Wells' Syndrome Associated with Coxsackievirus A6 Infection

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Wells' syndrome, also known as eosinophilic cellulitis, is a skin disease originally described as erythematous indurated plaques resembling bacterial cellulitis characterized by tissue eosinophilia and so-called "flame figures" (1). Pathological aetiologies have yet to be clarified, but insect bites, parasitic infections, and drugs have been implicated as trigger factors (2–6). Viral agents, such as human parvovirus B19, herpes simplex virus, and even influenza virus vaccination, have also been reported to trigger Wells' syndrome (7–9).

CASE REPORT

A 45-year-old man presented with a 5-day history of fever (38°C) and erythema of the extremities. Physical examination demonstrated various-sized erythematous lesions on his swollen hands and feet (**Fig. 1**A). Vesicle and bulla formation was observed on the dorsal aspects of his hands and feet. He also had urticarial erythema on the upper arms and trunk (Fig. 1B). No oral lesions or cervical lymphadenopathy were detected. Laboratory findings demonstrated blood neutrophilia (11,220/μl) and increased C-reactive protein (12.0 mg/dl; normal: <0.3 mg/dl). Histopathological examination of an upper arm erythematous lesion on day 6 showed relatively moderate levels of cellular infiltrate, comprising lymphocytes and eosinophils in the entire dermis with dilated capillaries. In the erythematous vesicular lesions, marked oedema in the papillary dermis and intra-epidermal vesicle formation were observed (Fig. 1C–E), in addition to dermal cellular infiltrates. No reticular or ballooning degeneration of keratinocytes was found. Within 10 days, the fever, erythema and vesicles/bullae had partially resolved, but swelling of the dorsal aspects of the hands persisted with severe pruritus (**Fig. 2**A). In addition, the patient had marked blood eosinophilia, up to 14,945/μl. A second biopsy specimen of the dorsum of the hand on day 14 showed a dense cellular infiltrate in the entire dermis and subcutaneous tissues, consisting of many eosinophils (Fig. 2B). Small foci of "flame figures" were also observed (Fig. 2C). The *FIP1L1-PDGFRA* fusion gene was negative. The patient was treated with oral prednisolone (40 mg/day), resulting in a dramatic improvement in the skin manifestations and blood eosinophilia. No recurrence has been observed. Investigations for viral titres demonstrated an increase in anti-coxsackievirus A6 (from ×8 up to ×128 within 2 weeks) (Fig. 2D). There were no significant changes in titres suggestive of other infectious agents, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), adenovirus, human parvovirus B19, or *Mycoplasma pneumoniae*.

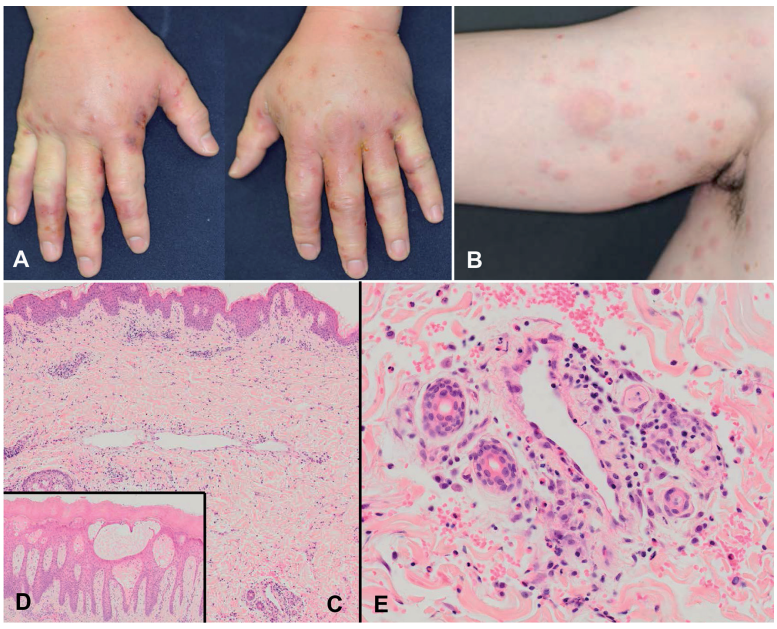

Fig. 1. Clinical and histopathological features of initial skin lesions on day 6. (A) Dorsal aspects of the hands are swollen with erythema and vesicles/bullae. (B) Urticarial erythema on the upper arms. (C) A weak or moderate cellular infiltrate and oedema are observed in the entire dermis (original magnification ×40). (D) Intraepidermal vesicles and marked oedema in the papillary dermis (original magnification ×40). (E) Lymphocytes and eosinophils around deep dermal vessels and eccrine glands (original magnification ×400).

DISCUSSION

This case showed bilateral erythematous swelling of the hands with pruritus or a burning sensation, which was histopathologically characterized by marked tissue eosinophilia in the entire dermis and subcutaneous tissues with flame figures. The patient also had severe blood eosinophilia. These manifestations appeared to be triggered by coxsackievirus A6 infection. The differential diagnosis should include the non-episodic type of angioedema with eosinophilia. We preferred to diagnose this patient with Wells' syndrome because of the marked dermal tissue eosinophilia with flame figures. However, the present case may lie somewhere on the continuum between these 2 diseases.

One of the unusual features of the present case was that the initial symptoms on day 6, such as the vesicular erythema of the hands/feet and urticarial erythema on the trunk (Fig. 1), were not necessarily accompanied by marked tissue eosinophilia. In this stage, he showed blood neutrophilia, but not eosinophilia. Thus, whether these initial symptoms can be regarded as an early stage of Wells' syndrome is unclear. One may assume that these were atypical forms of hand-foot-mouth disease or erythema exudativum multiforme associated with coxsackievirus A6 infection, as coxsackievirus A6 has recently been repor-

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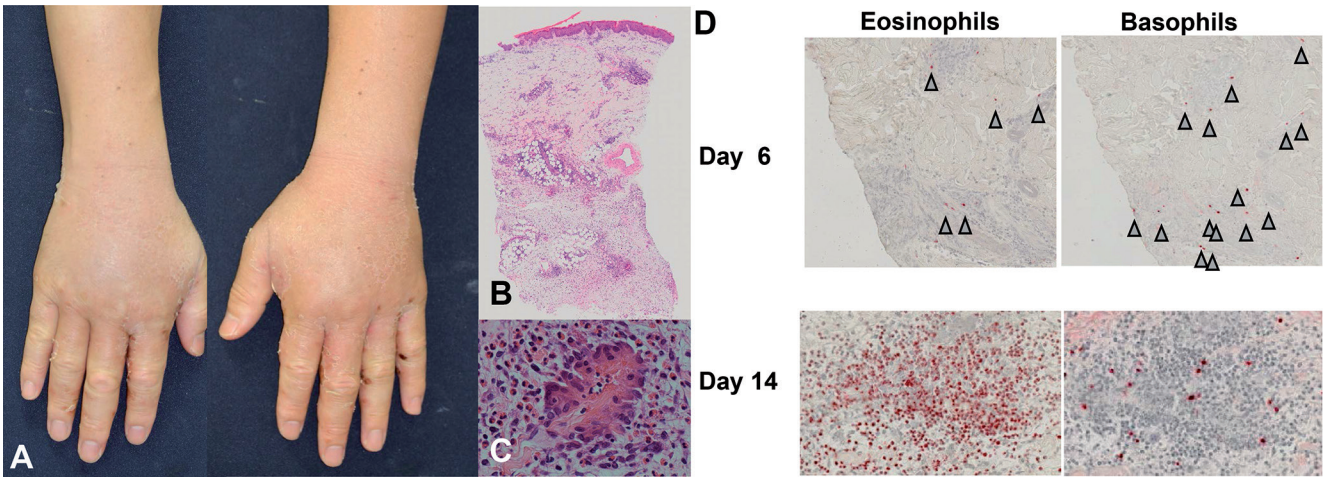

Fig. 2. Clinical and histopathological features on day 14. (A) Swelling with diffuse erythema of the hands and fingers. (B) Dermal cellular infiltrates become more prominent and extend into subcutaneous tissues (original magnification ×10). (C) Flame figures surrounded by numerous eosinophils (original magnification ×400). (D) Changes in antibody titres for coxsackievirus A6. (E) Eosinophil and basophil staining of skin lesions (original magnification ×40 and ×200, on days 6 and 14, respectively).

ted to induce not only typical hand-foot-mouth disease, but also atypical form of hand-foot-mouth disease characterized by widespread papular/vesicular eruptions on the trunk, face and dorsal hands, occasionally mimicking erythema multiforme, Stevens-Johnson syndrome and eczema herpeticum (10).

Recently, basophils have been shown to be present in a number of allergic diseases, such as urticaria, atopic dermatitis, prurigo and eosinophilic pustular folliculitis (11). In mouse models of irritant contact dermatitis and eosinophilic esophagitis, basophil infiltration was essential for eosinophilic inflammation (12, 13). Thus, the numbers of eosinophils and basophils were analysed immunohistochemically with anti-eosinophil major basic protein (BMK13, Santa Cruz Biotechnology Inc., CA, USA) and basophil-specific BB1 (kindly provided by Dr Andrew F. Walls, University of Southampton, Southampton, UK) antibodies, respectively (Fig. 2E). Numerous basophils were present (mean 16 cells/mm^2) in the initial lesion on day 6; they were more prominent than eosinophils (mean 7 cells/mm^2). Basophil infiltration subsequently increased in later skin lesions on day 14 (mean 95 cells/mm^2), but much higher numbers of eosinophils infiltrated the skin (mean 395 cells/mm^2). Basophils infiltrated early skin lesions, and they may have promoted subsequent accumulation of eosinophils. These findings also suggest that immunological events associated with Wells' syndrome occurred even during the initial skin lesions when tissue and blood eosinophilia was not so prominent.

Wells' syndrome is immunologically biased toward Th2 type immunity (14). It needs to be clarified how viral infections, such as coxsackievirus A6, which generally induce Th1 immunity, provoked eosinophilic inflammation, such as Wells' syndrome, in conjunction with basophil activation.

The authors have no conflicts of interest to declare.

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