CASE REPORT

A mysterious postoperative rash

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SUMMARY

This case report describes the development of a rash in a patient admitted with large bowel obstruction secondary to carcinoma of the sigmoid colon. The patient underwent a Hartmann's procedure and right hemicolectomy for a metastatic deposit at the terminal ileum. On postoperative day 3, the patient developed a bullous haemorrhagic rash on the thighs, flanks and abdomen, associated with a sharp drop in platelet count. Suspicion of heparin-induced skin necrosis was raised, and prophylactic enoxaparin was switched to fondaparinux. Skin biopsy results later confirmed the diagnosis. Clinical suspicion of heparin-induced skin necrosis is essential and should prompt a switch between prophylactic agents, in order to prevent potentiation of this life-threatening side effect.

BACKGROUND

This case describes the presentation of a rare, but severe side effect of a very commonly used medication. Clinical suspicion is crucial: therapeutic agent switch, while causing no harm, can prevent potentiation of this life-threatening side effect. This case report raises awareness about heparin-induced skin necrosis and will therefore benefit both patients and healthcare staff.

CASE PRESENTATION

A 54-year-old woman presented to the accident and emergency department with a 2-month history of abdominal discomfort associated with vomiting, constipation and significant weight loss. She had a medical history of schizophrenia, treated with risperidone, and no known drug allergies. Her surgical

history was significant for three caesarean sections. She was independent and lived with her daughters. On examination, her abdomen was distended, but soft and non-tender. A CT scan of the abdomen demonstrated large bowel obstruction secondary to a sigmoid stricture, with decompression into the small bowel. The patient was consented for a laparotomy and intraoperative findings were consistent with large bowel obstruction caused by carcinoma of the sigmoid colon; a metastatic deposit involving the terminal ileum was also seen. Intraoperatively, the patient became severely septic, requiring high doses of norepinephrine. A right hemicolectomy and Hartmann's procedure were performed, with formation of a double-barrel ileocolic stoma and an end-colostomy.

Subsequently, the patient required prolonged admission to the intensive care unit due to sepsis and hypotension with sustained inotrope requirement. On postoperative day 3, the nursing staff alerted the surgical team about the appearance of a rash. This was first noted on the left thigh, but later developed also on the right thigh, both flanks and right side of the abdomen (affecting approximately 5% of total body surface area). It consisted of extensive areas of non-blanching purple discolouration with large bullae (figures 1 and 2). Skin temperature was normal, and no crepitus was detected. Mucosal surfaces were intact. The patient reported no associated pain or pruritus, and her overall clinical status remained unchanged. At the same time, note was made of the patient's platelet count which had dropped from a normal preoperative level to $10 \times 10^9/L$.

INVESTIGATIONS

- ▶ Antiheparin/platelet factor-4 antibodies.
- ▶ Vasculitis and thrombophilia screen.
- ▶ Cryoglobulins, hepatitis B and C screen.
- ▶ Skin punch biopsies, from the centre and the edge of the affected areas, for histology.

DIFFERENTIAL DIAGNOSIS

The two diagnoses first considered on examination of the rash were Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); however, the absence of mucosal involvement and systemic symptoms, such as fever, were strongly in disavow of these diagnoses. SJS and TEN are most commonly caused by medications; in this case, no clear relationship could be established between medication received by the patient and the onset of the rash, further weakening this diagnostic hypothesis. The absence of systemic symptoms and other

Figure 1 Clinical appearance of the rash on the abdomen, right flank and right thigh on postoperative day 4.

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Figure 2 Clinical appearance of the rash on right thigh on postoperative day 4, after the rupture of large bullae.

organ or system involvement also militated against a diagnosis of vasculitis. The dermatology team felt that the appearance of the rash, absence of mucosal involvement and systemic symptoms, as well as the associated thrombocytopaenia, were compatible with a diagnosis of heparin-induced skin necrosis. Haematology was consulted and advised that the early onset of the rash and of thrombocytopaenia after heparin administration did not support the diagnosis. The absence of other thrombotic complications and the presence of a plausible alternative explanation for the thrombocytopaenia (ie, sepsis) were further clues pointing away from this diagnosis. Nevertheless, the haematology team advised that enoxaparin could be switched to fondaparinux, a factor Xa inhibitor, while further investigations were carried out.

TREATMENT

The rash stabilised after prophylactic enoxaparin was replaced with fondaparinux. However, the area of skin necrosis on the abdomen caused difficulties in the management of the double-barrel ileocolic stoma and faecal contamination of the abdominal and right flank wounds. In collaboration with plastic surgery, regular wound debridement and wash-out were performed, with application of vacuum-assisted closure (VAC) to isolate the wounds from the stoma (figure 3). Regular VAC changes were carried out until adequate amount of granulation tissue was obtained, and split-thickness skin grafting was performed.

Figure 3 Application of vacuum-assisted closure to isolate abdominal and right flank wound from ileocolic stoma.

Figure 4 H&E stain of skin (x125 magnification). The epidermis is partly detached from the dermis and shows some epidermal degeneration. Microthrombi are present in the superficial vessels with some adjacent red cell extravasation and some mild inflammation.

OUTCOME AND FOLLOW-UP

Skin biopsy results showed the presence of coagulative epidermal necrosis, diffuse dermal microthrombosis with marked red blood cell extravasation and mild mixed inflammatory infiltrate within the upper and middle layers of the dermis. No features of vasculitis were seen (figure 4). These results were consistent with the diagnosis of heparin-induced skin necrosis. After confirmation of skin graft take, the patient was discharged with daily dressing changes in the community and general surgery and plastic surgery outpatient follow-up.

DISCUSSION

Heparin-induced skin necrosis was first described in the 1970s in patients treated with unfractionated heparin and, later, in patients treated with low-molecular weight heparin.^{1,2} It typically presents as one or multiple discrete areas of skin erythema which progress to well-demarcated haemorrhagic lesions, with subsequent bulla formation and full-thickness necrosis.³

Heparin-induced skin necrosis usually occurs at sites of injection, but can also affect distant sites and involve a significant percentage of total body surface area.⁴ It is characterised by its time of onset in relation to heparin exposure: it typically occurs within 7–14 days. However, prior exposure to heparin can result in accelerated onset, as in our case.⁵

Differential diagnoses include other conditions which can cause full-thickness necrosis of the skin: for example, drug reactions, such as SJS and TEN, infection, thrombophilia, such as antiphospholipid syndrome, and vasculitides.⁶ Important clinical discriminants include the absence of mucosal surface involvement, of systemic symptoms, such as fever, and of other organ or system involvement. These clinical features, combined with the characteristic histological appearance, confirm the diagnosis of heparin-induced skin necrosis.

Most authors consider that heparin-induced skin necrosis shares the same aetiology as heparin-induced thrombocytopaenia: heparin binds to platelet factor-4 (PF-4) and forms heparin/PF-4 complexes which are recognised by circulating antibodies. These newly formed antigen–antibody complexes can induce platelet activation and thrombotic occlusion of the dermal microvasculature.⁷ Heparin-induced skin necrosis is usually associated with thrombocytopaenia, and the presence of

antibodies against heparin/PF-4 complexes, but cases have been described where both these features are absent.⁸

Treatment of heparin-induced skin necrosis consists of discontinuation of heparin therapy.⁹ Heparin can be substituted with other anticoagulant agents, such as fondaparinux. This intervention is simple, but yet essential: literature describes cases where heparin treatment was continued despite the appearance of a suggestive rash—the patients developed systemic thrombotic complications, such as cerebral and myocardial infarction.¹⁰

Heparin-induced skin necrosis resolves spontaneously after discontinuation of heparin therapy. Supportive management of skin lesions is essential to prevent complications, such as infection.

Wound debridement and, in some instances, split-thickness skin grafting can be used to accelerate wound healing.¹¹

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Learning points

- ▶ In the case of a suggestive rash appearing shortly after the initiation of heparin therapy, consider substituting heparin with another anticoagulant agent, such as fondaparinux, even if not all the characteristic features are present.
- ▶ When faced with a difficult clinical case, in the presence of diagnostic uncertainty, do not hesitate to seek opinions from colleagues in different specialties, so as to agree on the best course of action until an exact diagnosis is ascertained.
- ▶ While disagreement may exist between specialties about the most likely diagnosis, the different teams should consider each other's opinions when proposing therapeutic options.
- ▶ The primary team will then have an overview of available options when making a decision about the management plan.

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