A case of eczema coxsackium with erythema multiforme–like histopathology in a 14-year-old boy with chronic graft-versus-host disease

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INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a common, self-limited viral exanthem characterized classically by mild fever, small vesicles/erosions of the oral mucosa, and painful oval, gray vesicles involving the palms, soles, buttocks, and genitalia of young children. Coxsackievirus A16 (CVA16) and enterovirus 71 are the most frequently implicated pathogens.[1] However, there are increasing reports of atypical presentations caused by other viral serotypes, most commonly coxsackievirus A6 (CVA6).[2] Mathes et al[3] described 4 characteristic clinical morphologies of severe CVA6-associated atypical HFMD, including a widespread vesiculobullous eruption, localization of vesicles/erosions within areas of atopic dermatitis (eczema coxsackium [EC]), a Gianotti-Crosti–like eruption of vesicles and edematous papules in an acrofacial distribution, and petechial/purpuric papulovesicles on the palms and soles.[1,3] We report a case of EC presenting within lesions of chronic eczematous graft-versus-host disease (GVHD) with erythema multiforme (EM)/Stevens-Johnson syndrome (SJS)–like histopathology.

Abbreviations used:

CVA6:	Coxsackievirus A6
CVA16:	Coxsackievirus A16
EC:	eczema coxsackium
EV:	enterovirus
EM:	erythema multiforme
GVHD:	graft-versus-host disease
HFMD:	hand, foot, and mouth disease
HSV:	herpes simplex virus
RT-PCR:	reverse transcriptase polymerase chain reaction
SJS:	Stevens-Johnson syndrome

CASE REPORT

A 14-year-old boy presented to the emergency department with a 2-day history of a painful vesicular skin eruption along with a low-grade fever and sore throat. His medical history was significant for adrenoleukodystrophy/adrenal insufficiency treated 12 years prior with 2 myeloablative donor umbilical cord transplants and durable donor cell engraftment. Chronic eczematous GVHD was diagnosed by his transplant team during the first year after his transplant and managed with topical tacrolimus and oral methylprednisolone. His vesicular eruption involved the scalp, face, axillae, antecubital fossae, inguinal folds, penis, scrotum, buttocks, and dorsal hands (Fig 1). Notably, his eruption developed within sites at which he had known chronic GVHD (Fig 2). The patient's family increased his hydrocortisone from 5 mg 3 times a day to 30 mg 3 times a day. However, the rash continued to worsen with increasing pain, prompting his presentation to the emergency department. The patient was admitted for treatment of suspected eczema herpeticum.

Upon admission, he was afebrile, and a complete blood count and metabolic panel were normal. He was started empirically on intravenous acyclovir and continued on hydrocortisone, 30 mg 3 times a day.

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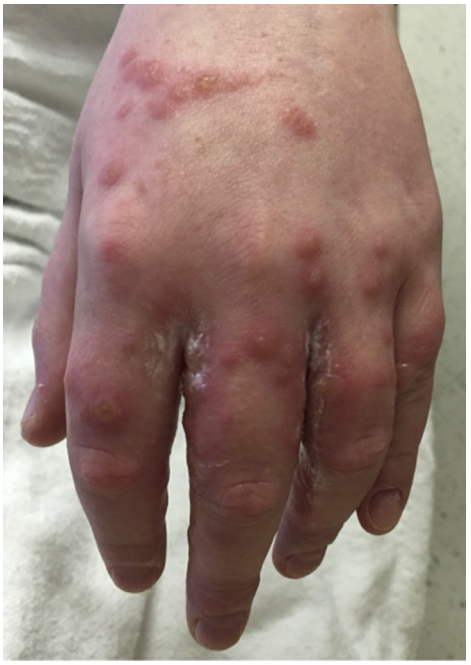

Fig 1. Atypical HFMD. Pink edematous papules and vesicles on erythematous bases to the dorsal hands and fingers. Macerated plaques in the interdigital spaces.

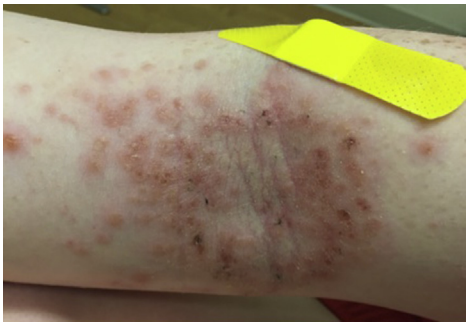

Fig 2. Eczema coxsackium. Background erythema and scaling in the antecubital fossa with overlying erythematous edematous papules, vesicles, and erosions.

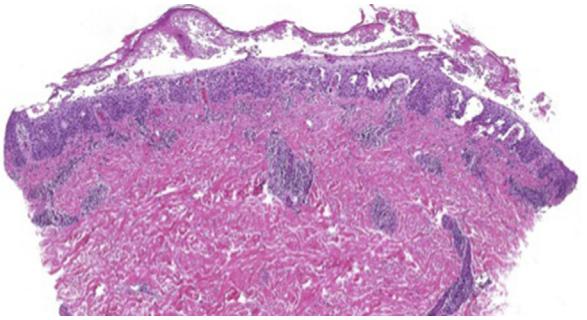

Fig 3. Coxsackievirus infection. Superficially necrotic epidermis with a papillary to mid-dermal inflammatory infiltrate. (Hematoxylin-eosin stain.)

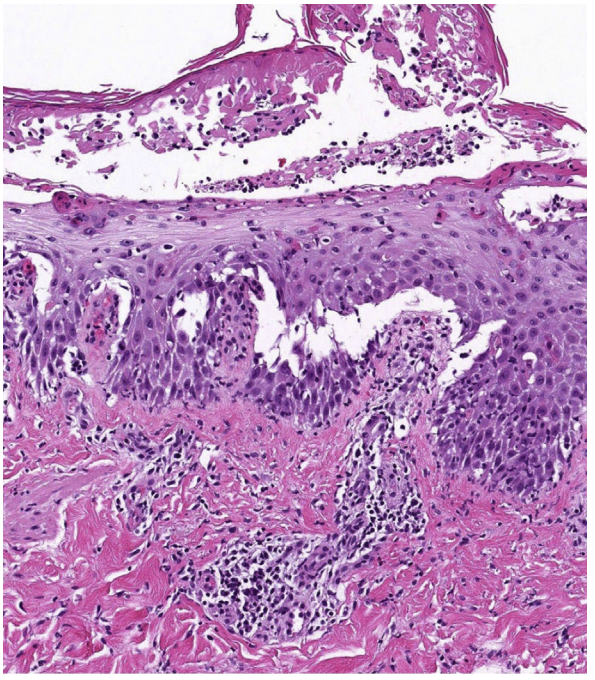

Fig 4. Coxsackievirus infection. Neutrophils present within the necrotic upper epidermis overlying scattered necrotic keratinocytes with associated lymphocytic vacuolar interface dermatitis. (Hematoxylin-eosin stain.)

On day 2, the patient had dusky violaceous macules on his palms, soles, and hard palate. No targetoid lesions were appreciated. The pediatric dermatology service favored a diagnosis of EC. Further history found that his school nurse had reported possible cases of HFMD within the last week.

A punch biopsy from the right arm found a prominent lymphocytic interface dermatitis with dyskeratotic keratinocytes at all levels. The superficial epidermis was necrotic and sloughed with associated neutrophilic aggregates. Within the dermis, there was a superficial to mid-dermal predominantly perivascular infiltrate composed of lymphocytes, histiocytes, and plasma cells along with rare eosinophils (Figs 3 and 4). No herpes viral cytopathic changes were noted.

Coxsackievirus A and B serum titers, enterovirus (EV) and herpes simplex virus (HSV) cultures from vesicle fluid, and rapid direct fluorescent antibody testing for HSV/varicella zoster virus from vesicle fluid were negative. However, EV serum reverse transcriptase polymerase chain reaction (RT-PCR) was positive, confirming the suspected diagnosis of an atypical presentation of HFMD, specifically

eczema coxsackium. Acyclovir was discontinued, and the patient was discharged home with supportive care. Six days after discharge, only a few thin scaly eczematous plaques remained along with postinflammatory hyperpigmentation.

DISCUSSION

The term *eczema coxsackium* was coined by Nahmias et al in 1968 who reported an extensive vesicular eruption caused by CVA16 in a child with a history of severe eczema.[4] Three cases of EC caused by CVA16 were subsequently reported; 1 in an adult patient with Darier's disease and 2 in children with atopic dermatitis.[3] Mathes et al[3] then reviewed 80 patients with atypical HFMD caused by molecularly confirmed (17 of 80) or clinically suspected CVA6 infection and found that 55% had lesions accentuated within areas of previous eczematous dermatitis. They also noted a tendency for localization to sites of skin injury or inflammation, such as sunburns, irritant/diaper dermatitis, healing lacerations, and tinea pedis.[3] Since then, multiple cases of EC have been reported in both children and adults; however, to our knowledge, besides one report of coxsackievirus A9 developing within lesions of mosaic epidermal ichthyosis,[5] no serotypes other than CVA6 and CVA16 have been reported to cause EC.[6]

Enteroviruses, in particular CVA6, are difficult to grow in conventional viral culture,[3,7,8] with false-negative rates ranging from 84% to 86%.[7] RT-PCR is a sensitive tool for diagnosis compared with viral culture[6-8] but cannot differentiate between various strains. EV subtyping requires viral protein capsid gene sequencing, necessitating the use of specialized research laboratories.[1,8] RT-PCR should preferably be performed on vesicle fluid followed by oropharyngeal swabs and stool samples.[8] In general, testing blood samples is not recommended given that viremia occurs early, resolves after the virus seeds the skin, and is therefore typically absent by the time patients present for evaluation. Furthermore, "commercially available" EV antibody assays are not recommended because the complement fixation methodology used is out of date, both acute and convalescent samples are needed to prove serologic conversion (in essence the acute sample is expected to be negative), and the number of EV serotypes included is often limited.[8] In our case, the coxsackie titers were checked early in the course of disease, and a convalescent sample was not obtained. All of the B subtypes were tested for, but the coxsackie A titer only checked 6 subtypes including A2, A4, A7, A9, A10, and A16. Although genotype subtyping would have been ideal, in our case, the sample was no longer available to send out for confirmation. The CVA6 subtype was suspected based on our patient's clinical presentation; however, given that the genotype was not confirmed, the possibility that another EV serotype may have been responsible cannot be excluded.

Although HFMD is often diagnosed clinically, when biopsied, the prototypical histologic features include spongiosis and ballooning of the upper epidermis leading to epidermal vesiculation with prominent reticular degeneration. Additional findings may include papillary dermal edema and a scant, mostly lymphocytic, superficial dermal inflammatory infiltrate. No virus-specific cytopathic changes or inclusions are seen in contrast to viruses in the differential diagnosis such as herpes and Orf.[9] Interestingly, Chung et al[10] reported a series of patients who presented with widespread mucocutaneous blistering eruptions during a HFMD epidemic in Taiwan. They identified a new variant of CVA6 within the vesicle fluid of 6 patients whose histopathology results showed extensive necrosis of the epidermis with dyskeratosis and bulla formation, mimicking a severe cutaneous adverse reaction, such as EM or SJS, and commented that the morphology of the oral lesions might be a helpful clue when distinguishing these entities clinically.[10] More recently, Laga et al[11] published a clinicopathologic study of 3 cases (2 proven CVA6) of atypical HFMD in adults. Histologically, a consistent pattern was identified including intraepidermal vesiculation with "specific involvement of the upper stratum spinosum and stratum granulosum" along with a predominantly neutrophilic intraepidermal infiltrate. They suggested that these characteristic findings along with the lack of a fundamental interface process should help distinguish EM/SJS from atypical HFMD microscopically. The histologic findings in our case were similar; however, because of the presence of an interface dermatitis, our differential diagnosis did include EM/SJS versus an exacerbation of the patient's GVHD. EM was thought to be very unlikely based on the morphology of his oral and cutaneous lesions, and the degree of dyskeratosis and epidermal necrosis present on biopsy would have correlated with a severe flare of his GVHD, which was not substantiated by his clinical presentation or laboratory findings. Furthermore, the presence of a mild viral prodrome, reported cases of HFMD at school, positive EV serum RT-PCR, and spontaneous resolution supported a diagnosis of atypical HFMD.

Many viruses, including varicella zoster virus and HSV, have a predilection for localization to areas of inflamed or traumatized skin. This case

underscores the point that atypical HFMD should be considered within the differential diagnosis not only for acute-onset febrile blistering diseases but also for new-onset vesicles/erosions within sites of skin injury/inflammation or dermatitis, including GVHD. Our case also further illustrates the possible histologic overlap between EM/SJS and atypical HFMD, highlighting the fact that coxsackievirus infection should be considered within the differential diagnosis for an EM-like interface reaction in the appropriate clinical scenario.

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