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Case Report



# Coxsackievirus A6-induced Hand-Foot-and-Mouth Disease Mimicking Stevens-Johnson Syndrome in an Immunocompetent Adult

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## ABSTRACT

Hand-foot-and-mouth disease, a highly contagious viral infection, occurs more common in children than in adults. However, there was a recent outbreak of Coxsackievirus A6-induced infection with an atypical presentation among the adult population. Stevens–Johnson syndrome is a severe mucocutaneous disease characterized by extensive necrosis and detachment of the epidermis, and this condition is commonly caused by medications. Herein, we describe a 30-year-old male patient taking allopurinol for the management of gout. The patient presented with numerous erythematous papules, vesicles, and patches with mucosal eruptions on the whole body, oral mucositis, and fever, and he was finally diagnosed with hand-foot-and-mouth disease.

**Keywords:** Adult; Coxsackievirus A6; Hand-foot-and-mouth disease; Stevens–Johnson syndrome; Allopurinol

## INTRODUCTION

Hand-foot-and-mouth disease (HFMD) is a highly contagious viral infection commonly affecting children [1]. It is caused by several enteroviruses, primarily Coxsackievirus A16 and Enterovirus 71. HFMD is typically characterized by fever, malaise, sore mouth or throat, and characteristic cutaneous eruptions on the hands, feet, and mouth [2]. With the appearance of skin lesions, this condition must be distinguished from other skin diseases, including erythema multiforme (EM), and other viral infections such as chickenpox and measles. Currently, the occurrence of atypical adult HFMD caused by Coxsackievirus A6 (CVA6) is increasing worldwide [3-5]. HFMD caused by CVA6 affects a higher number of adult patients compared with that caused by conventional viruses.

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**Conflict of Interest**
No conflicts of interest.

**Author Contributions**
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Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) constitute a disease spectrum of the severe mucocutaneous hypersensitivity reaction commonly caused by drugs [6]. This spectrum is characterized by skin detachment and mucosal involvement. SJS is a severe type of reaction characterized by skin detachment of less than 10% of the body surface area (BSA), widespread macules, and flat, atypical target lesions. Further, TEN involves more than 30% of the BSA. The SJS/TEN overlap syndrome is defined as skin detachment of 10 – 30% of the BSA [7]. Allopurinol, a drug used for the treatment of gout, has been well known to be associated with SJS [8]. Herein, we present a case of an adult male patient with an atypical presentation of CVA6-induced HFMD, which mimicked SJS caused by allopurinol.

## CASE REPORT

A 30-year-old male patient visited the emergency room due to fever for 5 days and whole-body skin eruption for 3 days. The skin eruption started in both hands and then spread to the whole body within 3 days. Moreover, he had labial vesicles, painful scrotal skin eruption, odynophagia, and dysphagia

The patient presented with acute ill-looking appearance upon check-up, and his vital signs were as follows: blood pressure, 110/70 mmHg; pulse rate, 100 beats/min; body temperature, 38.3°C; and respiration rate, 20 cycles/min.

Numerous erythematous papules were observed on the patient's torso, palms, perioral area, and scrotum. The lips were covered with crusts, and blisters were found around the area (**Fig. 1A-1C**). The patient also presented with oral mucosal lesions. There were three round-shaped non-tender lymph nodes measuring 0.5 cm on the left side of the neck. The patient claimed that he had been taking drugs for gout for 3 weeks before the visit, as well as vitamins and lutein supplements. Moreover, he had no close contact with any ill child or adult.

Laboratory test results were as follows: blood test (white blood cell [WBC] count: 8,190 $x10^6$/L, neutrophil count: 79.9%, lymphocyte count: 11%, eosinophil count: 0.0%, hemoglobin level: 15.5 g/dL, and platelet count: $148x10^9$/L), liver function test (aspartate aminotransferase level: 26 U/L, alanine aminotransferase level: 37 U/L, alkaline phosphate level: 73 U/L, and gamma-glutamyl transpeptidase level: 16 U/L), and kidney function test (blood urea nitrogen level: 12.3 mg/dL and creatinine level: 1.15 mg/dL). Only the C-reactive protein level was elevated at 2.1 mg/dL. The human immunodeficiency virus (HIV) and syphilis tests had negative results. . Based on the Epstein-Barr virus test, the patient tested positive for IgG and negative for IgM. Antipyretics (ketorolac, propacetamol) and antihistamines (hydroxyzine, levocetirizine) were administered, and ceftriaxone was provided as an empirical therapy. The fever persisted until the third day, and the skin lesions, including those on the dorsum of the hands, progressed with a merging pattern, and the lip and oral mucosal lesions were worse that the patient could not even drink water (**Fig. 1D-1F**).

The patient was then admitted on the third day of the emergency room visit, with consideration of viral infection and SJS caused by allopurinol. After 60 mg of methylprednisolone was administered in accordance with the treatment guidelines for SJS, the fever improved. A skin biopsy was performed on the second day of admission. On microscopic examination, superficial perivascular dermatitis and papillary dermal edema with epidermal necrosis (**Fig. 2A**), intra-epidermal vesicles containing neutrophils and epidermal necrosis of the upper third layer


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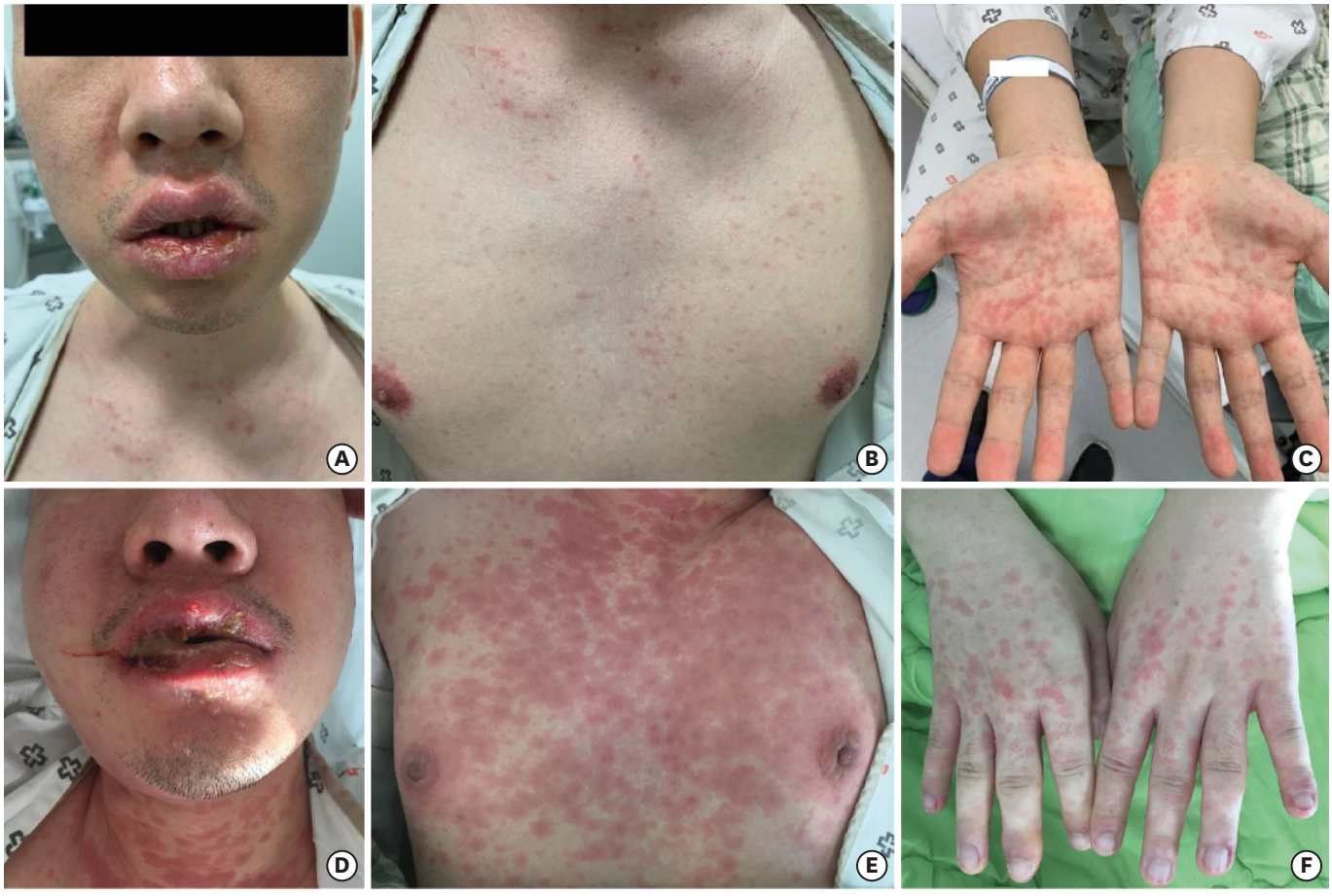


**Figure 1.** Skin lesions observed during the emergency room visit. (A) (left upper) Crusts covered lips, perioral viscles were shown. (B) (middle upper) Torso, and (C) (right upper) hands showing numerous erythematous papules.
Skin lesions on the third day of hospitalization. (D) (left lower) Labial crusts went worse. (E) (middle lower) Erythematous papules enlarged and merged with each other. (F) (right lower) Erythematous papules of the dorsum of the hands.

of the skin (**Fig. 2B, 2C**), scattered apoptotic keratinocytes and ballooning leading to reticular degeneration, and neutrophil dominant infiltration (about 10/high-power field) in the dermal interstitium (**Fig. 2D**) were shown. These findings are not suitable for diagnose SJS. Laboratory tests for measles and Varicella Zoster virus revealed that the patient tested positive for IgG but negative for IgM. Laryngoscopic examination showed that mucosal erosion and inflammation were noted in the epiglottis, aryepiglottic fold, and pyriform sinus, causing swelling and airway obstruction. On the eighth day, the laryngoscopic examination revealed bleeding, discharge, and blood clots around the lips, and the mucosal lesions in the larynx improved (**Fig. 3A-3C**). On the eleventh day, only focal lesions were observed on the lips. However, the lesions in the larynx were improved (**Fig 3D-3F**). He was then discharged after 14 days and was prescribed with oral antihistamines only.

He visited the hospital eight days after discharge, and the skin lesions and mucosal lesions improved. The result of the HLA-B*58:01 test for allopurinol-induced severe cutaneous adverse drug reactions (SCARs) was negative. Ten days after discharge, we found that the CVA6 neutralization test result was positive (1:32). The patient's sample was sent to LSI Medience Corporation, Tokyo, Japan, and tested. Moreover, the allopurinol patch test conducted 5 weeks after discharge was negative. Thus, the patient was finally diagnosed with


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adult HFMD. This case report had been approved by the Institutional Review Board of Inje University Haeundae Paik Hospital. (no. 2020-01-010).

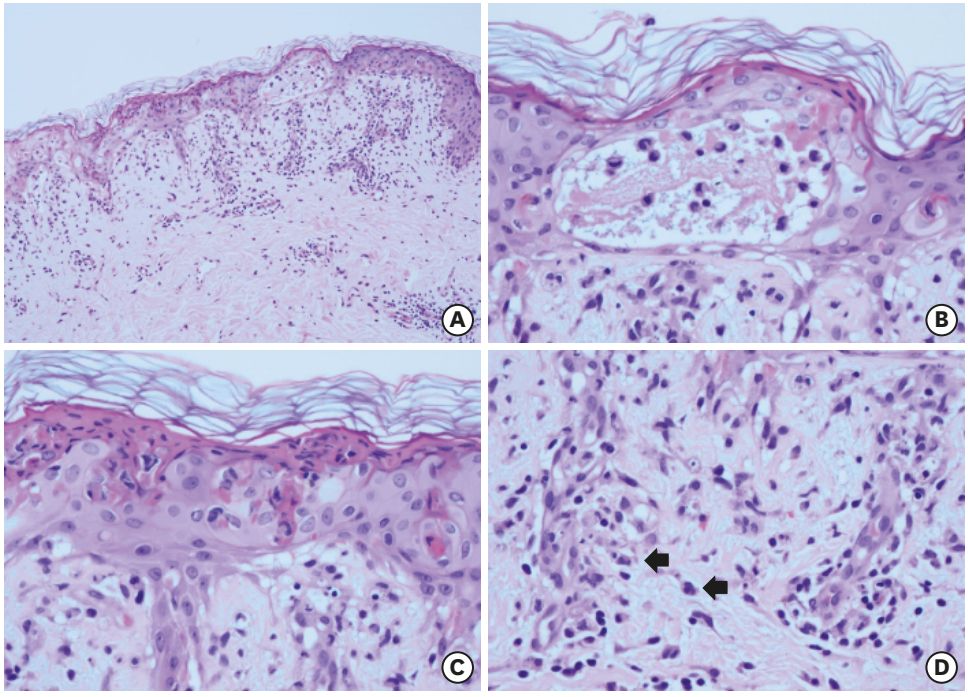


**Figure 2.** Pathologic findings of skin biopsy (hematoxylin and eosin stain).
(A) (left upper) Superficial perivascular dermatitis with spongiosis was predominantly noted. (x 100). (B) (right upper) Intraepidermal vesicle with neutrophils. (C) (left lower) Epidermal necrosis and reticular degeneration. (D) (right lower image) Superficial perivascular infiltrates comprising lymphocytes and neutrophils (arrow) were predominantly observed in the dermis.

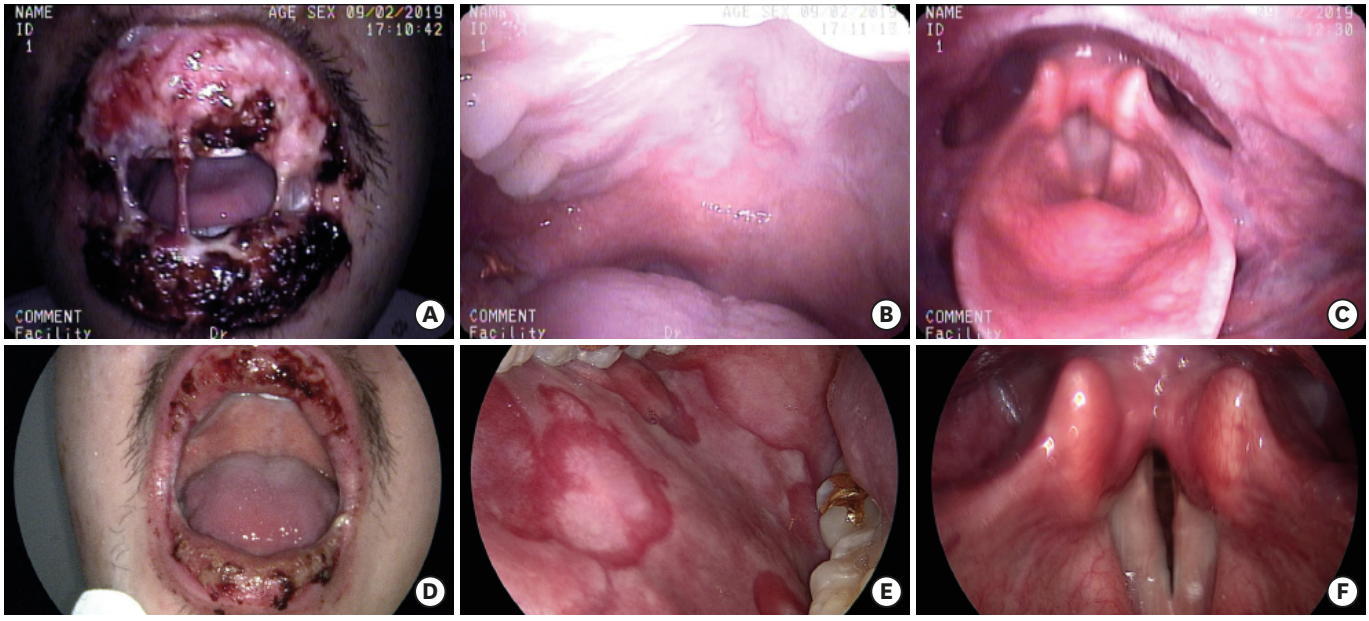


**Figure 3.** Laryngoscopic examination findings on the 8th day of admission. Lips (A) (left upper) Bleeding, discharge, and blood clots around the lips. (B) (middle upper) Palatine mucosal ulceration. (C) (right upper) Laryngeal mucosal ulceration.
Laryngoscopic examination findings on the 11th day of admission. (D) (left lower) Perioral discharge and blood clots were improved. (E) (middle lower) Buccal mucosal ulceration. (F) (right lower) Laryngeal mucosal ulceration were improved.


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## DISCUSSION

HFMD is a rare disease in adults. Only 11% of the adults exposed to the infection and less than 1% of infected adults develop HFMD [9]. In recent years, several cases of HFMD in adults were reported worldwide [3, 4]. Adult HFMD cases are often associated with CVA6, and the first case was identified in Finland after a major outbreak of HFMD in 2008 [4]. This strain caused outbreaks among both children and adults in Europe and Asia [3, 4].

The clinical manifestations of adult HFMD are quite different from those of the typical HFMD in children. Adult HFMD has atypical and more severe characteristics such as higher fever and gastrointestinal and catarrhal symptoms [5]. It often resembles EM or a disseminated herpetic eruption, indicating extensive cutaneous involvement and targetoid macules and papulo-vesicles. Thus, the clinical course of the condition is worse than that of classic cases [2, 3, 10]. Moreover, it is characterized by more widespread distribution of skin lesion in areas, including the perioral region, dorsum of the hands and feet, trunk, calves, forearms, and neck, and onychomadesis can occur [3, 10]. The rash in atypical HFMD often presents with ulcerations and scabs, and bullae can be observed [10].

SJS/TEN is a disease spectrum of severe hypersensitivity reaction involving the mucous membrane and epidermal tissue, causing the formation of bullae. It is commonly associated with drugs such as allopurinol, sulfamethoxazole, carbamazepine, phenytoin, sulfasalazine, sulfonamides, oxicam (non-steroidal anti-inflammatory drugs [NSAIDs]), and phenobarbital [6, 8]. The differential diagnosis of SJS/TEN includes EM, generalized bullous fixed drug eruption (GBFDE), and other cutaneous bullous diseases. EM is characterized by typical target lesions, bullae, and epidermal detachment. However, it is strongly associated with herpes simplex virus and rarely with drugs [11]. EM with severe mucosal involvement is referred to as erythema multiforme major, and it is often associated with systemic symptoms such as fever and arthralgias. Skin lesions of mild EM are limited to the arms, hands, and feet, but in severe cases it can spread to the mouth, genitalia, and mucocutaneous junction of the anus [12].

Allopurinol is a xanthine oxidase inhibitor used for gout management, as it reduces the production of uric acid. It is widely used despite the development of alternative agents such as febuxostat and probenecid [13]. Allopurinol can induce SCARs, including SJS/TEN, with an incidence rate of 0.69 per 1,000 person-years [14]. Allopurinol-induced SCARs are strongly associated with the HLA-B*58:01 allele and are relatively common among Asian populations [15]. In this case, with the patient's past medication history of allopurinol for gout, allopurinol-induced SCARs can be considered a major differential diagnosis in Korea. So, HLA-B*58:01 test can be meaningful although it is not a confirmatory test, drug provocation test (DPT) for excluding allopurinol-induced SCARs.

Because adult HFMD is quite uncommon and shows atypical presentations, it is often hardly distinguishable from SJS or EM. Therefore, skin biopsy with histopathologic analysis could be a useful diagnostic tool for differential diagnosis [16]. Adult HFMD and EM have similar histopathologic features such as epidermal necrosis and superficial perivascular lymphocytic infiltration. However, HFMD has quite distinct microscopic findings and clinical presentation, which are different from those of EM. For example, neutrophilic infiltration of both the epidermis and the dermis is significantly more common in HFMD than in EM. On the one hand, intraepidermal necrosis in HFMD is commonly localized in the upper third of


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the epidermis. On the other hand, EM is typically characterized by lymphocyte predominant interface dermatitis with necrosis in the lower third of the epidermis [17].

In this case, SJS was the primary clinical differential diagnosis. However, the patient was not diagnosed with the condition due to the presence of atypical features, which were as follows: (1) different patterns of skin lesions, including erythematous papules starting from the hands and feet to the thorax, unlike in SJS, which starts from the thorax to the extremities [18]; (2) severe erythematous papules and skin detachment in the hands and feet; (3) oral, pharyngeal, and laryngeal mucosal lesions that are significantly more severe than skin lesions on the same day; (4) enlarged cervical lymph nodes in the early phase; and (5) lack of abnormal laboratory results indicative of organ involvement in SJS, such as hematologic abnormalities, elevated aminotransferase levels, and decreased renal function [19]. Although we could not detect the virus in blood and tissue, clinical symptoms that were suitable for acute virus infection, and the serology test was positive, and the pathologic findings were more favorable to HFMD than SJS. Taken together, it was believed that this case was appropriate to diagnose HFMD. It is not possible to completely confirm the Coxsackievirus infection by pathologic findings, it is considered appropriate to diagnose HFMD if such pathological findings are confirmed in the context of the patient's clinical features and Coxsackievirus neutralization test result as in the case of this patient. Plus, as described above, histopathologic features were more suitable for HFMD than SJS [17].

In Korea, several cases of HFMD in immunocompetent adult patients were recorded [20]. However, this is the first case of CVA6-induced HFMD in an immunocompetent adult. The patient was initially diagnosed with SJS because he was taking a common causative drug and presented with vesiculobullous skin rash. However, he was eventually diagnosed with HFDM. This case showed that the diagnosis of adult HFDM is challenging. In addition, HFMD should be included in the differential diagnosis of patients with vesicular skin lesions with severe oral mucosal involvement.

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