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Case Report

Acenocoumarol Induced Cutaneous Leucocytoclastic Vasculitis with Fatal Outcome

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Received: March 18, 2019; **Published:** June 26, 2019

Abstract

Acenocoumarol is an oral coumarin anticoagulant that is widely prescribed for the prophylaxis and treatment of venous and arterial thromboembolic disorders. Their administration requires biological monitoring because of the risk of drug overdose and consequent haemorrhagic complications. Additionally, skin reactions associated with oral coumarin-derived anticoagulants are an uncommon occurrence. Although hypersensitivity reactions such as vasculitis are possible and have been previously described, they are very rare with only few cases in the medical literature reporting a Coumarin-induced vasculitis. We report a rare case of a 76-year-old Moroccan man presenting with an acenocoumarol-induced leukocytoclastic vasculitis with a fatal evolution after accidental reintroduction.

Keywords: *Acenocoumarol; cutaneous vasculitis; antivitamin K; leucocytoclastic vasculitis; coumarin; reintroduction*

Introduction

Acenocoumarol is an oral coumarin anticoagulant that is widely prescribed for the prophylaxis and treatment of venous and arterial thromboembolic disorders [1,2]. Their administration requires biological monitoring because of the risk of drug overdose and consequent haemorrhagic complications [3]. Additionally, skin reactions associated with oral coumarin-derived anticoagulants are an uncommon occurrence [2]. In fact, skin necrosis, purple toes, maculopapular vesicular urticarial eruptions and Lyell syndrome are regarded as acenocoumarol-related adverse effects [1]. However, vitamin K antagonist-induced leukocytoclastic vasculitis (LCV) has been rarely reported and its causal relationship is warranted to be elucidated [4]. We report a rare case of a 76-year-old Moroccan man presenting with a serious and unexpected adverse effect of antivitamin K (AVK) in form of an induced LCV, confirmed histologically and chronologically, with fatal outcome.

Case Report

A 76-year-old chronic smoker male patient with history of renal failure on hemodialysis and high blood pressure treated with diuretics, exhibited ischemic stroke that had required acenocoumarol therapy. He reported 15 days before his admission a bilateral edema of the feet with erythematous and purpuric infiltrated painful lesions on the legs, ulcerating thereafter, in a context of apyrexia and asthenia, appearing 3 months after acenocoumarol intake. He did not had a history of drug allergy and he was not taking any other medications. The physical examination revealed multiple round infiltrated and necrotic-hemorrhagic purpuric lesions on the lower limbs, locally ulcerated by places, associated to an edema of the feet (Figure 1). The remaining parts of the body were spared. Total body exam found signs of right heart failure. No other clinical features were noted. An infectious, inflammatory and immunological assessment was made and showed no abnormalities. Histological examination of the involved skin demonstrated fibrinoid necrosis of small vessel wall

surrounded by polymorphonuclear leukocytes, suggesting leukocytoclastic vasculitis. The acenocoumarol treatment was incriminated because of its chronological imputability and then interrupted and substituted by another anticoagulant, while all the other medications were continued. Skin lesions resolved spontaneously over the next 30 days and the patient had a good clinical evolution. However, 1 month after discharge, the patient accidently resumed acenocoumarol treatment by self-medication, which results in the reappearance of purpuric lesions associated to large necrotic associated patches of the limbs (Figure 2) with hemodynamic and Glasgow disorders that rapidly induced the death of the patient, before performing a cerebral-CT and other laboratory tests in order to seek for other systemic disorders, despite the introduction of systemic corticotherapy.

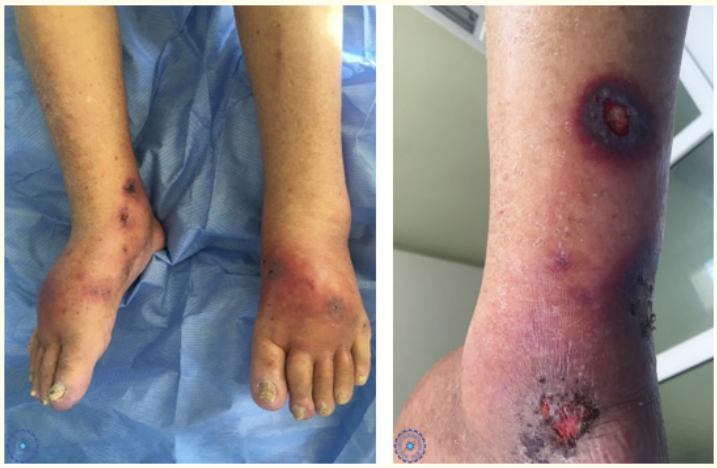

Figure 1: *Clinical examination showing multiple round infiltrated and necrotic-hemorrhagic purpuric lesions on the lower limbs, locally ulcerated by places, associated to an edema of the feet.*

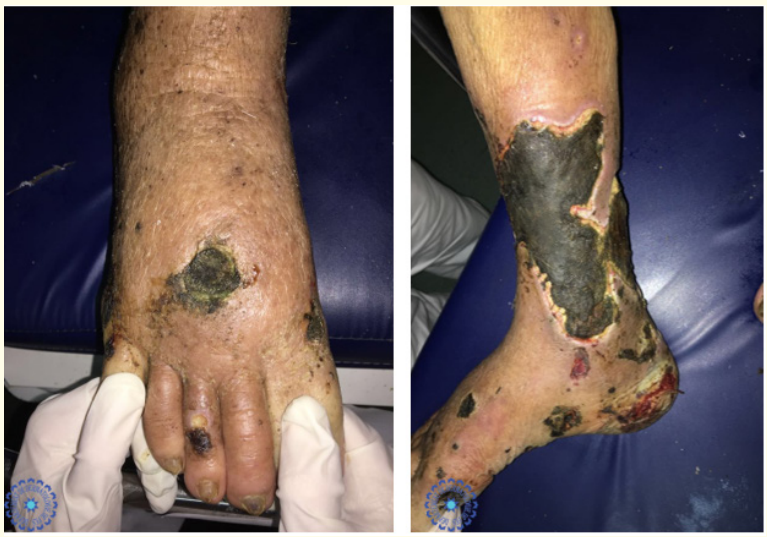

Figure 2: *Clinical features after accidental reintroduction of acenocoumarol showing multiple purpuric lesions associated to large necrotic associated patches on the lower limbs.*

Discussion

Cutaneous vasculitis is inflammation of the blood vessels and it can have a wide range of clinical features and etiologies [1]. These includes infections, inflammatory disease and malignancy or could be idiopathic in most cases [4]. Nevertheless, medication is associated with approximately 10 - 15% of all vasculitic dermatologic lesions, and the typical manifestation is cutaneous small-vessel vasculitis which usually occur with a long latent period [1,4].

Anticoagulants of the coumarin family are frequently administered for the treatment and prophylaxis of arterial and venous thromboembolic disease [5]. Hemorrhage is the main adverse effect related to acenocoumarol [1] due to excessive lowering of the procoagulant factors, but uncommon complications such as skin reactions have been described [5]. Cutaneous necrosis is a well-documented but infrequent complication of this drug [1]. Although hypersensitivity reactions such as vasculitis are possible and have been previously described [5], they are very rare with only few cases in the medical literature reporting a Coumarin-induced vasculitis [1].

The interval reported in the literature between the first exposure to acenocoumarel therapy and the symptoms of vasculitis was markedly varied, from days to years [4]. In fact, there are two groups according to the interval between first exposure to warfarin and the appearance of the symptoms [2]. The patients with symptom onset within 6 weeks are named "normal latency LCV," and the patients with latency of more than 6 weeks are called "late-onset LCV" [2]. In our case, the patient developed LCV after 3 months intake of coumarin drugs, which is within the time frame for the development of late-onset LCV.

The diagnosis is based on the clinical aspect of the lesions and the chronology of appearance and disappearance of lesions in the absence of other identifiable cause [6]. Actually, the disease spectrum ranges from relatively benign cutaneous symptoms requiring only discontinuation of acenocoumarel and supportive care, to a life-threatening condition requiring intensive care [4]. However, in most of the cases, it resolved after discontinuation of the drug [2]. Nevertheless, it may occur after re-exposure of the causative agent and be an element in favor of the diagnosis, which was the case in our patient [2].

To evaluate the causal link between AVK and the onset of LCV, extrinsic and intrinsic imputability can also be calculated using the current method in French pharmacovigilance centers obtained by the combination of chronological and semiological scores [3,6]. In fact, we believe that the present vasculitis could obviously be related to acenocoumarol in view of the following arguments: the clear temporal relation between the onset of acenocoumarol therapy and the skin rash, the spontaneous resolution of the vasculitis after acenocoumarol withdrawal and the absence of other attributable etiology or medication [1]. Thus, making this association very probable. We also insist on the obligation to report, without delay, any incident involving medication intake to the regional pharmacovigilance center [3]. Nevertheless, it is important to make a differential diagnosis from warfarin-induced skin necrosis, because the therapy of the two entities is different [5].

Pharmacological treatments include topical and systemic corticosteroids, antihistamines, nonsteroidal anti-inflammatory drugs and immunosuppressants [4]. Patients with severe or life-threatening manifestations require treatment with pulse corticosteroids, hemodialysis, cyclophosphamide, or plasmapheresis [2]. Furthermore, death generally occurred in 14.3% of Coumarin drugs-induced LCV cases, which is compatible with the mortality rate in all published drug-induced vasculitis cases [4]. Our case required, at first, only withdrawal of the suspected agent with good clinical improvement. However, after the accidental reintroduction of the drug by the patient, the evolution was rapidly fatal despite the introduction of systemic corticotherapy.

Conclusion

In summary, we present a very rare case of a coumarin drug-induced leucocytoclasic vasculitis. Clinicians should be very aware of this potential and serious side effect, so that they can think about it in case of any infiltrated purpuric lesions in patients under AVK medications. This will allow them to hold the drug intake when temporal relation is evocative, and thus to establish appropriated treatment. Additionally, we insist on the importance of the prompt and correct management of these serious toxidermias whose reintroduction of the responsible agent could lead to serious systemic involvement with possible fatal evolution.

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Volume 2 Issue 4 July 2019