Trousseau syndrome presenting with penile gangrene

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INTRODUCTION

Trousseau syndrome is a hypercoagulable state in association with an underlying malignancy. It is associated with myriad arterial and venous thrombotic events such as superior vena cava obstruction, noninfectious endocarditis, and myocardial infarction.[1] Here we describe an unusual presentation of Trousseau syndrome in a patient with underlying prostate adenocarcinoma.

Abbreviations used:

NSAID: nonsteroidal anti-inflammatory drugs
PSA: prostate-specific antigen

CASE REPORT

A 64-year-old Chinese man with poorly controlled, insulin-dependent diabetes mellitus, hypertension, and hyperlipidemia was referred for a 2-month history of glans penis gangrene. He had no known drug allergies. He had a history of prostate adenocarcinoma with bony metastases [stage T3, N4, M1, Gleason 9 (score 4+5)], serum prostate-specific antigen (PSA) levels of 272 μg/L (normal range, 0-4 μg/L) and had undergone bilateral subcapsular orchidectomy 6 years ago with improvement of serum PSA levels to 0.8 μg/L postoperatively. He defaulted follow-up for 5 years and re-presented with castrate-resistant prostate cancer with a PSA of 126.6 μg/L. He was started on bicalutamide (antiandrogen) tablets.

The penile lesions started as painful erosions surrounding the penile meatus, which gradually became necrotic over 2 months. There were no vesicles or bullae. The patient attempted to self-medicate with topical Baneocin powder (Bacitracin Zinc, Neomycin Sulfate). He also experienced worsening pain and required multiple courses of nonsteroidal anti-inflammatory drugs and tramadol. He denied any urinary symptoms or systemic symptoms before or during the onset of the erosions. There were no recent changes in his regular medication. His last sexual contact was more than 10 years ago.

Clinically, the patient was afebrile and had near-circumferential dry gangrene involving the glans penis associated with severe swelling of the foreskin and paraphimosis (Fig 1, *A* and *B*). The penile shaft and scrotal skin were unremarkable, with no significant dermatologic signs elsewhere. There were multiple small palpable inguinal lymph nodes.

Laboratory test results on admission were significant for normochromic normocytic anemia (hemoglobin level, 10.3 g/dL), leukocytosis with neutrophilia (white cell count, 12 $\times$ $10^3/\mu$L; neutrophils, 90%), and increased C-reactive protein level of 48.9 mg/L (reference range, 0-3 mg/L). The eosinophil count, renal panel, serum calcium, platelet count, international normalized ratio, prothrombin time, activated partial thromboplastin time, and urinalysis results were unremarkable. Urine cultures and penile swab cultures were negative for bacterial growth. Ultrasound Doppler scan of the penis did not find any collection or abscess, with normal blood flow seen in the glans penis. His serum PSA level was elevated at 166 μg/L.

Multiple biopsies of the lesion found spongiotic stratified squamous epithelium with large areas of basal necrosis. There were several thrombosed small to medium blood vessels with a neutrophilic infiltrate beneath the ulcer. No calcium deposits were seen in the walls of the blood vessels. Gomori methenamine-silver and Gram stain were negative,

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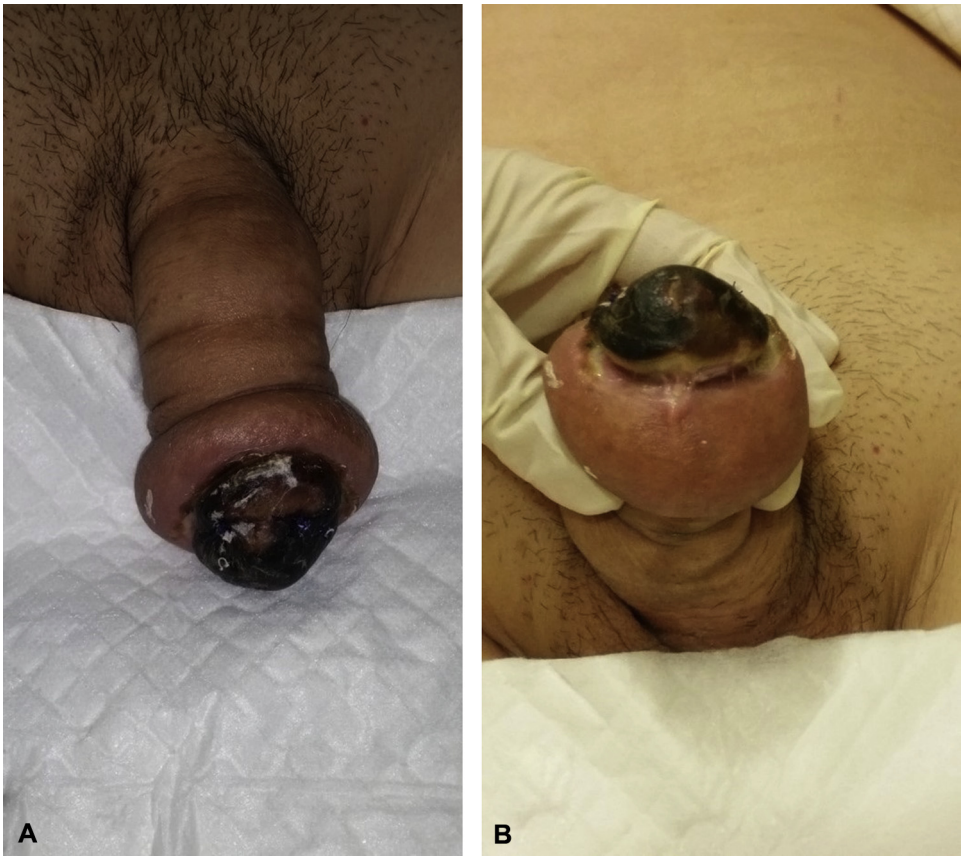

Fig 1. **A** and **B**, Dorsal and ventral views show near circumferential dry gangrene of glans penis, with foreskin swelling and paraphimosis. A small fissure can be seen beneath the ventral aspect of the glans penis.

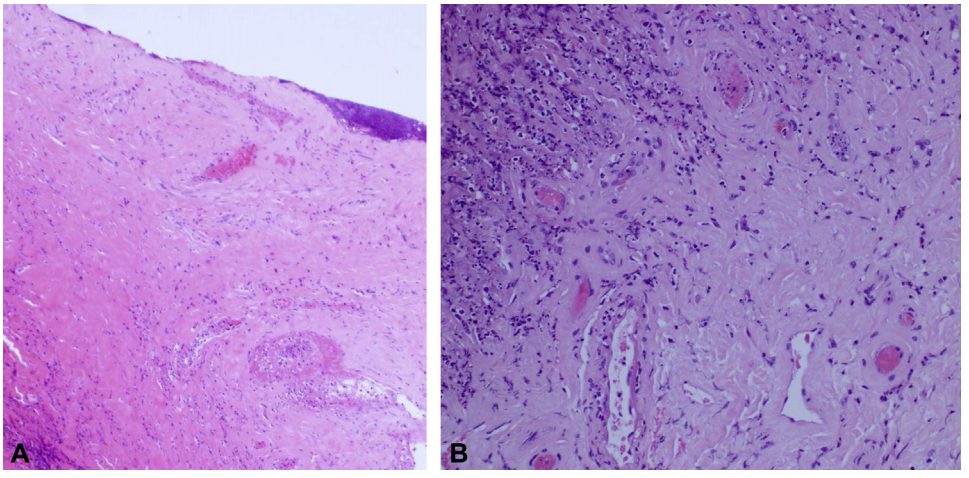

Fig 2. **A** and **B**, Photomicrographs show superficial thrombopheblitis with surface ulceration. (**A** and **B**, Hematoxylin-eosin stains; original magnifications: **A**, ×10; **B**, ×40.)

with no viral cytopathic changes observed (Fig 2, *A* and *B*).

The patient was treated empirically with intravenous augmentin (1.2 g, every 8 hours) while awaiting culture results. Unfortunately, he opted for discharge against medical advice soon after his admission. When reviewed in clinic a week later, his penile gangrene had progressed to encompass the entire circumference of the glans penis. Workup for his hypercoagulable state was planned in the outpatient setting 6 to 8 weeks after discharge. However, he declined to return to our department for follow-up.

He underwent an elective partial penectomy at a private hospital several weeks later, and was reported to have recovered well postoperatively.

DISCUSSION

This report discusses an unusual presentation of Trousseau syndrome resulting in penile gangrene in a patient with metastatic prostate adenocarcinoma. Historically, Trousseau syndrome referred to superficial migratory thrombophlebitis in the presence of malignancy.[1] The term now describes a florid hypercoagulable state encompassing arterial or venous thrombosis, nonbacterial thrombotic endocarditis, disseminated intravascular coagulation, or microangiopathic hemolytic anemia.[1,2] Clinical manifestations range from uncomplicated superficial thrombophlebitis to superior vena cava obstruction, stroke, and pulmonary embolism.[1] The most common cancers associated with Trousseau syndrome include pancreas, lung, prostate, and stomach cancers.[1] Dermatologic findings may include erythematous, tender papules, or nodules along the course of a vein. Histologic examination of the lesion may find an inflammatory infiltrate involving all layers of the affected vein and a thrombus within the lumen.[3] A variety of soluble factors, including mucins secreted by adenocarcinomas, cysteine protease (cancer procoagulant), and expression of tissue factor by cancer cells contribute to the pathogenesis of Trousseau syndrome.[4-6]

The mainstay of treatment in Trousseau syndrome is treatment of the underlying malignancy. Heparin is the drug of choice and is more effective than warfarin in preventing thrombosis. Heparin enhances the ability of antithrombin to inactivate factor Xa and thrombin, and blocks P-selectin on leukocytes and platelets, thus preventing the aggregation of platelets and leukocytes.[7] Low-molecular-weight heparins have been used in the management of Trousseau syndrome, though with varying efficacy.[7]

To our knowledge, there have been no reports of Trousseau syndrome causing penile gangrene. Superficial thrombophlebitis, deep venous thrombosis, and thrombosis of the internal jugular vein have been reported in patients with Trousseau syndrome associated with prostate carcinoma.[8,9]

We believe that our patient's penile gangrene caused by Trousseau syndrome, given his extensive history of prostate carcinoma that was left untreated for many years. The gangrene is unlikely to be caused by medication use, as the patient did not report any history of fixed drug eruption affecting the glans penis while on nonsteroidal anti-inflammatory drugs, and bicalutamide is not known to cause penile gangrene. Normal arterial penile flow was seen, and histologic examination of the glans penis was suggestive of thrombophlebitis with no evidence of infection. Calciphylaxis was excluded, as histologic examination did not show calcium deposits in the walls of small and medium blood vessels, and the patient had normal renal function, with normal serum calcium and phosphate levels. We planned to investigate further the patient's hypercoagulable state after his acute event. Unfortunately, he declined to return for further follow-up.

Malignancy is the second most common acquired cause of hypercoagulable syndrome.[10] Patients should receive screening for cancer in addition to complete blood count, prothrombin time and partial thromboplastin time studies, and evaluation for antiphospholipid antibodies before testing for common genetic disorders associated with hypercoagulable syndrome.[10] Laboratory investigations for these genetic disorders are generally unreliable during an acute thrombotic event and are best left to when the patient has recovered from the acute episode and is asymptomatic.[10] Hence, Trousseau syndrome should be considered as a differential diagnosis of penile gangrene, particularly in patients with underlying malignancy.

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