Man, 25, With Sinus Pain, Sore Throat, and Rash

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A 25-year-old white man presents to urgent care with a nine-day history of increasing sinus pressure, mild sore throat, dry cough, and low-grade fever. Physical exam of the ears, nose, throat, and chest is unremarkable, but the patient does display mild maxillary sinus tenderness. Sinus pain (and symptom duration) is the primary complaint. The patient was recently exposed to influenza B, but a rapid flu test is negative. A five-day course of amoxicillin-clavulanate is prescribed for a presumed diagnosis of bacterial sinusitis.

One week later, the patient returns with worsening sore throat and a morbilliform rash (see Figures 1 and 2), which covers the trunk, upper arms, and thighs. He has no known allergies to drugs, foods, or other environmental triggers. Examination reveals slightly tender, mobile anterior and posterior cervical lymphadenopathy, as well as bilateral tonsillar erythema and exudates, which were not present at the initial visit.

The rest of the exam is normal, and the patient's sinus symptoms have resolved. Heterophile antibody testing yields positive

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FIGURE 1

A diffuse morbilliform rash covers the patient's chest.

FIGURE 2

Diffuse morbilliform rash on the patient's back.

TABLE 1
Incidence of Rash After Varied Antibiotic Exposure in Patients with IM

	Ampicillin	Amoxicillin	Amoxicillin-Clavulanate	Cephalosporins	Macrolides	Tetracyclines
Study 1 incidence of rash[8]	8.5%	29.51%	15.56%	15.38%	9.09%	
Study 2 incidence of rash[10]	95%					11.7%
Study 3 incidence of rash[7]	Up to 95%	Up to 95%	40%-60%	40%-60%		

Sources: Luzuriaga & Sullivan. *N Engl J Med.* 2010[7]; Chovel-Sella et al. *Pediatrics.* 2013[8]; Forgie & Marrie. *Am J Med.* 2015.[10]

results, suggesting infection with Epstein-Barr virus (EBV).

DISCUSSION
EBV is a pervasive herpesvirus that infects approximately 95% of adults worldwide.[1] More than 90% of adults are seropositive for EBV antibodies by the age of 30.[2] Although affected individuals are often asymptomatic, some patients develop symptoms of infectious mononucleosis (IM).[2] An aminopenicillin rash can occur in patients with IM who are treated with amoxicillin or ampicillin, as was the case with this patient.

Incidence and pathophysiology
Infection with EBV most commonly occurs between the ages of 15 and 24.[1,2] Infection before the age of 1 is rarely seen due to circulating maternal antibodies; incidence of IM in those younger than 1 or older than 30 is < 1 per 1,000 cases annually.[2] The average annual incidence of infection is 0.5% in young adults (ages 15 and 24) but has been reported as high as 4.8%.[2] About 10% to 20% of people who never knowingly come into contact with the virus will become infected annually; of those, up to 50% will develop IM.[2] There are no known correlations in incidence based on sex or seasonal changes.[2]

Like all herpesviridae, EBV causes a latent infection that persists for a lifetime, specifically in replicating B lymphocytes.[1] Saliva is the most common mode of EBV transmission, as viral shedding occurs in the throat and mouth.[1,3] While the viral load in saliva is the highest during the first six months of infection, there are no clear data determining the risk for transmission throughout the course of asymptomatic shedding.[4] There is a 30-to-50–day incubation period of EBV infection before a patient experiences symptoms of IM.[1] During this period, B lymphocytes and epithelial cells (specifically in the tonsillar crypts) are believed to be the source of viral replication.[1,3]

Clinical presentation of IM
Common symptoms of IM include sore throat, fever, and fatigue. Approximately one in 13 patients ages 16 to 20 who present with a fever and sore throat will be diagnosed with IM.[6] However, symptomatology alone is more sensitive than specific and is not sufficient to diagnose IM.[6] Combined fatigue and pharyngitis is sensitive (81%-83%) but not specific, and posterior cervical lymphadenopathy increases the likelihood of IM (specificity, 87%).[6]

The classic triad associated with IM includes fever, pharyngitis, and cervical lymphadenopathy, with morbilliform rash and palatal petechiae appearing less commonly (3%-15% and 25%, respectively).[1,2,9] In affected patients, a transient truncal rash manifests within the first few days of disease onset.[7] Tonsillar enlargement is also a common, but not specific, sign of acute IM.[2]

Splenomegaly is found in 15% to 65% of patients, typically developing within three weeks of disease onset.[1,5,9]

Hematologic complications occur in 25% to 50% of cases.[5] Mild thrombocytopenia is common; however, more severe complications—such as hemolytic anemia, hemolytic-uremic syndrome, aplastic anemia, and disseminated intravascular coagulation—have also been associated with IM.[5] Fulminant and potentially fatal complications are more common in immunocompromised patients.[1,2]

Pediatric and geriatric patients (those older than 65) may present with atypical signs and symptoms. For example, children are commonly asymptomatic or may present with a nonspecific viral illness.[1] In addition, pediatric and elderly populations can develop elevated aminotransferase levels, and 26% of elderly patients present with jaundice (compared with 8% of young adults).[2,3,7]

Workup/differential diagnosis

Heterophile antibody testing is the most efficient and least expensive diagnostic test to confirm IM (sensitivity, 63%-84%; specificity, 84%-100%).[2] Within the first week of IM, however, 25% of patients will produce a false-negative antibody test; a complete blood count (CBC) with differential and peripheral smear are appropriate follow-up tests.[1,2,5] Detecting 10% or more atypical lymphocytes on a peripheral smear has a specificity of 95% and sensitivity of 61.3% for detecting IM, and a CBC with a lymphocyte count of less than 4,000 mm has a 99% negative predictive value.[2] Viral capsid IgM testing can confirm the diagnosis of IM in an unclear clinical situation, such as a negative heterophile antibody test with an absolute lymphocyte count > 4,000 mm or in which 10% or more atypical lymphocytes were detected.[2]

Pharyngitis is caused by group A streptococci in 15% to 30% of children and 10% of adults worldwide, and 30% of patients with IM have a concomitant infection with group A streptococci.[1,5] Because pharyngitis is a common presenting symptom of IM, rapid antigen strep test is appropriate when working up these patients.[2] In addition, HIV, cytomegalovirus, human herpesvirus-6, and *Toxoplasma gondii* should be considered in the differential for patients with pharyngitis, fatigue, malaise, and lymphadenopathy—especially if the group A streptococci/EBV workup is negative.[1,2,5]

EBV is also a known trigger of hemophagocytic lymphohistocytosis (HLH). In a Japanese study, half of all HLH cases correlated with a primary infection of EBV.[2,3,8] EBV is also the first confirmed oncogenic virus.[3] EBV DNA in the plasma is now a tumor marker for nasopharyngeal carcinoma (sensitivity, 96%; specificity, 93%).[8] Hodgkin lymphoma tumors are associated with EBV infection in 50% of cases.[4] However, EBV seropositivity is ubiquitous (approximately 95%), while these correlated conditions are relatively uncommon; patient education on these issues is therefore not needed.

Treatment/complications

Aminopenicillin rash classically occurs in patients with IM who are treated with amoxicillin or ampicillin. These antibiotics are most commonly prescribed for suspected group A streptococci infection.[7] Up to 95% of patients with IM who are exposed to these drugs develop this rash within two to 10 days of receiving the first dose of the antibiotic.[9,10] Similar eruptions are often reported following administration of other penicillins, but not with the same frequency seen with ampicillin or amoxicillin (see Table 1).[11]

The mechanism of the aminopenicillin rash is not completely understood, but one theory is that the activated CD8+ cells react with the drug antigens and deposit in the skin.[10] Another proposed mechanism is that antigens formed against activated polyclonal B cells create immune complexes with the drug, which then deposit in the skin.[10]

No known factors increase the incidence of this rash in patients after antibiotic exposure (eg, previous penicillin exposure, antibiotic dose or duration, patient age or ethnicity, atopic history).[7] The rash gener-

ally resolves within a week after antibiotic discontinuation.[7] Importantly, the development of a rash in a patient with EBV after administration of an aminopenicillin is *not* associated with an allergy nor is it a sign of an unfavorable reaction to such drugs in the future.[12]

The rash can be described as morbilliform or scarlatiniform and should be distinguished from the rash that acute IM can cause. Five percent of patients with an aminopenicillin rash will have an urticarial presentation, whereas 95% of patients have an exanthematous presentation.[1,9,10] Although it can be quite difficult to distinguish one rash from the other, the aminopenicillin rash is more widespread than that associated with acute IM, covering extensor surfaces and spreading to the face, trunk, neck, mucous membranes, and sometimes the palms and soles.[1,7,9,10] The rash caused by IM begins within the first few days of disease, whereas the aminopenicillin rash will manifest seven to 10 days after antibiotic exposure and is commonly pruritic.[1] Each rash will last about one week.[1]

CONCLUSION

The diagnosis of EBV can be challenging due to its similarity to group A streptococcal pharyngitis and other viral syndromes. In this case, the development of classic symptoms, along with the morbilliform eruption following administration of an aminopenicillin, was strongly suggestive of this diagnosis. This pairing of EBV infection and aminopenicillin rash does not indicate a penicillin allergy.   **CR**

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