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Delayed Onset Low Molecular Weight Heparin Induced Skin Necrosis on a Hemodialysis Patient

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Abstract

Delayed onset low molecular weight heparin induced skin necrosis is a rare adverse event. It usually occurs at the site of injection, and typically develops within 2 weeks of starting therapy. However, in our case, we presented a 62-year-old woman who is on Hemodialysis twice a week. Her hemodialysis prescription included Enoxaparine 0.2 cc IV as anticoagulant. On her third month of regular hemodialysis, she developed skin necrosis on her right leg and left hand. The diagnosis was made clinically and by exclusion of other possible causes of skin necrosis in a chronic kidney disease patient, such as calciphylaxis. The most important aspect of management, in this case, is early recognition and withdrawal of its use, which were done in our patient.

Keywords

Heparin, Skin Necrosis, Hemodialysis

1. Introduction

Low molecular weight heparins are anticoagulants commonly used as prophylaxis for venous thromboembolic diseases, and treatment of deep vein thrombosis, pulmonary embolism, or acute myocardial infarction. It has likewise gained popularity as an anticoagulant of choice during hemodialysis [1].

Heparin induced skin necrosis is a rare adverse effect of either subcutaneous or intravenous (IV) heparin administration. It usually occurs at the site of subcutaneous injection, and typically develops within 2 weeks of starting heparin therapy [2].

A case report by J. Humphries *et al.*, entitled Heparin Skin Necrosis: Delayed Occurrence in a Patient on Hemodialysis, published in the American Journal of

Kidney Diseases in February 1991, presented a similar case of skin necrosis in a patient receiving IV heparin during routine intermittent hemodialysis. The patient was in her third month of regular hemodialysis, and skin necrosis began 2 weeks starting therapy. This case report claimed that it has never been seen in patients receiving heparin with hemodialysis [2].

Another case report written by Katsourakis *et al.*, entitled Low Molecular Weight Induced Skin Necrosis: A Case Report, published in Hindawi 2011, it likewise presented a case of skin necrosis in a patient receiving low molecular weight heparin. However, the low molecular weight heparin was being administered subcutaneously, and the patient was not a hemodialysis patient. In this case report it was noted that skin necrosis at the injection site is a rare adverse effect, and is more commonly associated with unfractionated heparin rather than with low molecular weight heparin [1].

There are very few reports on this heparin induced skin necrosis occurring in hemodialysis patients. But, although rare, its recognition is vital as continued use, especially in a hemodialysis patient, who is subjected to heparin treatment 2 to 3 times a week, and is prone to develop life-threatening complications. Hence, the objective of this case report is to recognize heparin as a cause of skin necrosis in hemodialysis patients and to understand how it is diagnosed and managed.

2. Case Report

This is a case of a 62-year-old female, who is a diagnosed case of Acute Kidney Injury secondary to Obstructive Nephropathy secondary to Right Ureterolithiases s/p DJ stent placement, right (March 2019) on top of Chronic Kidney Disease secondary to Diabetic Nephropathy s/p IJ catheter insertion (March 2019) on Hemodialysis twice a week. Her hemodialysis prescription included Enoxaparine 0.2cc IV as anticoagulant.

On her regular hemodialysis day of June 2019, she was noted with chills during the first hour of her dialysis. Hence, blood culture and sensitivity were requested, and she was given Vancomycin 500mg IV, which was infused for one hour after a negative skin test.

After two days, she sought a consult due to severe right leg pain, which was erythematous and warm to touch. This was associated with swelling, erythema, and tenderness of the left hand and a palpable mass at the right forearm about 4 × 3 × 2 cm in size, mobile, non-tender, non-erythematous, and not warm to touch (**Figure 1**). She was then admitted and was treated as a case of Cellulitis right leg and left hand. She was started on Meropenem 500 mg IV OD. Her maintenance medications were continued.

Blood culture and sensitivity result showed growth of *Klebsiella pneumonia*. Intact Parathyroid Hormone was normal. IV antibiotics were continued. She continued to be dialyzed twice a week with Enoxaparine 0.2 cc IV as anticoagulant. It was noted that during and after dialysis, inflammation on both the right leg and left hand flares.

Within days, skin lesions on the right leg became confluent with bullae formation that eventually erupted drainage yellowish crusting fluid (**Figure 2**).

At this time, suspicion of a drug induced hypersensitivity reaction was entertained; hence, Prednisone 20 mg/tab 1 tab BID was started. Vancomycin IV Infusion and Enoxaparine 0.2 cc IV as anticoagulant were then discontinued. She then continued thrice weekly hemodialysis for 3 hours, using normal saline as flushing. No anticoagulant was given during hemodialysis.

There was noted resolution of fever and decrease in the inflammation of the right leg and left forearm.

After two-dialysis sessions without anticoagulant use, a trial of Tinzaparine 0.2 cc IV as anticoagulant was used. There was noted recurrence of severe pain in the right leg, with flaring of inflammation of the left hand and forearm. This was also associated with erythema and warmth of the right forearm (**Figure 3**).

She continued hemodialysis thrice a week, 3 hours per session, without

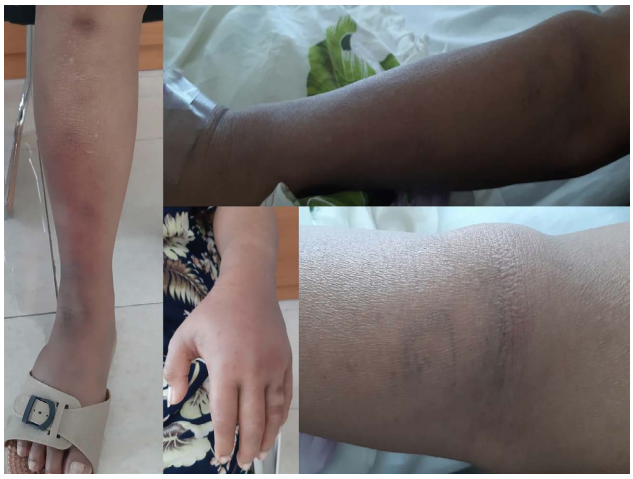

Figure 1. Right leg erythematous. Left hand swollen, erythematous, and tender. Right forearm with a palpable mass 4 × 3 × 2 cm, mobile, non-tender, and non-erythematous.

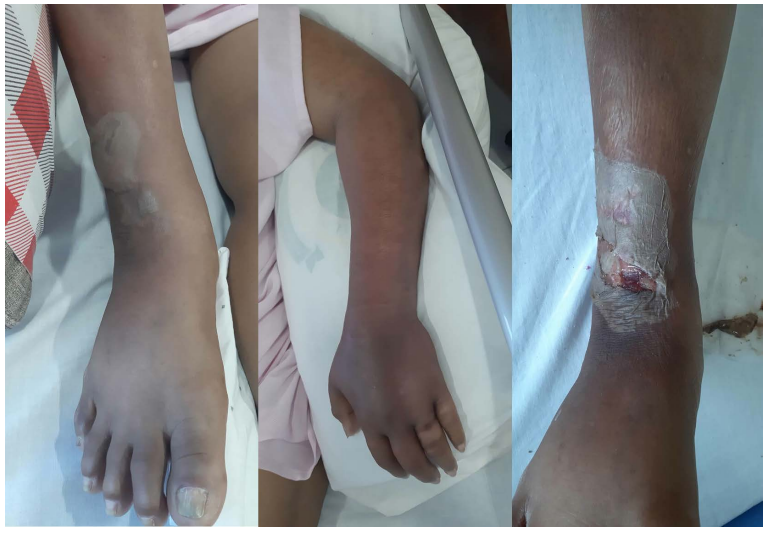

Figure 2. Right leg skin lesion transformed into a bullae.

anticoagulant. Progressive improvement of induration of both arms was noted. There was no recurrence of inflammation of the right leg. However, due to the initial necrotic changes, debridement was done. Biopsy of the left forearm induration showed superficial perivascular dermatitis without thrombosis or calcifications, while the right leg induration showed dermal necrosis with focal epidermal ulceration without thrombosis or calcifications (**Figure 4**).

After 3 months of no anticoagulation during hemodialysis, a trial of Fondaparinaux 2.5 mg SQ pre HD was done. After two succeeding hemodialysis session using fondaparinaux as anticoagulant, an induration was noted on the left foot which eventually eroded into a necrotic lesion (**Figure 5**). Hence, it was again discontinued, and she continued hemodialysis thrice weekly without anticoagulant. Since then, there was no recurrence of skin necrosis.

3. Discussion

Heparin induced skin necrosis is a rare adverse effect that usually affects middle

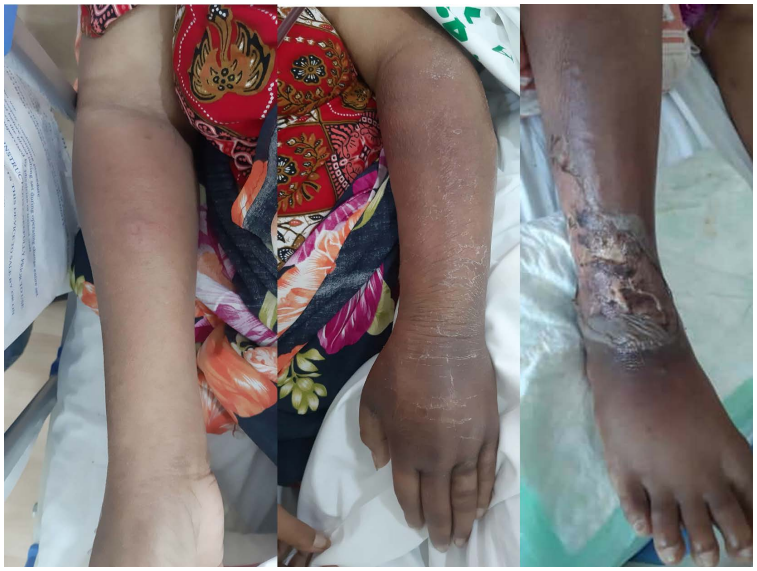

Figure 3. Inflamed right leg, left hand, and left forearm. Right forearm erythematous and warm.

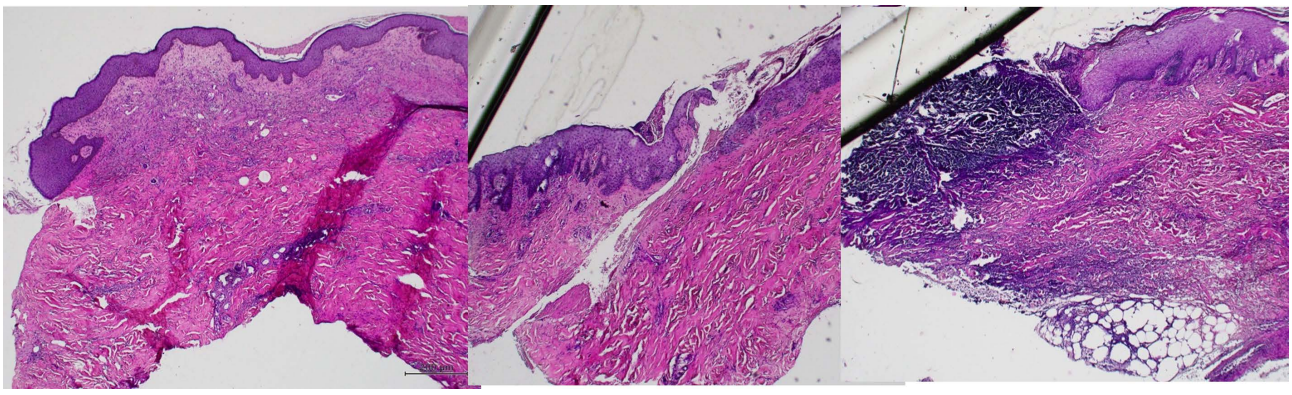

Figure 4. Skin biopsy of left forearm and right leg debrided tissue.

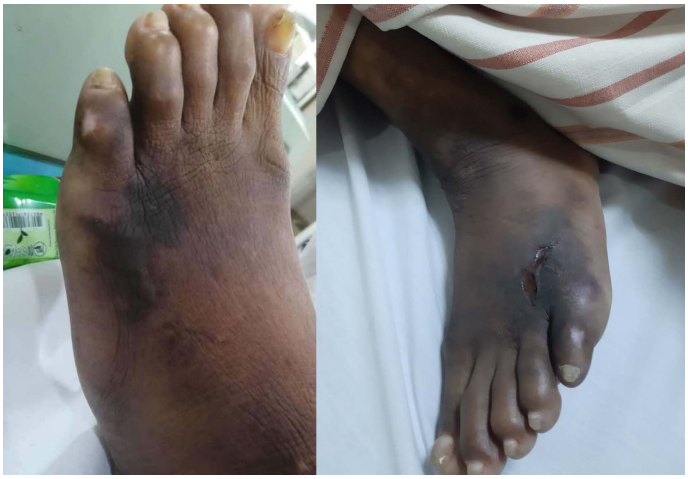

Figure 5. Left foot skin necrosis.

aged and obese women. [2] The skin necrosis usually appears between days 5 to 15 from initiation of therapy. A late onset of skin necrosis, as long as 3 months after the initiation of therapy in a hemodialysis patient was reported. It was concluded that this might be due to the intermittent administration of the heparin, which was only given during hemodialysis of the patient, thrice a week [2] [3].

The skin necrosis usually starts with erythema, edema, and severe pain, which eventually evolved into a bulla, and then necrosis. In most cases, it usually occurs locally at the injection site. [2] But distant distribution may also be seen, especially in those patients given intravenous administration of low molecular weight heparin, such as that seen in our patient [1] [5].

Skin necrosis commonly occurs at sites with abundant adipose tissue, such as the abdomen and thighs. This is postulated to be due to the fat tissue's poor blood circulation, hence, the heparin stays at the injection site longer. However, in our case it occurred in the right foot and bilateral forearms, which were sites not very rich in adipose tissue [2] [3] [4] [5].

There are multiple possible mechanisms for the skin necrosis to occur secondary to the use of low molecular weight heparin. Some older studies show the possibility of heparin induced platelet aggregation. Although, thrombocytopenia and thrombosis associated with heparin use usually involves larger arteries, and not associated with skin involvement. [6] [7] Other possible causes noted from older studies include, imbalances in coagulation factors, heparin induced decrease in antithrombin antigen and activity, and hemodialysis induced decrease in protein C levels contributing to a possible hypercoagulable state. [8] [9] [10] However, in this report, investigation of the possible pathophysiology of the skin necrosis secondary to the low molecular weight heparin was noted investigated.

Diagnosis of heparin induced skin necrosis in this case was merely done clinically. Because of the causal association of the patient receiving multiple intravenous antibiotics, initially it was regarded as the culprit for the hypersensitivity reaction that occurred in the patient. Likewise, since patient is diagnosed with end stage renal disease, a possibility of calciphylaxis was also entertained. Hence,

intact parathyroid hormone (PTH) was done and showed a normal result, and biopsy of the tissues involved also rules out the possibility of calciphylaxis, since no calcification was seen in the skin biopsy specimens of the patient presented in this report.

It was noted that with discontinuation of use of the low molecular weight heparin, there was resolution of the skin necrosis. Other modes of therapy are still to be elucidated, depending on the possible pathophysiology of the skin necrosis. [2] If heparin induced skin necrosis is noted, further hemodialysis should be done using an alternative anticoagulant, such as citrate or prostacyclin. [2] In this case report, flushing helped alleviate the skin necrosis. However, hemodialysis without anticoagulant will also result to several possible complications, such as, clotting, and inefficient dialysis due to early termination of treatment.

Considering the number of patients on hemodialysis using heparin as anticoagulant, it seems bothersome to note that only a few case reports have recognized skin necrosis secondary to its use. This may be due to poor recognition of the event. Hence, this leads to underestimation of the actual number of hemodialysis patients with skin necrosis induced by heparin use [2].

4. Conclusions

Delayed onset low molecular weight heparin induced skin necrosis is a serious adverse effect if not diagnosed early. Hence, the most important aspect in the management of this condition is early recognition and discontinuation of its use.

With regards to patients on hemodialysis who require long-term use of heparin as anticoagulant, it would be very difficult. As in our case, alternative anticoagulants such as fondaparinux also resulted in flaring of the skin necrosis. Hence, other alternatives should be sought, such as citrate and prostacyclin. It is also important to investigate the possible pathophysiology of the skin necrosis so that other treatment modalities could be employed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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