A Case of Heparin Necrosis

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Skin necrosis is a rare complication of heparin administration that is usually localized to injection sites.

We report a case of skin necrosis that was caused by minidose intraarterial infusion of porcine heparin which had been used in a touch to prevent coagulation in percutaneous intraarterial cannula. The skin necrosis appeared 35 days after starting heparin use.
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Key Words: Delayed onset, Heparin necrosis

Heparin has had an increasingly important role to play in therapy since 1916 when its anticoagulant properties was discovered.

As its uses increased, the spectrum of complications widened. Obviously, the most frequent complication of heparin therapy is hemorrhage of various organs, most commonly of the skin. Less commonly observed complications of heparin therapy include osteoporosis, telogen effluvium, anaphylaxis, thrombocytopenia and arterial embolism.[1] Skin necrosis is a rare but serious complication of heparin therapy that usually occurs at the site of subcutaneous injection,[2] but there are reports of skin necrosis induced by intravenously injected heparin.[3,4]

We report a case of cutaneous necrosis with delayed onset that was caused by intraarterial infusion of heparin.

As far as we know, no case of this disorder has been reported in Korean literature.

REPORT OF A CASE

A 16-year-old female patient had been admitted to surgical department for anoxic brain damage. After the development of skin lesion, she was seen in consultation by the authors. She had been inserted percutaneous arterial cannula to monitor close arterial blood pressure and arterial blood gas. The cannula had been inserted in both sides of the radial arteries, dorsalis pedis arteries and posterior tibial arteries by turns. Heparin had been used in a touch to prevent coagulation in the cannula. Coumarin had never been administered to this patient. The skin lesions appeared 35 days after starting heparin use and during this period dose of infused heparin was 12,000 I.U. The skin lesions appeared on the right dorsal foot and the right lower shin and the cannula had been inserted in the right dorsalis pedis artery until 5 days before skin lesions developed. There was no history of personal or familial drug hypersensitivity.

On physical examination, the patient was comatose and hemorrhagic bullae based on a well-defined irregularly-bordered brownish black purpuric oozing patch roughly measured 12×7cm were shown on the right dorsal foot and the right lower shin(Fig. 1).

Laboratory examinations showed anemia, leukocytosis and normal values for urinalysis, stool examination, blood chemistry, prothrombin time, activated partial thromboplastin time, bleeding time and fibrinogen. The platelet count was 251,000/cu mm before heparin use, 146,000/cu mm on the day of skin necrosis and 342,000/cu mm 28 days after heparin withdrawal(Table 1). On chest roentgenogram,

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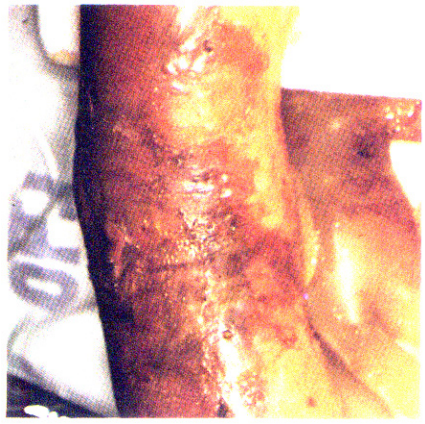

Fig. 1. Well-defined hemorrhagic bullae with purpuric patches on the right ankle area.

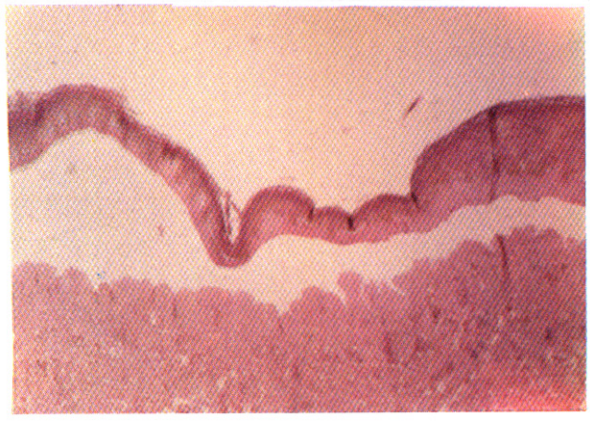

Fig. 2. The epidermal and upper dermal necrosis with upper dermal separation(H&E stain, × 40).

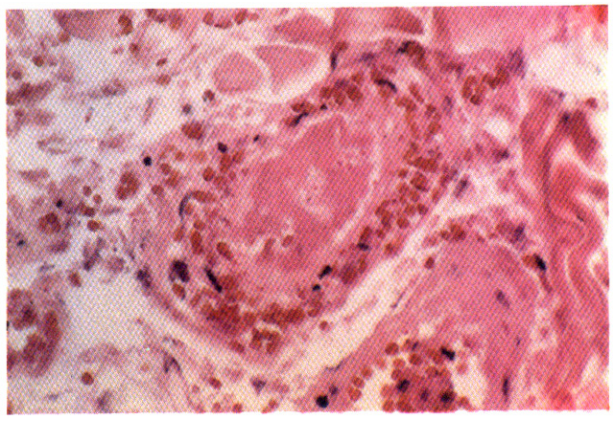

Fig. 3. Numerous extravasated RBCs but a few inflammatory cells are seen around necrotic and thrombosed blood vessels(H&E stain, × 40).

pneumonia was suspected. Histopathologic examination of a necrotic bulla disclosed the necrotic epidermis and upper dermis with upper dermal separation(Fig. 2). The dermis showed numerous extravasated RBCs but a few inflammatory cells infiltrate. The dermal blood vessels were necrotic, dilated and thrombosed(Fig. 3). Martius scarlet blue stain and phosphotungstic acid hematoxylin stain for fibrin showed positive results within the thrombosed blood vessels(Fig. 4, 5).

Under the impression of heparin necrosis, heparin was discontinued immediately. The skin le-

Table 1. Sequential platelet count

Time sequence	Platelet count
Before heparin use	251,000/cu mm
14 days after heparin use	273,000/cu mm
23 days after heparin use	308,000/cu mm
29 days after heparin use	165,000/cu mm
35 days after heparin use*	146,000/cu mm
28 days after heparin stop	342,000/cu mm

*The skin necrosis appeared 35 days after heparin use

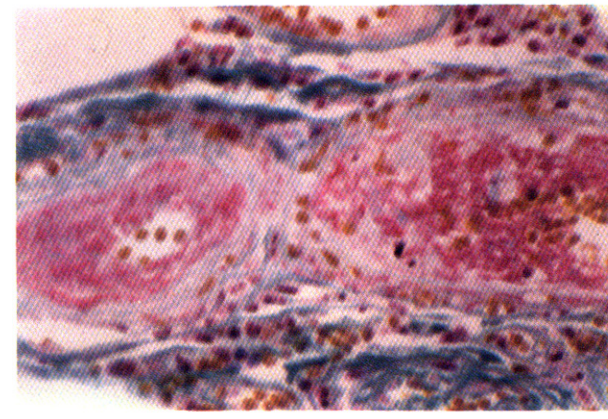

Fig. 4. Fibrin thrombi showing red color(Martius scarlet blue stain, × 400).

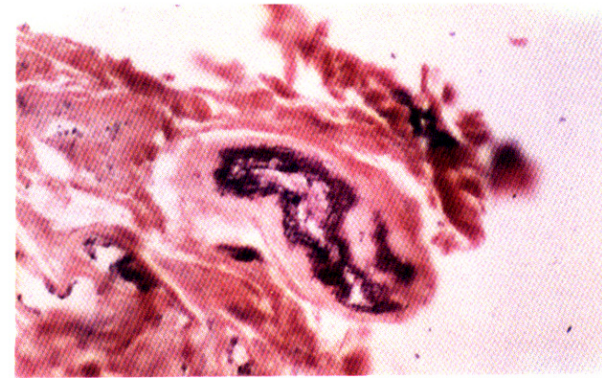

Fig. 5. Fibrin thrombi showing violet color(Phosphotungstic acid hematoxylinstain, × 200).

sions did not progress further. The eschar was debrided after 6 days, leaving a shallow ulcer.

Two months later she died of problems related to a metabolic acidosis and a pulmonary failure.

DISCUSSION

Heparin sodium, a mucopolysaccharide derived from porcine intestinal mucosa or beef lung, is used primarily for the prophylaxis and treatment of venous thrombosis and thromboembolic disorders. Since heparin is not effective orally, it is administered by intravenous injection or infusion and by deep subcutaneous injection. Heparin inhibits blood clotting both in vitro and in vivo, acting at multiple sites in the coagulation system.[5]

O'Toole[6] in 1973 first indicated that subcutaneously administered heparin could induce necrosis of the overlying skin. In the following year Hume and his associates[7] described four areas of necrosis occurring at sites of heparin administration within the subcutaneous fat. These two reports were made as letters to the editor, and the word "necrosis" was not used in the titles. They were largely ignored by a disbelieving readership. Not until White, Sadd and Nensel's classic paper in 1979[2] could the new entity of "heparin necrosis" be viewed as real, significant, and understandable.[8]

Heparin necrosis usually occurs in middle-aged women and has a predilection for heparin injection sites on the thighs, buttocks, and abdomen.[2,4,8] However, it has been reported in patients receiving intravenous heparin therapy.[3,4] Heparin necrosis follows an evolutionary course that begins with localize erythema and proceeds to bullae formation and frank necrosis. Burning pain begins six to 13 days within onset of treatment and heralds the development of well-delineated necrotic lesions by 12 to 24 hours. Clinically, the lesions are characterized by a black hue, a well-defined border, and a surrounding zone of erythema. Pain and erythema generally resolve within five days, but many of these lesions require debridement and grafting. Heparin necrosis has been described with heparin of both porcine and bovine origin.[2,3,4,6,7]

Histopathologic finding of heparin necrosis is extensive occlusion of dermal and subcutaneous capillaries, venules, and small arterioles with fibrin and platelet thrombi without signs of inflammation. This results in hemorrhagic infarcts, necrosis of the dermis, and subepidermal bullae due to dermal necrosis.[9]

According to current hypotheses,[2,3,4,8,10,11] the pathogenesis of heparin necrosis is as follows. Heparin induces heparin-dependent antiplatelet antibodies in heparin-sensitive persons which cause platelet aggregation should manifest itself by local skin necrosis in some patients and as arterial occlusion in others. In patients with skin necrosis there may be a factor independent of the primary aggregating effect of heparin which keeps the reaction localized. Poor absorption or poor circulation to subcutaneous fat may slow the clearing of heparin from the injection site. If skin necrosis is a localized manifestation of an individual's sensitivity to heparin, systemic thrombosis and thrombocytopenia should occur if these patients receive intravenous heparin.[2]

Patients receiving heparin should have platelet counts done frequently. When skin necrosis at heparin injection sites is the only manifestation of heparin-induced thrombosis, thrombocytopenia may not be present. However, when heparin is given intravenously to a sensitive patient or when systemic thrombotic symptoms are present, the platelet count is usually strikingly decreased. The development of thrombocytopenia should alert the physician to the possibility of heparin-induced aggregation of platelets in patients with nonspecific or minimal symptoms. Major complications may be averted by early recognition of the condition and immediate withdrawal of heparin.[2]

Coumarin necrosis is a rare condition that occurs in less than 1% of patients started on oral anticoagulant therapy.[12] Although heparin and coumarin necrosis are nearly indistinguishable clinically and histopathologically, there are striking dissimilarities. The initial symptoms of coumarin necrosis occur on the third to fifth day of treatment in the ninety percent, whereas heparin problems are never seen before the sixth to eighth day.[2,12] Coumarin necrosis seems to progress more slowly. Thirty-six to 72 hours usually elapse from the time of the onset of pain to the demarcation of coumarin-induced lesions, whereas heparin-induced lesions are demarcated at 18-36 hours.[2] Because coumarin necrosis is not related to an immunologic basis and is due to functional protein C deficiency, coumarin necrosis is not associated

with thrombocytopenia.[2,8,12,13,14]

In case of heparin necrosis, the occurrence of skin necrosis on an ankle area, as shown in our patient, is very rare, so we don't deny the possibility that heparin was leaked out from the right dorsalis pedis artery. However, it is interesting that the skin necrosis appeared 35 days after starting heparin use. We think that probably the occurrence of an immunologic process was delayed due to her poor general condition. Although the platelet count was not decreased below lower normal limit, it was strikingly decreased at the time of skin necrosis than before heparin use and markedly increased after heparin withdrawal.

Therapy centers on prophylaxis. The avoidance of heaprin of bovine lung origin may be prudent since it is associated with a higher incidence of thrombocytopenia.[15] Since the platelet appears to be the central mediator in heparin necrosis, all patients on heparin therapy should be monitored for a drop in platelet count. Any such significant and otherwise unexplained drop calls for prompt cessation of the heparin.[16] Once the infarct has formed, stopping the heparin is wise. The occurrence of skin necrosis is a warning-more serious problems may develop if systemic heparin is used. Platelet transfusion are probably contraindicated while heparin is still in the circulation.[2] Since the infarct is the result of a specific immune-induced type of clotting, coumarin or an antiplatelet drug seems worthy of trial.[2,4,8]

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