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Extensive Skin Necrosis Complicating Periprosthetic Knee Infection

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Abstract

Background: Soft-tissue necrosis after total knee arthroplasty is an uncommon and potentially severe complication, with a range of possible etiologies, tough to address and uncertain outcome.

Methods: The authors describe a very challenging case of an anticoagulated patient with acute onset periprosthetic knee joint infection complicated with severe skin necrosis around the knee and lower leg.

Results: Despite the range of possible causes, enoxaparin-induced skin necrosis was the main concern. The treatment approach consisted of treating the underlying infection, discontinuing enoxaparin, and reinstating dabigatran; beyond the first procedure of a two-stage revision with medial gastrocnemius muscle flap, it was additionally applied a negative pressure dressing and treatment within a hyperbaric oxygen chamber. The patient was ultimately managed with the second procedure one year after the original surgery. Two years after the second stage, the patient is infection-free with painless, well-functioning knee arthroplasty.

Conclusion: This report illustrates a challenging case of extensive lower limb skin necrosis complicating an acute periprosthetic knee infection. Despite a successful outcome, the necrosis's exact aetiology remains unproven, but enoxaparin-induced skin necrosis emerges as a diagnostic of exclusion.

Introduction

Severe wound complications following Total Knee Arthroplasty (TKA), though uncommon, are of major importance [1,2]. Clinical presentation ranges from wound problems and superficial infections to full-thickness wound dehiscence or skin necrosis that may originate deep infection and require additional surgeries. Those with early complications, rates of major surgery (component resection, muscle flap coverage, amputation), or deep infection within two years reach 5.3% and 6%, respectively [1].

The authors describe a very challenging case of acute onset periprosthetic knee joint infection complicated with severe skin necrosis around the knee and lower leg. It was performed surgical debridement of the necrotic tissues, medial gastrocnemius muscle flap, negative pressure dressing, complementary treatment within hyperbaric oxygen chamber, split-thickness skin graft for wound coverage. The patient was ultimately managed with a successful yet very eventful two-stage procedure, being able to walk autonomously and presenting a good knee range-of-motion, with complete wound healing. Despite a successful outcome,

the necrosis's exact aetiology remains unproven, but enoxaparin-induced skin necrosis emerges as a diagnostic of exclusion.

Case Presentation

A 78-year-old woman with a history of atrial fibrillation and arterial hypertension underwent left TKA for primary osteoarthritis (Figure 1a). Chronic medication included dabigatran, olmesartan/hydrochlorothiazide, and amlodipine. No history of diabetes, autoimmune disease, peripheral arterial or venous disease, or other relevant comorbidities.

Dabigatran was stopped three days before surgery and bridged to enoxaparin 60 mg bid. A tourniquet was used throughout the procedure (approximately one hour), and a drain was used for the first 24 hours. The patient was discharged on day 5 with a clean wound and recommendation to switch back to oral dabigatran.

On the 18th postoperative day, a significant wound skin necrosis was found (Figure 1b), and despite normal leukocyte count and relatively low C-Reactive Protein (CRP) levels 15.8 mg/L, the patient was switched back to enoxaparin and was scheduled for surgery within two days (Figure 1c). Doppler vascular ultrasonography at this point was normal.

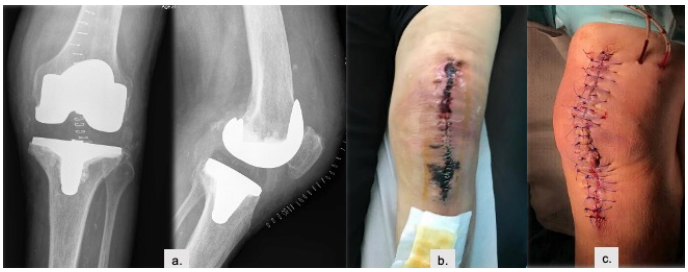

Figure 1: a. postoperative TKA X-Ray; **b.** skin necrosis on postoperative day 18th; **c.** surgical wound immediately after Debridement and Antibiotics with Implant Retention (DAIR).

After surgical debridement, including polyethylene exchange, broad-spectrum IV antibiotics were started (vancomycin and piperacillin-tazobactam), and given the apparent skin tension, an extension knee splint was used. Despite these efforts, skin necrosis progressed on the wound's distal part (Figure 2a).

Microbiological samples taken during surgery confirmed infection with *Enterococcus faecalis* and *Staphylococcus haemolyticus*. As such, we decided to remove the prosthesis, implant an antibiotic-loaded spacer, and perform a medial gastrocnemius muscle flap for wound coverage (Figure 2b-c). Microbiological samples, including implant sonication, isolated the same microorganisms, but broad-spectrum antibiotics were maintained for the entire six-weeks period given the unfavorable clinical course.

During the next couple of weeks emerged extensive superficial skin necrosis around the knee (sparing the gastrocnemius flap) and extending to the lower leg around the incision made to harvest the muscle flap (Figure 3).

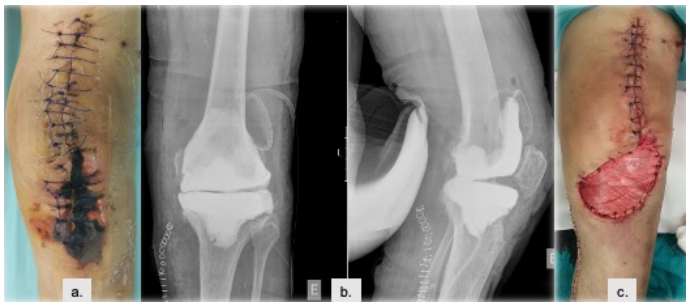

Figure 2: a. skin necrosis on day 5th after DAIR; **b.** X-Ray after the implant removal and application of an antibiotic-loaded cement spacer; **c.** medial gastrocnemius muscle flap for wound coverage.

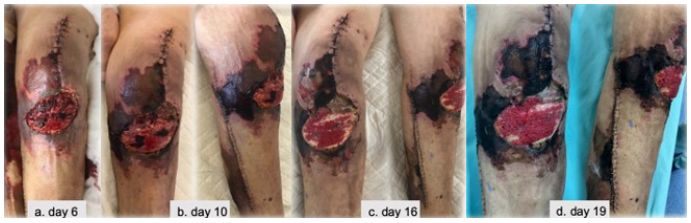

Figure 3: a-d. skin necrosis progression after TKA revision, extending to the lower leg around the incision made to harvest the muscle flap.

An exhaustive investigation was initiated. Formal arteriography was performed, and occlusive arterial disease was ruled out. Skin biopsy revealed microvascular thrombotic phenomena and ischemia without vasculitis. No other systemic signs or skin manifestations occurred except on the afflicted lower limb. Complete Blood Count (CBC) revealed normal leukocyte count and relative formula, persistently normal platelet values, and slight postoperative anemia. Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) levels were elevated but ran a favorable downwards trend. Kidney function was persistently normal, and there was no electrolyte or calcium phosphate metabolism imbalance. All coagulation parameters were normal. Autoimmune disease assessment was negative for Antinuclear Antibody (ANA), Anti-Neutrophil Cytoplasmic Antibodies (ANCAs), and antiphospholipid syndrome antibodies (including lupus anticoagulant). A hematology consult was also requested, thinking of Low Molecular Weight Heparin (LMWH) induced skin necrosis, but given the lack of thrombocytopenia and atypical clinical presentation, a decision was made not to pursue more specific testing regardless of our suspicion.

After three weeks, the surgical debridement of the necrotic tissues was undertaken. In the lack of an alternative diagnosis, a decision was made to discontinue enoxaparin and reinstate dabigatran. A negative pressure dressing was applied, and complementary treatment on a hyperbaric oxygen chamber was also initiated. Necrosis stopped progressing (Figure 4a-d), and eventually, a split-thickness skin graft of the thigh for wound coverage was performed (Figure 4e).

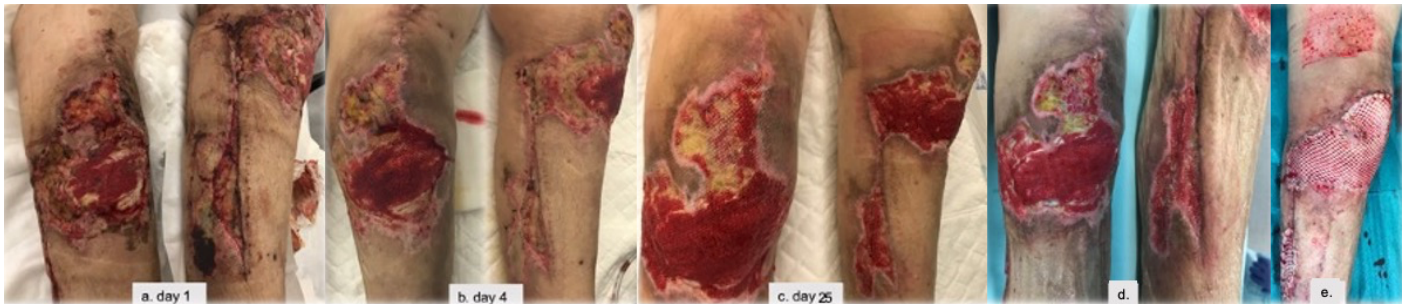

Figure 4: a. 3 weeks after DAIR it was performed a debridement of the necrotic areas interrupt enoxaparin and reinstate dabigatran hypocoagulation, negative pressure dressing applied and hyperbaric oxygen chamber was initiated; **b-c.** progressive healing of the wound; **d.** new debridement; **e.** split-thickness skin graft of the thigh for wound coverage.

During the outpatient follow-up, soft tissues showed slow but progressive improvements and eventually healed completely. A few weeks after hospital discharge, an ulcer on the leg's lateral aspect (unrelated to previous incisions) developed and progressed (Figure 5a-d). A biopsy was again performed that revealed unspecific findings suggesting infected venous leg ulcers, and a two-week course of oral amoxicillin/clavulanate was instituted with excellent clinical response (Figure 5e-h). A new immunological assessment showed positive ANA with a low anti-dsDNA's low value, without complement consumption and positive IgG anti-beta-2-glycoprotein I (anti-cardiolipin and lupus anticoagulant remain negative), but after twelve weeks, they were back to normal.

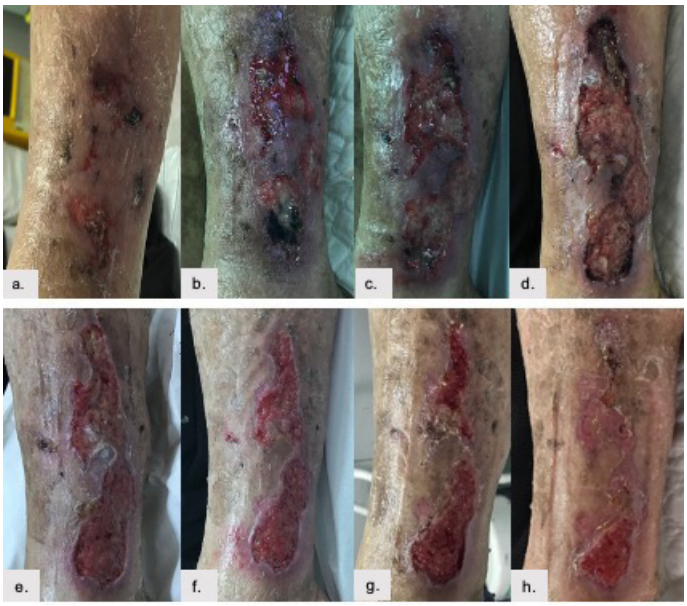

Figure 5: a-d. lateral leg wound developing and progression; **e-h.** response after institution of two-week course of oral amoxicillin/clavulanate.

Second stage surgery was consecutively postponed, but when satisfactory soft tissues were present (Figure 6a) and after an adequate discussion with the patient, a decision to go ahead with the second stage was taken one year after the original surgery. Dabigatran was discontinued for three days before and immediately resumed after surgery with no LMWH bridging. A lateral approach was used to avoid going through the muscle flap (Figure 6c). Intraoperatively, multiple deep tissue samples were collected and showed no bacterial growth. Postoperatively, a small superficial necrotic area on the knee's anterior aspect appeared, and considering the past history, hyperbaric oxygen therapy was resumed up to complete wound healing and hospital discharge after three weeks. Two years after the second stage, the patient is infection-free with a painless, well-functioning knee arthroplasty, and no systemic disorder was diagnosed (Figure 6b,d).

The patient was informed that data from the case would be submitted for publication and gave the consent.

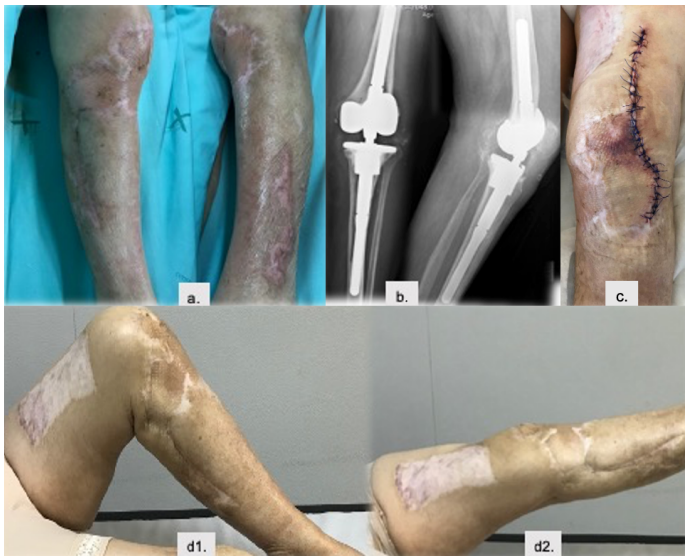

Figure 6: a. skin before the 2nd procedure; **b.** postop X-Ray; **c.** skin fully healed; **d1-2.** Left knee range-of-motion in the last evaluation 0-115º.

Discussion

Extensive skin necrosis such as the one presented, can originate in a wide range of aetiologies, and all of them were considered in this case:

1. Infection

In the setting of wound healing issues after joint replacement, Periprosthetic Joint Infection (PJI) should always be ruled out. We believe it is imperative to address these cases early and aggressively to obtain good results [3]. This principle was also observed in this case, and polymicrobial PJI was confirmed. Necrotizing Fasciitis (NF) may also be caused by polymicrobial infections [4] and was considered despite a non-compatible clinical presentation. As such, despite the favorable course of inflammatory blood markers such as CRP, we worried that some

"occult" microorganisms would be responsible for the ongoing skin necrosis and decided to keep broad-spectrum antibiotics for the entire six-weeks period.

Why we believe skin necrosis was not caused by the underlying infection (and no reason to prolong antibiotic therapy was present):

A. PJI was adequately addressed from the start. Debridement and antibiotics with implant retention were performed timely, and even if the persistent infection could be considered a contributing cause in the early stages, it would certainly not be responsible for what happened after prosthesis removal and spacer implantation.
B. NF initial clinical presentation resembles cellulitis that rapidly progresses within 24 to 72 hours [4]. This was not the case here, nor was there ever disproportionate pain and tenderness compared with physical findings (cardinal finding) [5,6]. Moreover, the biopsy did not reveal fascial necrosis, neutrophil infiltration, subcutaneous fat necrosis, vasculitis, or other suggestive features [7].

2. Arterial Disease/Embolic Phenomena

Although it is clear that skin necrosis is the final result of superficial microvasculature occlusion, we worried that some kind of major arterial disease could be responsible for the exuberant clinical presentation. Atrial fibrillation and patient's age mandated appropriate investigation. Blood vessel obstruction due to embolic phenomena was also a possible cause.

Why we believe skin necrosis was not caused by underlying arterial disease or embolic phenomena:

A. The patient underwent completely normal angiography.
B. Completely normal laboratory coagulation parameters and continuing anticoagulation medication exclude a primary hypercoagulable condition as the cause for skin necrosis.
C. Unlike other forms of necrosis, with embolic phenomena, the areas of involvement tend to be small, distal, and multiple.

3. Autoimmune Diseases

Several autoimmune diseases may present cutaneous involvement with skin necrosis. They could be associated with ANA positive test (like systemic lupus erythematosus – SLE – and scleroderma) or vasculitis ANCA-positive and negative. Systemic symptoms, laboratory findings, and positive auto-antibodies are useful to achieve a diagnosis. Skin biopsy is pertinent, demonstrating vasculitis.

Antiphospholipid Syndrome (APS) is an acquired thrombophilia caused by autoantibodies against phospholipids and/or phospholipid cofactors, causing arterial and venous thrombosis. Dermal capillary thrombosis develops into local or widespread necrosis, and the cutaneous manifestations are often the first presenting feature [8]. Diagnosis of APS involves the presence of thrombotic clinical events in addition to elevated auto-antibodies on at least two occasions, 12 weeks apart [9].

Why we believe it is not an autoimmune disease:

A. ANA and dsDNA were positive in the second study only (and not during acute postop skin necrosis), without systemic symptoms or laboratory findings to support SLE diagnosis. In addition, immunosuppression was not used in the acute event, and two years later, no other manifestations occur.
B. Vasculitis is completely absent in all biopsies taken.
C. The absence of previous thrombotic events, other suggestive clinical features 21, and the presence of positive anti-beta 2-glycoprotein in only one study does not support the diagnosis of APS.

4. Calciphylaxis

Calciphylaxis is an uncommon and devastating cause of acute cutaneous necrosis. It occurs due to metastatic calcification of small blood vessels leading to ischemic organ damage. Areas with extensive subcutaneous fat and high vascularity (e.g., breasts, buttocks, thighs, etc.) are commonly affected [10]. Areas of central ischemic necrosis develop and enlarge over weeks, usually with a distinctive excruciating pain. The gold standard in the diagnosis of calciphylaxis is a tissue biopsy [11].

Why we believe it is not calciphylaxis:

A. Histologic findings are very characteristic in this disorder (i.e., intravascular calcium deposits), and they were completely absent in all samples taken.
B. Lack of clinical characteristics and context for this disease (e.g., end-stage renal disease).

5. Pyoderma Gangrenosum

Pyoderma Gangrenosum (PG) is an ulcerating neutrophilic dermatosis that can occur in areas of trauma or following surgical procedures [12–14]. While the onset of PG is sudden, it tends to remain a chronic ailment. It classically presents on the lower extremities [7]. Diagnosis is often by exclusion, and although lesions appear infected, cultures are not useful [15]. While there are no specific histological features of PG, a biopsy is still necessary to exclude alternative etiologies [16].

Why we believe it is not PG:

A. Although it is clear there are no specific histologic findings to PG, there are, however, some suspicious/supporting features (e.g., inflammatory infiltrate) that are completely absent in our case [17].
B. After surgical debridement of the skin necrosis, there was no further progression of the ulcer. If PG was the culprit, one could expect postsurgical worsening is known as pathergy phenomenon, the reason why surgical debridement is usually contraindicated [7,17].
C. The spontaneous improvement despite the lack of corticosteroid/immunosuppressive therapy is also

against this diagnosis, as is the good clinical outcome after the second stage revision surgery.

6. Drug-induced

Heparin-induced skin necrosis is considered part of heparin-induced thrombocytopenia syndrome, although a decrease in platelet count is observed in only 50% of patients. Necrotic lesions typically appear between 5–15 days after treatment initiation. It usually presents close to the injection site, although it has been described at a distance on rare occasions [18–22]. Blood tests can reveal thrombocytopenia and the presence of anti-platelet factor IV antibodies, although their absence is insufficient to rule out this diagnosis. Treatment consists of discontinuation of heparin administration and replacement with other anticoagulants [7,19].

Why we believe it is LMWH induced skin necrosis, despite the atypical location of the necrotic lesions and the lack of classical thrombocytopenia and heparin-platelet factor 4 antibodies in this case:

A. Skin necrosis stopped progressing after we decided to discontinue enoxaparin and switch back to dabigatran.
B. Although the mechanism is not as clear, heparin-induced necrosis can occur in the absence of thrombocytopenia and responsible antibodies [7,19].
C. This is indeed an exclusion diagnosis, but we believe all other possible diagnoses were thoroughly excluded.

In conclusion, this report illustrates a challenging case of extensive lower limb skin necrosis complicating an acute periprosthetic knee infection. Difficulties around diagnosis and treatment were numerous, even within a well-trained multidisciplinary team. Despite a successful outcome, the necrosis's exact aetiology remains unproven, but enoxaparin-induced skin necrosis emerges as a diagnostic of exclusion.

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