Long-term steroid therapy can result in secondary adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal axis. Systemic intercurrent illness can often precipitate adrenal crisis in such patients if steroid therapy is not increased temporarily to tide over the period of metabolic stress.

The aetiology of adrenal insufficiency can be differentiated by checking serum ACTH which is high in Addison's disease and suppressed in secondary adrenal failure due to hypothalamic or pituitary causes. Adrenocortical autoantibodies to 21-hydroxylase are positive in 80% of patient's with Addison's disease.[4]

Our patient had taken prednisolone for seven years and presented with incipient adrenal crisis six months after this was discontinued. Secondary adrenal failure due to long-term adrenal suppression was initially considered as the cause of adrenal failure but the generalised hyperpigmentation and positive adrenal antibodies suggest a diagnosis of autoimmune Addison's disease. Our patient was fortuitously being partially treated for Addison's disease while on prednisolone for presumed polymyalgia rheumatica, but developed overt adrenal insufficiency when this was discontinued. We are aware of at least one other case in which primary adrenocortical failure was masked by exogenous steroid administration.[5] Our patient subsequently developed primary autoimmune hypothyroidism and this, along with the history of pernicious anaemia, supports a common autoimmune aetiology.

The ubiquitous long-term use of oral glucocorticoids to treat a variety of respiratory, rheumatological and haematological disorders carries the risk of causing adrenal insufficiency. Signs and symptoms of adrenal insufficiency in such patients should be anticipated and treated with 'crisis' dose steroid replacement during metabolic stress. Primary autoimmune Addison's disease often presents with non-specific symptoms and diagnosis is often delayed. A high index of suspicion remains the cornerstone of diagnosis.

References

1 Addison T. *On the constitutional and local effects of disease of the suprarenal capsules (1855)*. Birmingham, AL: Classics of Medicine Library, 1980.
2 Laureti S, Vecchi L, Santeusanio F, Falorni A. Is the prevalence of Addison's disease underestimated? *JCEM* 1999;84:1762.
3 Bleicken B, Hahner S, Ventz M, Quinkler M. Delayed diagnosis of adrenal insufficiency is common: a cross-sectional study in 216 patients. *Am J Med Sci* 2010;339:525–31.
4 Marzotti S, Falorni A. Addison's disease. *Autoimmunity* 2004;37:333–6.
5 Marston RA. Primary adrenocortical failure masked by exogenous steroid administration. *Clin Endo* 1992;36:519–20.

Address for correspondence: Dr S Nag, Department of Acute Medicine, The James Cook University Hospital, Marton Road, Middlesbrough TS4 3BW.
Email: Sath.Nag@stees.nhs.uk

lesson of the month (2)

Warfarin-induced skin necrosis

Warfarin-induced skin necrosis is a rare but serious complication of treatment with this commonly prescribed drug. This lesson presents the case of a patient with extensive skin necrosis after inappropriately prolonged warfarinisation and delayed recognition. The condition is briefly reviewed to highlight key features and risk factors.

Lesson

A malnourished 82-year-old woman was referred to the emergency department with an extensive, painful rash. This had worsened despite two weeks treatment for herpes zoster. A month prior to admission she had undergone patellar surgery with a brief interruption of warfarin treatment. Warfarinisation had been commenced a year previously for a postoperative pulmonary embolus. Examination revealed extensive tender and malodorous erythematous plaques with a violacious hue. Central necrotic eschars and vesiculobullous changes were evident and there was involvement of the face, breasts, trunk and limbs (Fig 1).

Warfarin-induced skin necrosis (WISN) was suspected necessitating the cessation of warfarin, and administration of vitamin K and low molecular weight heparin. Broad-spectrum antibiotics, enteral feeding and a three-day course of methylprednisolone, as vasculitis could not be excluded, were commenced. Biopsy of involved skin showed vascular thrombi, patchy necrosis and recent haemorrhage consistent with WISN. No evidence of vasculitis was seen. The erythematous plaques progressively became entirely necrotic. Despite prolonged treatment with intravenous antibiotics, the patient died from overwhelming sepsis and multi-organ failure.

Discussion

WISN typically occurs in obese middle-aged women. Lesions have a propensity for areas with increased subcutaneous fat and

Catherine R Mungalsingh, CT1; **Jamie Bomford,** FY2; **Jeremy Nayagam,** FY1; **Mirella Masiello,** FY1; **Ugo I Ekeowa,** specialist registrar; **Simon Webster,** consultant in respiratory medicine

Chest Unit, Kent and Sussex Hospital, Tunbridge Wells, Kent

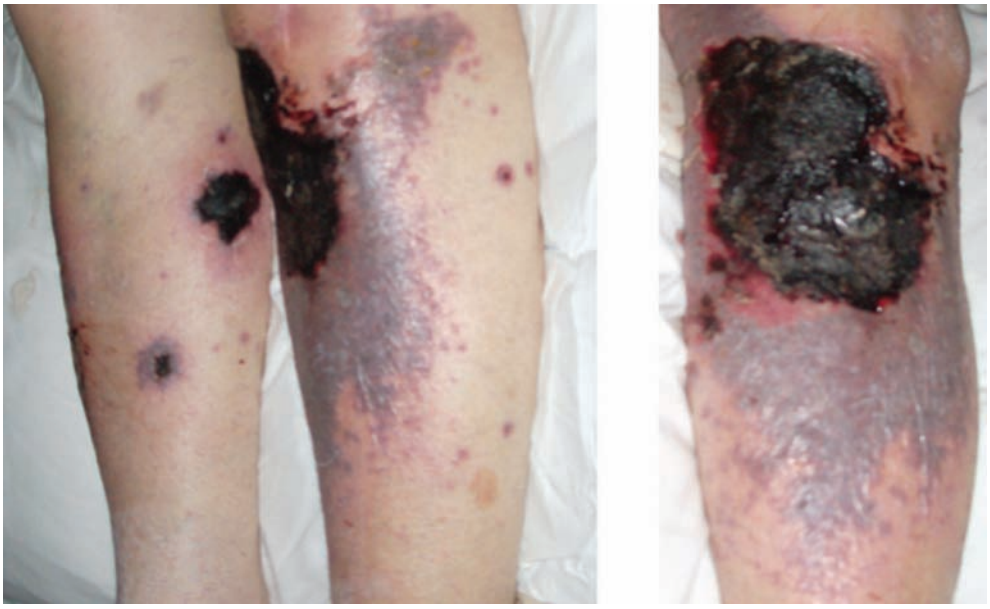

Fig 1. Multiple tender, malodorous necrotic lesions were found on the patient's trunks, limbs and face. Right panel: these were typically comprised an eschar with surrounding purpura. Approximately 20% of the patient's body surface area was eventually involved.

classically appear on the breast, buttocks, thighs and abdomen.[1–4] In the majority, lesions develop 3–6 days after starting warfarin therapy,[1,2,4–8] although cases are reported after up to three years.[5,7] Affected skin undergoes infarction evolving to necrotic eschar and full thickness skin loss.[1–4,8] Clinical history and cutaneous distribution in conjunction with histology helps distinguish WISN from other conditions such as heparin-induced skin necrosis, disseminated intravascular coagulation and necrotising fasciitis.[1]

Implicated aetiological mechanisms include protein C deficiency, hypersensitivity and a direct toxic effect of warfarin.[1,2,8] Histology typically shows diffuse microthrombi within dermal and subcutaneous capillaries, venules and deep veins, with endothelial cell damage resulting in ischaemic skin necrosis and red blood cell extravasation.[1] The lack of perivascular inflammation and arteriolar thrombosis, differentiates WISN from the vasculitides.[1,3]

The mainstay of management is supportive. Treatment is aimed at withdrawing warfarin and reversing its effect on protein C with vitamin K and fresh frozen plasma.[1–9] Heparin therapy is utilised to prevent further thrombosis in the postcapillary venules,[4] and protein C concentrate is effective although high cost has limited its use. Patients may require local debridement and occasionally skin grafting or even amputation.[2] The main causes of death are deep tissue necrosis, sepsis syndrome secondary to wound infection and multi-organ failure.[11]

Lessons to be elicited

One per cent of the UK population take warfarin.[11,12] WISN is a rare but important complication that requires high clinical suspicion and early recognition. Timely initiation of treatment may prevent extensive skin involvement and predisposition to overwhelming bacterial infection. Moreover, this case highlights the importance of determining treatment interval at initiation of anticoagulation and subsequently reviewing the indication for its continuation in all anticoagulated patients encountered in medical practice.

References

1 Nazarian R, Van Cott E, Zembowicz A, Duncan LM. Warfarin-induced skin necrosis. *J Am Acad Dermatol* 2009;61:325–32.
2 Mo J, Retzinger GS. Warfarin-induced skin necrosis. Lab lines – a publication of the Department of Pathology and Laboratory Medicine at the University of Cincinnati 2001:7.
3 Pero M, Verma S, Espeso A, Griffiths M, Jani P. An unusual case of warfarin-induced pinna skin necrosis. *J Laryngol Otol* 2009;123:685–8.
4 Gelwix T, Beeson M. Warfarin-induced skin necrosis. *Am J Emerg Med* 1998;16;5:541–3.
5 Essex DW, Wynn SS, Jin DK. Late onset warfain-induced skin necrosis: case report and review of the literature. *Am J Hematol* 1998;57:233–7.
6 Cole MS, Minifee PK, Wolma FJ. Coumarin necrosis: a review of the literature. *Surgery* 1988;103:271–7.
7 Sorensen D, Eilbert W. Warfarin-induced skin necrosis. *Ann Emerg Med* 2010;55:302–5.
8 Beitz J. Wound wise – anticoagulant-induced skin necrosis. *Am J Nurs* 2004;104:31–2.
9 Stewart A, Penman I, Cook M, Ludlam C. Short report: warfarin-induced skin necrosis. *Postgrad Med J* 1999;75:233–5.
10 Bhaijee F, Wainwright H, Meintjes G *et al.* Warfarin-induced skin necrosis in HIV-1-infected patients with tuberculosis and venous thrombosis. *S Afr Med J* 2010;100:372–7.
11 Kamali F, Pirmohamed M. The future prospects of pharmacogenetics in oral anticoagulation therapy. *Br J Clin Pharmacol* 2006;616:746–51.
12 Wadelius M, Pirmohamed M. Pharmacogenetics of warfarin: current status and future challenges. *Pharmacogenomics J* 2007;7:99–111.

Address for correspondence: Dr S Webster, Tunbridge Wells Hospital, Tonbridge Road, Pembury, Tunbridge Wells, Kent TN2 4QJ
Email: simonwebster1@nhs.net