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METHOTREXATE INDUCED BULLOUS PEMPHIGOID: A CASE REPORT

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ABSTRACT

Background: Bullous pemphigoid (BP) is an autoimmune cutaneous blistering disorder. The precise precipitating etiology is not clear. There has been documented Drug-induced BP in case reports.

Case report: We describe a case of a 44- year old female with a past medical history of Psoriasis, who developed bullous pemphigoid. She had previously been on maintenance dose of 10mg intravenous methotrexate injection once weekly since 2 years. She developed pustular rashes suddenly for which the methotrexate dose was increased to twice weekly. During the first week of increased dose of methotrexate after the second injection, she presented with the diffuse bullous eruptions. The drug was stopped immediately and the patient was managed with IV steroids, antibiotics first and then oral steroids, antibiotics with good clinical outcome. As per, Naranjo's Adverse Drug Reaction (ADR) score, there is a "probable" cause and effect association for this case.

Conclusion: The exact mechanism is not known for the above mentioned ADR. Immunosuppressants like Methotrexate should be used judiciously.

KEYWORDS: Methotrexate, Bullous pemphigoid, Drug induced.

INTRODUCTION

Adverse drug reactions (ADRs) have been reported to be accountable for 0.3 to 7 percent of deaths amongst hospitalized patients. Drug reactions can range from mild, moderate to severe. Bullous pemphigoid (BP) which is not rare, but severe cutaneous cell-mediated hypersensitivity reaction that is usually induced by medication or a virus. Drug-induced BP has been documented in case reports. There are multiple drugs causing BP including furosemide,[1-3] angiotensin-converting enzyme inhibitors (ACEIs),[4] β-blockers,[5] penicillins,[6] dipeptidyl peptidase IV inhibitors and more recently anti–tumor necrosis factor agents.[7]

Methotrexate is a folate antagonist used widely for various skin disorders. It ameliorates many inflammatory diseases but has various side effects.

Psoriasis is a chronic, inflammatory, hyperproliferative skin disease in which methotrexate is commonly used for treatment as well as for preventing relapse.

Bullous pemphigoid is most common autoimmune dermatosis usually seen in older adults. It is an immune bullous subepidermal dermatosis characterized by large, tense blisters on an erythematous skin. These usually occur on the flexural site of limbs and trunk.[8] Mucosal involvement is also common.

It is an immune bullous disease as IgG immunoglobulins (antibodies) and activated T lymphocytes (white blood cells) attack components of the basement membrane, particularly a protein known as the BP antigen BP180, or less frequently BP230.[9]

IgG autoantibodies bind to the skin basement membrane in patients with bullous pemphigoid. Binding of these antibodies at the basement membrane activates various complement and inflammatory mediators. Activation of the complement system plays a critical role in attracting inflammatory cells to the basement membrane.These inflammatory cells are postulated to release proteases which further degrades hemidesmosomal proteins and leading to erythema and blister formation.

CASE HISTORY

A 44 years old, female patient presented to the emergency with chief complaints of multiple erosions on upper and lower limb and buttocks with two fluid filled vesicles on each thigh along with oral erosions. The patient had been administered intravenous methotrexate

10mg/twice weekly for chronic plaque psoriasis. She presented with the above complaints within 24 hours of second weekly dose of methotrexate. A detailed history was taken.

Patient was a diagnosed case of chronic plaque psoriasis since 2 years and regularly visited local dermatologist who administered her intravenous methotrexate 10 mg once weekly since 2 years. A few days back, she developed pustular rashes again and visited the same dermatologist who increased the dose of methotrexate 10 mg from once to twice weekly. In the first week of increased dose of methotrexate after the second injection, she developed multiple erosions on upper and lower limbs and buttocks, with two fluid filled vesicles on each thigh, oral erosions and fever within 24 hours of injection. Thus she was brought to our hospital for further treatment.

On physical examination, patient was well oriented to time, place and person, with multiple bullous erosions on upper and lower limbs, buttocks, multiple bullous vesicles on each thigh and oral erosions (figure 1). Nikolsky's sign was negative (It is elicited as the extension of a bulla due to pressure applied in a sliding motion to the lateral aspect of the lesion).[10]

There was no pallor, icterus, cyanosis or lymphadenopathy. Her body temperature was 102°F, Pulse rate- 78/min, B.P- 110/70 mm of Hg and Respiratory rate- 22/min. Other past medical history for any medical illness, surgery or any drug allergy was insignificant. No other systemic abnormalities were detected.

The patient was admitted with diagnosis of Drug induced Bullous Pemphigoid and intravenous Methotrexate 10mg was immediately stopped. ADR was instantaneously reported and Causality assessment done using Naranjo's algorithm which categorized the adverse drug reaction as probable (score=6). [11] We also reported the ADR in the vigiflow software for further assessment by the National Coordinating Centre (NCC) under the Pharmacovigilance Programme of India (PvPI) 2010.

Patient was started with intravenous fluids (1.5 liters/day), intravenous Prednisolone 10mg TDS, intravenous Linezolid 600gm BD. Oral ulcer was managed with the Oral benzocaine gel and Condy's soaks mouth wash.

Patient started showing improvement after 4-5 days of treatment, had normal body temperature with BP-110/70 mm of Hg, pulse 70 beats/minute, respiration at 16/minute,

urinary output of 1.5-1.8 liters/day and with an overall improved general condition. Her skin lesions were also improving with post-inflammatory pigmentation. Systemic steroid were continued, Inj. Prednisolone 10 mg QID for 10 days, which was gradually tapered to 10 mg TDS for 10 days, 10 mg BD for 7 days, then Tab Prednisolone 10 mg once daily for 7 days respectively. Intravenous fluid was also stopped on day 4 as patient was comfortable taking orally. Inj. Linezolid was also stopped after 14 days. Patient recovered completely after 22 days and was discharged with a follow- up advice to dermatology OPD for further management of Psoriasis.

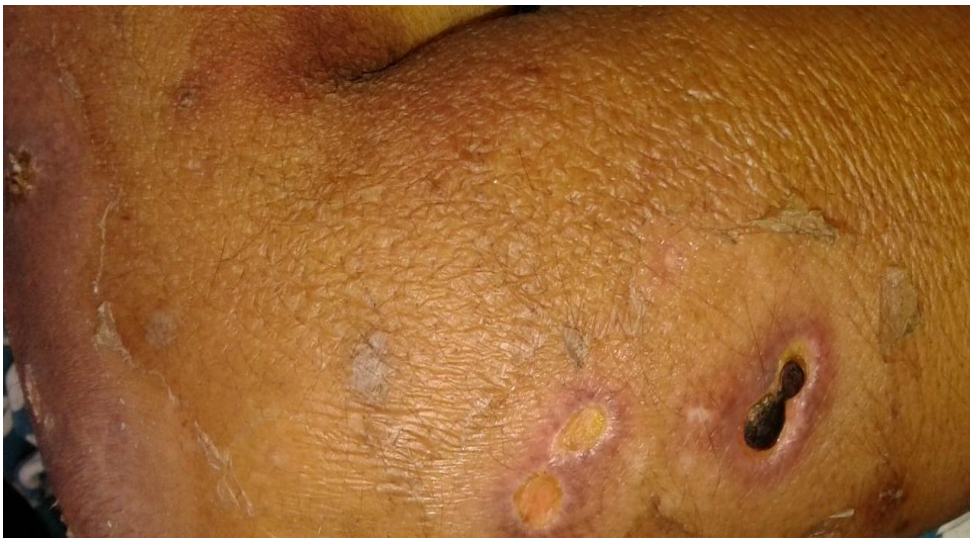

Figure 1: A close up image of healing bullae on right arm of the patient.

DISCUSSION

Methotrexate (MTX) is a folate antagonist that inhibits folic acid synthesis by blocking the function of dihydrofolic acid reductase. In presence of dihydrofolic acid reductase, dihydrofolates gets reduced to tetrahydrofolates before they can be used as carriers of one carbon groups in the synthesis of purine nucleotides and thymidylate. Thus by inhibiting utilization of folic acid, methotrexate interferes with DNA synthesis, DNA repair and cellular replication in rapidly proliferating cells.

Methotrexate apart from being used as an anticancer agent is also used for the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis and juvenile rheumatoid arthritis, pemphigus vulgaris, bullous pemphigoid, dermatomyositis, systemic lupus erythematosus, scleroderma, sarcoidosis, cutaneous polyarteritis nodosa, bechets disease, pyoderma gangrenosum, atopic dermatitis, keloids and lymphomatoid papulosis.

The most common side effects with methotrexate are liver dysfunctions, hepatitis, bone marrow suppression, nausea, gastric complaints and hair loss. [12]

Among most cases of psoriasis, plaque psoriasis is the most common form, accounting for approximately 90% of cases. Exacerbating factors include infection, endocrine factors, hypocalcaemia, medications, psychological stress and skin trauma. The aim of treatment is to minimize the extent and severity of the disease so as to improve the quality of life. Patients who discontinue treatments may experience a return of disease (relapse) or worsening of disease (rebound).[13]

Methotrexate in psoriasis acts through numerous mechanisms which might elucidate its effect. It is an antimetabolite which causes reduction in proliferation of skin cells, as it antagonises folic acid metabolism. It reduces pyrimidines, purines and methylation of DNA. Apart from this it also has weak immunosuppressive activity [14] and anti-inflammatory properties as well, possibly causing an increase in intracellular adenosine, a purine nucleoside.

Bullous Pemphigoid (BP) is a cutaneous autoimmune blistering disorder against the hemidesmosome, a part of the basement membrane that attaches the epidermis to the dermis.[15]

Discrepancy between autoreactive T helper (Th) and T regulatory cells, toll-like receptor activation and Th17/IL-17 pathway are the three probable autoimmunity triggers underlying BP.

The pathology of BP is mainly due to an autoantibody response toward structural components of the hemidesmosome (BP180 and BP230). The binding of autoantibodies leads to complement activation, recruitment of inflammatory cells which further releases proteolytic enzymes. Inflammatory cascade may be triggered by activation of Th17 cells with no interference of autoantibodies. The precise role of BP antigens in the pathogenesis of bullous pemphigoid is not completely clear. BPAg1 (BP230) is an intracellular component of the hemidesmosome; BPAg2 (BP180, type XVII collagen) is a transmembranous protein with a collagenous extracellular domain.

There are various factors which induce BP in genetically predisposed individuals like drug intake, physical agents and viral infections. Drugs may activate either by altering the immune

response or modifying the antigenic properties of the epidermal basement membrane. Common drugs reported to cause BP are Enalapril, Furosemide, Vildagliptin, Sitagliptin etc. A causative role of infections in inducing BP, is particularly seen with human herpes virus (HHV), Cytomegalovirus, Epstein-Barr virus, Hepatitis B and C viruses, Helicobacter pylori and Toxoplasma gondii. [16]

Drug induced BP is not uncommon though Methotrexate induced BP reports are rare. Hence methotrexate administration should be done carefully under expert supervision so that the ADR can be managed appropriately to prevent fatality.

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