Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

A Rare Case of Mortality Following Heparin-induced Necrotizing Skin Lesions as Thromboprophylaxis After Total Abdominal Hysterectomy

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Article Info

10.30699/jogcr.4.4.151

Received: 2020/02/1;
Accepted: 2020/04/28;
Published Online: 19 May 2020;

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ABSTRACT

Background & Objective: Anticoagulant therapy has been used for the prevention and treatment of deep vein thrombosis and pulmonary embolism. Heparin-induced necrotizing skin lesion is a serious complication that can be potentially life-threatening.

Case Report: We report a 55-year-old female presenting with skin necrosis without thrombocytopenia after prescribing heparin prophylaxis. She had died as it was not possible to discontinue her heparin therapy.

Conclusion: Heparin-induced skin necrosis should be suspected in all patients who undergo UFH or LMWH. Observation of platelet count is recommended at the onset of skin lesions. Early diagnosis of this condition can be helpful for the management of this potentially mortal disease.

Keywords: Anticoagulants, Heparin, Necrotic Skin lesions

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Introduction

Anticoagulant therapy has been used for the prevention and treatment of deep vein thrombosis and pulmonary embolism **(1)** after major surgery **(2, 3)**. Heparin-induced skin necrosis is a rare complication **(4)**, which was first observed in 1973 **(5)** and their frequency is estimated to be less than 0.2% **(6)**. It usually happens about 8-11 days after heparin therapy. It could also occur sooner if the patient has any history of the previous reaction to Heparin administration **(4)**.

The diagnosis is usually clinical and the biopsy can be helpful otherwise. Pathologic report includes a small dead superficial skin with occlusive vasculitis. Heparin is discontinued as soon as possible during the therapy and surgery may be required to remove the necrotizing. Skin graft may be needed if the necrotic area would be widespread. In this study, we report an unusually severe case of heparin-induced skin necrosis after total abdominal Hysterectomy.

Case Report

A 55-year-old obese (body mass index 36 kg/m2) female (G8P7L7Ab1) was admitted to Imam- Khomeini hospital, a university hospital affiliated with Tehran University of Medical Sciences (TUMS) with complaints of dizziness, anemia (hemoglobin= 7) and menometrorrhagia since five months ago. She had a history of chronic hypertension for 10 years as well as dyslipidemia, diabetes mellitus and chronic renal failure (GFR=16) with no history of the previous dialysis.

Her medication included *Furosemide* (40 mg twice a day), Asprin (80 mg daily), Amlodipine (5mg twice a day), Metoral (25 mg twice a day), Prazosin (5mg daily), Atorvastatin 20 (mg daily), Nephrovit daily, and Insulin. She had no positive history of using heparin or low molecular weight heparin in the past.

She was admitted to Imam- Khomeini hospital with the same complaint in July 2018. Her treatment included D&C after transfusion of 8 pack cells. Hysterectomy was planned due to complex atypical hyperplasia reported by pathologic study. Hysterectomy was operated after her general condition met stable criteria.

Hemoglobin level was 7 gr/dl at the time of admission and the platelet count was 276000/µL. Therefore, transfusion of four units of pack cells ordered to correct her anemia. As a result, the patient laboratory study met the normal ranges (Hb:10.2gr/dl,

plt:167000/µL). Furthermore, Hysterectomy and bi-lateral Salpingoophorectomy was done on 09.27.2018. The surgery lasted less than an hour and with no complication. The estimated blood loss was less than 1000 mL. The incision was Pfannenstiel with 16cm in diameter and skin repaired with nylon sutures by far and near method.

Thromboprophylaxis was started with unfractionated heparin (UFH) 24h after surgery (7500 unit BD subcutaneous). The injection was located beside the umbilicus, in the abdominal wall. The patient experienced fever (40 degrees) and shivering after three days. No source of infection was found by the first visit after the complication had occurred and the incision looked normal.

An area of erythema associated with pain was found around the incision area, located 1 cm above the incision on the 4th day after surgery-14 hours after the fever had initiated. The lesions manifested by the sudden development of pain and erythema leading to the sharply defined plaques progressing to purpuric plaques, which tend to be necrotic within a short period time (Figure 1). A biopsy was obtained to document the pathologic features besides the clinical findings.

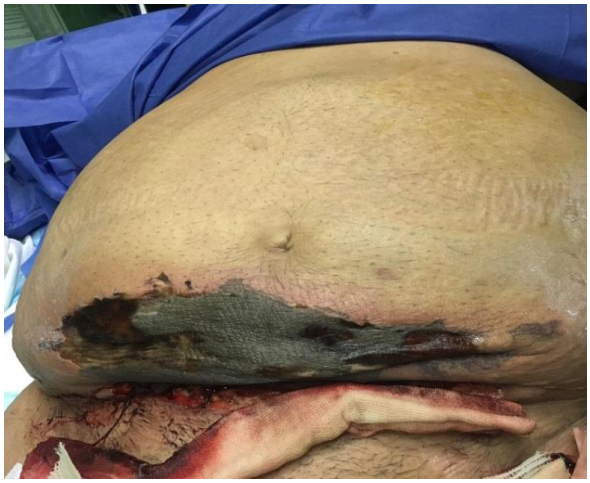

Figure 1. Skin necrosis

Hematologic study revealed a normal platelet count of 192000/µL with Hemoglobin count of 8.1gr/dl and WBC count of 7900/µL (the same as previous CBC) and her coagulation screen was normal. Oliguria occurred in less than a day after the fever, fallowing with hypotension. Although, she was oriented, we decided to admit her to the intensive care unit for sepsis workups as she became lethargic and her GCS felt to 13. Broad-spectrum antibiotic therapy (Vancomycin and Imipenem) started and Norepinephrine and Dopamine were prescribed for the management of hypotension. After a few hours her Creatinine raised (cr=5.9 mg/dl) and she became Anuric. Therefore, we planned dialysis. She went under intubation and mechanical ventilation in less than 24h due to decrease in O_2 saturation as well as altered cautiousness. We did not found any source of infection in the meantime and all sepsis studied and cultures were negative. Laboratory findings included C3, C4, CH50, Protein C, antiphospholipid antibody and viral hepatitis serology were all normal. The only positive finding was the level of protein S which decreased to 34 (the normal range is more than 40). Re-laparotomy was scheduled to explore the intra-abdominal cavity for any probable source of pathology.

During the surgery, subcutaneous small vessel thrombosis associated with necrosis and infection of subcutaneous fat tissue was apparent. The fascia was intact (Figure 2).

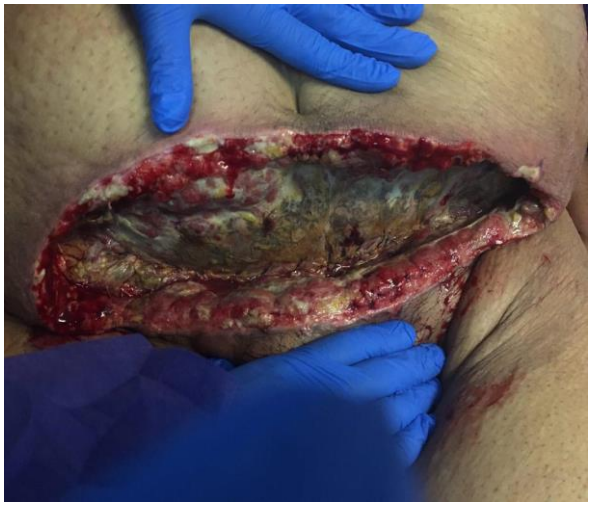

Figure 2. Skin debridement

The specimen from subcutaneous tissue was obtained for culture and pathologic study, before the massive debridement of the necrotic area. Debridement was operated twice after the re-laparotomy. Also, the affected area was treated three times a day with antibiotic therapy (Meropenem, Amikacin, and Vancomycin). After 3 days, her ECG showed AF rhythm leading to heparin infusion as a result of cardiology consultation. After 14 days, the biopsy finding revealed cutaneous occlusive vasculitis with sub-epidermal bullae with heparin-induced occlusive vasculitis (Figures 3 and 4). Although the heparin had to be stopped because of the cardiac rhythm, it was not possible to discontinue heparin therapy. Unfortunately, the cardiac arrest happened after 24 days of TAH+BSO because of prolonging and resistance hypotension and she died after 40 minutes of CPR

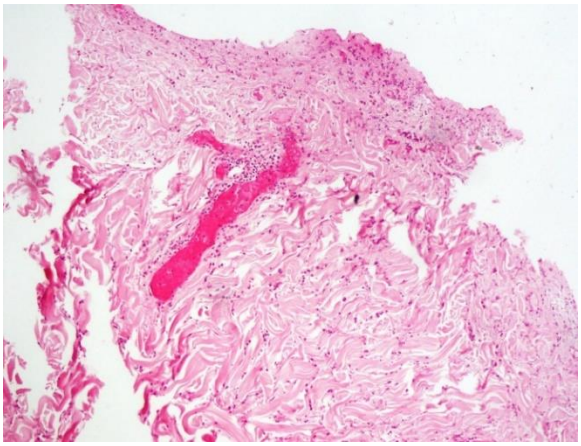

Figure 3. Denuded epidermis with necrosis of reticular dermis and occlusion of superficial vessels. (H&E × 10 magnification)

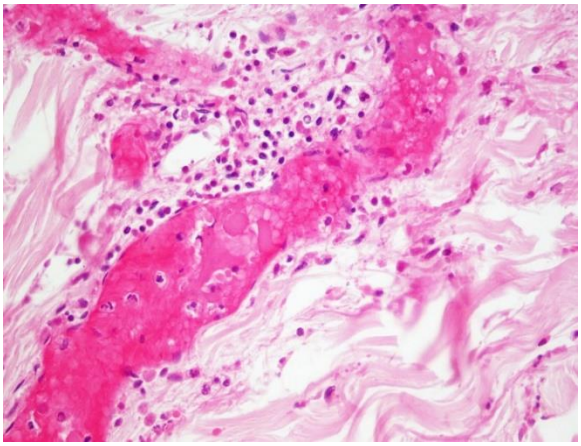

Figure 4. Occlusion of venules by fibrin-platelet thrombi and scant infiltrate of lymphocytes and neutrophils around the vessels. (H&E × 40 magnification)

Histopathologic examination of skin biopsy revealed thrombotic occlusion of small blood vessels with association of scant inflammation characterized by fibrin-platelet thrombi occluding dermal venules and arterioles with variable hemorrhage. There is scant mixed cell inflammation composed of predominantly lymphocytes and some neutrophils around the vessels. Ulceration and infarction of overlying epidermis and reticular dermis also identified. Interstitial infiltrate of neutrophils and histiocytes also present along with dermal edema and microhemorrhage (Figure 3).

Discussion

Heparin-induced necrotizing skin lesion is an extremely rare complication of the administration of LMWH **(7)**. Heparin-induced necrotizing skin was first observed in 1973 **(5)** and their frequency is estimated to be less than 0.2% **(6)**. Usually, Heparin-induced necrotizing skin starts 8-11 days after Heparin therapy and it could occur earlier if the previous history of reaction to Heparin existed **(4)**. So it is a potentially serious complication that could be even life-threatening.

The sign of this reaction is an erythematous, edematous and painful plaque in a site of injection, however, it could occur far from the site of injection before the complete skin necrotic bullous transformation is observed **(8)**.

The etiology of Heparin-induced skin necrosis includes immunologically mediated either via intravascular thrombosis resulting from Heparin-induced immune aggregation of platelet (Heparin-induced thrombocytopenia syndrome) or an Arthus type reaction due to the formation of an antigen-antibody complex in cutaneous blood vessels (type III hypersensitivity syndrome) **(9)**.

Diagnosis is usually clinical, and the biopsy could be useful. Pathologic feature is usually a small dead superficial skin with occlusive vasculitis. Heparin injection is usually discontinued as soon as possible and surgery may be required to remove the necrotic skin with a skin graft in case of an extensive necrotic area.

The finding of our study showed that the patient's platelet count does not significantly change in days before and after operations. These findings are not met the same finding of Tassava and Warkentin **(10)** study who found the patient's platelet count decreased from 480 to 299 * 10 9 /L in the next day after skin necrosis. In spite of the normal platelet count values, a decreasing platelet count by 29% on Day 5 and 38% on Day 6 after surgery is worrisome, particularly given the concomitant appearance of multi-centric necrotizing skin lesions; and a study which found the platelet count was dropped from 365 to 93*109/L (11). This result is reinforced by three corroborative studies performed by T. Godet *et al.* **(7)**, Patel *et al.* **(12)**, Khan *et al.* **(13)** where platelet count did not change before and after injection.

It's good to know that the several acute conditions which can lead to ICU admissions such as sepsis, inflammation, and trauma can cause thrombocytopenia to be masked and misdiagnosis of HIT, like what happened in our case **(14)**.

The site of a skin lesion in this study is close to the site of injection which is similar to previous studies **(7, 11,13)**. In a prospective study of Schindewolf *et al.* with over 87 patients, Heparin induced skin lesions at the injection site (or elsewhere) are not strongly associated with immunoallergic HIT, but most likely due to delayed-type hypersensitivity **(15)**. Patel *et al.* **(12)** described a 69-year-old woman for whom 5000 IU twice a day heparin was commenced as prophylaxis against venous thromboembolism and arm skin necrosis appeared on day 7 of injection SC UFH. The same as this study, Arnold **(11)** described an 84-year-old diabetic woman whose skin necrosis was noted after 7 days of prophylactic UFH in the left arm (near injection side). Furthermore, the presence of a circulating IgG antibody against heparin-platelet factor

4 was found in previous researches **(7,11,13)**, however, we did not investigate this factor in our study.

Conclusion

Heparin-induced skin necrosis should be suspected in all patients who undergo UFH or LMWH. Observation of platelet count is recommended at the onset of skin lesions. Early diagnosis of this condition can be helpful for the management of this potentially mortal disease.

Acknowledgments

The authors would like to thank all those who helped them writing this paper.

Conflict of Interest

Authors declared no conflict of interests.

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How to Cite This Article:

Deldar Pasikhani M, Ghotbizadeh F, Akbari R, Shooshtari M, Pajouhi A. A Rare Case of Mortality Following Heparin-induced Necrotizing Skin Lesions as Thromboprophylaxis After Total Abdominal Hysterectomy. J Obstet Gynecol Cancer Res. 2019; 4 (4) :151-154

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