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Case Report

Erythema Multiforme Major Caused by Amoxicillin and Ceftriaxone in Patient Suffering from Respiratory Infection: A Case Report

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ABSTRACT

Erythema Multiforme (EM) is an acute, self-limited, and occasionally recurrent skin disorder that is caused by a variety of infections, drugs, and other stimuli. Infections account for 90% of cases of erythema multiforme, which is brought on by a cell-mediated immune response. The adverse drug reaction reported is rare and is caused by amoxicillin and ceftriaxone. A 49-year-old male patient visited the outpatient department with a chief complaint of breathlessness, cough, dyspnea, fever, itching, redness, and skin allergic reaction on the stomach, hands, and legs. He has had a history of type 2 Diabetes Mellitus (DM) from the past eight years. He had been prescribed oral amoxicillin 875 mg twice a day, ceftriaxone 2g/daily, paracetamol 625mg (SOS), pantoprazole 40mg/daily, and multivitamin once a day for a chest infection, and metformin 500mg + glimepiride 2mg in morning and insulin glargine 10 IU (SOS) for type-II diabetes. On the assessment of causality this Adverse Drug Reaction (ADR) was found probable by both the WHO-UMC scale and Naranjo scale. It was observed that ADRs like blisters following erythema multiforme major can be lethal and can cause anxiety and stress to the patients and also their quality of life is reduced. This present case report will help the physicians, clinicians and other healthcare professionals to get aware and vigilant about the adverse drug reaction caused by amoxicillin and ceftriaxone and also helps them in the early detection and management of ADR.

Keywords: Erythema multiforme major, Adverse drug reaction, Amoxicillin, Ceftriaxone, Case report.

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BACKGROUND

A type IV hypersensitivity reaction, erythema multiforme is an acute, self-limited, and occasionally recurrent skin disorder that is caused by a variety of infections, drugs, and other stimuli.[1] EM minor and EM major are the two primary types of erythema multiforme. Only one mucous membrane is affected by EM minor (EMm), and symmetrical target cutaneous lesions are visible on the extremities. Whereas, the cutaneous lesions in EM Major (EMM) involves two or more mucosal membrane and are quite different.[2] Infections account for 90% of cases of erythema multiforme, which is brought on by a cell-mediated immune response. Although erythema multiforme is most frequently associated with Herpes Simplex Virus (HSV) type 1, HSV-2 has also been found to be a contributing factor.[3] Drugs known to cause EMM are amoxicillin,[4] cefotaxime,[5] barbiturate, hydantoins, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and sulfonamides.[6]

CASE PRESENTATION

A 49-year-old male visited the outpatient department with a chief complaint of breathlessness, cough, dyspnea, fever, itching, redness, and skin allergic reaction on the stomach, hands, and legs. Afterward, he was referred to the dermatology department for further diagnosis. On interviewing it was found that he had a history of type 2 DM from the past eight years and a chest infection from the last 15-20 days. The eruption started from the stomach, and both hands initially with itching and redness that progressed to the lower region legs. The development of blister measuring 0.2-0.6 cm in diameter and varies in size as shown in Figure 1.

On interviewing the patient, about medical and past history, it was revealed that the patient visited a private clinic with a primary complaint of fever, chest tightness, dyspnea, and cough, fifteen days back for the treatment. As per his medical history, he was on oral amoxicillin 875 mg twice a day, ceftriaxone 2g/daily, paracetamol 625mg (SOS), pantoprazole 40mg/daily, and

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multivitamin once a day for chest infection for the last 5 days. However, the patient was also taking a combination of metformin 500mg + glimepiride 2mg in the morning and insulin glargine 10 IU (SOS) for type-II diabetes.

On evaluation, it was found that the erythema multiforme major reaction appeared in the initial stages of treatment with multiple blisters when he started treatment with amoxicillin 875mg and ceftriaxone 2g prescribed for Chest infection.

Investigation

He was physically diagnosed with erythema multiforme major, but no other abnormality and deformity were found. On the recommendation of a pulmonologist, dermatologist, and endocrinologist various diagnostic tests were conducted in the hospital as Complete Blood Count (CBC) for a blood infection, Fasting Blood Sugar (FBS), HbA_1C for diabetes, Serum Glutamic Oxalacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT) for hepatic cell injury, urinalysis for infection and diabetes, chest X-ray for a chest infection, Pulmonary Function Test (PFT) for lung capacity. The blood pressure was found 125/85 mmHg normal.

In CBC, White Blood Cells (WBC) were found at 12000 cells/mcL indicating infection or inflammation, Erythrocyte Sedimentation Rate (ESR) 42 mm/hr indicating inflammation, and Red Blood Cells (RBC) values of 5.26 million cells/mcL were found normal.

Figure 1: Erythema multiforme major in a 49-year-old male patient with a blistering.

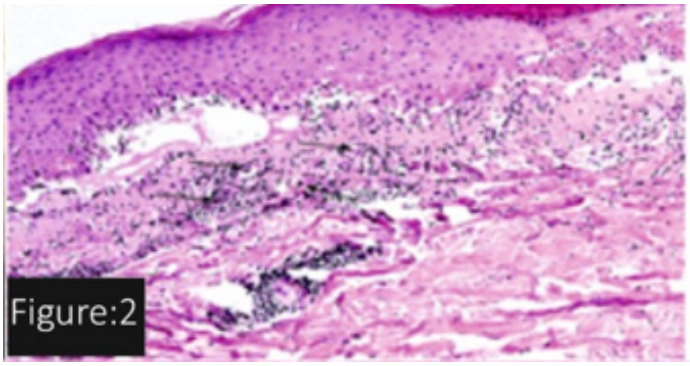

Figure 2: Histopathologic features of EMM Stain: hematoxylin and eosin (x 200) Epidermal necrosis seen overlying subepidermal vesicles with upper dermal lymphohistiocytic perivascular dermatitis as EMM.

The FBS: 185 mg/dL and HbA_{1c} 7.2% indicating diabetes. The values for SGOT and SGPT 32 units per liter of serum and 23 units per liter of serum respectively were found normal. Urinalysis was found normal. In the chest X-ray report, white spots were observed which indicates infection. In PFT, forced vital capacity, and total lung capacity was found to be decreased and SpO_2 value was found 86% which is less than the normal value. Other investigations like HSV and Human Immunodeficiency Virus (HIV) were found negative and Anti-Nuclear Antibody (ANA) was found negative. On evaluation for Sexually Transmitted Infection (STI) reports were found negative. The results for bacterial and viral blood culture and serology were awaited. The skin biopsy of the targeted blister revealed intraepithelial edema associated with exocytosis as indicated in Figures 2, 3, and 4.

Following the reaction, amoxicillin and ceftriaxone were discontinued, the alternatives of these drugs were prescribed to treat the chest infection and the treatment for skin blisters was initiated as a result the patient recovered from the reaction. After three weeks, the patient's consent was asked for re-challenging the drugs but the patient did not agree due to a lack of time and money.

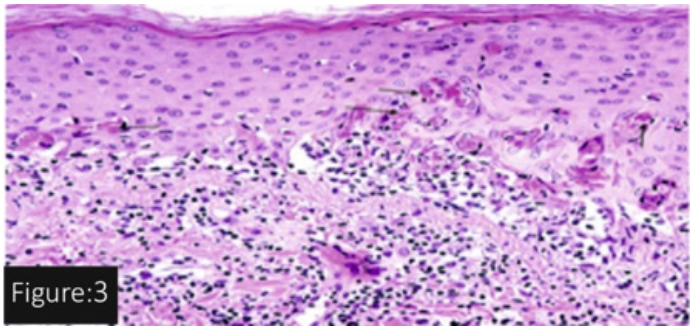

Figure 3: Showing basal layer vacuolar damage. Keratinocyte necrosis in both basal and suprabasal, superficial sparse perivascular infiltrate. Early blistering because of damage at the basement membrane in erythema multiforme results in interphase reaction pattern infiltrate of lymphocytic T cells attacking the dermoepidermal (DE) junction.

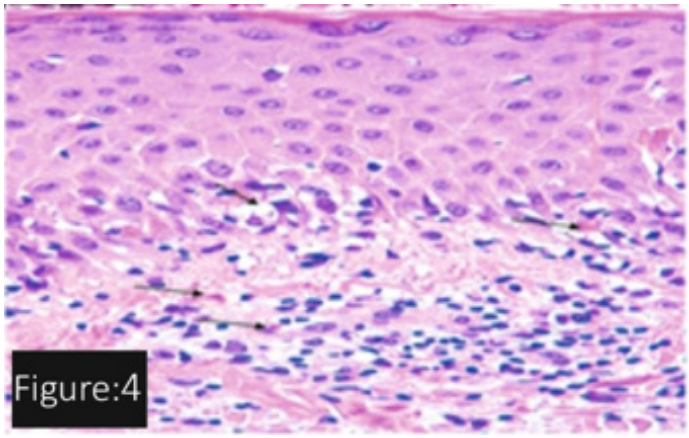

Figure 4: Showing basal hydropic changes, individual keratinocyte necrosis, and focal lymphocytic spongiosis, Stain: hematoxylin and eosin (x 400).

Treatment

The vital signs, electrolyte levels, and FBS were monitored daily. The progression of skin blisters was also observed on daily basis. The treatment includes oral antihistamines levocetirizine 5mg, β-methasone diproprionate 0.05% ointment, methylprednisolone 32mg/day for five days, and topical calamine lotion at night. The dose of methylprednisolone was reduced to 16mg, followed by 8mg after five days. On assessing the adverse drug reaction, oral amoxicillin and ceftriaxone were suspected drugs for causing an ADR blistering following erythema multiforme major. Amoxicillin 875mg twice a day and ceftriaxone 2g/day was stopped immediately as it was confirmed by assessing the causality of the ADR. A causality assessment of ADR was conducted using the WHO-UMC scale and Naranjo scale. On examination, it was found that ADR was found to be probable in both causality assessment scales and caused by amoxicillin and ceftriaxone. On evaluation and assessing ADR, it was found that there is no role of paracetamol, multivitamins, metformin + glimepiride, and insulin glargine in this ADR.

Outcome and Follow-Up

The patient took amoxicillin 875mg twice daily, ceftriaxone 2g/day along with paracetamol 625mg (SOS), multivitamins once a day, metformin 500mg + glimepiride 2mg, and insulin glargine (SOS). On follow-up, it was observed that the signs were diminished when the amoxicillin and ceftriaxone were withdrawn, treatment was initiated and the patient started to recover.

DISCUSSION

EM, first reported by Ferdinand Von Hebra in 1866, is a self-limited, acute skin condition that occurs as symmetrically spread "target lesions" on the extremities.[7] Analytical studies of EM linked with HSV have served as a foundation for understanding the pathogenesis of EM. It is believed to be the result of a cell-mediated immune response against cells that are positive for viral antigen and contain the HSV DNA polymerase gene (pol). Mononuclear cells with the skin homing receptor cutaneous lymphocyte antigen, such as macrophages and CD_{34}^{+} Langerhans cell progenitors, phagocytose the virus in peripheral blood. The HSV DNA that has been engulfed is carried to the epidermis, where it is delivered to the keratinocytes in fragmented form. Increased E-cadherin expression enhances the adhesion of HSV- containing Langerhans cells to endothelial cells. The inflammatory response is also caused by the increase of adhesion molecules on endothelial cells. Contrarily, drug-related EM appears to be connected with $CD8^{+}$ T-cell assault and lesion TNF-expression.[8,9]

Cases reported: In a case report by Mamatha *et al.* shows a case of ciprofloxacin-induced erythema multiforme in a 33-year-old male patient.[10] In another case, it was reported that eslicarbazepine caused erythema multiforme in a 41-year-old woman by Massot *et al.*[11]

CONCLUSION

The patient taking amoxicillin and ceftriaxone for treating infections is at the risk of developing erythema multiforme major reaction. The blisters can take a longer time to heal due to diabetes. The physician should be more vigilant while prescribing amoxicillin and ceftriaxone to patients, especially diabetes patients.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

EM: Erythema multiforme; **EMM:** Erythema multiforme major; **DM:** Diabetes mellitus; **ADR:** Adverse drug reaction; **HSV:** Herpes simplex virus; **FBS:** Fasting Blood sugar; **DE:** Dermoepidermal; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **CBC:** Complete blood count; **SGPT:** Serum glutamic pyruvic transaminase; **SGOT:** Serum glutamic oxaloacetic transaminase; **PFT:** Pulmonary function test; **WBC:** White blood cell; **ESR:** Erythrocyte sedimentation rate; **RBC**: Red blood cell; **HIV:** Human immunodeficiency virus; **ANA:** Anti-nuclear antibody; **STI:** Sexually transmitted disease.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This case was reported during the study which was approved by Institutional Ethics Committee. The study was carried out after taking permission from the Institutional Ethics Committee of ISF College of Pharmacy (Ref. no.: ISFCP/IEC/2015-16/P-17 and IEC-ISFCP/17-18/35, Moga. The consent was taken from the patient to participate in the study.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

AUTHORS CONTRIBUTIONS

Dr. Amit Sharma collected data of the case, Mr. Mohammad Amir is the major contributor in the writing, literature, and drafting the manuscript, Ms. Manisha Vohra and Mr. Ian Osoro is the major

contributor in editing and drafting the manuscript, all authors read and approved the final manuscript.

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