



Acenocoumarol-induced leukocytoclastic vasculitis

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We report a case of a acenocoumarol (Sintrom[®])-induced vasculitis in a 54-year-old white female receiving oral anticoagulant therapy for atrial fibrillation, secondary to mitral stenosis. She was given digoxin, furosemide and acenocoumarol. In the third week of acenocoumarol treatment the patient was feverish (38°C) and both legs became tender and swollen. The skin was initially erythematous and later showed purpuric lesions and hemorrhagic bullae (Figure 1). Histologic examination of the involved skin demonstrated vascular changes of small vessels with fibrinoid necrosis of the walls. Polymorphonuclear leukocytes were found within and around the vessel wall with many scattered nuclear fragments (leukocytoclastic vasculitis) (Figure 2). The INR, being 2.35, was within the normal therapeutic range. Antinuclear antibody and anti-neutrophil cytoplasmic antibody tests were negative. Two months after withdrawal of acenocoumarol, the levels of protein C and S (total and free) were determined, being 88%, 78% and 70%, respectively. The coumarin was stopped and prednisone was started at a dose of 1 mg/kg/day IV. The skin lesions and fever resolved. The patient refused treatment with another coumarin drug and she was discharged on digoxin, furosemide and aspirin (100 mg/day).

Anticoagulants of the coumarin family are frequently administered for the treatment and prophylaxis of arterial and venous thromboembolic disease. The most common side effect of these drugs is bleeding due to excessive lowering of the procoagulant factors, but uncommon complications such as skin reactions have been described.¹ Among the cutaneous side effects of oral anticoagulant therapy, the most frequent are the *purple toes syndrome* and warfarin-induced skin necrosis,² although hypersensitivity reactions such as vasculitis are possible and have been previously described in several reports.³⁻⁶ In severe cases of vasculitis, the cutaneous manifestations may mimic skin necrosis: erythematous lesions that expand and evolve into red-purple zones with hemorrhagic bullae. In this situation, it is important to make a differential diag-



Figure 1. Hemorrhagic lesions with surrounding normal tissue.

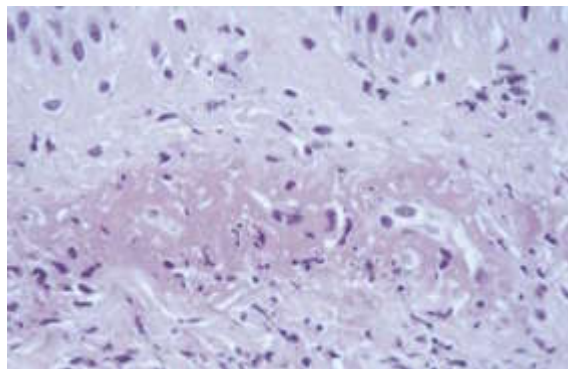


Figure 2. Skin biopsy. Fibrinoid necrosis of the vessel wall with infiltration by neutrophils and nuclear fragments (H&E 400 \times).

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nosis from warfarin-induced skin necrosis, because the therapy of the two entities is different.

Warfarin-induced skin necrosis typically presents between the third and eighth day of therapy, although it can appear later.⁷ It is more common in females, and frequently affects areas where there is abundant subcutaneous fatty tissue: breast, thighs and buttocks. In males the penis is affected, while the breast is spared. Histopathologically, there is microvascular thrombosis in the areas of skin involved. Declining protein C and S levels are thought to be important in the pathogenesis because of a rapid fall in the levels of these anticoagulant proteins before the anticoagulant effect is obtained, although other factors may be involved.⁸⁻¹⁰ By contrast, vasculitis appears later, is accompanied by an inflammatory infiltrate, its localization is different and the treatment is based on discontinuation of the drug plus administration of steroids.

References

1. Hirsh J, Dalen JE, Deykin D, et al. Oral anticoagulants. Mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1995; 108(suppl.): 231S-246S.
2. Sallah S, Thomas DP, Roberts HR. Warfarin and heparin-induced skin necrosis and the purple toe syndrome: infrequent complications of anticoagulant treatment. *Thromb Haemostasis* 1997; 78:785-90.
3. Tamir A, Wolf N, Brenner S. Leukocytoclastic vasculitis: another coumarin-induced hemorrhagic reaction. *Acta Derm Venereol (Stockh)* 1994; 74:138-9.
4. Howitt AJ, Williams AJ, Skinner C. Warfarin-induced vasculitis: A dose related phenomenon in susceptible individuals? *Postgrad Med J* 1982; 58:233-4.
5. Tanay A, Yust I, Brenner S, et al. Dermal vasculitis due to coumarin hypersensitivity. *Dermatologica* 1982; 165:178-85.
6. Susano R, Garcia A, Altadill A, et al. Hypersensitivity vasculitis related to nicoumalone. *Br Med J* 1993; 306: 973.
7. Essex DW, Wynn SS, Jin DK. Late-onset warfarin-induced skin necrosis: case report and review of the literature. *Am J Hematol* 1998; 57:233-7.
8. Gelwix TJ, Beeson MS. Warfarin-induced skin necrosis. *Am J Emerg Med* 1998; 16:541-3.
9. Gallerani M, Manfredini R, Moratelli S. Non-haemorrhagic adverse reactions of oral anticoagulant therapy. *Int J Cardiol* 1995; 49:1-7.
10. Dahlback B. Factor V and protein S as cofactors to activated protein C. *Haematologica* 1997; 82:91-5.