A New Trigger of Morbilliform Eruption in the Setting of Atypical Infectious Mononucleosis

Roxanne Rajaii, DO,* Megan Furniss, DO,** John Pui, MD,*** Brett Bender, DO****

*Dermatology Resident, PGY2, Beaumont Hospital - Farmington Hills, Farmington Hills, MI
**Dermatology Resident, PGY4, Beaumont Hospital - Farmington Hills, Farmington Hills, MI
***Dermatopathologist, Beaumont Hospital - Farmington Hills, Farmington Hills, MI
****Dermatologist, Beaumont Hospital - Farmington Hills, Farmington Hills, MI

Disclosures: None
Correspondence: Roxanne Rajaii, DO; rrjaii@atsu.edu

Abstract
Morbilliform eruptions, also commonly referred to as exanthematous or maculopapular drug eruptions, are the most common type of hypersensitivity reaction and can vary in etiology. Antibiotics are a common trigger, most notably amoxicillin or ampicillin in the setting of a concomitant and acute Epstein-Barr virus (EBV) infection. However, other antibiotics have been identified to cause a similar reaction in the setting of EBV. Cefalexin, a commonly used cephalosporin, is the only antibiotic in its class that has been implicated in causing such a phenomenon. We present a unique case of a morbilliform eruption in the setting of EBV secondary to the use of cefepime, further outlining the importance of conservative antibiotic use and awareness of such a reaction in this specific patient population, not only with penicillins but also with a wider spectrum of antibiotics.

Introduction
Epstein-Barr virus (EBV) infects more than 98% of the world’s adult population and is the most common cause of infectious mononucleosis (IM).1,2 IM is a clinical syndrome characterized by prominent fever, fatigue, malaise, lymphadenopathy, and sore throat.2 It is a self-limiting disease most commonly seen in older children and young adults. Symptoms persist over a period of weeks to months, typically without sequelae; however, neurologic, hematologic, hepatic, respiratory, and psychological complications may occur. In this patient population, a rash can develop with concomitant use of an antibiotic, most commonly amoxicillin or ampicillin. Clinically, a generalized maculopapular, urticarial, or petechial rash develops within five to 14 days of antibiotic treatment in a patient with an acute EBV infection.1,2

This eruption -- particularly in response to amoxicillin or penicillin administration -- is well known among clinicians, especially dermatologists and infectious-disease specialists.1,2 Lesser known is the ability of other classes of antibiotics to trigger this immunologic phenomenon. Although amoxicillin and ampicillin are most commonly the causative agents of this eruption, other penicillin derivatives and other antibiotic classes have also been cited in the literature. These include methicillin, pivampicillin, talampicillin, cephalexin, minocycline, sulfonamides, quinolones, and macrolides including erythromycin and azithromycin. To date, although cefalexin, a commonly used cephalosporin, has been cited to cause this reaction, cefepime, another well-known cephalosporin, has not been implicated in this phenomenon, making this case report novel in adding another antibiotic to the list of potential causes for a morbilliform rash in the setting of infectious mononucleosis.1

Case Report
A 29-year-old woman presented to the emergency department with left-sided back and leg pain, leg weakness, fever, rash, nausea, vomiting, and malaise and was admitted for further work-up. Approximately one week prior, she had been admitted to a nearby hospital with similar complaints plus pelvic pain and dysuria, for which she was treated with intravenous (IV) cefepime and vancomycin for presumed hospital-acquired pyelonephritis, as she had been admitted a month prior to that for status asthmaticus. Four days later, she presented with an urticarial morbilliform rash. She was told she was allergic to cefepime, was prescribed diphenhydramide and a weeklong course of ciprofloxacin, and was discharged home the day prior to presenting at our hospital.

On examination, the patient had a diffuse morbilliform and urticarial eruption, with accentuation on the trunk, neck and upper extremities. The truncal eruption had overlying marked purpura (Figure 1), while the neck and extremity eruptions were indurated and urticarial in nature (Figure 2). The patient’s skin was notably sensitive to touch, and she complained of generalized itching and stinging. There was an absence of mucosal involvement, including the throat, and the face was spared. The exam was also positive for left costovertebral angle pain and tenderness of the spleen on palpation. The spleen was palpable 1 cm below the left ribcage.

Work-up included the following laboratory tests: complete blood count, complete metabolic panel, anti-nuclear antibody, creatinine phosphate kinase, lactic acid, blood cultures, rapid plasma reagent, immunoglobulin (Ig) G and immunoglobulin M titers for rubella, human immunodeficiency virus, cytomegalovirus, EBV, and parvo B19. All labs were within normal limits and demonstrated expected adult immunities, with the exception of a white blood cell count of 12.4 and EBV titers positive for IgM and negative for IgG, indicating an acute Epstein-Barr virus infection, also known as infectious mononucleosis. A computed tomography scan of the abdomen and pelvis noted the spleen to be at “top normal size,” measuring 13 centimeters.

A skin biopsy was taken from each of the representative areas, one purpuric and the other urticarial. The biopsy of the left dorsal hand showed a focal vacuolar interface dermatitis with occasional lymphocytes present at the dermal-epidermal junction and a sparse underlying superficial perivascular lymphocytic infiltrate. These

![Figure 1. Eruption on the neck and acral sites with an indurated, urticarial appearance.](image1)

![Figure 2. Eruption on the back, diffusely covered in a tender, morbilliform, markedly purpuric rash.](image2)
findings were consistent with a morbilliform viral exanthem. The biopsy of the left lower abdomen revealed a different histologic pattern consisting of a superficial to mid perivascular and interstitial mixed-cell infiltrate composed of lymphocytes and neutrophils with extravasated erythrocytes, with minimal epidermal changes. These findings were consistent with an urticarial drug eruption.

Based on the positive acute EBV titers, biopsy results, and clinical presentation, the patient was diagnosed with acute infectious mononucleosis complicated by a morbilliform drug eruption elicited by administration of cefepime. The patient was treated with a two-week steroid taper, beginning with topical corticosteroids, antipyretics, and anti-inflammatory oral prednisone on discharge. She was also treated with IV methylprednisolone and transitioning to a two-week steroid taper, beginning with topical corticosteroids, antipyretics, and anti-histamines, and fared well. She was discharged home after a five-day admission.

Discussion

Exanthematous drug eruption, also known as morbilliform or maculopapular drug eruption, is the most common type of hypersensitivity reaction and can have a variety of etiologies. It often manifests as a diffuse and symmetric eruption of erythematous macules or small papules that can be triggered within approximately one week of drug initiation. Roughly 2% of individuals exposed to drugs will experience a cutaneous drug reaction, most commonly with antibiotics as the causative agent. Although most often confined to the skin, severe cases may exhibit involvement of the mucosa and appendages.3,4

The pathophysiology of exanthematous drug eruptions is variable. Many are believed to be a result of a delayed-type T-cell mediated (type IV) immune reaction.5 However, the exact mechanism by which drugs cause an immune response resulting in a maculopapular eruption is poorly understood. The number of drugs that have been cited as culprits for such a reaction is vast. The penicillins, cephalosporins, and agents with sulphhydryl groups, for instance, are among the most commonly used drugs that cause a drug eruption.1,2 These specific classes of drugs act as haptons, bind to macromolecules, and then become full antigens.6 Aromatic sulfonamides (trimethoprim–sulfamethoxazole), anticonvulsant drugs such as carbamazepine and phenytoin, some nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol are other agents that are notorious for causing a drug eruption. However, these specific drug classes require biotransformation to form reactive metabolites.1,6

Although drugs play a crucial role in exanthematous drug eruptions, concomitant diseases, namely viral infections, may predispose an individual to such an eruption as well.7-9 Diseases cited in current literature that increase an individual’s risk of such an eruption include infection with Epstein-Barr virus, cytomegalovirus, and human herpes viruses 6 and 7. In the setting of EBV-caused infectious mononucleosis, a maculopapular rash almost always occurs following the administration of ampicillin or amoxicillin.2 In addition, immunocompromised patients, namely those afflicted with human immunodeficiency virus (HIV) infection, cystic fibrosis, and autoimmune disorders, are also at increased risk of developing an exanthematous drug eruption.2,7,11,12

While the pathophysiology is not fully understood, the histopathology of these drug eruptions has been better described.13 At the dermoepidermal junction, a vascular interface dermatitis with scattered dyskeratotic keratinocytes is often observed. A superficial perivascular and interstitial infiltrate of lymphocytes, neutrophils, and eosinophils is often seen under histology as well. Other features that may be seen include extravasation of erythrocytes, foci of lymphocytes at the dermoepidermal junction, and fibrin deposition within the blood vessel walls of the papillary plexus.

Epstein-Barr virus is the most common cause of infectious mononucleosis, which is characterized by prominent fever, fatigue, malaise, lymphadenopathy, and sore throat. However, other viruses, such as cytomegalovirus (CMV), HIV, human herpesvirus type 6 (HHV-6), and hepatitis B virus (HBV), can also spread through bodily fluids and cause this disease.11 Symptoms of infectious mononucleosis persist over a period of weeks to months, typically without sequelae; however, neurologic, hematologic, hepatic, splenic, respiratory, and psychological complications can arise.2,15

In patients with infectious mononucleosis, a rash can develop with concomitant use of an antibiotic, most commonly ampicillin and amoxicillin.14 The rash presents as erythematous macules and papules, closely resembling eruptions of viral exanthems. Pustules and bullae may be seen, although very rarely. Acral sites are often spared in mild cases. However, the face, palms, and soles may be affected. Aside from this maculopapular rash, patients often experience pruritus, low-grade fever, elevation of acute-phase proteins, and mild eosinophilia.12 Timing of these eruptions is variable; the consensus, however, is that the rash commonly develops within five to 14 days of antibiotic initiation.2 In those individuals who have been previously sensitized, the eruption may appear within only two or three days.

If antibiotics are postulated to be the causative agent, the eruption may even appear up to several days after treatment termination. Although the eruption in many individuals evolves rapidly, it reaches its maximum intensity approximately two days after discontinuation of the causative agent and resolves within one to two weeks. Many individuals experience desquamation throughout the process of resolution, and some may suffer from post-infectious hyperpigmentation.

Diagnosis is often clinical in nature and should be suspected in an individual who is receiving drug therapy and presents with a new-onset rash.8 History of present illness, clinical features, laboratory testing, and sometimes histopathologic examination of a skin biopsy are used to confirm a suspected diagnosis.13 Treatment involves prompt withdrawal of the offending drug along with symptomatic treatment including topical corticosteroids and oral antihistamines for the pruritic eruption. Systemic corticosteroids are typically only indicated in severe cases.

This case demonstrates the importance of accurate diagnosis and early identification of mononucleosis, particularly in the setting of a new-onset rash after antibiotic initiation. Although not among the numerous antibiotics previously reported to cause a maculopapular eruption in individuals infected with EBV, this case demonstrates that cefepime can be added to the long list of antibiotics that can cause an immune response in this patient population. While this reaction can be severe, it is important to note that it does not imply a true allergy to that specific antibiotic or even the general drug class, as patients often tolerate the antibiotic of concern without an adverse reaction in the absence of mononucleosis.3 In this case, the marked reaction to the antibiotic provided a clue to pursuing the correct diagnosis in a less-than-typical presentation of acute mononucleosis. Ultimately, the severity and sudden onset of the rash after antibiotic administration was the key clue to the unifying diagnosis.

Conclusion

This case report documents a new and previously undocumented trigger of morbilliform eruption, cefepime, in the setting of infectious mononucleosis. While antibiotics such as amoxicillin and ampicillin have commonly been associated with the development of a maculopapular rash in the setting of an acute EBV infection, this clinical scenario demonstrates the important role other antibiotic classes may play in similar drug eruptions. This further supports the importance of conservative antibiotic use and awareness of such a reaction in this patient population with all antibiotics, not just the penicillins. Further research documenting a morbilliform eruption after treatment with cefepime in the setting of infectious mononucleosis are needed for a more definitive association.

Figure 3. H&E (200x): Skin biopsy of the left dorsal hand showing a focal vascular interface dermatitis with occasional lymphocytes present at the dermal/epidermal junction and a sparse underlying superficial perivascular lymphocytic infiltrate.

Figure 4. H&E (200x): Skin biopsy of the left lower abdomen showing a superficial to mid-perivascular and interstitial mixed-cell infiltrate composed of lymphocytes and neutrophils with extravasated erythrocytes; minimal epidermal changes are noted.
References


Abbreviations and acronyms:
EBV: Epstein Barr Virus
CMV: Cytomegalovirus
IM: Infectious mononucleosis
CBC: Complete blood count
UA: Urinalysis
CMP: Complete metabolic panel
CT: Computed Tomography
ANA: Anti-nuclear anti-body
CPK: Creatinine phosphate kinase
HIV: Human Immunodeficiency virus
RPR: Rapid plasma reagent

Acknowledgment
Author Contributions: Drs. Rajaii and Furniss had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Drs. Rajaii, Furniss and Bender

Acquisition, analysis, and interpretation of data: Drs. Rajaii, Furniss, and Pui

Drafting of the manuscript: Drs. Rajaii, Furniss, and Bender

Critical revision of the manuscript for important intellectual content: Drs. Rajaii, Furniss, Bender, and Pui