Skin Rash During Epstein-Barr Virus–Induced Infectious Mononucleosis in Adolescents and Adults: Incidence, Predisposing Factors, and Prognostic Implications

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Skin rash is a potential complication of Epstein-Barr virus (EBV)–induced infectious mononucleosis (IM) [1]. Classic studies from the 1960s reported skin rash in most IM patients receiving aminopenicillins, with frequencies of up to 100% for children [2], 94% for adolescents [3], and 69% for university students [4], compared with 10%-16% for patients not receiving antimicrobials [2-4]. This frequency of the so-called ampicillin rash or amoxicillin rash is still assumed in reviews [1,5-6], although recent studies reported a lower incidence (<30%), at least in children [7,8]. The rash was later reported to occur with ß-lactams and antimicrobials [9]. It is generally assumed that while antibiotic-related rash during IM does not indicate long-term hypersensitivity, it may reveal true allergy in some children [8,10]. The median age of IM patients with rash is lower than that of those without [11]. In the general population, however, drug allergy is more common in adults than in children [6]. We aimed to investigate the frequency, associated factors, and implications of skin rash in adolescents and adults with IM.

This retrospective study included 396 patients (208 male [52.5%]; median age 19 years [range, 15-87 years]) who were admitted to Santiago de Compostela University Hospital, Santiago de Compostela, Spain (1995-2018), as reported elsewhere [12]. Patients were diagnosed as having IM when a compatible clinical syndrome was accompanied by positive values for IgM antibodies against the capsid antigen of EBV and/or a positive heterophile antibody result [1,12].

Forty patients developed skin rash (10.1%). This was present on admission in 36 cases and appeared shortly thereafter in 4 cases. The rash was maculopapular in 36 patients, urticarial in 3, and purpuric in 1 patient and was more frequent in females than in males (26/188 [13.8%] vs 14/208 [6.7%]; *P*=.019) (Table). Age was similar in patients with and without rash (Table). Rash was more common in patients who received antibiotics prior to admission than in those who did not (34/202 [16.8%] vs 6/194 [3.1%]; *P*<.001) (Table). Rash developed in 29 of 162 (17.9%) patients receiving ß-lactams (amoxicillin in 10 cases, amoxicillin-clavulanic acid in 14 cases, and phenoxymethylpenicillin in 5 cases). Specifically, rash developed in 24/116 patients (20.6%) previously treated with amoxicillin (with or without clavulanic acid [Table]). Rash was more frequent in patients who received ß-lactams than in those who were treated with other antibiotics, although the difference was not statistically significant (*P*=.668), because fewer patients were receiving non–ß-lactam antibiotics (Table; Supplementary Figure 1). The rash developed after a median of 7 days of antibiotic therapy (range, 1-11 days). Duration of treatment did not differ significantly between rash related to ß-lactams and rash related to other antibiotics (data not shown). A total of 234 patients later received antibiotics during hospital admission owing to bacterial superinfection of the tonsils (macrolides in 119 cases, clindamycin in 45, quinolones in 14, and ß-lactams in 56 [amoxicillin in 11 of these cases]); none of them developed skin rash.

Clinical and immuno-hematological characteristics were similar in patients with and without rash (Table). Among patients who had previously received ß-lactam therapy, rash was more frequent in heterophile-negative patients (5/8, 62.5%) than in heterophile-positive patients (22/149, 14.7%; *P*=.003). An age-adjusted multivariate model (logistic regression) revealed female sex (OR, 2.45; 95%CI, 1.16-5.18; *P*=.018), previous ß-lactam therapy (OR, 5.46; 95%CI, 2.37-12.6; *P*<.001), and negative heterophile antibodies (OR, 3.54; 95%CI, 1.26-9.90; *P*=.016) to be independently associated with rash. To our knowledge, the effects of sex and heterophile antibodies on the risk of rash during IM have not previously been described. However, both females and patients without heterophile antibodies may display specific manifestations during IM [12,13].

None of the 29 patients who developed skin rash after receiving ß-lactams reported previous drug allergy. Nine patients underwent a complete allergy work-up, including prick and intradermal tests with penicilloyl-polylysine, benzylpenicilloate, cefuroxime, penicillin-G, amoxicillin, and amoxicillin-clavulanate, followed by a drug provocation test if the result was negative. ß-Lactam allergy was diagnosed in 4 patients based on delayed positive skin tests to penicilloyl-polylysine in 1 case and both amoxicillin and amoxicillin-clavulanate in the remaining 3. One of these patients had already experienced a skin reaction to amoxicillin several months after the IM episode. Allergy was ruled out in the remaining 5 cases. In the following years, 9 additional patients tolerated the same ß-lactam involved in the reaction (amoxicillin), 2 patients with phenoxymethylpenicillin as the

Table. Clinical and Biological Characteristics of Patients With Infectious Mononucleosis, Stratified by the Presence of Cutaneous Rash.[a]

	Skin rash				*P* Value[b]
	Present		Absent		
	No.		No.		
Age, y	40	19 (17-23)	356	20 (17-24)	.339
Female sex	40	26 (65.0)	356	162 (45.5)	.019
Corticosteroid therapy before admission	40	4 (10.0)	354	22 (6.2)	.361
Antibiotic therapy before admission					
Any antibiotic	40	34 (85.0)	356	168 (47.2)	<.001
ß-Lactam antibiotic[c]	40	29 (72.5)	356	133 (37.3)	<.001
Amoxicillin[d]	40	24 (60.0)	356	92 (25.8)	<.001
Macrolides	40	3 (7.5)	356	21 (5.9)	.687
Quinolones	40	1 (2.5)	356	7 (1.9)	.820
Other[e]	40	1 (2.5)	356	7 (1.9)	.820
Sore throat	39	28 (71.8)	356	256 (71.9)	.988
Nausea or vomiting	40	10 (25.0)	355	89 (25.1)	.992
Lymphadenopathy	40	30 (75.0)	355	264 (74.4)	.931
Heterophile antibodies	37	30 (81.1)	340	304 (89.4)	.130
Blood leukocytes, $\times 10^9$/L	40	10.6 (7.0-15.5)	356	12.2 (7.6-17.2)	.225
Blood lymphocytes, %	40	50.3 (38.3-55.8)	356	52.9 (41.6-61.7)	.060
Serum IgG, mg/dL	22	1280 (1030-1680)	230	1330 (1090-1580)	.896
Serum IgA, mg/dL	22	323 (216-446)	230	274 (192-354)	.180
Serum IgM, mg/dL	22	237 (188-360)	230	236 (171-329)	.736

[a]Values are shown as median (IQR) or absolute numbers (percentages).
[b]Mann-Whitney or χ^2 test.
[c]Six of these patients had also received antibiotics from other groups (clindamycin in 2 cases, and moxifloxacin, azithromycin, clarithromycin, and erythromycin in 1 case each).
[d]With or without clavulanic acid.
[e]The patient who developed rash in this group had received cotrimoxazole.

culprit antibiotic tolerated amoxicillin, and 1 patient with amoxicillin as the culprit tolerated cloxacillin. The cause of ß-lactam allergy remained undetermined in 8 patients, although 4 later tolerated cephalosporins not related to the culprit drug. Allergy was confirmed in 4/29 patients (13.8%) with rash after ß-lactam therapy. Regarding other antibiotics, only 1 patient who had received ciprofloxacin and 2 who had received azithromycin were assessed; the open challenge test result was negative in all 3 cases (Supplementary Figure 1).

Our study is limited by its retrospective design. In addition, since the skin rash of IM is sometimes mild, its frequency may have been underestimated. Moreover, the patients were adolescents and adults who were admitted to the hospital (ie, with severe IM); thus, the conclusions can only be applied to similar populations. Nevertheless, our findings help to disprove some myths about skin rash during IM. First, as previously pointed out [7-9,11], rash associated with antibiotics (specifically, ß-lactams) seems much less frequent than reported in older series (69%-100% of those treated with amoxicillin) [2-4]. In our experience, only a minority of patients receiving antibiotics develop rash (a fifth in the case of amoxicillin). Second, it is generally assumed that ß-lactam-related rash in IM patients does not indicate allergy but a transient loss of tolerance [9,14,15]. In our experience, this is true for most patients, although it may be the first manifestation of allergy in a sizeable proportion of adolescent and adult patients, as recently reported in children [8,10]. Most IM patients are youths who will probably require antibiotics throughout their lives. Our findings suggest that adolescent and adult patients with EBV-induced IM who develop a skin rash after receiving antibiotics should undergo a specific allergy work-up.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Lennon P, Crotty M, Fenton JE. Infectious mononucleosis. BMJ 2015;350:h1825.

2. Patel BM. Skin rash with infectious mononucleosis and ampicillin. Pediatrics. 1967;40:910-1.
3. Pullen H, Wright N, Murdoch JM. Hypersensitivity reactions to antibacterial drugs in infectious mononucleosis. Lancet. 1967;2:1176-8.
4. Brown GL, Kanwar BS. Drug rashes in glandular fever. Lancet. 1967;2:1418.
5. Ciccarese G, Trave I, Herzum A, Parodi A, Drago F. Dermatological manifestations of Epstein-Barr virus systemic infection: a case report and literature review. Int J Dermatol. 2020;59:1202-9.
6. Abrams EM, Khan DA. Diagnosing and managing drug allergy. CMAJ. 2018;190:E532-E538.
7. Chovel-Sella A, Ben Tov A, Lahav E, Mor O, Rudich H, Paret G, et al. Incidence of rash after amoxicillin treatment in children with infectious mononucleosis. Pediatrics. 2013;131:e1424-7.
8. Dibek Misirlioglu E, Guvenir H, Ozkaya Parlakay A, Toyran M, Tezer H, Catak AI, et al. Incidence of antibiotic-related rash in children with Epstein-Barr Virus infection and evaluation of the frequency of confirmed antibiotic hypersensitivity. Int Arch Allergy Immunol. 2018;176:33-8.
9. Thompson DF, Ramos CL. Antibiotic-induced rash in patients with infectious mononucleosis. Ann Pharmacother. 2017;51:154-62.
10. Mori F, Fili L, Barni S, Giovannini M, Capone M, Novembre EM, et al. Sensitization to amoxicillin/clavulanic acid may underlie severe rashes in children treated for infectious mononucleosis. J Allergy Clin Immunol Pract. 2019;7:728-31.
11. Hocqueloux L, Guinard J, Buret J, Causse X, Guigon A. Do penicillins really increase the frequency of a rash when given during Epstein-Barr Virus primary infection? Clin Infect Dis. 2013;57:1661-2.
12. Páez-Guillán EM, Campos-Franco J, Alende R, Lázare H, Beceiro C, Gonzalez-Quintela A. Jaundice in relation to immune activation during Epstein-Barr virus-induced infectious mononucleosis. Am J Med Sci. 2023;365:270-8.
13. Sasaki Y, Ishii T, Maeda T, Mori T, Shigeta T, Kashiwagi K, et al. Sex difference in clinical presentation of patients with infectious mononucleosis caused by Epstein-Barr virus. J Infect Chemother. 2020;26:1181-5.
14. Renn CN, Straff W, Dorfmüller A, Al-Masaoudi T, Merk HF, Sachs B. Amoxicillin-induced exanthema in young adults with infectious mononucleosis: demonstration of drug-specific lymphocyte reactivity. Br J Dermatol. 2002;147:1166-70.
15. Jappe U. Amoxicillin-induced exanthema in patients with infectious mononucleosis: allergy or transient immunostimulation? Allergy. 2007;62:1474-5.

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