DOI: 10.7860/JCDR/2015/14669.6972

Case Report

Pharmacology Section

Metronidazole-Induced Bullous Pemphigoid: A Case Report

SAIBAL MOITRA[1], SUKANTA SEN[2], INDRANIL BANERJEE[3], AYAN SIKDER[4], PRASANTA DAS[5]

ABSTRACT

Bullous pemphigoid is an autoimmune cutaneous blistering disorder, the exact pathogenesis of which is still not fully elucidated. Drug-induced bullous pemphigoid eruptions are rare but have been reported earlier with the use of frusemide, psoralens, ibuprofen, galantamine hydrobromide, ACE inhibitors like captopril, spironolactone, penicillin, ampicillin, levofloxacin, penicillamine. We hereby report a case of metronidazole induced bullous pemphigoid (BP) in a 52-year-old male patient suffering from liver abscess following 4 days of drug administration. The skin biopsy findings obtained from the patient were consistent with the diagnosis of bullous pemphigoid (BP). Metronidazole was discontinued and symptomatic treatment was offered to the patient. Following withdrawal of metronidazole, the bullae subsided in the next 7-10 days without any significant residual scarring. The causality assessment performed as per the Naranjo algorithm revealed the case to be probable (Naranjo score 7).

Keywords: Adverse drug reaction, Cutaneous drug eruptions, Drug-induced bullous pemphigoid

CASE REPORT

A 52-year-old male patient was admitted in a tertiary care hospital with fever, chills and rigour since last 1 week and headache and body ache for 3 days. He was put on antibiotic and antipyretic. Fever subsided within three days but the patient developed loss of appetite, pain in right hypochondrium region and distension of abdomen. Routine blood count and ESR revealed decrease Hb 10.32gm%, increased WBC count and increased ESR (115 mm in 1st hour). His differential leukocyte count was significant for 9% eosinophils (normal range is 1-4%). Electrolytes were all within normal limits. There was normal serum billirubin with slightly increased liver enzymes.

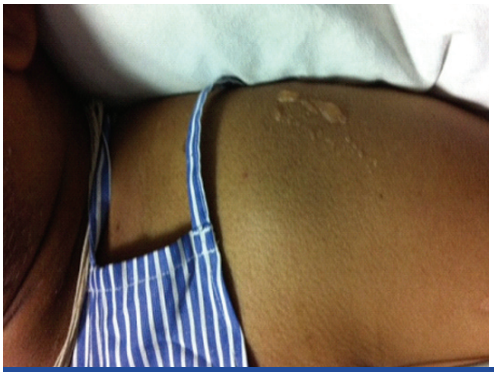
USG abdomen showed a space-occupying lesion in the liver which may be liver abscess, so USG guided percutaneous aspiration was done. Aspirate sent for serology for *E. Histolytica* (IgM and IgG), microscopy for trophozoites of *E. Histolytica* and culture and sensitivity. Aspirate was positive for amebic serology and negative for bacterial growth. He was started inj metronidazole 750 mg i.v. Q8H. After 4 days, blisters appeared on the non-pressured areas, which were non-pruritic and non-tender in nature.

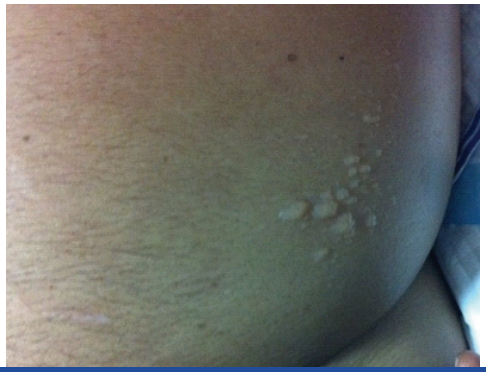
On examination, vital parameters including pulse, blood pressure were stable. There were blisters over left shoulder joint, lower abdomen and mild edema over face, dorsae of hands and feet. Blisters were of different size with multiple intact bullae of sizes, ranging from 2x1 to 2x2 cm [Table/Fig-1-3]. A careful physical examination demonstrated bullous eruptions mostly on an erythematous base with no target lesions. The oral and genital mucosa was not involved. The patient had no history or evidence of autoimmune, neoplastic, or infectious diseases. No earlier episode of allergy to any medication was reported. Inj metronidazole was discontinued as the patient developed multiple blisters all over body following its administration. The patient was treated with IV fluids, tab paracetamol 500mg SOS, and inj cefipime plus tazobactum (1.125 gm) i.v. twice daily, tab levocetriizine 5 mg once daily, gentian violet paint over intact bulla and fusidic acid plus betamethasone cream topical application twice daily over eroded lesions. Upon withdrawal of inj metronidazole, there was improvement of eruption and no new lesions appeared.

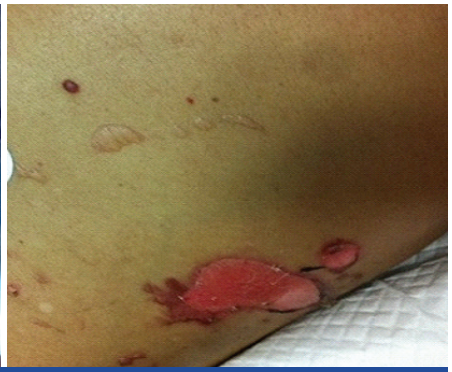
A skin biopsy was performed and but direct immunofluorescent staining could not be done. The finding of a subepidermal vesicle supports our diagnosis of bullous pemphigoid. One week later, all the skin lesions started resolving with hyperpigmented spots without scarring [Table/Fig-4,5]. Patient and his attendants were counseled to avoid metronidazole use in future. The causality assessment was performed using the Naranjo algorithm [1] where the score was 7 suggestive of a probable association. The severity of the ADR as per the Modified Hartwig scale was found to be Moderate (Level 3) [2].

DISCUSSION

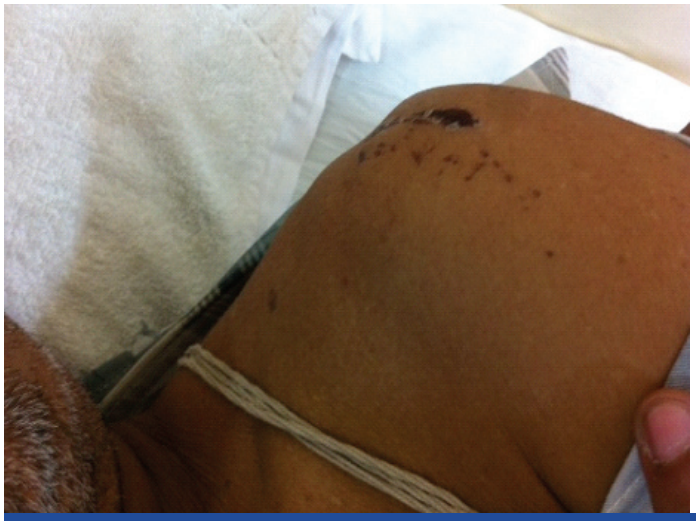
Cutaneous drug eruptions (CDR) constitute the most common type of adverse drug reactions (ADR) with an overall incidence rate

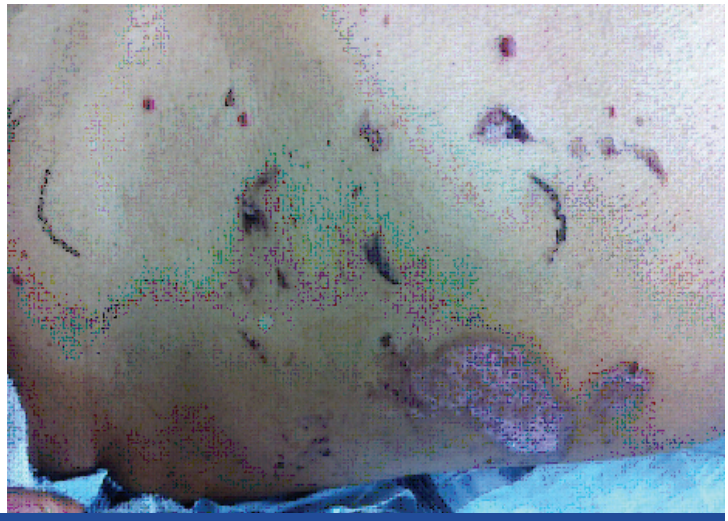






[Table/Fig-1]: Multiple blisters of varying size on left shoulder region **[Table/Fig-2]:** Multiple blisters of varying size on abdomen **[Table/Fig-3]:** Ulceration on blister site during remission





[Table/Fig-4]: Remission of blisters on left shoulder region after drug withdrawn **[Table/Fig-5]:** Discoloration and pigmentation of skin on blisters area during remission phase

of 2–3% in hospitalized patients [3]. A CDR is suspected when a patient who develops rash or blisters during a course of drug therapy. Commonly drug induced blistering eruptions are drug-induced pemphigus and pemphigoid, linear IgA bullous dermatosis and pseudoporphyria cutanea tarda [4].

BP is an autoimmune, subepidermal, blistering disease characterized by tense blisters containing haemorrhagic fluid developing on an erythematous base [5]. It mainly affects the skin although the eyes, mouth, and genitals also can be affected. The disease usually occurs spontaneously, however certain medications also can precipitate its development. Itching and blisters occur in almost all patients early in the course of the disease. Blisters may break, and the exposed skin can be raw and painful. The skin can return to normal with darker spots may remain after the blisters go away. Scars usually do not develop.

Drug-induced BP eruptions are rare but have been reported with the use of frusemide [5], psoralens [5], ibuprofen, galantamine hydrobromide [6], ACE inhibitors like captopril [5], spironolactone [5], penicillin [5], ampicillin [5], levofloxacin [7], penicillamine [5], chloroquine [5], sulfasalazine [5], Efalizumab [8], levetiracetam [9], sitagliptin and vildagliptin [10]. Metronidazole, a synthetic nitroimidazole drug, is indicated in the prevention and treatment of systemic infections caused by anarobic microorganisms. BP is a rare complication of metronidazole therapy. The hallmark of BP is the production of autoantibodies against two antigens (BPAG1 and 2) which can be induced by drugs and clinically manifested as blisters of varying degree [10].

Blisters are a well-known manifestation of cutaneous reactions to drugs. Blistering disorder like pemphigus vulgaris was ruled out to negative Nikolsky sign. Cicatricical pemphigoid is a rare variant in which mouth ulcers, eye problems and other complications may develop, with subsequent scarring was also ruled out clinically as there was no involvement of blisters in oral cavity and eyes. There are isolated reports of bullus eruption due to Metronidazole [11-13]. Idiopathic BP is characterised by large tense blisters developing on an erythematous base and often haemorrhagic fluids was also clinically excluded. The finding of a subepidermal vesicle supports our diagnosis of BP. Presence of subepidermal blisters excluded intra-epidermal or subcorneal lesions like Impetigo, Staph “scalding skin” syndrome, friction induced, viral infections like (Herpes, Varicella Zoster) and suprabasal lesions like pemphigus vulgaris.

Most bullous drug reactions result from an immunologically mediated inflammatory response. Suggested mechanisms include local drug-induced metabolic disturbance (possibly in the cyclic AMP system) at the level of the basal cells which might lead to the formation of immunogens and be one of the initiating factors in subepidermal bullous immune dermatoses [10]. Very recently, it was explained that autoimmune damage via altered antigenicity of structures within the lamina lucida, negative action on immune suppressor cells, or direct splitting of skin without development of antibody [14].

The interest of this case report is the clinical presentation, temporal relationship and histopathological findings. Although metronidazole is rarely involved agent in drug-induced BP, this form of presentation has been rarely reported. Recently, BP was reported in diabetic patients treated with dipeptidyl peptidase-4 inhibitors (gliptins) [10]. On extensive literature search revealed only one other report of metronidazole associated BP [15]. We take this opportunity to publish this unique metronidazole induced BP. Like other drug-induced disease, after the suspected agent was interrupted a spontaneous remission of lesions was noticed. This evolution is not observed in the idiopathic form.

Further studies are now warranted to validate our observations, definitely evaluate the potential of metronidazole to cause BP, and to elucidate the corresponding pathogenesis.

CONCLUSION

We presented this case of metronidazole induced bullous pemphogoid as it was detected in the initial days of starting the inj metronidazole and gradually recovered after withdrawal of suspected drug. Bullous eruptions were gradually resolved after discontinuation of suspected drug. Patient was counseled and advised not to use metronidazole for any future indication and report to us in case similar incidence cutaneous drug reaction develops. Prompt recognition, exclusion and stopping of culprit drug (s); early diagnosis, evaluation of the severity and prognosis of disease condition; rapid initiating supportive care and then specific care are the crux for the management of drug-induced severe cutaneous reactions. Patient and family members should be adequately counseled. Health care professionals and patients should be educated on potential danger symptoms and signs of cutaneous drug reactions to look out for when taking high-risk drugs.

REFERENCES

[1] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roborts EA. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1991;30:239-45.
[2] Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm*. 1992;49:2229-32.
[3] Lau PM, Stewart K, Dooley MJ. Comment: hospital admissions resulting from preventable adverse drug reactions. *Ann Pharmacother*. 2003;37(2):303-04.
[4] Crowson AN, Brown TJ, Magro CM. Progress in the understanding of the pathology and pathogenesis of cutaneous drug eruptions. *Am J Clin Dermatol*. 2003;4:407–28.
[5] Lee A, Thomson J. Drug-induced skin reactions. In: Lee A, editor. Adverse Drug Reactions. 2nd ed. London: Pharmaceutical Press; 2006. pp. 126–55.
[6] Diab M, Coloe J, Bechtel MA. Bullous pemphigoid precipitated by galantamine hydrobromide. *Cutis* 2009;83(3):139-40.

[7] Ma HJ, Hu R, Jia CY, Yang Y, Song LJ. Case of drug-induced bullous pemphigoid by levofloxacin. *J Dermatol*. 2012;39(12):1086-87.
[8] Duong TA, Buffard V, André C, Ortonne N, Revuz J, Bagot M, et al. Efalizumab induced bullous pemphigoid. *J Am Acad Dermatol*. 2010;62:161–62.
[9] Karadag AS, Bilgili SG, Calka O, Onder S, Kosem M, Burakgazi-Dalkilic E. A case of levetiracetam induced bullous pemphigoid. *Cutan Ocul Toxicol*. 2013;32(2):176-78.
[10] Pasmatzi E, Monastirli A, Habeos J, Georgiou S, Tsambaos D. Dipeptidyl Peptidase-4 Inhibitors Cause Bullous Pemphigoid in Diabetic Patients: Report of Two Cases. *Diabetes Care*. 2011;34:e133.
[11] Bhargava P, Mathur DK, Agarwal US, Bhargava R. Severe bullous fixed drug eruption due to metronidazole mimicking a localized form of toxic epidermal necrolysis. *Indian J Dermatol Venereol Leprol*. 1996;62(1):55-56.
[12] Puneet B, Agarwal US, Bh. Severe bullous fixed drug eruption due to metronidazole mimicking a localized form of toxic epidermal necrolysis. *Indian J Dermatol Venereol Leprol*. 1996;62(1):55-56.
[13] Sehgal VN, Khandpur S, Sardana K, Bajaj P. Bullous fixed drug eruption (BFDE) following per-oral metronidazole. *J Eur Acad Dermatol Venereol*. 2003;17:607-09.
[14] Perry A, Sparling JD, Pennington M. Bullous pemphigoid following therapy with an oral beta-blocker. *J Drugs Dermatol*. 2005;4(6):746-48.
[15] Gupta S, Alam K, Palaian S, Singh M, Dwari B, Prabhu S, et al. Metronidazole Induced Bullous Fixed Drug Eruptions: A Case Report And A Review Of Literature. *The Internet Journal of Dermatology*. [Internet] 2006;5(1):1-5. Available from: http://ispub.com/IJD/5/1/5786.

PARTICULARS OF CONTRIBUTORS:
1. Pulmonologist, Department of Pulmonary Medicine, Charnock Hospital & Research Centre Pvt. Ltd., Kolkata, West Bengal, India.
2. Associate Professor, Department of Pharmacology, ICARE Institute of Medical Sciences & Research, Haldia, West Bengal, India.
3. Assistant Professor, Department of Pharmacology, Lady Hardinge Medical College, New Delhi, India.
4. ICU Registrar, Department of Emergency Medicine, Chittaranjan Seva Sadan, Bhawanipur, Kolkata, West Bengal, India.
5. Respiratory Therapist, Department of Pulmonary Medicine, Charnock Hospital & Research Centre Pvt. Ltd., Kolkata, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sukanta Sen,
Associate Professor, Department of Pharmacology, ICARE Institute of Medical Sciences & Research,
Haldia-721 645, West Bengal, India.
E-mail: drsukant@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Apr 27, 2015**
Date of Peer Review: **Aug 01, 2015**
Date of Acceptance: **Oct 05, 2015**
Date of Publishing: **Dec 01, 2015**