Concurrent Coxsackie Virus A6 Infection and Kawasaki Disease

Hand-foot-mouth disease (HFMD), a highly contagious viral infection commonly affecting children younger than five years, usually shows maculopapular or vesicular eruptions on the hands, feet, and the oral mucosa. Coxsackievirus A16 and Enterovirus 71 are the predominant HFMD pathogens. Of them, Coxsackievirus A6 (CVA6) manifests the more severe or atypical variant of HFMD, characterized by high fever with vesiculobullous exanthema often spreading more widely on the trunk and extremities, with perioral zone involvement [1]. Kawasaki disease (KD), the most common childhood vasculitis, preferentially involves coronary arteries. The KD etiology remains obscure despite extensive research undertaken to elucidate it. Infections may be the potential trigger for KD, especially in genetically susceptible children [2]. Our patient presented with concurrent occurrence of HFMD and KD. We therefore attempt to address comorbidity between CVA6-associated HFMD and KD.

A previously healthy Japanese 3-year-old boy was hospitalized for fever, left cervical swelling, and rash, which began 3 days before admission. His temperature was 39.4°C. Left cervical lymph nodes were tender and enlarged. Oral examination revealed 1-2 mm fine petechiae on the soft palate and erosions on the buccal mucosa. There were diffuse 1-3 mm discrete, monomorphic, erythematous papules concentrated primarily on the face in the perioral region and forehead, palms and soles, dorsal hands, fingers, and buttocks. Cardiac, respiratory, and abdominal examinations were normal at admission. The patient's elder sister had a past history of KD.

Laboratory findings included hemoglobin of 11.1 g/dL, white blood cell count of 18.1×10^9/L (neutrophils 84.4%, lymphocytes 15.6%), platelet count of 347×10^9/L, C-reactive protein of 8.74 mg/dL, and procalcitonin of 0.68 ng/mL. Coronavirus disease 2019 (COVID-19) antigen determined by the automated immunoassay system HISCL-800 (Sysmex Corp.) using nasopharyngeal swab was negative. Other laboratory tests to examine electrolytes, liver function, and kidney function yielded normal results. Intravenous ceftriaxone (100 mg/kg/day for 3 consecutive days) failed to reduce fever. Periungual hemorrhagic bullae became evident on several digits of the hands and feet.

On the 5th hospital day, an additional diffuse erythematous maculopapular rash, bilateral non-purulent conjunctival hyperemia, injected, dried and fissured lips, and strawberry tongue were found. Echocardiography showed a hyperechogenous aspect of both coronary arteries with mild dilatation. A diagnosis of KD was made. The patient was treated with intravenous immunoglobulins (IVIG, 2 g/kg over 24 hours of infusion) along with oral acetylsalicylic acid (33 mg/kg/day) [3]. Fever improved promptly on the following day. On the 7th hospital day, cutaneous desquamation of fingers and toes developed. C-reactive protein became normal. Acetylsalicylic acid was decreased to a single dose of 3.3 mg/kg/day. The patient was discharged on the 9th hospital day, after which the clinical course was uneventful. Echocardiography findings were completely normal after 35 days. Neutralizing antibody levels for CVA6 measured at admission were 512-fold higher than normal.

This case underscored two clinical issues: concomitant HFMD and KD, and provocation of KD by CVA6-associated HFMD. Concurrent occurrence of HFMD and KD is uncommon. A severe outbreak of HFMD associated with CVA6 in Japan occurred in the autumn of 2021. During that HFMD outbreak, none of the other affected individuals developed KD. Rigante, et al. [2] first reported KD with concurrent Coxsackievirus B3 infection. Widespread papulovesicular eruptions, the ongoing pandemic of CVA6, and markedly increased viral antibody titers all indicated CVA6-associated HFMD. All six diagnostic signs of KD with hyperechogenicity of coronary arteries were well consistent with KD. It is possible that CVA6-associated HFMD might trigger KD development. The associations among approximately 15 viruses and KD were investigated using serological and polymerase chain rection (PCR) assay [4]. Coxsackieviruses interact with components of the innate immune system, which can destroy peripheral tolerance and can ultimately induce autoimmune diseases including myocarditis and diabetes following infection [5]. The elder sister had KD at three years of age, and progressed well with IVIG and oral acetylsalicylic acid without any concurrent disease. Siblings of affected patients with KD tended to be more susceptible to developing KD than those without a sibling history [6]. Although the etiology of KD remains unknown, it presumably results from abnormal immunologic response to various infections in genetically susceptible individuals [2,4,7]. Reportedly, CVA6-associated HFMD that is severer than ordinary HFMD might elect excessive systemic inflammation or dysregulate innate immune response. Along with the sibling history of KD, it might eventually have predisposed this patient to develop KD [1, 7].

A four-fold or greater increase in antibody titer is inferred as serologically significant when the acute and convalescent phases are measured simultaneously, but antibody titer of CVA6 was assessed only once at the acute phase in this case. Secondly, PCR analysis to evaluate the association between CVA6 infection and KD were not performed. Third, cytokine profiles to monitor immunomodulation during the acute phase of HFMD and KD were not obtained.

In conclusion, although cases of concurrent HFMD and KD are uncommon, they are expected to be likely. Further investigations must be conducted to ascertain true immunomodulation to various inciting infections and/or genetic factors in KD. Knowledge in those areas would be appreciated to establish promotion of innovative treatments and precautionary measures against KD.

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