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A case of erythema multiforme major following administration of ciprofloxacin ophthalmic drops

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Abstract

A 49-year old woman was hospitalized for generalized rash and pruritus following the administration of ophthalmic drops containing ciprofloxacin to treat conjunctivitis. Physical examination demonstrated diffuse erythematous papules and plaques with a targetoid appearance, injected sclera, and multiple erosions in the oropharynx. Skin biopsy confirmed a diagnosis of erythema multiforme major. The eye drops were discontinued and supportive treatment was initiated; the patient recovered in four weeks and was discharged from the hospital. Although cases such as this are rare, it is important that physicians take a thorough medication history from all patients with suspected erythema multiforme, including topical and ophthalmic medications. Prompt discontinuation of the offending agent can hasten patient recovery and optimize outcomes.

Keywords: drug-induced, eye drops, ophthalmic drops, erythema multiforme, fluoroquinolones

Introduction

Erythema multiforme major (EMM) is an acute, self-limited, type IV hypersensitivity reaction to certain drugs, pathogens, and other allergens. It is thought to lie on a spectrum with Stevens-Johnson syndrome and toxic epidermal necrolysis and presents with characteristic targetoid lesions with mucosal erosions or bullae. Indeed, currently it is considered by several investigators to be synonymous with Stevens-Johnson syndrome having less than 10 percent body surface area involvement and 2 mucous membranes affected [1]. Since the terminology for this spectrum of diseases is still debated, we will refer to our patient's diagnosis as "EMM" because her clinical features (e.g., targetoid lesions, oral mucosal involvement) align closely with the classic description of EMM [2]. Herein we describe an unusual case of EMM triggered by the use of ciprofloxacin ophthalmic drops.

Case Synopsis

A 49-year-old woman presented to the emergency department for evaluation of sudden-onset diffuse rash and pruritus. The patient had an extensive past medical history including hypertension, Type II diabetes mellitus requiring left-sided below-knee amputation, Stage IV chronic kidney disease, asthma, congestive heart failure, and coronary artery disease. Notably, after a 2009 quadruple bypass graft she had an allergic reaction to the sternotomy wires leading to wound dehiscence and requiring removal of a majority of her sternum and subsequent reconstructive surgery. One week prior to admission the patient developed injected sclera and eye pain bilaterally. Her primary care physician diagnosed her with conjunctivitis and prescribed ciprofloxacin eye drops three times daily. Despite use of these eye drops, her eye pain progressively worsened throughout the week. She took diphenhydramine 12.5 mg twice daily without improvement. On the day of admission, the patient awakened with odynophagia, diffuse rash, and intense pruritus. The rash started on her stump and spread over the rest of her body during the course of the day. She had a cold three weeks prior to admission but it resolved without treatment. Besides the eye drops, the patient was taking no new medications. Family history revealed the presence of systemic lupus erythematosus in the patient's mother.

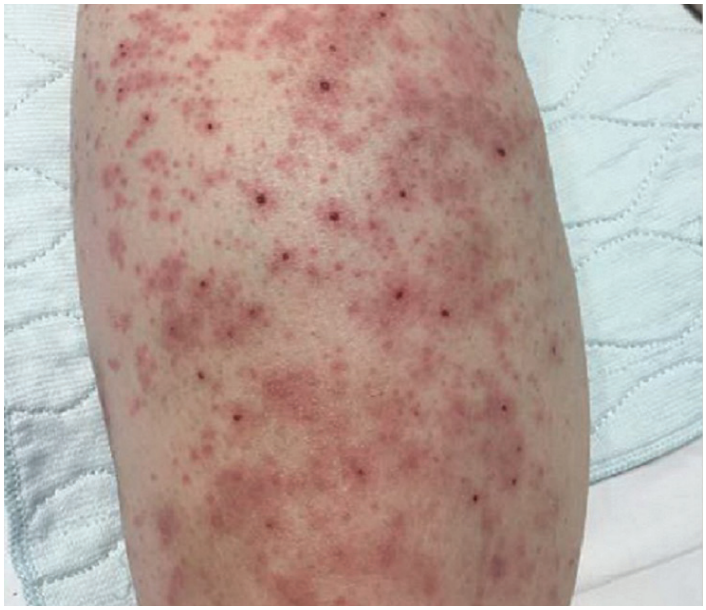

Figure 1. *Diffuse, pruritic, erythematous papules and plaques with dusky centers on right leg.*

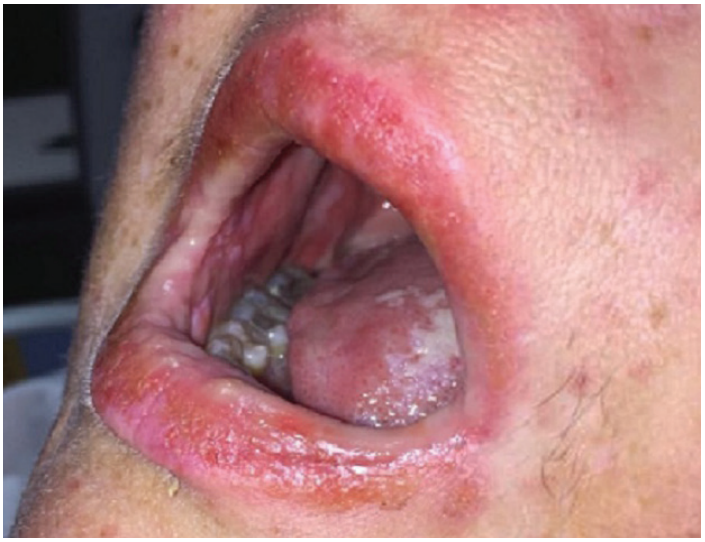

Figure 2. *Mucosal erosions causing odynophagia.*

On physical examination, the patient demonstrated diffuse, symmetric, annular, erythematous papules and plaques with dusky centers (**Figure 1**). Sclera were injected bilaterally. Oral examination revealed mucositis with multiple erosions present (**Figure 2**). Laboratory values were significant for an elevated erythrocyte sedimentation rate of 52 mm/HR (RR 0-20 mm/HR) on the day of admission. Measurement of serum Mycoplasma IgM was within normal limits. Chest X-rays were taken three times during the patient's admission; all chest X-rays were negative. Punch biopsy of lesions on the patient's right shoulder and right wrist revealed interface dermatitis with central areas of full-thickness epidermal necrosis consistent with EMM (**Figure 3**).

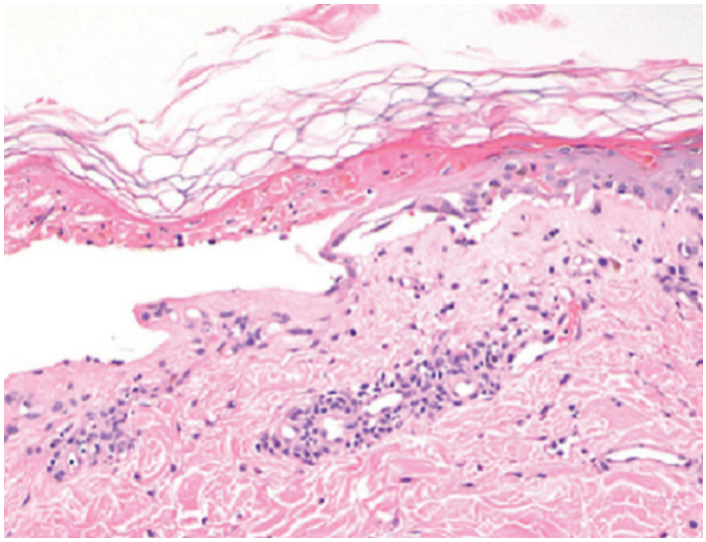

Figure 3. *Punch biopsy of the patient's right shoulder revealing interface dermatitis with central areas of full-thickness epidermal necrosis. H&E,* **200.**

After the diagnosis of EMM was confirmed by biopsy, the ciprofloxacin eye drops were discontinued and the patient was treated with topical triamcinolone 0.1% ointment twice daily on the body and lips and hydrocortisone 1% ointment twice daily on the face until the lesions resolved. On hospital day 22 the patient was discharged with significant improvement of her symptoms.

Case Discussion

Erythema multiforme major is a cutaneous hypersensitivity reaction that may be caused by various agents, such as drugs, diseases, or household products. Common culprits include herpes simplex virus infections, M. pneumoniae infections, antibiotics, sulfonamides and antiepileptics [3]. Thought to lie on a spectrum with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), erythema multiforme major severe enough to require hospitalization has an incidence of less than 7.4 per 106 person-years [4]. The disease often begins with prodromal symptoms such as cough, fever, malaise, and headache, followed by the eruption of a rash. The skin lesions of EMM classically begin with discoid, erythematous macules that quickly become papular. These edematous papules evolve into the targetoid lesions characteristic of EMM. These lesions typically erupt on the extremities and move centrally, often appearing on the mucosa as well as the skin. Given

the extensive mucosal and cutaneous involvement of EMM, numerous complications may arise. The most common complications are ocular, including keratitis, loss of vision, and uveitis. Myocardial, renal, hematologic, and pulmonary complications are rare but have been reported. Attacks of EMM are self-limited, typically lasting 1-6 weeks [3].

Fluoroquinolones such as ciprofloxacin, levofloxacin and norfloxacin are well-documented triggers of EMM/SJS/TEN [5-7] However, in most instances, the inciting fluoroquinolone is administered orally or intravenously. Several documented cases exist in which sulfacetamide ophthalmic drops resulted in toxic epidermal necrolysis [8, 9]. To the best of our knowledge, only two other cases of EMM/SJS/TEN induced by fluoroquinolone eye drops have been reported [10, 11]. The first of these cases was a 20-year-old man who developed TEN 48 hours after starting ofloxacin eye drops for a left-sided hordeolum [10]. In the second case, a 12-year-old girl began having symptoms of SJS (e.g., mouth ulcers, conjunctival injection) 2 days following the administration of ofloxacin eye drops; she presented for treatment 2 days after the onset of symptoms [11]. In both cases, the patients had no chronic medical conditions [10, 11], although the male patient had a history of lip swelling during treatment of a lower respiratory tract infection with oral ciprofloxacin three years prior [10]. Neither patient reported using any medications besides the ophthalmic drops [10, 11]. In our case, the identification of the eye drops as the causative agent was supported by the temporal association between the onset of symptoms and the administration of the eye drops and the lack of any other medications recently started by the patient. Mycoplasma-induced EMM was considered owing to the patient's recent history of a "cold," although in EMM due to Mycoplasma infection, mucosal lesions rather than cutaneous lesions often predominate. However, acute Mycoplasma infection was ruled out by normal serum Mycoplasma IgM levels. Complete withdrawal of the offending agent, along with copious use of topical corticosteroids, resulted in the patient's remission.

Conclusion

Erythema multiforme major should be considered in any patient with a sudden, diffuse eruption of pruritic targetoid lesions after the administration of fluoroquinolone ophthalmic drops. The pathogenesis of EMM is unclear, but it is thought to be the result of a cutaneous type-IV hypersensitivity reaction. Laboratory findings are usually non-specific [3]. Histopathologic evaluations of EMM show focal liquefactive degeneration of the epidermal basal zone along with inflammatory changes such as exocytosis and spongiosis [12]. Because such a wide array of agents may lead to EMM, it is important that physicians be aware of the potential for even topical medications to cause severe drug reactions. Ciprofloxacin ophthalmic drops should be added to the list of causative agents that may induce EMM, and dermatologists should be aware of this to avoid misdiagnosis.

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