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Case report

Massive tissue necrosis can be induced by heparin or warfarin

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Massive skin and soft tissue necrosis is a rare but potentially fatal complication of warfarin therapy in 0·01 to 0·1% of patients receiving the drug,[1] but is not usually associated with heparin therapy unless limited to the site of subcutaneous injection.[2] In warfarin therapy, the aetiology of this complication remains unknown but has been associated with the protein C/protein S system. Protein C and protein S are naturally occurring vitamin K dependent plasma proteins which regulate blood coagulation. Deficiencies of one or other, whether acquired or hereditary, have been associated with spontaneous clinical thrombosis.[3] Where anticoagulation is required in the presence of protein C deficiency, heparin has been recommended as an alternative, which may also arrest the progression to frank necrosis.[4] We report two cases in which massive necrosis of skin and soft tissue was induced, in one case by heparin and in the other by warfarin. We speculate on a possible common aetiology which may limit the use of heparin as an alternative to warfarin in some patients.

CASE HISTORIES

Case 1. A 55-year-old caucasian female was admitted with an exacerbation of ulcerative colitis which she had suffered for 4 years. She was treated with corticosteroids (but with no other drugs known to have a haemorrhagic potential), and developed deep venous thrombosis for which intravenous heparin was given. Warfarin was not administered. After seven days, in which adequate control of anticoagulation had been maintained, she developed painful skin discoloration in both breasts, whereupon the heparin was discontinued; despite this the skin underwent necrosis. On transfer to the Plastic Surgery Unit she was toxic and febrile. At surgery the left breast was found to be completely necrotic with gas bubbles in the pectoralis muscles (Fig 1) and mastectomy was required. The right breast was less severely affected, requiring local débridement only. The wounds were left open but subsequently covered with split skin graft on the left and directly closed on the right. Pre- and postoperative coagulation screens were within normal limits; there was no evidence of thrombocytopenia. Histology of

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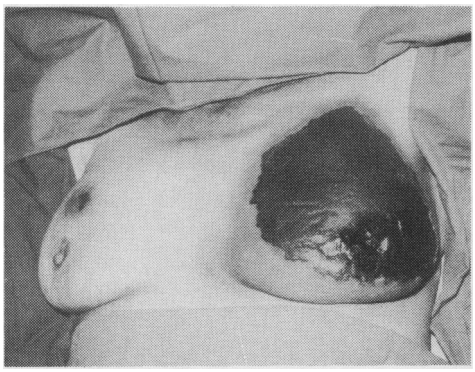

Fig 1. Case 1. Preoperative chest wall.

the specimens showed haemorrhagic necrosis of skin and soft tissue with no evidence of pyoderma gangrenosum or malignancy. *Staphylococcus aureus* and *streptococcus fragilis* were cultured but no *clostridia.* The patient made an uneventful recovery.

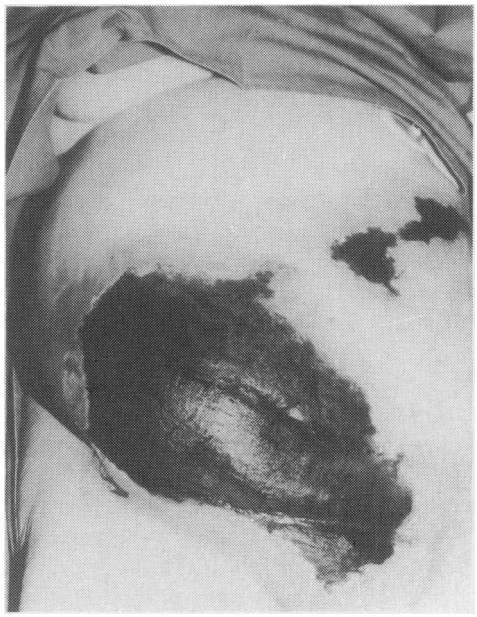

Fig 2. Case 2. Preoperative abdominal wall.

Case 2. A 68-year-old obese caucasian female in atrial fibrillation underwent successful femoral embolectomy for acute arterial occlusion. She was initially anticoagulated with intravenous heparin and commenced on warfarin. After 5 days she developed painful skin discoloration over the lower abdomen, whereupon warfarin was discontinued. The skin subsequently became necrotic (Fig 2). On transfer to the Plastic Surgery Unit her anticoagulation screen was normal, and there was no evidence of thrombocytopenia. At surgery the skin and soft tissue of the anterior abdominal wall were found to be necrotic and required débridement to the level of fascia over the musculature. The wound was left open but subsequently covered with split skin graft. Histology of the specimen showed haemorrhagic necrosis of skin and soft tissue from which staphylococci and coliforms were cultured. The patient made an uneventful recovery.

DISCUSSION

Heparin and warfarin are important therapeutic agents but have a number of recognised adverse effects.[5] Massive skin and soft tissue necrosis induced by warfarin anticoagulation, though rare, is well documented. Although the aetiology of this complication remains unknown, a direct toxic effect, hypersensitivity and thrombosis related to vasculitis and deficiency of protein C have been suggested.[1] An acquired deficiency of the protein C/protein S system, a similar deficiency inherited in autosomal dominant or recessive fashion, the absence of thrombocytopenia or concurrent medication which may contribute to enhanced bleeding, should result in thrombosis. Both our cases demonstrate haemorrhagic changes only. Where the microscopic appearances are that of thrombosis, it has been suggested that heparin may be indicated as an alternative agent, which may also arrest the progression to frank necrosis.[2] We report here (Case 1) heparin-induced

massive skin and soft tissue necrosis seen previously only as a complication of warfarin therapy. Interestingly, our patient had ulcerative colitis. This disease may be relevant, as its autoimmune nature results in thrombo-embolism. We can find no reference in the literature to deficiencies in the protein C/protein S system in patients with this disease, but the changes that occur are known to result in thrombosis rather than haemorrhage. In addition, this patient was on maintenance dose of corticosteroids, which are associated with an increased tendency to bleed in the presence of heparin, although it is unlikely that this would be sufficient to cause the degree and localization of necrosis in the breast. *Clostridia* and other gram positive organisms are known to cause tissue necrosis but their absence in either of these cases makes this explanation unlikely. Skin necrosis may occur with heparin therapy as a complication of thrombocytopenia or may be localized to the site of subcutaneous injection, and may be medicated by IgG.[2,6] We would suggest that the postulated mediators in warfarin-induced necrosis may be related to the inflammatory and immunological mediators involved in heparin-induced complications. Thus, in those patients who require continued anti-coagulation in the presence of warfarin-induced skin or soft tissue necrosis and who also have an autoimmune disease or are at risk of generalized thrombo-embolic phenomenon, heparin may not be an appropriate alternative agent. However, the new low molecular weight heparins may offer such an alternative and could be given as a trial subcutaneous dose which would produce an immediate localized reaction in the small number of patients who are truly hypersensitive to heparin, which remains a possible explanation for the massive necrosis in our cases.

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