Late-onset rash in patients with group A beta-hemolytic streptococcal pharyngitis treated with amoxicillin

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Abstract

We observed late-onset rashes in patients with group A beta-hemolytic streptococcal (GAS) pharyngitis. Of 1028 patients with GAS pharyngitis, which was principally treated with amoxicillin, we evaluated those who developed a late-onset rash and excluded those with scarlet fever alone. Twenty-one patients developed a rash (2.0%, 95% confidence interval, 1.3-3.1%), 7 to 20 days (median, 8 days) after GAS pharyngitis onset. The rashes were characterized by maculopapules, which increased in size with coalescence and some developing into plaques, with a symmetrical distribution with a propensity for the extremities, including the palms and soles. The clinical courses of the patients were good, and the rashes subsided within 14 days. A non-immediate reaction to β -lactams, which usually manifests as a maculopapular rash, is a possible cause in our patients, however, repeated courses of amoxicillin in 3 patients did not induce the rash. The underlying mechanism of the late-onset rash after GAS pharyngitis with amoxicillin treatment remains unclear.

Introduction

Group A beta-hemolytic streptococci (GAS) are common pathogens causing pharyngitis. These organisms are responsible for around 20% and 10% of pharyngitis cases in children adults respectively.¹ The skin manifestations of GAS infection are well known as scarlet fever. Other skin manifestations of GAS infection, such as erythema marginatum in rheumatic fever and erythema nodosum, are rare.² Among patients with GAS infection, we observed patients with late-onset rash characterized by macules or papules, which later coalesce 7 days or more after the onset of pharyngitis. The rash was self-limiting and had a good clinical course. Although GAS infection is common, this phenomenon is rarely reported.

Case Report

At Kimura Children and Family Clinic, Izumo, Japan, we treated three patients who developed a late-onset maculopapular rash with coalescence 7 days after the onset of GAS pharyngitis in July 2006. They were examined by dermatologists and diagnosed with erythema multiforme. They had GAS pharyngitis 7 days before the rash. Since these three patients, we have observed several patients with similar clinical courses. From April 1, 2006 to May 31, 2014, we evaluated the clinical course of these patients including the first three patients. We excluded patients who had scarlet fever alone in the acute phase. We also reviewed all cases of GAS pharyngitis. A diagnosis of GAS pharyngitis was made according to the presence of clinical features such as tonsillopharyngeal erythema and exudate, and tender anterior cervical lymphadenopathy (with or without fever), necessarily accompanied by a positive assay for rapid GAS antigen (ImmunoCARD EX STREP A, TFB Inc., Tokyo, Japan), which is an enzyme-linked immunosorbent assay kit with 95.1% sensitivity and 99.0% specificity compared with a standard throat culture according to the product information. We did not perform viral or immunological investigations for any of the patients.

Results

During the study period, 1,028 patients presented with GAS pharyngitis at our clinic. They were treated with a 10-day course of amoxicillin (AMPC), except oral cephalosporins in some recurrent cases. Twenty-one patients showed a rash after the acute phase (7 days or more after the pharyngitis onset), representing an incidence of 2.0% (95% confidence interval, 1.3-3.1%; Table 1). Twelve patients were male and 9 were female, with the ages ranging from 4 to 62 years (median, 7 years). AMPC was administered to 20 patients as a 10-day course. The course was completed in 17 patients and was discontinued in 3 patients after the skin rash appeared. One patient (Patient 7) was treated with cefcapene pivoxil for 3 days followed by AMPC for 7 days. The acute symptoms of GAS pharyngitis subsided within a few days after the treatment in 20 patients, although 1 patient (Patient 20) had fever for 3 days and abdominal pain at GAS pharyngitis onset.

The rash appeared 7 to 20 days (median, 8 days) from GAS pharyngitis onset (Figure 1). Initial manifestations included red or pink macules or papules, which gradually increased in size and coalesced. It had a symmetrical dis-

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tribution on the extremities (where it was prominent and involved both the palms and soles), trunk, and face (Figure 2). It was fixed and progressed over a few days. One patient (Patient 2) had erythema of the oral mucosa, and itching was observed in 15 patients (71%). The first three patients (patients 1, 2, and 3) were diagnosed erythema multiforme by dermatologists. However, typical target lesions were not observed in either of the 3 patients or the other 18 patients. Two patients (patients 4 and 6) with scarlet fever in the acute phase had a longer latency until the rash appeared 15 and 20 days after GAS pharyngitis onset, respectively. At the emergence of the rash, none of the patients showed any signs or symptoms such as hepatosplenomegaly except for the skin manifestations and itching. They were all in good clinical condition. Twenty of the 21 patients were given antihistamines and 3 were given oral prednisolone. The rash duration was 3 to 14 days (median, 7 days). Three patients (Patients 6, 13, and 19) were given further courses of AMPC for recurrent GAS infection, although the rash did not recur.

Discussion

We reported cases of late skin manifestations after GAS pharyngitis onset in 21 of 1028 patients. These cases were characterized by i) the onset of rash around 8 days after GAS pharyngitis onset; ii) red macules or papules, which increased in size and coalesced; iii) symmetric distribution with a propensity for

the extremities, including the palms and soles; iv) no clinical features other than the rash and itching; and v) rash duration of 4 to 14 days.

The rash resembled that of erythema multiforme, which is characterized by a polymorphous eruption of macules, papules, and characteristic target lesions. The target lesions are the diagnostic hallmark of erythema multiforme and have three concentric zones that consist of a central darker red area, a paler pink or edematous zone, and a peripheral red ring.³ However, none of our patients showed such typical target lesions. In contrast to typical erythema multiforme, the skin manifestations of the present patients were short lived. Moreover, as skin biopsy was not performed,

Figure 1. Time to onset of rash from the beginning of group A beta-hemolytic streptococcal pharyngitis.

Figure 2. A) A 8-year-old boy (Patient 18): papules with partial coalescence on the trunk and upper extremity on the second day of the rash. B) A 6-year-old boy (Patient 21): scattered macules on the palms on the second day of the rash; C) A 7-year-old girl (Patient 11): numerous red papules with coalescence on the back on the third day of the rash on the third day of the rash.

Table 1. Patients' characteristics.

	Sex	Age, years	Onset, days	Duration, days	Itching	10 day-AMPC treatment	Antihistamine /steroid	Remarks
1	M	6	7	7	-	Complete	-/-	Dermatologist examined
2	F	7	7	5	+	Incomplete	+/-	Dermatologist examined, oral exanthema
3	F	6	7	7	-	Incomplete	+/+	Dermatologist examined
4	M	8	8	NA	+	Complete	+/-	Cefcapene pivoxil for 3 days followed by AMPC for 7 days
5	F	5	15	4	-	Complete	+/-	Scarlet fever in the acute phase
6	F	4	8	3	-	Complete	+/-	No event in the two further courses of AMPC
7	M	9	20	NA	+	Complete	+/-	Scarlet fever in the acute phase
8	F	31	8	14	+	Complete	+/+	-
9	M	12	9	7	+	Complete	+/-	-
10	F	62	9	7	+	Complete	+/-	Household infection
11	F	4	7	6	-	Complete	+/-	-
12	M	9	9	4	+	Complete	+/-	-
13	M	9	7	10	+	Complete	+/-	No event in the one further course of AMPC
14	M	5	8	7	-	Complete	+/-	-
15	M	7	8	NA	+	Complete	+/-	-
16	F	11	7	NA	+	Complete	+/-	-
17	F	13	8	NA	+	Complete	+/-	-
18	M	8	7	7	+	Incomplete	+/-	-
19	M	4	9	4	+	Complete	+/-	No event in the one further course of AMPC
20	M	5	7	4	+	Complete	+/-	Fever for 3 days and abdominal pain at the onset GAS pharyngitis
21	M	6	9	4	+	Complete	+/-	-

Onset: days from the disease onset to the rash appearance, Duration; rash duration, NA: not available, Incomplete: stopping the medication at the rash appearance; AMPC, amoxicillin.

we were unable to diagnose erythema multiforme. Urticaria, in which lesions are transient and typically last less than 24 hours, is also a differential diagnosis. However, the rash was fixed rather than migratory. Scarlet fever has a typical rash characterized by diffuse, finely papular, erythematous eruptions, which usually appears within 24 to 48 hours after GAS pharyngitis onset.² The late-onset rash was different from that of scarlet fever regarding the skin finding and timing of appearance. Two patients (patients 4 and 6) had both scarlet fever and late-onset rash.

Co-infection with Epstein-Barr virus is also one possible reason for the rashes in the present cases. However, this seems unlikely because the clinical symptoms were quickly resolved with the initial antibiotic therapy in the acute phase. Moreover, no features other than skin manifestations (*e.g.*, hepatosplenomegaly, malaise or fatigue) were present at the emergence of the rash. In infectious mononucleosis, a more rapid onset, within 3 days after aminopenicillin administration, is usual for drug-eruption,⁴ whereas our patients showed rash after 8 days.

Kodo reported that among 1245 patients with streptococcal pharyngitis, 32 developed rashes in a prospective study.⁵ Out of 32 patients, 18 were treated with AMPC (3.1%, 18/580 patients); 9, with cephalosporin antibiotics (3.2%, 9/275 patients); and 3 with penicillin G (0.9%, 3 out of 325 patients). The rash appeared during the course of antibiotics treatment in 76% of them and after antibiotics treatment in 24% of them. The patients treated with AMPC tended to have severe and showed a varied nature of the rash compared with those treated with cephalosporin antibiotics or penicillin G. The incidence of the rash (3.1%) was nearly the same as ours (2.0%). However, in our study, some patients with late-onset skin rashes were probably lost to follow up and might have consulted a dermatologist, so the incidence is possibly higher.

Because all the patients in this study took AMPC, drug eruptions should be considered. Allergy to β -lactams are well-known, consisting of 2 types of reactions, namely immediate reactions, which are mediated by specific Ig-E antibodies, and non-immediate reactions, which are suggested because of their cell-mediated pathological mechanism.⁶ In the non-immediate reactions, maculopapular rashes are common.⁷ In a prospective study of 933 patients who received ampicillin treatment, 68 (7.3%) of the patients developed rashes that were mostly maculopapular, but not urticarial.⁷ The rashes appeared 9 days from the beginning of the treatment, almost

the same as that in our study (8 days after GAS pharyngitis onset). The rashes were not accompanied by skin exfoliation, significant mucous membrane involvement, or anaphylaxis. The authors mentioned that the future treatment with ampicillin was not a contraindication.⁷ Bierman *et al.* reported that all 34 patients with maculopapular rashes treated with ampicillin had no reaction to the re-administration.⁸ Moreover, Romano *et al.* reported that 38 (90%) of 42 children with histories of maculopapular rashes during aminopenicillin treatment had negative results both in allergologic tests and oral challenges.⁹ Ponvert *et al.* reported that oral challenge tests yielded positive results in 19 (7%) of 264 patients with a history of β -lactam hypersensitivity who presented with maculopapular rashes.¹⁰ These findings indicated that allergy to β -lactams in patients with maculopapular rashes of non-immediate reactions could be hardly proved by allergologic tests and oral challenges. Three patients in our study (patients 6, 13, and 19) did not have recurrence of the rash after further courses of AMPC.

The late-onset rashes in our patients were most likely caused by non-immediate type of AMPC hypersensitivity. However, a drug provocation test, which is thought to be the most reliable diagnostic tool, had a low yield in patients with non-immediate reactions to β -lactams.⁸⁻¹⁰ Prolonged oral provocation test also had a low yield.¹¹ Moreover, three of our patients showed no recurrence of the rash with repeated courses of AMPC. Therefore, it is difficult to explain the pathophysiological mechanism only with AMPC hypersensitivity. Some factors other than drug-specific T cells, such as infection itself or nonspecific activation of innate immunity by drugs, can cause maculopapular rashes during a drug treatment.¹² If this late-onset rash is truly due to allergy to AMPC, tolerance to AMPC may develop after appearance of the rash in patients with a negative provocation test.¹²

GAS pharyngitis is common in daily practice. It is important to know that at least 2% of patients with GAS pharyngitis treated with AMPC will develop late-onset rash. Because our patients had a good natural course, a better understanding of the underlying mechanism behind this late-onset skin rash is clinically relevant to avoid unnecessary further laboratory tests and anxiety of the patient and their family.

Conclusions

We reported late-onset rashes appearing 7 to 9 days after GAS pharyngitis onset in 2% of our patients. The rashes were maculopapular, increasing in size and coalescing, with some developing into plaques. The rashes were likely to be caused by non-immediate type of AMPC hypersensitivity; however, repeated courses of AMPC in 3 patients did not induce the rash. The underlying mechanism of the late-onset rash after GAS pharyngitis treated with AMPC remains unclear.

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