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10.5005/jp-journals-10015-1073

CASE REPORT

Drug-Induced Bullous Pemphigoid: Expect the Unexpected

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ABSTRACT

Several systemic factors are known to contribute oral diseases. At same time, the drugs used for the treatment of such systemic diseases itself might cause spectrum of clinical conditions. The identification of a positive agent becomes difficult when the patient is on multiple drug regimens.

Reporting a case of an elderly female patient, who was on regular medication for hypertension over 5 years, developed generalized bullous eruptions in couple of weeks after being treated with Ciprofloxacin and Paracetamol for urinary tract infection. The dermal lesion worsened with administration of Dapsone.

Keywords: Bullous pemphigoid, Oral ulcers, Ciprofloxacin, Dapsone, Corticosteroid.

INTRODUCTION

Bullous pemphigoid is a chronic, autoimmune, subepidermal, blistering skin disease. It is characterized by the presence of immunoglobulin G (IgG) autoantibodies specific for the hemidesmosomal bullous pemphigoid antigens BP230 (BPAg1) and BP180 (BPAg2).[1] If untreated, the disease can persist for months or years, with periods of spontaneous remissions and exacerbations. Involvement of oral mucous membrane is seen only in 10 to 25% of patient leading to limited oral intake secondary to dysphasia. Erosions secondary to rupture of the blisters may be painful and may limit patient's daily living activities. Because the average age of onset of bullous pemphigoid is about 65 years, patients with bullous pemphigoid frequently have other co-morbid conditions that are common in elderly persons. Also, increased age make them more vulnerable to the adverse effects of corticosteroids and immunosuppressive agents which are commonly used for management. The onset of bullous pemphigoid may be either subacute or acute with widespread, tense blisters. Bullous pemphigoid has been reported to be precipitated by ultraviolet irradiation, radiotherapy and exposure to some drugs. Ciprofloxacin shows relatively few side effects, like photosensitivity, hypersensitivity, Stevens-Johnson syndrome and erythema multiforme,[2] only few cases are reported with ciprofloxacin induced bullous pemphigoid.[3,4]

CASE REPORT

A 69-year-old female patient reported to the department of oral medicine and radiology with chief complain of painful ulceration in oral cavity since 3 months. She also reported occurrence of dermal lesions a month later. She reported of consuming tablet Ciplox^{TM} 500 mg (ciprofloxacin) twice daily and tablet Crocin^{TM} (paracetamol) SOS, both for 1 week, for the management of urinary tract infection. Three weeks later, after medication she noticed vesicle formation in oral cavity rupturing to form ulcers. Lesion was associated with prodromal symptoms of itching and burning sensation. Patient reported with history of hypertension since five years, for which she was consuming tablet Losium H (Angiotensin II inhibitors). No earlier episode of allergy to any medication was reported. The general physical examination was within normal limits. On extraoral examination, multiple vesicular urticated excoriation were observed with ulceration of varying size on the flexor surface of lower extremities (Fig. 1). Recently, ruptured vesicles on back and upper extremities showed serum discharge. Mucous membrane of eyes, genitalia and lips appeared to be healthy. On intraoral examination, multiple oval shaped ulcers were seen on the gingiva of both upper and lower arch (Fig. 2). Other parts of oral cavity were free from ulceration.

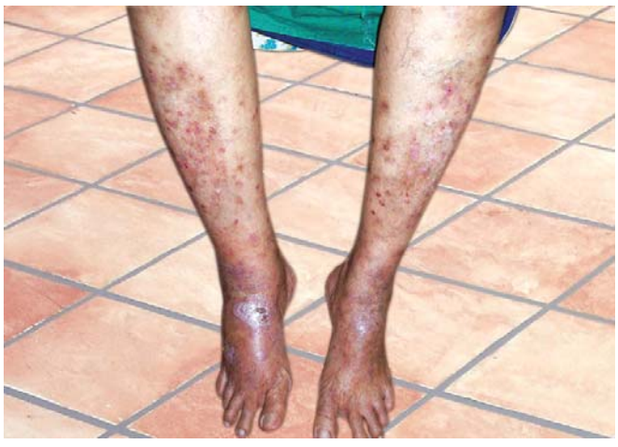

Fig. 1: Multiple vesicular urticated excoriation with ulceration of varying size

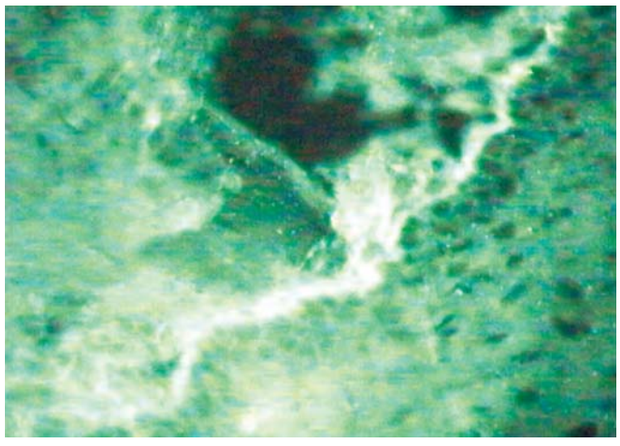

Fig. 3: Immunofluroscence test revealed deposition of IgG and C3 at the dermal epidermal junction

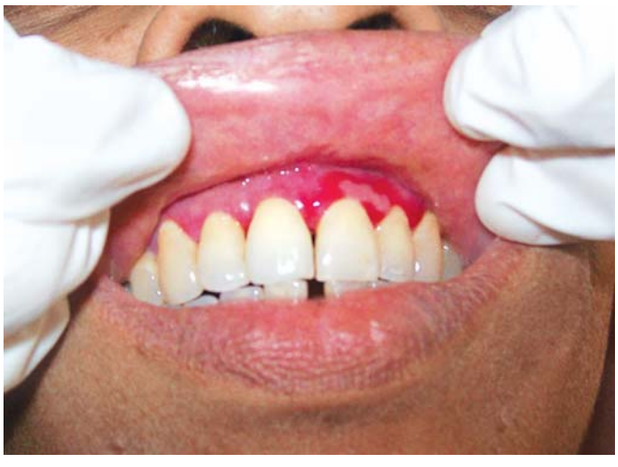

Fig. 2: Oval-shaped ulcers on the gingiva of upper arch

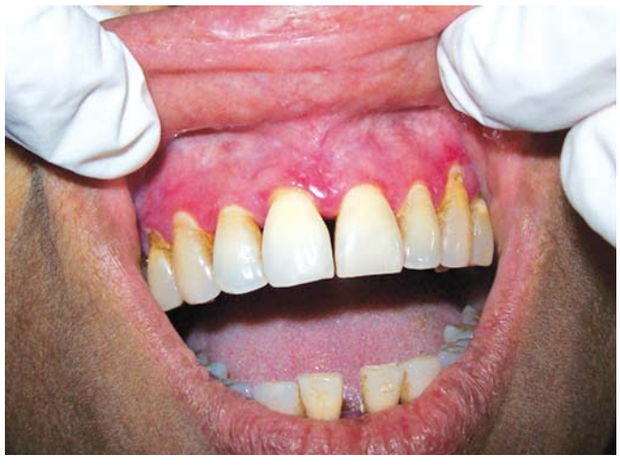

Fig. 4: Complete remission of oral ulcers

Conditions like herpes simplex, cicatrical pemphigoid, mucocutaneous diseases, like Reiters syndrome and Bechets syndrome, were ruled out clinically. Blistering disorder like pemphigus vulgaris was ruled out due to negative Nikolsky sign. Routine complete blood count, ESR, urine and liver analysis were done revealing increased ESR (80 mm/hr) and increased serum albumin level (4.8 gm/dl). Biopsy of perilesion area revealed subepithelial blister with infiltration of inflammatory cells. Direct immunofluroscence test revealed deposition of IgG and C3 at the dermoepidermal junction (Fig. 3). Based on these investigations, reported patient was diagnosed as having bullous pemphigoid.

Patient was prescribed tablet Dapsone 100 mg once daily for 30 days and topical application of steroids for oral ulcers. She reported back within 10 days with worsened dermal lesion. Dapsone was discontinued and Prednisolone 8 mg in three divided dose for 3 weeks was prescribed. For dermal lesions topical corticosteroids was advised. Oral lesion was managed with topical application of intermittent potency steroids along with Hexidine mouthwash. On recall, no new oral or dermal lesion was reported. Systemic steroid was further continued for complete remission. On next recall, patient reported with generalized weakness. Blood investigation revealed increased fasting sugar level (205 mg/dl), postprandial sugar level (411 mg/dl) and HbA1-c 8.4, hence, systemic steroids were tapered and discontinued. In a month duration blood sugar level was under normal range managed by hyperglycemic medication. For oral and dermal lesion topical steroid was continued. Complete remission was noticed within a span of 2 months (Fig. 4).

DISCUSSION

A wide spectrum of drugs can sometimes give rise to numerous orofacial and cutaneous manifestations. Although the true incidence of adverse drug reactions is difficult to quantify, the highest reported frequency consistently is found to be with antimicrobial agents like trimethoprim-sulfonamide combination (2.1%), fluoroquinolones (1.6%) and penicillins (1.1%).[5] Drug-induced bullous pemphigoid is a well-known complication of many drugs and represent a spectrum from an acute and self-limited condition to a chronic disease. At least 30 drugs can give rise to conditions resembling bullous or mucous membrane pemphigoid. These drugs belong to a variety of pharmacological (thiol and non-thiol) and therapeutically

targeted groups, including ACE inhibitors, furosemide, NSAIDs, penicillamine, psoralens, sulphonamides, cardioactive agents and penicillin-related antibiotics.[6] Chloroquine, captopril, spironolactone, terbinafine,[7] serratiopeptidase, mefenamic acid,[8] metoprolol[9] (beta-blocker), celecoxib[10] and ciprofloxacin[3,4] are other reported drugs inducing bullous pemphigoid. Possible mechanisms of drug-induced bullous pemphigoid include autoimmune damage via altered antigenicity of structures within the lamina lucida, negative action on immune suppressor cells, or direct splitting of the skin without development of antibody formation.[9] It has been suggested that multiple genetic and environmental influences are involved in disease induction, where in the drug act as heptan inducing immunological dysfunction. Precipitation of preexisting subclinical bullous pemphigoid has also been hypothesized to explain drug-induced lesions.

In drug-induced bullous pemphigoid the clinical, histological, and immunopathologic features are identical to those in idiopathic bullous pemphigoid. The induced forms are usually transient seen in younger age group, often localized and generally disappears after discontinuation of the drug. Oral mucosa is frequently affected, although patients often also have cutaneous lesions distributed over lower leg areas.[11] Patient also exhibits rapid improvement on systemic steroids with no recurrence and no dermal eosinophilic infiltrates. All these features supported the present reported case.

In present case, patient had no previous history of drug allergy reaction, hence, bullous pemphigoid associated with her hypertensive medication was ruled out. Angiotensin II inhibitors reports low incidence of adverse reaction mainly causing angioedema, dry mouth and ulcerations as main side effects. Paracetamol though safe and well-tolerated belongs to NSAID group, which account for 27% dermatological reactions with rare incidence of urticaria and Stevens-Johnson syndrome/toxic epidermal necrolysis.[5] As patient reported consuming paracetamol several times in her life span with no adverse reaction, and bullous pemphigoid associated with ciprofloxacin reported in literature, ciprofloxacin was suspected to be the offending drug. Worsening of dermal lesion during administration of Dapsone was due to bioactivation of drug in/near keratinocytes. Literature review states that bioactivation of Dapsone generate haptens that are recognized by sensitized lymphocytes evoking delayed type of immune-mediated reaction.[5] The temporal relationship between administration of ciprofloxacin-paracetamol and development of bullae, followed by resolution after discontinuation of suspected drug and management with steroid therapy suggested that bullous pemphigoid was associated with either drugs. Also, the history, clinical findings and investigations supported the diagnosis.

Note: This is the evidence based report of ciprofloxacin-induced bullous pemphigoid and health care professionals should be aware of this possibility, as ciprofloxacin is the most widely used medication in India.

ACKNOWLEDGMENT

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