

Skin rash during Epstein-Barr virus-induced infectious mononucleosis in adolescents and adults: Incidence, predisposing factors and prognostic implications

Páez-Guillán EM¹, Campos-Franco J¹, Alende R¹, Vidal C², Gonzalez-Quintela A¹

¹Department of Internal Medicine, Complejo Hospitalario Universitario, University of Santiago de Compostela, Spain

²Department of Allergy, Complejo Hospitalario Universitario, University of Santiago de Compostela, Spain

Corresponding author:

Dra. Carmen Vidal

Department of Allergy. Hospital Clínico Universitario.

15706 University of Santiago de Compostela, Spain.

E-mail: carmen.vidal.pan@sergas.es

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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, reaching 100% of children [2], 94% of adolescents [3], and 69% of university students [4], compared to 10%-16% of patients not receiving antimicrobials [2-4]. Such 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 (less than 30%), at least in children [7,8]. The rash was later described with different beta-lactams and a variety of antimicrobials [9]. It is generally assumed that antibiotic-related rash during IM does not indicate long-term hypersensitivity, although 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 it [11]. In the general population, however, drug allergy is more common in adults than in children [6]. We aimed to investigate the frequency, factors, and implications of skin rash in adolescents and adults with IM.

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

Skin rash developed in 40/396 patients (10.1%). Rash was present on admission in 36 cases and developed shortly thereafter in 4 cases. It was maculopapular in 36 patients, urticarial in 3, and purpuric in 1 patient. Rash was more frequent in females (26/188, 13.8%) than in males (14/208, 6.7%; $P=0.019$; Table 1). Age was similar in patients with and without rash (Table 1). Rash was more common in patients who received antibiotics prior to admission (34/202, 16.8%) than in those who did not (6/194, 3.1%; $P<0.001$; Table 1). Rash developed in 29 of 162 (17.9%) patients receiving beta-lactams (amoxicillin in 10 cases, amoxicillin-clavulanic acid in 14 cases, and phenoxymethylpenicillin in 5 cases). Specifically, rash developed in 24/116 (20.6%) of patients previously treated with amoxicillin (with or without clavulanic acid, Table 1). Rash was more frequent in patients who received beta-lactams than in those who were treated with different antibiotics, although the difference was not statistically significant ($P=0.668$) because there were fewer patients receiving non-beta-lactam antibiotics (Table 1; Supplementary Figure 1). The rash developed after a median of 7 days of antibiotic therapy (range, 1-11 days). Duration of treatment was not statistically different between rashes related to beta-lactams and those related to other antibiotics (data not shown). A total of 234 patients later received antibiotics during hospital admission due to tonsillar bacterial superinfection (macrolides in 119 cases, clindamycin in 45, quinolones in 14, and beta-lactams in 56 [amoxycillin 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 1). Among patients who received previous beta-lactam therapy, rash was more frequent in heterophil-negative patients (5/8, 62.5%) than in heterophil-positive patients (22/149, 14.7%; $P=0.003$). In a multivariate model (logistic regression) female sex (OR 2.45; 95% CI 1.16-5.18; $P=0.018$), previous beta-lactam therapy (OR 5.46; 95% CI 2.37-12.6; $P<0.001$), and negative heterophil antibodies (OR 3.54; 95% CI 1.26-9.90; $P=0.016$) were independently associated with rash after further adjusting for age. To our knowledge, the effects of gender and heterophile antibodies on the risk of rash during IM were not previously

described. It is known, however, that both females and patients without heterophile antibodies may display specific manifestations during IM [12,13].

None of the 29 patients who developed a skin rash after beta-lactam therapy reported previous drug allergy. A complete allergy workup was performed in 9 patients, including prick and intradermal tests with penicilloyl-polylysine, benzylpenicilloate, cefuroxime, penicillin-G, amoxicillin, and amoxicillin-clavulanate, followed by drug provocation test if negative. Beta-lactam allergy was diagnosed in 4 patients by means of delayed positive skin tests to penicilloyl-polylysine in one case and both amoxicillin and amoxicillin-clavulanate in the remaining 3. One of these patients had had another skin reaction after amoxicillin therapy 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 beta-lactam involved in the reaction (amoxicillin), 2 patients with phenoxymethylpenicillin as culprit antibiotic tolerated amoxicillin, and 1 patient with amoxicillin as culprit tolerated cloxacillin. Eight patients remained undetermined for beta-lactam allergy, although 4 later tolerated cephalosporins non-related to the culprit drug. As a whole, allergy was confirmed in 4/29 (13.8%) patients with rash after beta-lactam therapy. Regarding other antibiotics, only 1 patient who had received ciprofloxacin and 2 who had received azithromycin were studied, with a negative open challenge test in all cases (Supplementary Figure 1).

The study has limitations inherent to the retrospective design. Since the skin rash of IM is sometimes mild, its frequency may have been underestimated. Patients were adolescents and adults who were admitted to the hospital (i.e., with severe IM); thus, the conclusions can be only applied to similar populations. The study helps to disprove some myths about skin rash during IM. First, as previously pointed out [7-9,11], rash in relation to antibiotics (specifically, beta-lactams) seems much less frequent than reported in old series (69%-100% of those treated with amoxicillin) [2-4]. In our experience, only a minority of patients receiving

antibiotics (a fifth in the case of amoxicillin) develop a rash. Secondly, it is generally assumed that the beta-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 the majority of patients, but it may be the first manifestation of allergy in a sizeable proportion of adolescent and adult patients, as recently reported in children [8,10]. The majority of 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 study.

Conflict of interest statement

None to declare.

Financial statement

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Table. Clinical and biological characteristics of patients with infectious mononucleosis, stratified by the presence of cutaneous rash.

	Cutaneous rash				P-value
	Present		Absent		
	No.		No.		
Age (years)	40	19 (17-23)	356	20 (17-24)	0.339
Sex (female)	40	26 (65.0)	356	162 (45.5)	0.019
Corticosteroid therapy before admission	40	4 (10.0)	354	22 (6.2)	0.361
Antibiotic therapy before admission					
Any antibiotic	40	34 (85.0)	356	168 (47.2)	<0.001
Beta-lactam antibiotic ¹	40	29 (72.5)	356	133 (37.3)	<0.001
Amoxicillin ²	40	24 (60.0)	356	92 (25.8)	<0.001
Macrolides	40	3 (7.5)	356	21 (5.9)	0.687
Quinolones	40	1 (2.5)	356	7 (1.9)	0.820
Other ³	40	1 (2.5)	356	7 (1.9)	0.820
Sore throat	39	28 (71.8)	356	256 (71.9)	0.988
Nausea or vomiting	40	10 (25.0)	355	89 (25.1)	0.992
Lymphadenopathy	40	30 (75.0)	355	264 (74.4)	0.931
Heterophil antibodies	37	30 (81.1)	340	304 (89.4)	0.130
Blood leukocytes (x10⁹/L)	40	10.6 (7.0-15.5)	356	12.2 (7.6-17.2)	0.225
Blood lymphocytes (%)	40	50.3 (38.3-55.8)	356	52.9 (41.6-61.7)	0.060
Serum IgG (mg/dL)	22	1280 (1030-1680)	230	1330 (1090-1580)	0.896
Serum IgA (mg/dL)	22	323 (216-446)	230	274 (192-354)	0.180
Serum IgM (mg/dL)	22	237 (188-360)	230	236 (171-329)	0.736

Figures are medians and interquartile ranges (within parentheses) or absolute numbers and percentages (within parentheses). No., number of patients with available determination. P-values were obtained with the Mann-Whitney test or the chi-square test.

¹Six of these patients had also received antibiotics from different groups (clindamycin in two cases, and moxifloxacin, azithromycin, clarithromycin, and erythromycin in one case each).

²With or without clavulanic acid.

³The patient developing rash in this group had received cotrimoxazole.