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Amoxicillin-Induced Exanthem Unmasking Acute Epstein–Barr Virus Infection in a Young Adult with a Positive Group a Streptococcus Antigen Test: A Case Report and Review

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Abstract | **Case Report**

Background: Acute infectious mononucleosis (IM) caused by Epstein–Barr virus (EBV) is a common cause of pharyngotonsillitis in adolescents and young adults and is clinically indistinguishable from streptococcal sore throat at the bedside. The development of a maculopapular eruption after exposure to an aminopenicillin is a classical, though now less frequent, clue to underlying EBV. ***Case presentation:*** A 24-year-old woman presented with fever, cervical lymphadenopathy and exudative tonsillitis on a background of incidental lymphocytosis. A rapid Group A Streptococcus (GAS) antigen test was positive and she was treated sequentially with a macrolide and then amoxicillin. Three days into amoxicillin she developed a widespread, pruritic maculopapular rash without angioedema. The aminopenicillin was stopped and EBV serology subsequently returned viral capsid antigen (VCA) IgM-positive, confirming acute EBV infection. The rash settled with antihistamine and a short course of corticosteroid. ***Conclusion:*** This case illustrates genuine diagnostic overlap between streptococcal and EBV pharyngitis, the limitations of a positive GAS antigen test against a background of asymptomatic carriage, and the evolving understanding of the aminopenicillin–EBV exanthem. It reinforces the value of considering EBV before prescribing an aminopenicillin for sore throat in this age group, and of labelling the reaction accurately rather than as a fixed penicillin allergy.

Keywords: Epstein–Barr virus; infectious mononucleosis; amoxicillin; aminopenicillin rash; Group A Streptococcus; pharyngitis; drug eruption.

INTRODUCTION

Epstein–Barr virus (EBV) is a ubiquitous human gamma-herpesvirus acquired through salivary contact; the great majority of adults worldwide are seropositive by middle age [1]. Primary infection in early childhood is usually subclinical, whereas infection delayed to adolescence or young adulthood produces the classical syndrome of infectious mononucleosis (IM) (fever, pharyngitis, lymphadenopathy and marked fatigue) [2]; because the tonsillo-pharyngeal appearance of IM can mimic bacterial tonsillitis, affected patients are frequently treated with antibiotics, including aminopenicillins, before viral aetiology is recognised [2].

The eruption that may follow ampicillin or amoxicillin in this setting was first described in the 1960s and was historically quoted as occurring in 80-100% of treated patients [3]. More recent data place the figure considerably lower [4,5]. We present a case in which an amoxicillin-associated exanthem prompted recognition of acute EBV infection, despite an initially positive Group A Streptococcus (GAS) antigen test, and use it to review the natural history of EBV, the differentiation of bacterial from viral sore throat, the interpretation of EBV serology, and the contribution of background streptococcal carriage.

CASE REPORT

A 24-year-old woman presented with a two-day history of fever and tender neck swellings, preceded by a 5–7-day prodrome of sore throat and malaise. A complete blood count performed the previous day (Table 1) as part of a routine employment medical fitness assessment had shown a lymphocytosis. She had no significant past medical history and was on no regular medication.

Table 1: Laboratory results

Test	Result
Haemoglobin	11.9 g/dL
White blood count	9.4 x 10^3/uL
Platelets	226 x 10^3/uL
Neutrophils	3.36 x 10^3/uL
Lymphocyte	5.39 x 10^3/uL

Day 0. On examination by Physician 1, she was noted to be febrile with bilateral cervical glandular swelling and enlarged, exudative tonsils. A clinical diagnosis of acute tonsillitis was made and she was started on sustained-release clarithromycin (1 g daily). At this first encounter, she was advised that a viral cause, including possible EBV, could coexist.

Day 2. With no clinical improvement after 48 hours of clarithromycin, she was reviewed by Physician 2. Given the exudative tonsils, a rapid GAS antigen swab was performed and returned positive. Due to the apparent treatment failure, therapy was switched to amoxicillin 500 mg three times daily.

Day 5. Three days after starting amoxicillin, she re-presented with a widespread, itchy maculopapular rash (Figure 1). Physician 3 noted no lip swelling, angioedema, mucosal involvement, blistering or systemic compromise, and by this point, she was afebrile with resolving sore throat. EBV was suspected, and thus viral capsid antigen (VCA) IgM and IgG were requested. As the antibiotic was no longer clinically necessary, amoxicillin was stopped. She was given intramuscular hydrocortisone 100 mg, oral fexofenadine, and a subsequent four-day course of oral prednisolone 40 mg daily.

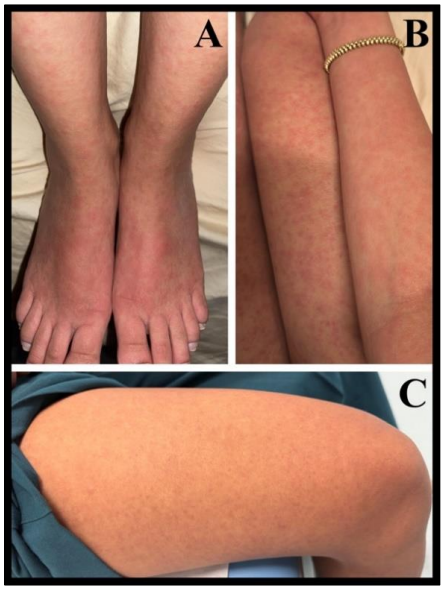

Figure 1: Morbilliform rash. (A, B) At the time of presentation. (C) Marked fading three days later

Day 7. At review with Physician 3, the rash had faded substantially. EBV VCA IgM and IgG returned positive, confirming acute EBV infection (see Table 2); the eruption was attributed to the aminopenicillin in the context of acute IM.

Table 2: Natural history of EBV-specific antibodies and stage of infection [3].

Marker	Appears	Persists / disappears	Interpretation
VCA IgM	First 1-2 weeks	Wanes by ~4-6 weeks (up to ~3 months)	Best single marker of acute / recent primary infection
VCA IgG	Acute phase peaks 2–4 weeks	Persists for life	Indicates infection at some point; not useful alone for timing
EA (early antigen) IgG	Acute phase	Falls by 3-6 months; persists in ~20%	Marker of active replication; variable, not required for diagnosis
EBNA IgG	Late, appears ~6-12 weeks (2-4 months) after onset	Persists for life	Its presence early effectively excludes acute infection
Stage		**VCA IgM / VCA IgG**	**EBNA IgG**
Susceptible (never infected)		Negative / Negative	Negative
Acute primary infection		Positive / Positive	Negative
Past infection / immunity		Negative / Positive	Positive

DISCUSSION

Investigations and serology

The peripheral lymphocytosis, exudative pharyngotonsillitis and cervical lymphadenopathy were in keeping with infectious mononucleosis. The positive GAS antigen test raised the possibility of true streptococcal co-infection but, as discussed below, could equally reflect asymptomatic pharyngeal carriage. Acute EBV infection was confirmed serologically by a positive VCA IgM [3].

In this patient, a positive VCA IgM with the expected absence of EBNA IgG (which does not appear until several weeks to months after onset) is diagnostic of acute primary infection [3]. Heterophile (Monospot) testing was not used; it has reduced sensitivity in the first week of illness and a negative result would not have excluded EBV.

Epstein–Barr virus and infectious mononucleosis

IM caused by EBV most often affects those aged 15–24 years and is usually self-limiting over two to eight weeks, though fatigue may persist longer [1]. Initial laboratory assessment classically shows a lymphocytosis with atypical (reactive) lymphocytes [7]. Management is supportive; neither antivirals nor corticosteroids are recommended for uncomplicated disease [1, 8]. Patients should be counselled about splenic rupture risk and advised to avoid contact and collision sport for several weeks [9]. Antibiotics are not warranted unless there is concurrent streptococcal infection [10].

Distinguishing EBV from streptococcal and other sore throats

No individual symptom or sign reliably separates viral from bacterial pharyngitis, which is why validated clinical prediction rules are used. In the UK, NICE recommends FeverPAIN and Centor to estimate the likelihood of streptococcal infection and guide antibiotic decisions [11]. Centor awards a point each for tonsillar exudate, tender anterior cervical nodes, history of fever and absence of cough; FeverPAIN scores fever, purulence, rapid attendance (≤3 days), severely inflamed tonsils and absence of cough/coryza [11]. Higher scores increase the probability of isolating streptococcus but neither tool distinguishes true infection from carriage, and both perform only modestly against throat culture in adults [12].

Crucially for this case, several Centor/FeverPAIN features (exudate, fever, tender nodes) are equally produced by potential EBV infection, so a high score does not exclude IM. Features that should actively raise suspicion of EBV instead include posterior (as well as anterior) cervical lymphadenopathy, prominent fatigue, palatal petechiae, splenomegaly, a lymphocytosis with atypical lymphocytes and failure to respond to an antibiotic. Other mimics of exudative tonsillitis worth bearing in mind are cytomegalovirus, acute HIV seroconversion, pseudomembranous diphtheria, toxoplasmosis and, when symptoms are unilateral or progressive, peritonsillar abscess and more rarely, Lemierre syndrome.

Background Group A Streptococcus carriage and the limits of a positive antigen test

A positive GAS antigen test is often equated with streptococcal disease, but asymptomatic pharyngeal carriage is common, and antigen tests and cultures cannot distinguish a carrier with an intercurrent viral illness from true streptococcal pharyngitis. In a meta-analysis of 285 studies, asymptomatic GAS carriage in children from high-income countries was around 10–11% [12], and a separate paediatric meta-analysis found carriage of roughly 12%, with GAS detected in about 37% of children presenting with sore throat [13]. Among symptomatic children swabbed in clinical settings, only about 10% have serologically confirmed GAS pharyngitis even though a far higher proportion are culture-positive, implying that many culture/antigen-positive patients are carriers rather than acutely infected [14].

Applied to this patient, a young adult with a lymphocytosis, an exudative pharyngitis unresponsive to a macrolide, and serologically confirmed acute EBV, the positive GAS antigen test may well represent carriage rather than active streptococcal co-infection. This does not exclude genuine dual pathology, although the two can coexist, but it reframes the decision to escalate to amoxicillin: the swab result, rather than the clinical trajectory, drove the antibiotic switch, and the clinical picture pointed to EBV as the dominant process. The wider learning point is that a positive GAS test neither confirms streptococcal disease nor excludes EBV, and in this demographic should prompt rather than dispel consideration of mononucleosis before an aminopenicillin is chosen.

The aminopenicillin–EBV exanthem

The eruption is a widespread, often intensely pruritic, morbilliform (maculopapular) rash that characteristically appears around three to nine days after starting the antibiotic (consistent with the day-3 post-antibiotic onset here) and resolves over roughly a week, sometimes with desquamation [4, 15, 16]. Although long taught as occurring in 80-100% of EBV patients given ampicillin, contemporary studies report much lower rates: approximately 30% with amoxicillin in one frequently cited cohort, and a pooled range of about 15-33% across recent series [4, 17]. The historical figures could reflect methodological limitations and possibly impurities in early antibiotic preparations.

Although the exact mechanistic basis for the EBV-amoxicillin is not known, the prevailing explanation is not classical IgE-mediated allergy but a transient, virus-driven alteration in immune regulation during acute EBV infection that lowers antigenic tolerance and provokes a delayed-type (T-cell-mediated)

hypersensitivity reaction to the drug [18, 19]. Importantly, the reaction is therefore usually self-limited and does not always predict lifelong penicillin allergy [18]. However, a minority of patients have positive aminopenicillin patch or intradermal tests months after recovery, indicating that true, persistent hypersensitivity can occasionally be unmasked [20]. Recent data also show that comparable rashes occur with non-aminopenicillin antibiotics during IM, so the eruption may not strictly specific to amoxicillin, and avoiding aminopenicillins alone may not abolish the risk [21].

A practical consequence concerns documentation. Recording this episode bluntly as "penicillin allergy" risks committing the patient to lifelong, often unnecessary, avoidance of first-line beta-lactams. It is preferable to document a viral-associated (EBV) maculopapular exanthem following amoxicillin, to note the absence of features of immediate or severe reaction, and to consider formal allergy assessment or de-labelling once the acute illness has resolved.

Management of the rash and the role of corticosteroids

The uncomplicated aminopenicillin-EBV exanthem is benign and self-limiting. Standard management is to stop the offending drug (which is usually no longer required) and provide symptomatic relief with oral antihistamines, emollients and, if needed, topical corticosteroids; reassurance about the expected course is important [2, 5]. This patient received intramuscular hydrocortisone followed by a short oral prednisolone course, and the rash settled quickly. It is worth noting, however, that the evidence base does not support systemic corticosteroids for either uncomplicated IM or the benign exanthem: a Cochrane review of seven randomised trials found insufficient evidence of benefit for symptom control, with any effect on sore throat not maintained beyond about 12 hours, and a lack of safety data [8]. Systemic steroids in EBV are conventionally reserved for specific complications, including impending airway obstruction from tonsillar hypertrophy, autoimmune haemolytic anaemia and severe thrombocytopenia, rather than for the rash itself [2, 8]. Recognising the eruption as benign can therefore help avoid escalation that confers little additional benefit.

Clinical learning points

1. Consider EBV first: In adolescents and young adults with exudative tonsillitis, cervical lymphadenopathy and a lymphocytosis, suspect infectious mononucleosis and avoid aminopenicillins until EBV is excluded.
2. A positive GAS test is not the end of the story: Background asymptomatic carriage (~10%) means antigen tests and cultures cannot distinguish a carrier with a viral illness from true streptococcal infection; a positive result should not dispel consideration of EBV.
3. Clinical scores have limits: Centor and FeverPAIN predict streptococcal isolation but do not separate carriage from infection or identify EBV; posterior cervical nodes, fatigue, splenomegaly and atypical lymphocytosis favour IM.
4. Treatment failure is a clue: Lack of response to an appropriate antibiotic, especially with lymphocytosis, should prompt reconsideration of a viral aetiology.
5. The amoxicillin rash is now less common than taught: Modern incidence is roughly 15-33% (not 90%); it is morbilliform, appears around day 5-9, and is self-limiting.
6. Manage supportively: Stop the drug; use antihistamines, emollients and topical steroids. Reserve systemic corticosteroids for genuine IM complications, not the rash.
7. Label carefully: Document a viral-associated exanthem rather than a fixed penicillin allergy, and consider allergy review before committing the patient to lifelong beta-lactam avoidance.

CONCLUSION

This case captures a recurring clinical trap: an exudative sore throat with a positive GAS antigen test in a young adult, treated with an aminopenicillin, followed by a maculopapular rash that unmasked acute EBV infection. It highlights the genuine overlap between streptococcal and EBV pharyngitis, the importance of interpreting a positive GAS test against the background of carriage, the contemporary (lower) incidence and immunological basis of the aminopenicillin-mediated EBV exanthem, and the need to document such reactions accurately. Considering EBV before reaching for an aminopenicillin in this age group remains a simple and effective safeguard.

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