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Multicentric Warfarin-Induced Skin Necrosis Complicating Heparin-Induced Thrombocytopenia

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Two patients developed catastrophic multicentric skin necrosis while receiving warfarin to treat venous thromboembolism complicated by immune-mediated heparin-induced thrombocytopenia (HIT). Patient 1 developed skin necrosis involving the breasts, thighs, and face, as well as venous limb gangrene and bilateral hemorrhagic necrosis of the adrenal glands, resulting in death. The second patient developed bilateral mammary necrosis necessitating mastectomies, as well as skin necrosis involving the thigh. Neither patient had an identifiable hypercoagulable syndrome, other than HIT. HIT may represent a risk factor for the development of multicentric warfarin-induced skin necrosis (WISN). Am. J. Hematol. 62:44–48, 1999. © 1999 Wiley-Liss, Inc.

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INTRODUCTION

Warfarin-induced skin necrosis (WISN) is a rare complication of anticoagulant therapy characterized by skin and subcutaneous tissue necrosis that typically begins 3–6 days after initiating warfarin treatment [1–3]. The pathogenesis of skin necrosis caused by warfarin and other oral anticoagulants is uncertain, but is believed to involve failure of one or more natural anticoagulant factors to down-regulate thrombin in the microvasculature. During initiation of oral anticoagulant therapy, a disturbance in procoagulant/anticoagulant balance can develop, caused in part by differences in the half-lives of the key anticoagulant (protein C) and procoagulant (prothrombin) factors (9 and 60 hr, respectively) [4]. Supportive evidence includes the observation that many patients with WISN have a congenital abnormality of one of the natural anticoagulant factors, such as deficiency of protein C [5–7], protein S [8–10], or antithrombin [11,12]; some patients have activated protein-C resistance (factor V Leiden) [13]. In many patients, however, no congenital hypercoagulable state can be identified, and it is suspected that acquired hypercoagulable states might predispose patients to WISN. We report 2 patients whose clinical course suggests that immune-mediated heparin-induced thrombocytopenia (HIT) may be a risk factor for the development of WISN.

MATERIALS AND METHODS

Case Reports

Patient 1 (Fig. 1A). An obese 59-year-old woman developed right calf vein thrombosis after a minor injury to the leg. Intravenous heparin was started with rapid achievement of a therapeutic activated partial thromboplastin time (aPTT), and warfarin was started on day 8. Heparin was discontinued on day 11 when the platelet count was 77×10^9/l. On day 10, a "bruise" developed on the left anterior thigh. By day 13, the ecchymosis on the left thigh had expanded, with increasing cyanosis and pain in the right foot, despite palpable pulses. Extension of the right lower limb deep venous thrombosis (DVT) was proven by repeat duplex ultrasonography. An inferior vena cava filter was placed on day 15. On day 18, when the INR rose to 9.6, warfarin was discontinued. The patient developed extensive hemorrhagic skin necro-

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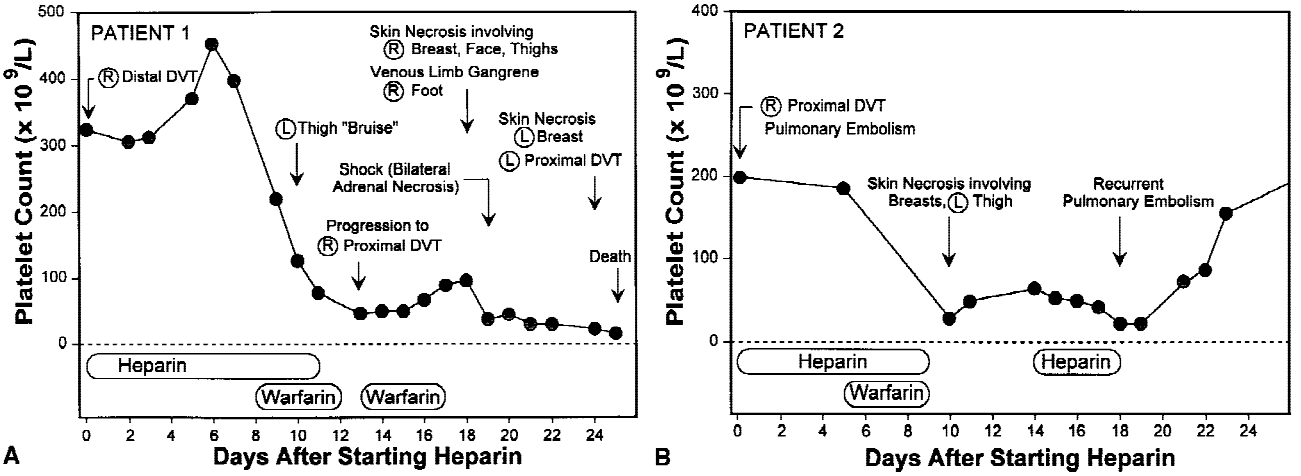

Fig. 1. (A) Clinical course of patient 1. R, right; L, left; DVT, deep vein thrombosis. (B) Clinical course of patient 2. R, right; L, left.

sis at multiple sites, including the right thigh (17 × 3 cm), left thigh (8 × 6 cm), right breast (17 × 11 cm), and right side of the face. On day 19, hypotension, metabolic acidosis, and multi-system organ failure developed; an exploratory laparotomy failed to identify the cause of the hypotension. A right above-the-knee amputation was performed for extensive venous limb gangrene. Plasma cortisol measured 0.8 μg/ml (normal, 4.0–18.0 μg/ml), but the hypotension proved refractory to corticosteroids and inotropes. Edema and cyanosis of the left distal leg developed, and duplex ultrasonography showed extensive DVT. Necrosis of the left breast (8 × 4 cm) and a new necrotic lesion of the left thigh also occurred. She died on day 25. Post-mortem examination revealed massive bilateral hemorrhages and complete necrosis of both adrenal glands, extensive bilateral lower limb DVT, bilateral pulmonary emboli with pulmonary infarction, splenic infarcts, and multiple areas of hemorrhagic bullous skin and subcutaneous fatty tissue necrosis. Microscopic examination showed thrombi in multiple veins and medium-to-small-size muscular arteries. No occult neoplasm was found.

Patient 2 (Fig. 1B). A 67-year-old woman developed right lower limb DVT and pulmonary embolism 7 days following right total knee replacement. Intravenous therapeutic-dose unfractionated heparin was given for 9 days. During the last 4 days of heparin use, warfarin was given (10 mg daily for 2 consecutive days, followed by 7.5 mg on the third day, and 2.5 mg on the fourth day). The INR rose to a maximal level of 2.8 on day 5, and 10 mg of vitamin K was given on the day that heparin was stopped when it was noticed that progressive swelling and dusky discoloration was developing on both breasts. Within 24 hr, the patient developed massive necrosis of both breasts (Fig. 2) and also skin necrosis involving the left thigh. The platelet count was 29×10^9/l, and rose to

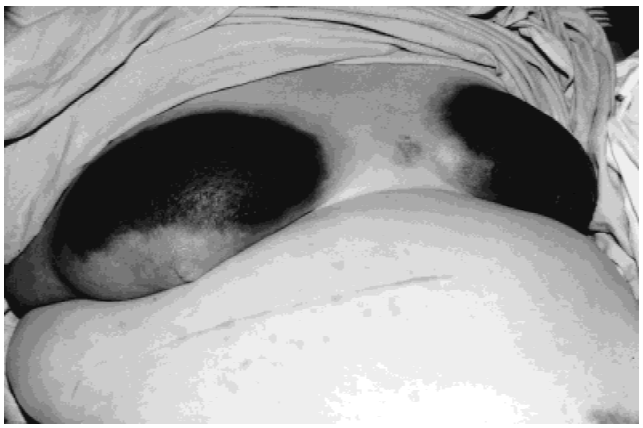

Fig. 2. Bilateral mammary necrosis complicating warfarin treatment during heparin-induced thrombocytopenia.

65×10^9/l over the next 4 days. Heparin was restarted, and the platelet count fell again to 22×10^9/l over the next 4 days (Fig. 1B), together with recurrent pulmonary embolism. Following discontinuation of the heparin, the platelet count recovered to 255×10^9/l over the next 10 days. The patient required bilateral mastectomies. Pathologic examination revealed extensive hemorrhagic necrosis of the epidermis and underlying dermis, without evidence for vasculitis. No neoplasm or any other chronic hypercoagulable state has been identified, and the patient remains in excellent health 8 years after this event.

Testing for Heparin-Induced Thrombocytopenia Antibodies

Testing for heparin-induced thrombocytopenia was performed by using the ^{14}C-serotonin release assay, as described [14,15]. Positive results by using this assay have been shown to correlate strongly with thrombocytopenia that begins on day 5 or later of heparin therapy [16].

Review of Patients With Heparin-Induced Thrombocytopenia

Serum or plasma from both patients described in this report was referred to McMaster University for laboratory investigations for HIT antibodies. To estimate the frequency of WISN complicating HIT, a database of 260 patients with serologically-confirmed HIT treated in Hamilton (15 year period ending June 30, 1998) was reviewed. Part of this database was reported in previous publications [17–19]. All patients who developed clinical features consistent with either WISN or venous limb gangrene were identified. WISN was defined as 'central' (non-acral) skin and subcutaneous skin necrosis that began 2 or more days after starting warfarin therapy that had no other apparent explanation [20]. Venous limb gangrene was defined as acral (i.e., involving the most distal parts of the extremities) skin necrosis complicating a DVT without clinical or radiologic evidence for large-vessel arterial occlusion [19,20]. Skin necrosis that was noted to have occurred at heparin injection sites were excluded, as this is a distinct syndrome known to occur in the absence of coumarin anticoagulation ("heparin-induced skin necrosis") [18]. We identified all patients who received one or more doses of warfarin, or who had persisting effects of recently administered warfarin (INR > 1.5), at a time when the platelet count was less than 150 $\times 10^9$/l attributable to HIT.

RESULTS

Testing for HIT antibodies by using the ^{14}C-serotonin release assay gave strong positive results in both patients. Plasma from patient 1 produced 84% serotonin release at 0.1 U/ml heparin that was inhibited by Fc receptor-blocking monoclonal antibody (1% release) and 100 U/ml heparin (0% release). Serum from patient 2 produced 97% serotonin release at 0.1 U/ml heparin that was inhibited by Fc receptor-blocking monoclonal antibody (0% release) and 100 U/ml heparin (0% release). These reaction profiles are characteristic of HIT antibodies.

For patient 1, moderate reduction of protein C (1.1 μg/ml; normal, 2.7–5.6 μg/ml) and protein S (8 μg/ml; normal, 13–32 μg/ml) were observed on plasma obtained on day 21. However, the antithrombin level was severely reduced: 17% by immunologic measurement (normal, 63–150%) and 41% by activity measurement (normal, 80–120%). As this patient died, it was not possible to determine whether a congenital deficiency of a natural anticoagulant was present.

For patient 2, following recovery from the episode of HIT and WISN, protein-C functional activity was normal (0.9 U/ml), as was the protein C antigen level (1.21 U/ml). The total protein-S antigen level was 1.71 U/ml (normal range for all three assays in Kingston, 0.75–1.5 U/ml). Antithrombin levels were also normal (1.16 U/ml). The patient was recently evaluated for factor V Leiden and the prothrombin 20210 variant: DNA sequencing revealed only wild-type sequences.

Review of the 260 patients with serologically-confirmed HIT identified 136 patients who received warfarin at a time when their platelet count was less than 150 $\times 10^9$/l attributable to HIT. There were 8 patients with warfarin-associated venous limb gangrene, including 1 patient who also had concomitant central WISN affecting a single 4 × 5 cm site on the abdomen. These 8 patients have been reported previously [19]. Thus, 8/136 (5.9%; 95% CI, 2.6–11.3%) patients with HIT developed tissue necrosis at least partially attributable to treatment with warfarin, although only 1 patient (0.7%; 95% CI, 0.02–4.0%) developed a central lesion that is more typical of WISN.

DISCUSSION

We describe two patients who developed catastrophic, multicentric WISN associated with serologically-confirmed HIT. One patient who died also had venous limb gangrene and bilateral adrenal hemorrhagic necrosis. Both patients had extensive necrosis involving both breasts, with the surviving patient requiring bilateral mastectomies. Mammary gangrene is a rare event in WISN that was reviewed by Isenberg and colleagues in 1996 [21]. Of 22 patients with breast necrosis complicating WISN they reviewed, only one had WISN involving both breasts, with one breast only minimally involved.

Only a few reports have described a possible association between WISN and HIT [22–26]. However, most of these reports [22–25] either did not perform diagnostic laboratory testing for HIT antibodies, or described patients who had other underlying disorders, such as adenocarcinoma [27] or congenital protein C deficiency [5–7], that are known to predispose to warfarin-induced prothrombotic complications. There have also appeared reports of apparent WISN, in which unexplained thrombocytopenia that began during heparin therapy was noted by the authors [6,28,29]. It is possible that undiagnosed HIT may have contributed to the WISN in these instances.

Recently, one of us has reported that the syndrome of venous limb gangrene complicating HIT may be the result of a transient disturbance of procoagulant-anticoagulant balance resulting from warfarin treatment [19,20]. The evidence implicating warfarin treatment in the pathogenesis of venous limb gangrene included the observation that affected patients had the combination of lower protein-C activity and higher thrombin-antithrombin complexes (a marker of in vivo thrombin generation), compared with control subjects [19]. Increased

thrombin-antithrombin complex levels is a recently recognized feature of HIT [19,30]. The increased thrombin generation that occurs in HIT could be related to a number of procoagulant effects of HIT antibodies, including endothelial injury that produces a procoagulant endothelial response [31,32], and the generation of procoagulant, platelet-derived microparticles [33]. Procoagulant, platelet-derived microparticles may contribute to an increase in thrombin generation in vivo, possibly beyond the capacity of the protein-C/protein-S pathway to down-regulate the thrombin generation. Further, microparticles could accelerate the rate of protein-C consumption [34], thus increasing the probability of early critical post-warfarin protein-C deficiency. Thus, the increased thrombin generated in HIT could predispose patients to the development of microvascular thrombosis during warfarin treatment, as there could be failure of the natural anticoagulant pathways to down-regulate thrombin in the microvasculature. Severe antithrombin deficiency that was noted in patient 1 might also have been related to consumption of this anticoagulant factor related to increased thrombin generation in HIT (although we cannot exclude a congenital antithrombin deficiency in this patient).

Both patients with multicentric WISN complicating HIT that we are reporting were identified when blood samples were referred to McMaster University for HIT antibody testing. Review of 260 patients with serologically confirmed HIT in Hamilton did not lead to identification of other patients with two or more central lesions of skin necrosis. However, we did identify 8 patients with warfarin-induced venous limb gangrene, previously reported [19], of whom 1 patient also had a single lesion of central (abdominal) skin necrosis. This suggests that the typical 'central' localization of WISN, e.g., typically involving breast, abdomen, thigh, and other non-acral tissues in about 90% of cases [1], may be relatively less common in HIT than the 'peripheral' (acral) localization of necrosis that is characteristic of the syndrome of warfarin-induced venous limb gangrene [19,20]. We have suggested that active DVT that is commonly observed in patients with HIT may help localize progressive microvascular thrombosis to the affected limb. This could occur either by direct propagation of thrombi from large proximal vessels to smaller, more distal vessels, or via reduction in venous blood flow from the limb affected by proximal DVT that predisposes to stasis-induced microvascular thrombosis in the area subtended by the thrombosis. These factors could help explain why patients with HIT appear to be predisposed to the variant syndrome of warfarin-associated venous limb gangrene [19,20].

Danaparoid and lepirudin are two drugs that are currently available in the United States to treat HIT. These agents either inhibit thrombin generation via factor Xa inhibition (danaparoid) [30] or directly inhibit thrombin (lepirudin) [35]. The observation that HIT could represent a risk factor for WISN and venous limb gangrene suggests that physicians should avoid using warfarin as single therapy for patients with acute HIT who may have increased thrombin generation. However, warfarin appears to be relatively safe once adequate anticoagulation is achieved with a drug that reduces thrombin generation or inhibits thrombin, or following resolution of the thrombocytopenia [36].

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