

Disseminated coxsackievirus A6 affecting children with atopic dermatitis

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Summary

Coxsackievirus A6 (CV-A6) is an emerging pathogen that has in recent years been associated with atypical hand, foot and mouth disease. This manifests as a generalized papular or vesicular eruption, which may be associated with fever and systemic disturbance. We report a series of six children presenting to a single centre in the UK with disseminated CV-A6 infection on a background of atopic dermatitis (AD). Our patients exhibited a widespread papular or vesicular eruption in association with exacerbation of AD. Several of our cases mimicked eczema herpeticum, but the extent was more generalized, and individual lesions were discrete rather than clustered and were less circumscribed in character. This series highlights that CV-A6 infection may be encountered in the UK, and should be considered in the differential diagnosis of an acute exacerbation of AD, particularly in children.

Enteroviruses are a group of positive-strand RNA viruses within the Picornavirus family, for which 12 species have been delineated. Coxsackie A viruses are associated with hand, foot and mouth disease.¹ Classic hand, foot and mouth disease (HFMD) is predominantly caused by coxsackie virus (CV)-A16 and enterovirus 71. It is typically localized to the oral cavity, hands and feet, and has an incubation period of 3–6 days with a prodromal phase of fever, pharyngitis and malaise.¹ Since 2008, a novel cutaneous phenotype associated with the CV-A6 strain has been observed in the East Asia² and Finland;³ more recently, cases have also been reported in the USA⁴ and Sweden.¹ This novel presentation has been referred to as atypical HFMD, and characteristically manifests as a widespread vesicular or papular eruption that may be associated with fever and systemic disturbance. We report a series of six children with a background of atopic dermatitis (AD) presenting with

a widespread papular or papulovesicular eruption. To our knowledge, this is the first series of cutaneous CV-A6 infection reported in the UK, and comparison with previous series reveals preferential involvement of children with AD. This series emphasizes the importance of this condition in the differential diagnosis of an exacerbation of AD in children.

Report

We report a series of six children aged from 3 months to 3 years (Table 1) presenting to the Dermatology service at a single centre in London between September and December 2013. Cases were identified retrospectively, and all patients, irrespective of age, with virologically confirmed CV-A6 identified by skin swab during this period were included in the series. Swabs were taken from intact vesicles where present, otherwise they were taken from involved areas of skin. Enterovirus typing was performed by the Virus Reference Laboratory at Public Health England. Briefly, viral RNA was extracted and reverse-transcribed to cDNA. PCR was performed with primers specific to the VP1 domain and sequenced. The resulting sequence was compared with known VP1 sequences within the coxsackievirus phylogenetic tree.

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Patients 1–5 had a previous diagnosis of well-controlled AD, and a diagnosis of AD was made for patient 6 at the time of presentation. Full details of these cases are given in Table 1. Swabs from patients 1–4 also grew *Staphylococcus aureus*. All were negative for herpes simplex virus (HSV) and varicella zoster virus (VZV).

Clinical features were similar between the six cases. In addition to an exacerbation of eczema, three of the six cases exhibited a papulovesicular eruption, with the remaining three exhibiting papules in the absence of clinically apparent vesicles (Fig. 1). In all cases, the eruption was generalized, with accentuation over limbs and face. In two cases there was prominent involvement of the hands, and another two cases exhibited involvement of the oral cavity. The initial clinical diagnosis in two cases was of a flare of AD with superimposed viral exanthem, while in a further two cases the initial diagnosis was of eczema herpeticum, and the remaining two cases were thought to have either HFMD or eczema herpeticum. Three of the six children were systemically unwell, and were admitted to hospital and treated with intravenous aciclovir and intravenous flucloxacillin. The other children were treated with oral antimicrobials; all received moderate-

potency topical steroids. All of the children were followed up and exhibited a good response to treatment, with resolution of the eruption and return of the severity of eczema to baseline levels by 4 weeks from initial presentation.

We have described a series of six cases of cutaneous CV-A6 infection, with *S. aureus* coinfection in four of these cases, preferentially affecting children with AD and presenting to a single UK centre in London from September to December 2013. The manifestations of cutaneous CV-A6 infection are protean; common features are systemic disturbance and a generalized vesicular or papular eruption.¹ By contrast, an outbreak in Taiwan was characterized by oral ulcers, with vesicular eruptions on the palms, soles, knees and buttocks;⁵ other Taiwanese patients have exhibited severe mucocutaneous blistering mimicking Stevens–Johnson syndrome.⁶ Patients in Singapore had predominantly oral lesions with few cutaneous lesions.⁷

Our patients were all young children. They manifested a distinctive clinical phenotype consisting of a widespread vesicular or papular rash eruption with prominent involvement of the upper and lower limbs (Table 1). This can be differentiated from the main differential diagnoses of conventional HFMD disease,

Table 1 Patient demographics.

Patient	Sex	Age, months	Date	Comorbidities	Morphology	Microbiology	Initial clinical diagnosis
1	Male	22	Dec 2013	Eczema	Flare of eczema with papules and erosions on face, forehead, extensor surfaces and periumbilical area	<i>Staphylococcus aureus</i> CV-A6	Flare of eczema with impetiginization and possible viral exanthem
2	Male	6	Sep 2013	Eczema	Flare of eczema with generalized papular eruption	<i>S. aureus</i> CV-A6	Impetiginized eczema/eczema herpeticum
3	Male	40	Oct 2013	Eczema, multiple allergies, asthma	Flare of eczema with vesicles on arms, hands, legs and face	<i>S. aureus</i> CV-A6	Eczema herpeticum with secondary staphylococcal infection
4	Male	3	Nov 2013	Eczema	Crusted, excoriated papules trunk, limbs, palms and oral cavity	<i>S. aureus</i> CV-A6	Flare of eczema with superimposed viral exanthem and impetiginization
5	Female	23	Oct 2013	Eczema	Vesicles on the dorsum of hands and feet, ankles and knee; flexures on buttocks and perioral area	CV-A6	Hand, foot and mouth disease, eczema herpeticum or chickenpox
6	Male	30	Oct 2013	–	Excoriated vesicles on elbows, wrists and knees; vesicles on hard palate with papules on buttocks and groin flexures	CV-A6	Hand, foot and mouth disease or eczema herpeticum



Figure 1 Patient 1: (a) This 22-month-old child presented with a papular rash particularly prominent on the face, forehead, extensor surfaces of the knees and shins and periumbilically. He was irritable but otherwise systemically well; (b) Close-up view of excoriated papules.

impetiginized eczema and eczema herpeticum on clinical grounds. Oral and acral involvement was variable.

Five of the six children had a previous diagnosis of AD, and the remaining child had a flexural rash suggestive of eczema at the time of presentation. Although patients with AD have previously been reported as affected by CV-A6 outbreaks in the USA,^{8,9} and accentuation of the eruption has been noted in body areas previously affected by eczema,^{8,9} the extreme preference seen in our series is unusual. However, we note that while this manuscript was in preparation, a series of patients with CV-A6 was reported in Edinburgh, of which a subset exhibited similar clinical features mimicking eczema herpeticum.¹⁰ All cases referred to our Dermatology service were included in this series; however, we cannot exclude the possibility that milder cases of atypical

HFMD were not referred. Nevertheless, this would suggest a more severe presentation in children with AD.

Several of our cases mimicked eczema herpeticum; however, eruptions were more generalized, and individual lesions were discrete rather than clustered and were less circumscribed in character. Staphylococcal co-infection was detected on swabs from four of the six cases. It is known that many patients with AD will exhibit staphylococcal carriage; nevertheless, there is a rationale for positing a pathological infection analogous to the situation in eczema herpeticum, reflecting a combination of epidermal barrier disruption and immune dysregulation. It is important that dermatologists are aware of CV-A6 in the differential diagnosis of vesicular eruptions, particularly in the context of childhood AD. Viral swabs should be tested for enterovirus RNA, in addition to HSV and VZV DNA. Of note, all of our patients were initially treated with aciclovir to cover the possibility of eczema herpeticum. Aciclovir targets the herpesvirus thymidine kinase, which is not present in coxsackieviruses; nevertheless, aciclovir should be initiated pending swab results if there is any clinical suspicion of HSV.

In summary, we have described atypical HFMD caused by CV-A6 preferentially affecting children with AD in the UK. Although serious complications are rare, it is essential that this condition is recognized.

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Learning points

- Coxsackieviruses are a common cause of classic HFMD.
- CV-A6 causes a distinct clinical phenotype with a widespread papular or vesicular eruption.
- Previous cases of CV-A6 have been reported predominantly in East Asia and the USA.
- We report a series of children presenting with CV-A6 in the UK.
- All but one of the cases in this series involved children with a background of AD.
- The clinical presentation of coxsackievirus A6 infection can mimic eczema herpeticum, and should be considered in the differential diagnosis of this condition.

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