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Erythema Multiforme vs Steven Johnson Syndrome: A Challenging Diagnosis and Threat to Patient Safety

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Abstract

This case observes the presentation and management of a 19-year-old female who was treated for cellulitis with Bactrim and subsequently developed conjunctivitis and a diffuse macular rash with irregular two-tone lesions. She was urgently referred to the hospital where she received care from dermatology and ophthalmology in the burn unit. This case highlights the complexity in differentiating erythema multiforme vs. Steven Johnson syndrome, which are drug reactions that may be indistinguishable based on patient history and physical exam yet carry a different prognosis. Steven Johnson syndrome is associated with a high mortality rate, while the rash of erythema multiforme is typically self-limiting. Nevertheless, the therapeutic relationship may be damaged if an adverse reaction such as erythema multiforme were to occur. Finally, we recommend that health care professionals briefly inquire about a family history of drug reactions to sulfa drugs before prescribing, especially if there are other first line medications available with similar efficacy and safety profiles.

Keywords: Drug Reaction, Erythema Multiforme, Bactrim

Background

Erythema multiforme is a type IV hypersensitivity reaction to viral infections, bacterial infections, medications, or immunizations that occurs with an incidence of <1% per year [1]. Erythema multiforme typically presents with erythematous macules or papules that evolve into target shaped lesions with darkly pigmented centers that correlate with epithelial necrosis. Moreover, these lesions typically self-resolve within a month [2]. Erythema multiforme must be distinguished from a more severe drug reaction known as Steven Johnson syndrome. A retrospective study estimated that 9.2 million adults suffer from Steven Johnson syndrome every year [3]. Moreover, Steven Johnson syndrome will cause a mortality of 4-19% depending on patient comorbidities and total body surface area [3]. Considerable overlap in etiology and clinical presentation makes these drug reactions difficult to distinguish in select patients. This case report details a case of a 19-year-old young woman who developed an adverse drug reaction to Bactrim after several days of exposure.

Case Presentation

Ms. Harbor is a 19-year-old African American female with a past medical history of insulin dependent type II DM, polycystic ovarian syndrome, early cataracts, and asthma who presented to her primary care physician with a blistering rash across her face, erosion of her lower lip, and excoriated papular lesions disseminated across her body after taking Bactrim for approximately two weeks. Her family history is significant for two aunts that had a similar reaction to Bactrim.

The patient was originally seen at an urgent care 14 days prior to her presentation. There she received a 10-day course of Bactrim for a cellulitis on her right anterior shin. The patient took the Bactrim as prescribed and had no improvement, so she returned to the urgent care and was prescribed another course of Bactrim. On the 12th day of taking Bactrim, the patient developed a constellation of symptoms all at once that included facial swelling, red eyes, purulent eye discharge, a painful erosion on her lower lip, blistering facial rash, and a diffuse rash. The patient received care at the Beaumont emergency department on day 12 and received a course of steroids, which provided mild improvement of her symptoms. She received a second dose of steroids on day 13 as well, however her symptoms persisted. On day 14 the patient was evaluated in our office. She developed a transient sore throat during this encounter.

Eye and full body skin exam in our office showed minimal conjunctival injection and absence of purulent discharge (Figure 1). However, this picture correlates to day 3 of her drug reaction and after receiving multiple courses of systemic steroids. Moreover, there is dry, excoriated skin involving the forehead and midface in a malar distribution (Figure 1). There is a shiny erosion of the lower lip that does not involve the vermillion border and does not involve the alveolar or buccal mucosa (Figure 2). There was also a diffuse macular rash with two tone lesions. The center of the lesions is necrotic and dark, consistent with atypical target lesions. These lesions involve the distal extremities; however, they are much less densely populated (Figure 3).

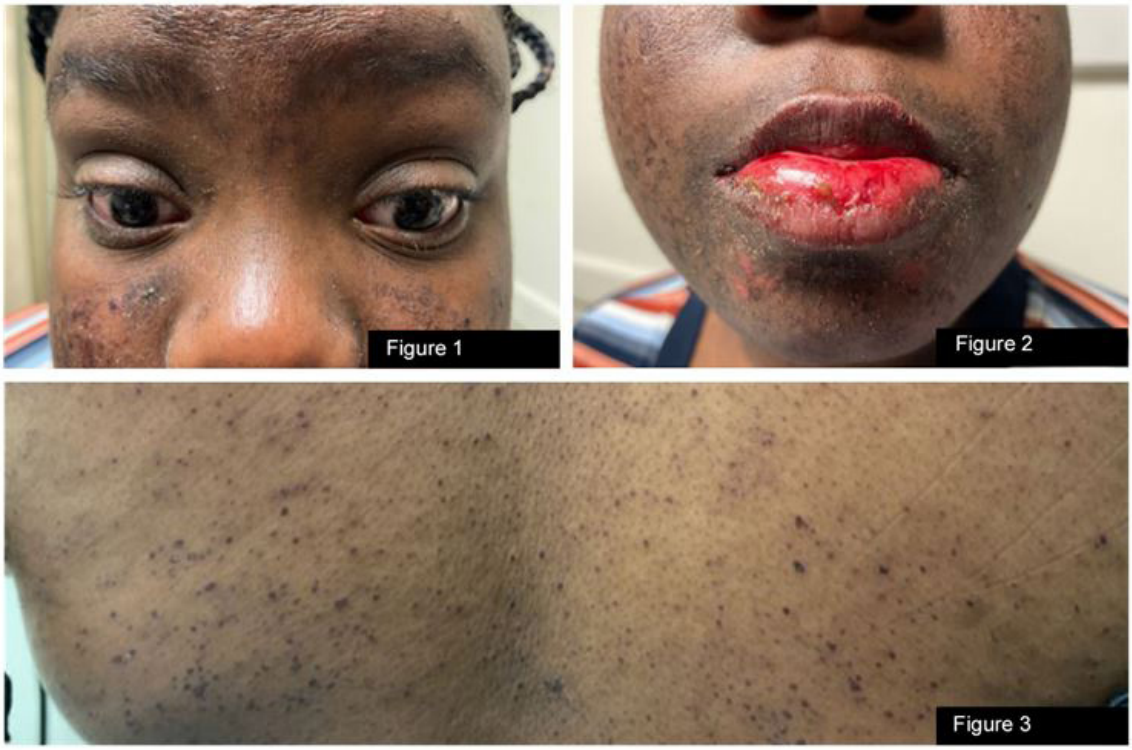

Figure 1-3: Full Body Skin and Eye Exam.

Investigations

Ms. Harbor was immediately referred from our office to the burn unit for evaluation by dermatology and ophthalmology. She was afebrile (37 C) and tachycardic (124 bpm) on presentation. Basic metabolic panel demonstrated hyponatremia (133mMol/L) and hypochloremia (92mMol/L), and elevated random blood glucose (24.6 mMol/L). ENA screen and fluorescent ANA testing were negative.

Ophthalmology saw the patient and performed a full exam including anterior and posterior segment exam. The patient was found to have no lid or lash involvement, no conjunctival pseudo-membrane, and clear cornea, conjunctivae, and sclerae. Pseudophakia was noted, however the patient has a history of early cataracts and lens replacement. The patient was diagnosed as erythema multiforme major vs. grade 0 SJS without ocular involvement.

Differential Diagnosis

Ms. Harbor's clinical presentation shows elements of both erythema multiforme and Steven Johnson syndrome. The cutaneous lesions of erythema multiforme are typically target shaped and spread centripetally from the distal extremities to the trunk [2]. Atypical lesions contain only two tones and an irregular border [2]. Mucosal involvement may include the conjunctivae and the labial, buccal, and tongue mucosa. Extension to the pharynx is rare [4]. Steven Johnson syndrome may also produce atypical target lesions, however the lesions are typically centrifugally spreading erythematous macules that evolve after several days into flaccid blisters [5]. Also, unlike erythema multiforme, conjunctival involvement is more severe and may be associated with purulent discharge [6]. Labial mucosal erosions are more likely to form a pseudo-membrane and mucosal involvement nearly always involves the pharynx [7]. Patients typically develop flu like symptoms with a high fever several days after cutaneous lesion onset. Ms. Harbor developed prominent conjunctival injection with purulent discharge, painful labial mucosal erosion without formation of a pseudo membrane, and many atypical target lesions with an unknown direction of spread. The lesions appear to have originated on her head and neck and spread centripetally based on the density of lesions. Ms. Harbor did not develop a flu like illness or blistering; however, these manifestations may have been prevented by early intervention with systemic steroids. Therefore, Ms. Harbor's dermatological presentation favors erythema multiforme, however report of her initial eye presentation was severe and would be expected in a patient with Steven Johnson syndrome.

Treatment

The patient had a SCORTEN score of 2 on presentation. However, her SCORTEN score diminished to 0 on the second day of admission. Moreover, she did not develop extensive skin detachment or rapidly progressing disease, so she was discharged home with recommendations to follow up with ophthalmology and a burn clinic.

Outcome and Follow Up

Ms. Harbor's had complete resolution of her rash and mucosal erosions within a month. Moreover, Ms. Harbor had a normal anterior compartment exam with ophthalmology and is unlikely to develop eye sequelae.

Discussion

A review estimates that 90% of erythema multiforme eruptions are caused by viral, bacterial, and fungal infections with herpes simplex virus being the most common implicated infection [1]. Moreover, targetoid lesions have been observed in patients after COVID-19 infection [8] and vaccination [9]. Drugs are estimated to cause less than 10% of erythema multiforme eruptions. In contrast, an analysis of 100 case reports estimates that 66% of Steven Johnson syndrome cases can be attributed to drug exposure. Allopurinol, lamotrigine, sulfa antimicrobials, nevirapine, and NSAIDs are the most common implicated medications[10]. Ms. Harbor's reaction was likely caused by Bactrim given the temporal relationship between medication administration and symptom development. We believe this is one of a minority of erythema multiforme cases caused by an adverse drug reaction. Moreover, this case is unlike other sulfa-antimicrobial induced erythema multiforme cases in the literature. Previous reports have detailed presentations of extensive irregular ulcerations of the palate and pharynx [11], vesicular lesions of the oropharynx and interdigital areas of the fingers [12], and a generalized maculopapular rash with epidermal sloughing [13]. Sulfa antimicrobial induced atypical targetoid lesions in erythema multiforme has not yet been described.

Genetic susceptibility plays an important role in developing erythema multiforme and Steven Johnson syndrome. The HLA-DQB1*0301 was found to be significantly associated with 66% of erythema multiforme patients vs. 31% of randomly selected asymptomatic controls in a case-control study [14]. An association between variants HLA-B:*15:02 [15], HLA-B*15:11 [16], HLA-A*31:01 [17], HLA-A*24:02 [18] and development of Steven Johnson syndrome after taking anti-epileptics that include carbamazepine, phenytoin, and phenobarbital is documented. However, no genetic association is well established between development of Steven Johnson syndrome after taking sulfa antimicrobials. Ms. Harbor has a family history of similar sulfa induced drug reactions in two aunts. Her family history strongly suggests a genetic predisposition to her adverse drug reaction.

The prevalence of erythema multiforme induced drug reactions are far less than 1% per year, however the potential for one to occur and damage the physician-patient relationship may warrant an adjustment in the way we prescribe antibiotics for cellulitis. Preferred agents in the treatment of uncomplicated cellulitis include Bactrim (TMP-SMX), clindamycin, and doxycycline (or) minocycline, which all have coverage against Methicillin-resistant Staphylococcus aureus [19]. TMP-SMX is generally considered in favor of clindamycin due to risk of c. difficile infection [20]. Moreover, doxycycline and minocycline provide unknown coverage of s. pyogenes and typically must be supplemented with amoxicillin [21]. Alternatively, medical providers should obtain a full history from patients before prescribing antibiotics. The history should include a family history of drug reactions. Knowledge of Ms. Harbor's family history of similar drug reactions to Bactrim may have guided the decision to choose either clindamycin or doxycycline and amoxicillin. This subtle change in her management would have prevented her adverse drug reaction.

Patient's Perspective

After 2 weeks of taking medicine for my leg infection, I abruptly developed a whole-body rash and had thick tears in my eyes. My lower lip also started to blister and bleed. My mouth was very painful. I initially received help in the emergency department, however my symptoms did not improve much. That's when my grandmother made a doctor's appointment, and I came in to get help. This was a frightening experience, and I know now that I can never take Bactrim again. A similar thing happened in both of my mom's sisters, however they were never hospitalized. I am thankful that I was given close observation in the hospital and that my eyesight is the same.

Learning Points

1. Steven Johnson syndrome carries a high rate of mortality and is more likely to be associated with severe conjunctival involvement with purulent discharge, high fever, and sloughing lesions.

2. Erythema multiforme is typically associated with target shaped lesions, however both Steven Johnson syndrome and erythema multiforme may produce atypical target shaped lesions with two tones and an irregular border.

3. This report provides a novel presentation of atypical target shaped lesions in a patient with sulfa antimicrobial induced erythema multiforme.

4. HLA alleles are an example of genetic susceptibility that predisposes individuals to developing Steven Johnson syndrome and erythema multiforme, and therefore we encourage health care professionals to inquire about a family history of drug reactions before prescribing an antibiotic to treat cellulitis.

Conflicts of Interest

The authors collectively deny any conflicts of interest.

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