Case Report

Asia Pacific Allergy

OPEN

A 14-year-old boy with severe erythema multiforme due to amoxicillin

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ABSTRACT

The most common cause of erythema multiforme (EM) in children is infectious diseases which account for approximately 90% of cases. Drug eruptions are another common cause. Here we are reporting about a male patient aged 14 years with lymphadenitis who developed severe diffuse erythema during the course of treatment with medications including several antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs). Based on the pathological findings of the skin biopsy, the skin rash was due to EM. Upon investigating the underlying cause of EM, viral antibody was positive for Coxsackie A6, lymphocyte transformation testing (LTT) was positive for one of the NSAIDs, and the patch test (PT) was positive for amoxicillin. Based on the pattern of distribution of the skin rash, the cause of EM was considered to be drug-induced eruption due to amoxicillin. In this case, we did not derive a diagnosis of drug eruption without investigating the possibility of drug induction, because most cases of EM in children are induced by infection and the antibody against Coxsackie A6 was elevated. To diagnose the possibility of amoxicillin-induced EM, it was important to distinguish between the distribution patterns of infectious versus drug-induced EM and to evaluate the possibility of drug induction by both LTT and PT. If the diagnosis of amoxicillin-induced EM, had not been made, the potential recurrence of EM with amoxicillin could have occurred.

Keywords: Coxsackie virus A6; drug eruption; erythema multiforme; lymphocyte transformation testing; patch test

1. Introduction

Erythema multiforme (EM) is an acute, self-limiting skin disease characterized by the abrupt onset of symmetric fixed red papules, some of which evolve into typical and/or occasionally atypical papular targets [1]. Infectious diseases account for approximately 90% of the causes of EM in children. Other causes include drugs, autoimmune diseases, and malignancies [2]. There are few cases in which the cause of EM is identified in children [3].

Up to 10% of children treated with antibiotics have cutaneous adverse drug reactions, but drug allergy is confirmed in <20% of patients [4]. Since drug allergy to penicillin accounts for the highest rate, skin rash developing during use of penicillin should be suspected as drug eruption [5]. However, it is difficult to diagnose drug allergy due to low sensitivity and difficulty in timing of several tests including lymphocyte transformation testing (LTT) and patch test (PT). For diagnosis of the drug allergy in EM, the clinical course, shape and distribution pattern of the skin rash, and skin pathology are also important [6].

We present a case of diffuse erythema associated with antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) and infection with Coxsackie A6 and discuss how to evaluate the cause of the rash.

2. Case presentation

2.1. Present history

A 14-year-old Japanese boy visited our hospital due to persistent fever, cervical lymphadenopathy, and diffuse skin rash. He did not have a medical history of allergy. Based on his family history, his father had allergic rhinitis, and his mother and sister had atopic dermatitis. He had a history of having taken all scheduled vaccinations.

Fourteen days before the onset of the rash, he noticed a swelling and tenderness on the left side of his neck. Upon visiting his local doctor 11 days before the onset of the rash, he was prescribed cefteram pivoxil and planoprofen. He revisited the doctor due to a low-grade fever 10 days before the onset of rash, when both the antibacterial drug and the NSAID were changed to Amoxicillin hydrate and potassium clavulanate hydrate, Loxoprofen sodium hydrate. However, due to persistent fever, he revisited the doctor 5 days before the onset of rash, both the SARS-CoV-2 PCR test and rapid influenza antigen test were negative. The doctor changed both the antibiotic and the NSAID again to cefditoren pivoxil, lornoxicam, and teprenone along with antacids. Since the fever persisted and skin rash was observed on the trunk, 3 days before the admission, he was referred to our department. At the time, lymphadenitis was diagnosed, and the antibiotic was further changed to faropenem, tranexamic acid, L-carbocysteine, and acetaminophen, with antacids. In light of the persistent fever and extended skin rash, he was admitted to our hospital for further investigations and treatment of suspected severe drug eruption. He had no

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previous history of exposure to drugs administered during the course of his disease.

2.2. Physical examinations and laboratory examinations

On admission, vital signs demonstrated a body temperature of 38.2°C, pulse rate of 80/minutes, respiratory rate of 20/minutes, blood pressure of 114/72 mmHg, and oxygen saturation of 98% (room air). Physical examination showed clear consciousness, no ocular conjunctival hyperemia, no ocular discharge, no ocular pain, no pharyngeal redness, and 2 stomatitis, 2–5 mm in size on the lower lip and the tip of tongue. Enlarged lymph nodes (2 cm in size) were detected bilaterally under the auricles and in the right axilla. Large lymph nodes of 1 cm were detected bilaterally in the inguinal region. Enlarged lymph nodes were tender, not erythematous, marginated, and not fixed. The skin rash was diffuse erythema all over the body, with a tendency of fusion on the trunk and edematous on lower limbs, accompanied by itching and heat sensation (Fig. 1). The Nikolsky's sign was negative. Hepatosplenomegaly was not found, and other abnormal findings were not observed.

Laboratory findings of peripheral blood showed white blood cell count of 4300/μL, aspartate aminotransferase was 91 IU/L, alanine transaminase was 123 IU/L, lactate dehydrogenase 469 IU/L, shown in Table 1. Ultrasonography demonstrated an internal homogeneous low-echo mass with a maximum diameter of 15 × 30 mm located in the neck, with no internal debris.

Pathological findings from the skin biopsy led to the diagnosis of EM (Fig. 2). There was no sign of Stevens-Johnson syndrome (SJS).

2.3. Disease course during admission

Since severe drug eruption such as SJS/toxic epidermal necrosis (TEN) was suspected due to diffuse erythema observed on the face, trunk, and extremities, a skin biopsy was performed at the time of admission. However, Nikolsky's sign was negative and there was no mucous membrane rash. Furthermore, the general condition was not markedly severe. Therefore, there was less likelihood of a severe drug eruption. Antibacterial agents and NSAIDs were discontinued considering the possibility of drug eruptions. Intravenous fluids, intravenous antihistamines, and topical ointments were started. The patient's mucosal symptoms and skin rash did not increase after admission. From the third day of hospitalization, the fever subsided, and the cervical lymph node swelling and skin rash decreased in size. On the sixth day of hospitalization, the cervical lymph node swelling disappeared and only a small amount of skin rash remained on the lower legs. He was therefore discharged. The dermatopathological diagnosis from the skin biopsy was EM. To investigate the cause of the EM, in this case, the cause might be infections or drugs. Regarding infections, several antibodies against pathogens that can possibly induce EM were measured. Only the IgG antibody against Coxsackie virus A6 was elevated (Table 1). Regarding drugs, LTT and PT were performed. LTT examines drug-sensitized lymphocytes in vitro. For LTT, lymphocytes were isolated from the patient's peripheral blood, to which the suspect drug and 3H-thymidine, a DNA precursor, were added and cultured for a certain time, and the amount of 3H-thymidine incorporated during DNA synthesis was measured. We use ampicillin sodium was 10%, amoxicillin hydrate was 5%, amoxicillin hydrate, potassium clavulanate hydrate, and NSAIDS as is. LTT for antimicrobial drugs which was performed on the ninth day after admission showed that Amoxicillin hydrate and potassium clavulanate hydrate, cefteram pivoxil, and faropenem were negative. Only lornoxicam among LTT for NSAIDs including loxoprofen sodium, lornoxicam, and pranoprofen performed on 1 month after onset was positive. (SI value: 180%) PT for the antimicrobial drug series including 34 drugs were performed approximately 1 month after the onset of illness, and PTs for the NSAIDs series including 14 drugs were performed approximately 3 months after the onset of illness. While PT was positive

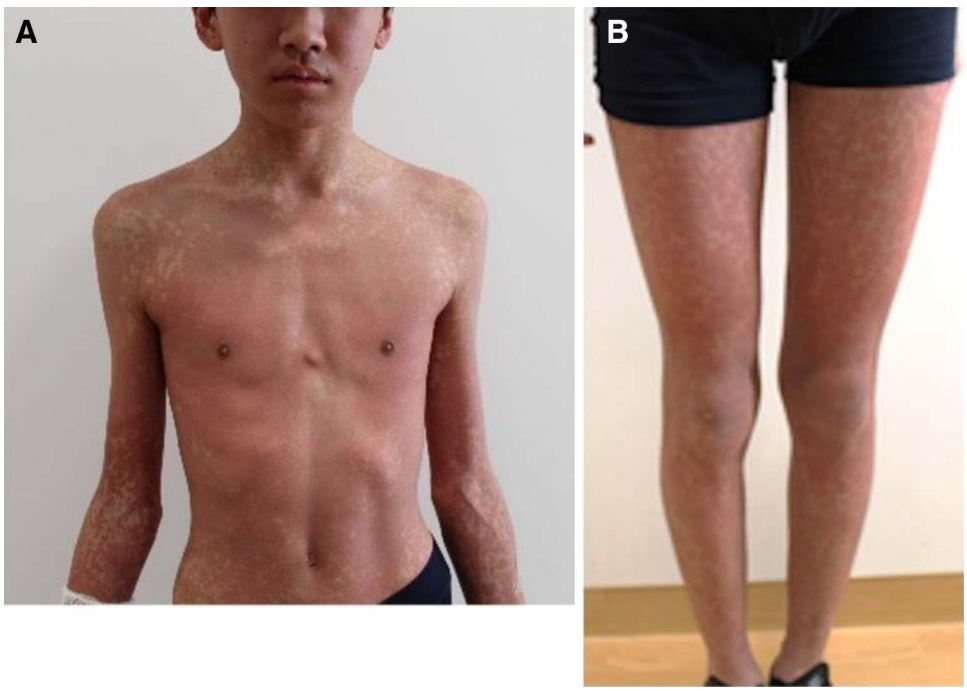

Figure 1. **(A)** Skin rash of ventral trunk. **(B)** Skin rash of lower extremities. Diffuse erythema was seen on the whole body. Erythema on the trunk showed a tendency to fusion and that on the lower extremities showed edematous changes.

Table 1.

Laboratory data at admission

Blood cell count	
WBC	4300/μL
RBC	$476 \times 10_4$/μL
Hb	13.5 g/dL
Plt	26.1 × 10/μL
Seg	51.50%
Ly	36.00%
Mono	8.00%
Eosino	3.50%
Serum biochemical data	
BUN	12.8 mg/dL
Cre	0.55 mg/dL
AST	91 IU/L
ALT	123 IU/L
LDH	469 IU/L
Na	141 mEq/L
K	4.4 mEq/L
Cl	103 mEq/L
CRP	0.07 mg/dL
C3	98 mg/dL
C4	23 mg/dL
CH50	41 U/L
sIL-2R	1293 U/ml
Coagulation fibrinolytic system	
PT/INR	1.29
APTT	43.4 seconds
D-dimer	1.0 ug/mL
Fibrinogen	343 mg/dL
Infection data	
ASO	39 UI/mL
Anti-*M. pneumonia* antibody	160 times
Anti-HBs antibody	Negative
Anti-HCV antibody	Negative
EBV viral capsid antigen IgM	Negative
EBV viral capsid antigen IgM	Negative
EBV unclear antigen IgG	Negative
Anti-HTLV-1 antibody	Negative
Anti-HIV antibody	Negative
Coxsackie A6/NT	128 times
Coxsackie A 16/NT	6 times

ALT, alanine transaminase; APTT, activated partial thromboplastin time; ASO, anti-streptolysin O; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CH50, 50 % hemolytic unit of complement; CK, creatine kinase; CRP, C-reactive protein; EBV, Epstein-Barr virus; FDP, fibrin degradation products; HBs, hepatitis B surface; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV-1, human T-cell leukemia virus type 1; Ig, immunoglobulin; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; PT-INR, international normalized ratio of prothrombin time; RBC, red blood cells; sIL-2R, soluble interleukin 2 receptor; WBC, white blood cells.

only for amoxicillin among the antimicrobial drugs, it was negative for all NSAIDs.

3. Discussion

We report here a case of a 14-year-old Japanese boy with lymphadenitis, who was treated with antimicrobial drugs and NSAIDs and was suspected to have severe drug eruption such as SJS/TEN because of developing diffuse erythema during the course. Skin rash was diffuse erythema with a tendency to fuse on the face, trunk, and extremities. Although 2 stomatitis, 2–5 mm in size on the lower lip and the tip of tongue were observed, no mucosal eruption was observed on the lips, eyelid conjunctiva, or vulva, His symptoms improved without glucocorticoid medication and only with discontinuation of the suspected drugs and administration of antihistamines.

In this case, the pathological diagnosis from the skin biopsy performed on admission was EM. The pathological findings of EM are characterized by lymphocytic infiltration into the epidermal-dermal junction and liquid degeneration of basal cells in

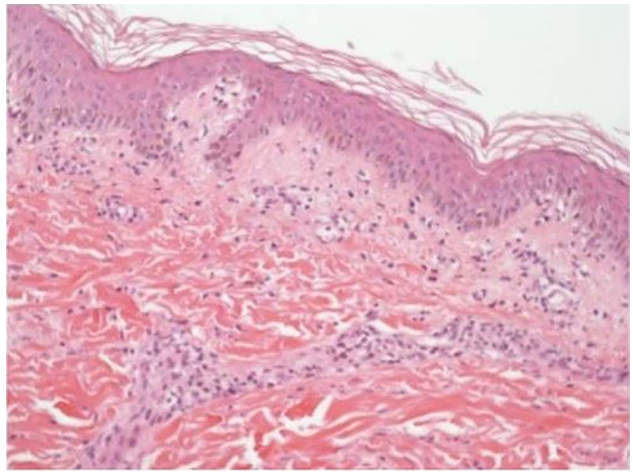

Figure 2. Histological examination showed keratinocyte vacuolar lesion (black arrow) at the dermo-epidermal border with necrosis of keratinocytes. Infiltration of few lymphocytes and histocytes around enlarged vessels in the dermal epithelium. (hematoxylin-eosin; original magnification ×10).

the early stage, and lymphocytic infiltration into the epidermis, leading to abnormal keratinization and subepidermal blistering in the advanced stage [6]. On the other hand, in SJS/TEN, the pathological findings are characterized by the detachment of the epidermis from the basement membrane and the observation of epidermal necrosis in all layers [6]. However, such findings in SJS/TEN were not observed in this case. EM associated with infectious diseases can be caused by a wide variety of factors, such as herpes simplex virus, mycoplasma, streptococcus, and coxsackie virus [6]. In this case, Only IgG antibody against coxsackie virus type A6 was elevated, suggesting that cervical lymphadenitis and EM were caused by coxsackie virus infection.

The distribution pattern of EM caused by infection is predominantly on the extremities, while that of drug-induced EM is predominantly on the face and trunk. This is an essential point in estimating the cause of the disease [7]. In this case, the skin rash was predominantly on the face and trunk. Therefore, the possibility of drug-induced skin rash should be considered.

The positivity rate of LTT is around 40% in Japan, 48% in disseminated severer erythema, and 40% in erythema exudative multiforme, depending on the nature of the rash [8]. The positivity rate of PT is 20%–60% in Japan, 9%–23% in severe drug eruptions in France, and 55% in Germany in some reports [9, 10]. LTT is more likely to be positive in the acute phase of the disease for SJS/TEN, and in the decompensation phase for DIHS [11–13]. Therefore, LTT is preferred over PT because it is safer and has a higher positive rate, but the timing of the test should be carefully considered.

Although LTT is considered to have a high positivity rate in erythrocytosis, in this case, all results were negative. This result may be due to the late timing of the LTT. However, only amoxicillin among antimicrobial agents was positive in PT, suggesting that amoxicillin was the cause of the rash. NSAIDs are known to have PGE2 inhibitory effects, which may result in a higher SI [14]. Since the SI for lornoxicam was slightly above the borderline and the PT for lornoxicam was negative, the LTT for lornoxicam was determined to be false positive.

Penicillin allergy accounts for the highest rate of drug eruptions, accounting for 5%–10% of all drug allergies in adults and children [5]. The most common type of drug eruption caused by penicillin antibiotics is the disseminated papulovesicular type, but the EM type is also frequent.

On advising patients through these results, regarding all betalactams except amoxicillin used in this study, LTT and PT are negative, and many other types of betalactams have been tested for PT, all with negative results. For this reason, we do not believe it is necessary to avoid all other betalactams. Although the possibility that lornoxicam may cause drug allergy cannot be ruled out completely based on the LTT result, there is little need to conduct drug-induced tests, and there are several alternative drugs that can be used in the form of alternative drugs.

4. Conclusion

In this case, amoxicillin administered during the course of cervical lymphadenitis caused by Coxsackie A6 infection was thought to be the cause of severe EM. The following 2 points are thought to be important in diagnosing the cause of EM in this case. One is to differentiate between infectious and drug-induced EM based on the characteristics of the distribution pattern of the skin rash. The other is to evaluate the possibility of drug-induced EM by multiple tests because the positivity rate of a single test was low. Due to the movement of patients for job or schooling reasons, it is also useful to note that there are disparities in the pattern of penicillin allergy in the Asia Pacific region [15]

Informed consent

Written informed consent was obtained from the 15-year-old patient and his parents for the publication of this article. It is available for submission at the request of the editorial office.

Conflict of interest

The authors have no financial conflicts of interest.

Author contributions

Conceptualization: Mami Kurihara, Shingo Yamanishi, and Ruby Pawankar. Investigation: Mami Kurihara, Shingo Yamanishi, and Saeko Ozaki. Clinical treatment: Mami Kurihara and Shingo Yamanishi. Project administration: Shingo Yamanishi and Ruby Pawankar. Writing original draft: Mami Kurihara, Shingo Yamanishi, and Ruby Pawankar. Review and edits: Shingo Yamanishi and Ruby Pawankar. Final version: all approved.

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