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Case Report

Ciprofloxacin induced erythema multiforme: a case report

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ABSTRACT

Erythema multiforme (EM) is an acute, self-limited, and sometimes recurring skin condition that is considered to be a type IV hypersensitivity reaction associated with certain infections, medications, and other various triggers like flavorings and preservatives, such as benzoic acid and cinnamon, immunologic disorders, such as transient selective C4 deficiency of infancy, collagen diseases, vasculitides, sarcoidosis, non-Hodgkin lymphoma, leukemia, multiple myeloma, myeloid metaplasia, and polycythemia, physical or mechanical factors, such as tattooing, radiotherapy, cold, and sunlight, foods, including salmon berries and margarine, malignancy, and hormonal. EM may be present within a wide spectrum of severity. EM minor represents a localized eruption of the skin with minimal or no mucosal involvement. According to a consensus definition, Stevens-Johnson syndrome (SJS) was separated from the EM spectrum and added to toxic epidermal necrolysis (TEN). The two spectra are now divided into the following: (1) EM consisting of erythema minor and major and (2) SJS/TEN. Ciprofloxacin is a second generation fluoroquinolone. Fluoroquinolones are rapidly bactericidal *in vitro* and are considerably potent against *Escherichia coli* and various species of *Salmonella*, *Shigella*, *Enterobacter*, *Campylobacter,* and *Neisseria*. Mainly used in urinary tract infections, prostatitis, sexually transmitted diseases, gastrointestinal and abdominal infections, respiratory tract infections, bone-joint and soft tissue infections. Metronidazole is a nitroimidazole antimicrobial medication used particularly for anaerobic bacteria and protozoa. It is on the World Health Organizations list of essential medicines, a list of the most important medications needed in a basic health system. Here we report the case of a 39-year-old male patient who presented with EM to the dermatology outpatient department, Adichunchanagiri Hospital and Research Centre. The patient gave a history of taking antimicrobials ciprofloxacin and metronidazole for the treatment of a non-healing wound on the right leg which he sustained in a road traffic accident. The review of the literature has revealed very rare associations of metronidazole and pantoprazole with EM, but cases of ciprofloxacin-induced EM have been reported. Hence, the reported adverse drug reaction has been attributed to ciprofloxacin. In this event, casualty assessment using Naranjo's scale revealed that ciprofloxacin was a probable cause for the adverse drug reaction.

Keywords: Erythema multiforme, Erythema multiforme minor, Erythema multiforme major, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Ciprofloxacin, Metronidazole, Pantoprazole, Hypersensitivity, Target lesions, Casualty assessment, Naranjo scale, Probable cause, Adverse drug reaction

INTRODUCTION

Erythema multiforme (EM) is an acute, self-limited, and sometimes recurring skin condition that is considered to be a type IV hypersensitivity reaction associated with certain infections, medications, and other various triggers.[1]

EM may be present within a wide spectrum of severity. EM minor represents a localized eruption of the skin with minimal or no mucosal involvement.[2]

EM major and Stevens-Johnson syndrome (SJS), however, are more severe, potentially life-threatening disorders. Lesions of SJS typically begin on the face and trunk. They are flat, atypical lesions, described as irregular purpuric macules with occasional blistering. Most patients also have extensive mucosal involvement. More than 50% of all cases are attributed to medications.[2]

Controversy exists in the literature with regard to the clinical definitions of EM and SJS and whether they are distinct

entities or whether they represent a spectrum of one disease process.[3-8]

International collaborators have suggested that EM and SJS could be separated as 2 distinct clinical disorders with similar mucosal reactions but different patterns of cutaneous lesions.

According to a consensus definition, SJS was separated from the EM spectrum and added to toxic epidermal necrolysis (TEN).[4]

The two spectra are now divided into the following: (1) EM consisting of erythema minor and major and (2) SJS/TEN.

The clinical descriptions are as follows:

- EM minor – Typical targets or raised, edematous papules distributed acrally
- EM major – Typical targets or raised, edematous papules distributed acrally with involvement of one or more mucous membranes; epidermal detachment involves less than 10% of total body surface area
- SJS/TEN – Widespread blisters predominant on the trunk and face, presenting with erythematous or pruritic macules and one or more mucous membrane erosions; epidermal detachment is less than 10% for SJS and 30% or more for TEN.[2]

Ciprofloxacin is a second generation fluoroquinolone. Fluoroquinolones are rapidly bactericidal *in vitro* and are considerably potent against *Escherichia coli* and various species of *Salmonella*, *Shigella*, *Enterobacter*, *Campylobacter,* and *Neisseria*. Mainly used in urinary tract infections, prostatitis, sexually transmitted diseases, gastrointestinal and abdominal infections, respiratory tract infections, bone-joint and soft tissue infections.[9-11]

Metronidazole is a nitroimidazole antimicrobial medication used particularly for anaerobic bacteria and protozoa. It is on the World Health Organizations list of essential medicines, a list of the most important medications needed in a basic health system.

Pantoprazole is a proton pump inhibitor drug that inhibits gastric acid secretion. The uses of pantoprazole includes gastroesophageal reflux disease, duodenal or gastric ulcers, treatment of pathological hypersecretory conditions, *Helicobacter pylori* infections, etc.

Cases of ciprofloxacin-induced EM have been reported.[12,13]

EM associated with the use of metronidazole and pantoprazole has been relatively very rare.

CASE REPORT

A 39-year-old male patient presented to the dermatology outpatient department, Adichunchanagiri Hospital and Research Centre, B.G. Nagar, with complaints of rashes all over the body since 1-day. The patient gives a history of road traffic accident following which he injured his right leg. The patient was prescribed tablet lakcip (ciprofloxacin) 500 mg BD, tablet flagyl (metronidazole) 400 mg BD, and tablet PAN (pantoprazole) 40 mg BD before food for the non-healing wound in his right leg. The consumption of these medications resulted in the appearance of the rashes for which he sought medical help. The rashes were characterized by central hyperpigmented area surrounded by dusky red papillae. The rashes were associated with itching. On examination, random blood sugar was 304 mg/dl. General physical examination and systemic examinations revealed no abnormality. The patient was treated with calosoft (calamine) lotion, tablet atarax (hydroxyzine) 25 mg HS, injection dexona (dexamethasone) 2 ml i.m stat, injection avil (chlorpheniramine) 2 ml i.m stat. Rashes reduced. Rechallenge was not done (Figure 1a and b).

DISCUSSION

EM is a type of hypersensitivity reaction, which occurs in response to medicines, infections or illnesses. EM minor presents with localized eruptions of the skin with minimal or no mucosal involvement. The papules evolve into pathognomonic target lesions or iris lesions that appear within a 72 hrs period and begin on the extremities. Lesions remain in a fixed location for at least 7 days and then begin to heal. Lesions may also appear as arcuate lesions. Precipitating factors include herpes simplex virus, Epstein-Barr virus, and histoplasmosis. Because this condition may be related to a persistent antigenic stimulus, recurrence is the rule rather than the exception, with most affected individuals experiencing 1-2 recurrences per year.[2]

Many suspected etiologic factors have been reported to cause EM.[14]

- Infections: bacterial (including Bacillus Calmette-Guérin vaccination, hemolytic streptococci, legionellosis, leprosy, *Neisseria meningitidis*, *Mycobacterium, Pneumococcus*, *Salmonella* species, *Staphylococcus* species, *Mycoplasma pneumoniae*), *Chlamydial*.
- Fungal (*Coccidioides immitis*)
- Parasitic (*Trichomonas* species, *Toxoplasma gondii*),
- Viral (especially Herpes simplex)
- Drug reactions, most commonly to: antibiotics (including, sulfonamides, penicillin), anticonvulsants (phenytoin, barbiturates), aspirin, antituberculoids, and allopurinol, and many others.

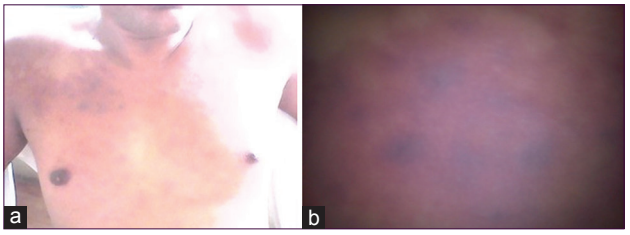

Figure 1: (a and b) Ciprofloxacin induced erythema multiforme.

- Physical factors: radiotherapy, cold, sunlight
- Others: collagen diseases, vasculitides, non-Hodgkin lymphoma, leukemia, multiple myeloma, myeloid metaplasia, polycythemia

The pathophysiology of EM is still not completely understood, but it is probably immunologically-mediated and appears to involve a hypersensitivity reaction that can be triggered by a variety of stimuli, particularly bacterial, viral, or chemical products.[2]

Cell-mediated immunity appears to be responsible for the destruction of epithelial cells. Early in the disease process, the epidermis becomes infiltrated with CD8 T-lymphocytes and macrophages, whereas the dermis displays a slight influx of CD4 lymphocytes. These immunologically active cells are not present in sufficient numbers to be directly responsible for the epithelial cell death. Instead, they release diffusible cytokines, which mediate the inflammatory reaction and resultant apoptosis of epithelial cells. In some patients, circulating T-cells transiently demonstrate (for <30 days) a T-helper cell type 1 cytokine response (interferon gamma, tumor necrosis factor [TNF] alpha, interleukin-2). Results of immunohistochemical analysis have also shown lesion blister fluid to contain TNF, an important proinflammatory cytokine.[2]

Other evidence supports the hypothesis that the disease is the result of cell-mediated immune reactions. Individuals possessing human leukocyte antigen–B12 are 3 times more likely to develop this disorder. The classic timing for a primary cell-mediated immune reaction is 9-14 days after the initiation of the offending drug. In recurrent exposure, the reaction occurs within several hours to 1-2 days, which is consistent with the timing of a secondary cell-mediated immune response.[2]

The review of literature has revealed very rare associations of metronidazole and pantoprazole with EM. Hence the reported adverse drug reaction has been attributed to ciprofloxacin.[15,16]

In this event, casualty assessment using Naranjo's scale revealed that ciprofloxacin was a probable cause for the adverse drug reaction.[17]

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