Clinicopathologic analysis of atypical hand, foot, and mouth disease in adult patients

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Background: Hand, foot, and mouth disease is a contagious viral infection usually affecting children. A resurgence of cases in adults, mainly caused by coxsackievirus A6 and with an atypical and more severe presentation, has taken place.

Objective: The goal was to examine the clinical, histologic, and immunohistochemical features of this disease in adults.

Methods: This is a retrospective study on documented cases of adult hand, foot, and mouth disease from France's Dermatology Department of Strasbourg University Hospital and Bel-Air Hospital in Thionville.

Results: Six patients with severe and atypical presentation were included, 4 caused by coxsackievirus A6. The histologic features were: spongiosis, neutrophilic exocytosis, massive keratinocyte necrosis, shadow cells in the upper epidermis, vacuolization of basal cells, necrotic cells in follicles and sweat glands, dense superficial dermal infiltrate of $CD3^+$ lymphocytes, and strong granulysin expression.

Limitations: This is a retrospective case series.

Conclusion: In adult patients presenting with atypical hand, foot, and mouth disease caused by coxsackievirus A6, biopsy specimens show distinctive changes in the epidermis but also in adnexal structures. The inflammatory infiltrate is made of T cells with a cytotoxic profile, with numerous granulysin-positive cells, as observed in severe drug-induced eruption with necrosis of keratinocytes. (J Am Acad Dermatol 2017;76:722-9.)

Key words: atypical; coxsackievirus A6; *Enterovirus*; granulysin; hand, foot, and mouth disease; keratinocyte necrosis.

Hand, foot, and mouth disease (HFMD) usually affects children younger than 5 years. It is characterized by vesicles in the oral cavity and on the palms and soles, with a moderate fever. Recovery occurs in 7 to 10 days.[1] A resurgence of this disease was recently observed in adults, however, associated mainly with coxsackievirus A6.[2-6] Presentation in adults is atypical and more severe, with a higher fever. Given this difficult diagnosis, skin biopsies are performed more often in adults, as other viral exanthema or drug-induced reactions may be suspected. There is little information and few microphotographic illustrations in the literature or in

Abbreviations used:

CTL:	cytotoxic T lymphocyte
HFMD:	hand, foot, and mouth disease
NK:	natural killer
SJS:	Stevens-Johnson syndrome

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Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication October 11, 2016.

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Published online December 24, 2016.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2016.10.022

dermopathology reference works regarding the detailed histologic aspects of HFMD.[2,4,5,7-11] Over the last 4 years, an unusually high number of cases of severe HFMD in adults has been observed in our hospitals.

The goal of this study was to examine the clinical, histologic, and immunohistochemical features of this disease in adults, working from well-documented cases. We attempted to characterize the inflammatory infiltrate, including granulysin expression, as HFMD may be mimicking Stevens-Johnson syndrome (SJS) or other drug-induced eruptions.[9]

CAPSULE SUMMARY

- Hand, foot, and mouth disease in adults is often severe and clinically atypical.
- Characteristic histology includes intense edema, necrotic or shadow keratinocytes, and neutrophilic exocytosis with T-cell infiltrate. Granulysin may play a role.
- The histologic changes of hand, foot, and mouth disease in adults can assist in the diagnosis.

METHODS

We performed a retrospective study of HFMD in adults occurring between July 2011 and July 2015 in 2 French dermatology departments. The patients were selected by consultation of hospitalization files, photographs, or biopsy specimens.

The criteria for inclusion were: age 18 years or older and HFMD proven by serology, positive polymerase chain reaction for enterovirus RNA, or a suggestive clinical picture with performance of a skin biopsy. The clinical criteria required in the absence of laboratory confirmation were vesicular eruption of the hands and feet and infection from a documented case of HFMD.

Enterovirus RNA was detected from vesicular fluid. RNA sequencing was performed at the Eastern Virology Laboratory of the National Reference Center for Enterovirus and Parechovirus, at the Lyon University Hospital, by sequencing the 5' (300-350 pb) region of 1D gene coding for capsid VP1 protein.

Histologic analysis was supplemented by routine immunohistochemical analyses with monoclonal or polyclonal antibodies against CD3 (NeoMarkers, Fremont, CA, clone SP7), CD8 (Dako, Glostrup, Denmark, clone C8/144B), CD56 (Ventana, clone 123C3), CD20 (Dako, clone L26), CD68 (Dako, clone KP1), CD30 (Dako, clone Ber-H2), CD31 (Dako, clone JC/70A), granzyme B (Dako, clone GrB-7), and granulysin (MBL Clinisciences, Nanterre, France, clone RF10).

RESULTS

Nine cases were identified, of which 3 were excluded owing to the absence of virologic confirmation or biopsy specimen.

The main clinical data are presented in Table I. All patients had painful or pruritic erythematous lesions (sometimes grayish) and palmoplantar papulovesicles that spread to the back of the hands or feet (Fig 1, *A* and *B*). One had bullous lesions (Fig 1, *B*). In 5 patients the skin was diffusely affected: face (Fig 1, *C*), scalp, buttocks, thighs, genitalia, back, and upper limbs.

Oral mucosa were not affected in 3 patients. In all patients, the course of the exanthema was shorter than 10 days. Coxsackievirus A6 was identified by sequencing in all the patients with a positive polymerase chain reaction result. In patient 6, enterovirus seroconversion was noted at day 19, with an initial negative serology. HIV serology performed in 4 patients was negative.

The skin biopsies were performed between the second and fourth day of the eruption. The histopathological presentation was very similar in all cases. The epidermis showed spongiosis, vesicles or bulla, and major neutrophilic exocytosis, mainly around the vesicles (Fig 2). There was massive keratinocyte necrosis, most prominent in the upper layers, and frequent vacuolized cells in the basal layers (Fig 2, *C* and *D*). In 2 cases there were keratinocytes with clear cytoplasm and light eosinophilic nucleus, like shadow cells. There was severe edema and perivascular infiltrate of the papillary dermis. Two cases showed erythrocyte extravasation in the dermis, and moderate leukocytoclasia in 1 case. The infiltrate of the papillary dermis was made of lymphocytes and histiocytes, admixed with neutrophils. Eosinophils were present in the mid and reticular dermis in 3 cases.

Follicular and apocrine gland involvement was conspicuous in 1 case, with vesicle formation, keratinocyte necrosis, and vacuolized infundibular basal cells (Fig 3, *A*). There was also perifollicular and perisudoral neutrophilic infiltrate (Fig 3, *B*). An eccrine sweat gland was involved in another case, with keratinocyte necrosis in the acrosyringium and neutrophilic infiltrate in the lumen, around the excretory duct and coil (Fig 3, *C* and *D*).

Immunohistochemistry showed that the dermal infiltrate was predominantly $CD3^+$, with $CD3^+$ cells found in exocytosis (Fig 4, *A*). These cells were $CD8^+$ and $CD56^-$. There were a minority of $CD20^+$ cells (Fig 4, *B*) and a few cells expressing CD30 (Fig 4, *C*) in 2 cases. CD68 expression was strong in histiocytes,