European Journal of Case Reports in Internal Medicine

Bullous Pemphigoid-like Skin Eruption during Treatment with Rivaroxaban: A Clinical Case Study

Cristiana Ferreira[1], Ana Oliveira[2], Antonia Furtado[3], Natividade Rocha[2], José Almeida Ribeiro[3]

[1] Serviço de Imunoalergologia, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal
[2] Serviço de Dermatologia, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal
[3] Serviço de Anatomia Patológica, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal
[4] Serviço de Medicina Interna, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal

Doi: 10.12890/2018_000724- European Journal of Case Reports in Internal Medicine - © EFIM 2018

Received: 15/08/2017
Accepted: 28/11/2017
Published: 15/01/2018

How to cite this article: Ferreira C, Oliveira A, Furtado A, Rocha A, Ribeiro J. Bullous pemphigoid-like skin eruption during treatment with rivaroxaban: a clinical case study. *EJCRIM* 2018;**5**: doi:10.12890/2018_000724.

Conflicts of Interests: The Authors declare that there are no competing interests.

ABSTRACT

Little has been documented about hypersensitivity reactions caused by treatment with rivaroxaban. This paper reports a bullous pemphigoid-like skin eruption that occurred in a 76-year-old female patient during rivaroxaban treatment. This case highlights the vigilance required by healthcare workers in recognising potential adverse effects of newly marketed drugs and in making medication changes when necessary. A bullous pemphigoid-like eruption due to treatment with rivaroxaban has not, to the best of the Authors' knowledge, been reported previously in the literature.

LEARNING POINTS

- Rivaroxaban can cause a bullous eruption apparently similar to epithelial toxic necrolysis (or to Stevens-Johnson syndrome).
- There is an apparent similarity between skin adverse events caused by the different anticoagulants.
- The anticoagulant responsible for the skin side-effects can be identified on clinical grounds by the correct differential diagnosis.

KEYWORDS

Rivaroxaban, bullous pemphigoid-like, cutaneous drug eruptions

INTRODUCTION

Cutaneous drug eruptions are among the most common adverse drug reactions and may often represent a challenging diagnostic problem. While a single drug can elicit a range of reaction patterns, no reaction pattern is specific to a particular drug. Although the temporal link between initiation of drug therapy and the onset of a drug rash is critical for the diagnosis, drug reactions may also occur during chronic drug administration.

Blisters are a well-known manifestation of cutaneous reactions to drugs. In many types of drug reactions, bullae and vesicles may be found in addition to other manifestations. Bullae are usually noted in erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, vasculitis, porphyria cutanea tarda, and phototoxic reactions[1]. Although drug-induced bullous pemphigoid eruptions are rare, they can be caused by certain drugs, such as furosemide, heparin, ibuprofen, captopril, and many others[2-6].

European Journal of Case Reports in Internal Medicine

Rivaroxaban (Xarelto®, Bayer Corporation, Pittsburgh, PA) is a new oral anticoagulant drug. It acts as a direct factor Xa inhibitor and is used in venous thromboembolism prophylaxis. This drug is increasingly prescribed because, as an oral drug, it is easily handled during therapy; moreover, no coagulation monitoring is needed, and it has a wide therapeutic index. However, phase III studies have listed hypersensitivity to rivaroxaban as 'undetermined'[7].

CASE DESCRIPTION

A 76-year-old female patient with a medical history of paroxysmal atrial fibrillation and depression was hospitalised on 10 January 2016 due to a pulmonary thromboembolism. During hospitalisation, the patient started sertraline 100 mg daily, rivaroxaban 20 mg daily, and furosemide 10 mg twice daily. Fifteen days after the start of therapy, the patient developed a rash characterised by urticarial plaques on her back, upper limbs, and anterior surfaces of her thighs. In addition, tense, sero-haemorrhagic blisters developed on both legs (*Figs. 1 and 2*). No lesions were observed on mucosae.

The patient was followed in the Internal Medicine and Dermatology Service. The tentative diagnosis was that of a bullous pemphigoid secondary to drug use or neoplastic aetiology. Given the known association between furosemide and bullous pemphigoid, its use was discontinued and the patient started on therapy using a topical corticosteroid, betamethasone cream, twice a day.

The results on the patient's diagnostic exams were as follows: a WBC of 7220 with 14.4% eosinophils, platelets 197,000/µl, and ESR 60 mm/hr. The CEA, Ca 15-3, Ca 19-9, and Ca 125 results were within normal ranges. The search for anti-skin, anti-basement, epidermal membrane and anti-keratinocyte autoantibodies (indirect immunofluorescence [IIF] in peripheral blood) was negative. Histological examination disclosed intraepidermal blistering with eosinophils and apoptotic keratinocytes inside, with significant spongiosis in the neighbouring epidermis *(Fig. 3)*. Discrete infiltrates of eosinophils were diffusely represented among spongiotic areas and throughout the upper part of the dermis in a perivascular and interstitial infiltrate pattern (*Fig. 4*). Immunofluorescence was negative for IgA, IgG, IgM, C3, and C1q.

Two weeks after the use of furosemide had been discontinued, the cutaneous condition worsened; bullous lesions now appeared on the forearms (*Fig. 5*). At that time, rivaroxaban was discontinued and replaced with warfarin, while furosemide was reintroduced. A rapid improvement in the lesions was noted within 1 week, and no relapse occurred during the 12-month follow-up.

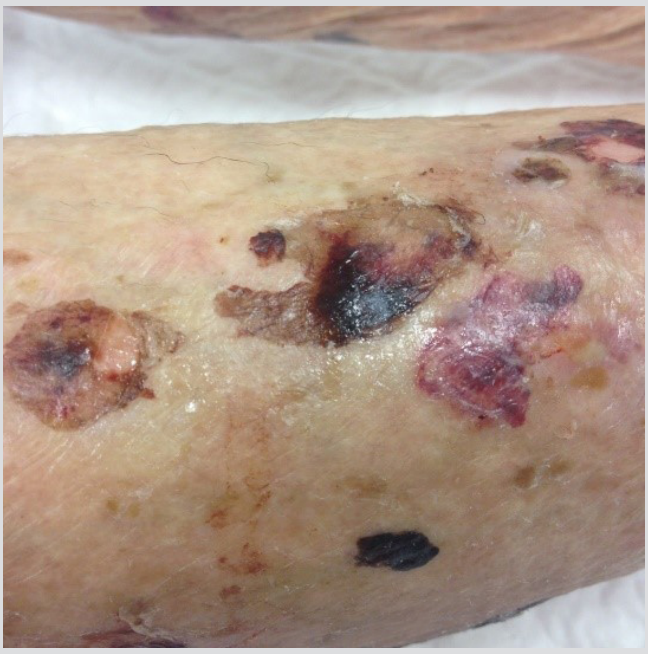

Figure 1. Bullous pemphigoid-like skin eruption on the legs

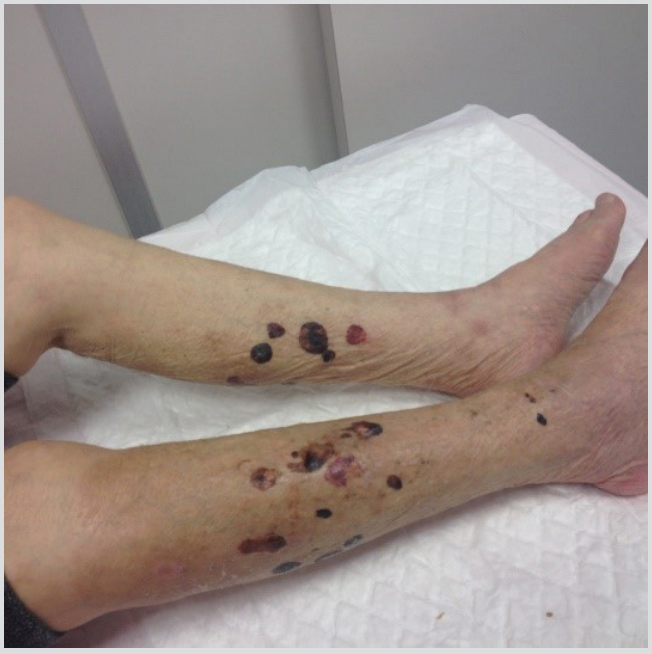

Figure 2. Bullous pemphigoid-like skin eruption on the legs

DOI: 10.12890/2018_000724

European Journal
of Case Reports in
Internal Medicine

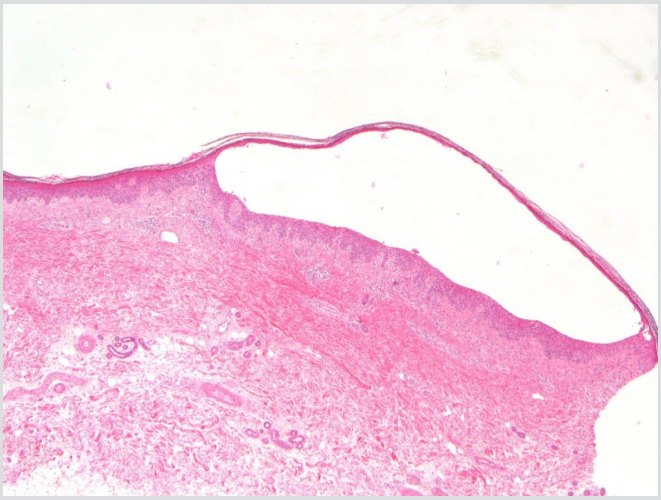

Figure 3. Histological examination using H&E staining and low power magnification revealed intraepidermal blistering

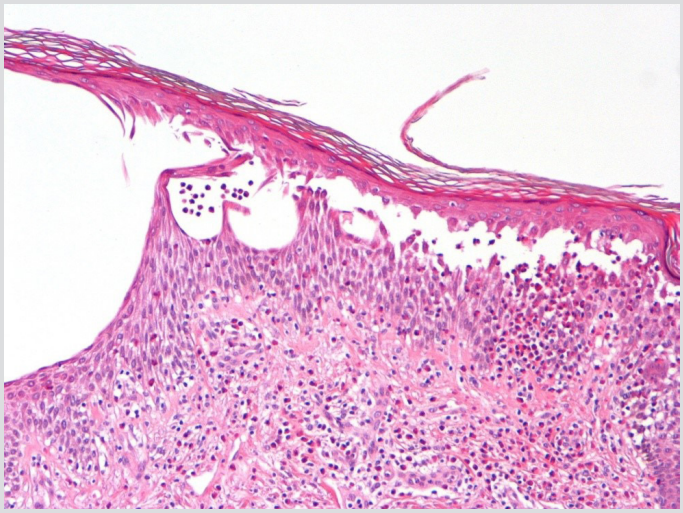

Figure 4. Histological examination using H&E staining and medium power magnification revealed eosinophils in tiny collections that were abundantly present among spongiotic areas in the epidermis (arrow) and throughout the upper part of the dermis (arrowhead)

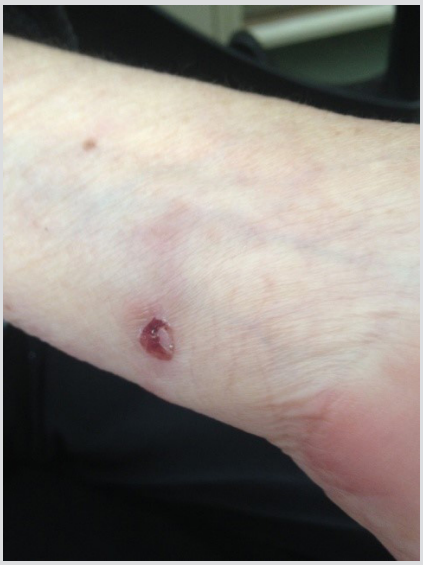

Figure 5. Bullous pemphigoid-like skin eruption on forearm

DISCUSSION

The diagnosis of bullous pemphigoid-like skin eruption due to rivaroxaban was established. Our differential diagnoses included haemorrhagic toxic necrolysis / heparin-induced thrombocytopenia and Stevens-Johnson syndrome (*Table 1*). However, the patient's normal platelet count, negative Nikolsky's sign, results on the direct immunofluorescence test, bullous eruption in the dermis-epidermis junction, and histologic findings ruled out these diagnoses. Histologically, drug-induced variants of bullous pemphigoid are similar to the typical form and are characteristically composed of eosinophil-rich subepidermal blisters[8]. In the initial stage, only eosinophilic spongiosis and numerous dermal eosinophils are present, with eosinophils lining up along the basement membrane[9]. At later stages, the blisters may appear to be intraepidermal as a result of keratinocyte regeneration. In the present case, these various morphological features were present and, in a concordant clinical context, were diagnostic for the disease. Negative immunofluorescence studies, as in this case, occur in 4% of the patients with bullous pemphigoid[1, 8].

Cutaneous reactions have been reported during anticoagulant therapy with coumarin derivatives and with unfractionated and low-molecular-weight heparins and heparinoids[10-12]. However, very few data regarding hypersensitivity reactions to rivaroxaban are available;

we were only able to find two such cases in the literature[13, 14]. Even though heparins, warfarin, and rivaroxaban have very different mechanisms of action, the clinical similarity of their epithelial side-effects is remarkable. In spite of this similarity, a differential diagnosis between the offending agents can be made with high confidence (*Table 2*).

	Steven-Johnson syndrome (SJS)	*Bullous pemphigoid*		*Haemorragic skin eruptions*	
		Idiopathic	*Drug-induced*	*Heparin-induced skin necrosis*	*Coumarin-induced skin necrosis*
Clinical features	• *Rusty macules with or without epidermal detachment (<10% BSA)* • *Atypical target lesions (papular lesions with two zones of colour changes, with papular, vesicular or flaccid bullous centre)*	• *Multiple tense bullae arising on normal or erytemathous skin* • *Bullae can rupture, leaving circular erosions with haemorragic crusts* • *Urticarial papules and plaques, along with bullae containing serous fluid* • *Pruritus and nonspecific eczematous lesions can precede* • *At least 50% of patients have peripheral eosinophilia*		• *Often associated with heparin-induced thrombocytopenia with thrombosis* • *Necrosis starts with a small, erythematous and painful lesion that later extends to areas of necrosis*	*Pain, oedema and small subcutaneous haematoma, followed by erythematous or haemorrhagic changes in demarcated lesions that become bullous and can progress to gangrenous necrosis*
Mucosal involvement	*Severe*	*Rare*	*No*		
Distribution	*Face, neck, trunk*	*Lower abdomen, thighs, forearms, legs*		*Injection site, but can also be generalised*	*Subcutaneous fatty tissue, eg breasts, thighs, abdomen and buttocks*
Histological findings	• *Subepidermal blister with overlyng confluent necrosis of the entire epidermis; keratinocyte apoptosis is a hallmark of SJS* • *Sparse perivascular infiltrate composed primarily of lymphocytes*	• *Subepidermal bullae* • *Infiltrate composed of neutrophils and eosinophils in the dermis and bulla cavity*	*Subepidermal bulla or intraepidermic*	*Microvascular thrombi in small vessels with minimal inflammation*	*Areas with thrombosis, microvascular injury and fibrin deposits in the postcapillary veins and small vessels*
Presence of autoantibodies	*Negative*	• *DIF with IgG and/or C3 in the basement membrane zone* • *IIF (+) in 70% of patients*	*DIF and IIF can be negative*	*Antibodies against heparin platelet factor-4 complexes*	
Others	• *Systemic symptoms are usually present (fever, hepatitis, cytopenias)* • *Progression to toxic epidermal necrolysis is possible* • *Nikolsky (+/-)*	*Nikolsky (-)*		*Platelet count drops by 50% compared with the baseline value within first 10–14 days of treatment*	• *10 days after the onset of therapy* • *Protein C or protein S deficiencies*

Table 1. Differential diagnosis of a bullous skin eruption in patients undergoing anticoagulant therapy

European Journal of Case Reports in Internal Medicine

Substance group according to site of action	*Chemical name*	*Bullous skin reaction*
Vitamin K antagonists	*Coumarins*	• *Haemorrhagic bullous eruption* • *Skin necrosis*
Antithrombin-III activators (heparins)	*Glycosaminoglycans*	• *Haemorrhagic bullous eruption* • *Bullous-like eruption* • *Stevens–Johnson syndrome / Toxic epidermal necrolysis* • *Bulbous pemphigoid* • *Skin necrosis*
Direct factor Xa inhibitors	*Xabans*	*Toxic skin eruption*

Table 2. Bullous skin reactions to various substance groups with anticoagulant effects

REFERENCES

1. Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. Fitzpatrick's dermatology in general medicine, 8th ed. New York: McGraw-Hill, 2012.
2. Lee A, Thomson J. Drug-induced skin reactions. In: Lee A, ed. Adverse drug reactions. 2nd ed. London: Pharmaceutical Press, 2006, pp. 125–56.
3. Ma HJ, Hu R, Jia CY, Yang Y, Song LJ. Case of drug-induced bullous pemphigoid by levofloxacin. *J Dermatol* 2012;**39**:1086–87.
4. Miguel-Gomez L, Fonda-Pascual P, Carrillo-Gijon R, Muñoz-Zato E. Bullous hemorrhagic dermatosis probably associated with enoxaparin. *Indian J Dermatol Venereol Leprol* 2016;**82**:319–20.
5. Perry A, Sparling JD, Pennington M. Bullous pemphigoid following therapy with an oral beta-blocker. *J Drugs Dermatol* 2005;**4**:746–48.
6. 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. *Internet J Derm* 2006;**5**:1–6.
7. Bayer HealthCare AG. Xarelto (rivaroxaban): Summary of product characteristics as approved by the European Commission, 2011. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf
8. Calonje JE, Brenn T, Lazar A, McKee PH. McKee's pathology of the skin. 4th ed. Philadelphia: Elsevier Saunders, 2012.
9. Weedon D, Strutton G, Rubin AI. Weedon's skin pathology. 3rd ed. Edinburgh: Churchill Livingstone/Elsevier, 2010.
10. Maldonado Cid P, Alonso de Celada RM, Noguera Morel L, Feito-Rodríguez M, Gómez-Fernández C, Herranz Pinto P. Cutaneous adverse events associated with heparin. Clin *Exp Dermatol* 2012;**37**:707–11.
11. Scherer K, Tsakiris DA, Bircher AJ. Hypersensitivity reactions to anticoagulant drugs. *Curr Pharm Des* 2008;**14**:2863–73.
12. Bircher AJ, Harr T, Hohenstein L, Tsakiris D. Hypersensitivity reactions to anticoagulant drugs: diagnosis and management options. *Allergy* 2006;**61**:1432–40.
13. Vernon HM, Nielsen AK, O'Bryan EC. Hypersensitivity reaction after administration of rivaroxaban (Xarelto). *Am J Emerg Med* 2016;**34**:1325.e1-2.
14. Yates J, Choudry M, Keys G. A case report describing a suspected rivaroxaban hypersensitivity reaction in a surgical patient. *J Clin Pharm Ther* 2013;**38**:159–61.