discharged. Tests results for herpes simplex virus/varicella zoster virus polymerase chain reaction (PCR), syphilis IgG, tissue aerobic culture, fungal culture, and acid-fast bacillus cultures were all negative. Test results for enterovirus PCR of a skin lesion and blood sample were both positive. Shortly after discharge, the patient developed desquamation of the hands and feet along with several focal areas of discoloration on the legs.

Discussion

Hand-foot-mouth disease (HFMD) is one of the many manifestations of enterovirus infection and has classically been associated with Coxsackie virus strain A16 and Enterovirus 71.[1] The disease is characterized by low-grade fever, vesicular enanthem of the oral mucosa, and peripherally distributed cutaneous lesions. It is seen most commonly in children and only rarely affects adults, with less than 1% of infected adults demonstrating clinical signs of infection.[1,2] The virus is transmitted through fecal-oral, oral-oral, and respiratory routes and most commonly manifests in summer and early autumn.[2] It is typically a benign, self-limiting illness, although more severe manifestations do occur.[3]

Since 2008, a new enterovirus strain, Coxsackie virus A6 (CVA6), has been linked to several worldwide outbreaks of HFMD.[2,4] The febrile, mucocutaneous syndrome associated with CVA6 was first identified in Finland and was subsequently reported in Europe and Asia.[5] The illness reached the United States in 2011 and has since been identified in several states.[4] Infection with CVA6, which has classically been associated with herpangina, results in a distinct presentation of HFMD, termed *atypical HFMD*.[6] Atypical HFMD seems to have a higher manifestation rate in adults compared with classic HFMD, and the clinical presentation is often more severe.[3] More severe infection could be attributable to immunosuppression or an altered immune system as observed in this patient with CLL, although no strong associations with lymphoproliferative disorders have been established. Rates of hospital admission are higher with atypical HFMD than with typical HFMD, although most cases of A6 have been self-limiting.[1,2,7]

Unique clinical features of atypical HMFD include high fever; involvement of the dorsal hands and feet, calves, and trunk; extensive cutaneous involvement; periorificial lesions; localization in areas of atopic dermatitis; vesiculobullous and erosive eruptions; Gianotti-Crosti–like lesions; petechial or purpuric eruptions; delayed onychomadesis; and palmoplantar desquamation.[1-3,7-9] Atypical HFMD can also result in systemic symptoms, such as headaches, arthralgias, gastrointestinal tract symptoms, and fatigue.[1] Differential diagnosis may include varicella zoster virus infection, eczema herpeticum, erythema multiforme major, eczema herpeticum, bullous impetigo, and even cutaneous small vessel vasculitis. Characteristic histological findings include spongiotic and interface dermatitis with edema leading to subepidermal separation, reticular and ballooning degeneration of the epidermis, necrosis, papillary dermal edema, and a mixed dermal, sometimes perivascular, inflammatory infiltrate.[1,10] Treatment is symptomatic and includes hydration and pain control and with atypical forms, admission is sometimes necessary to control symptoms.

ARTICLE INFORMATION

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Published Online: November 2, 2016. doi:10.1001/jamadermatol.2016.3751

Conflict of Interest Disclosures: None reported.
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