Pyoderma gangrenosum of the penis

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Pyoderma gangrenosum (PG) is a cutaneous inflammatory disorder that results in painful ulcers. Isolated penile PG is an exceedingly rare entity that has only been reported in a handful of cases.

This case highlights the course of a 71-year old man with a locally destructive, nonhealing penile ulceration who was ultimately diagnosed with PG. He underwent extensive work up to reach the diagnosis. His disease progression was halted with systemic steroids and Methotrexate. We present his clinical course and a review of the literature to highlight the need for early recognition of this potentially devastating condition and to outline management options.

Key Words: pyoderma gangrenosum, scarring, immune, urethra, penile, stenosis

Introduction

Pyoderma gangrenosum (PG) is a rare, chronic inflammatory skin disease in which a painful nodule breaks down to form a progressively enlarging ulcer. PG typically occurs in conjunction with an underlying systemic disease, commonly inflammatory bowel disease (IBD), polyarthritis, or gammopathy.[1] It is estimated to affect between 3-10 patients per million per year,[2] with a peak incidence in patients aged 20-50 years old and a slight predominance in women.[3] PG is a diagnosis of exclusion in the setting of a progressing necrolytic ulcer. There are currently no established diagnostic criteria for the disease.[4] Additionally, the treatment for PG involves immunosuppresive therapy, which would be detrimental in the setting on an infectious or malignant etiology for penile ulcer.

There exist several subtypes of PG including pustular, bullous, and vegetative variants. The classic form, ulcerative PG, often requires aggressive systemic immunosuppressive therapy for management.[2] Genital PG is a rare phenomenon, typically involving the vulva. PG of the penis represents an extremely rare entity that has been reported in less than 30 cases in the literature. Here, we report the case of a 71-year old man who presented initially with a non-healing penile ulcer that progressed despite several medical treatments. After a lengthy work up, consultation with multiple specialists, and secondary histologic review of biopsy specimens the consensus diagnosis was PG. He was started on immunosuppressive therapy and demonstrated marked improvement.

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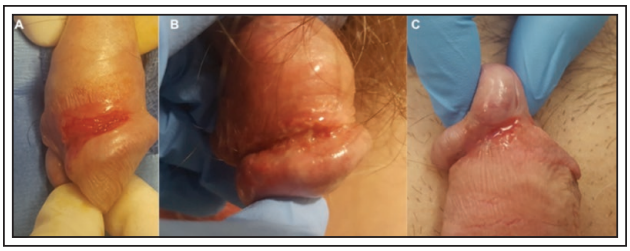

Figure 1. (A) Penile ulceration along the coronal sulcus at presentation with **(B)** non-healing of ulcer following biopsy **(C)** Follow up exam with persistent ulceration under the coronal sulcus at the right lateral aspect.

Case report

A 71-year old male with history of prostate cancer 3 years status-post prostatectomy presented with a 2-month history of a penile ulcer just under the right lateral aspect of the coronal sulcus. Physical exam revealed a narrow hypospadiac meatus that opened at the coronal margin and an ellipsoid penile ulceration along the coronal sulcus, 2-3 mm deep and 1 cm in length. The surrounding glans and underlying corpora for the distal 1 cm of the phallus were indurated with superficial scarring and retraction of the penile shaft. There was no inguinal lymphadenopathy appreciated. A work up for an infectious etiology was negative. This included PCR for herpes simplex virus, treponemal antibody testing for syphillis, fungal and gram stain of swabs of the wound. He denied any recent travel to suggest a more exotic etiology. Laboratory findings including a complete blood count and basic metabolic panel were unremarkable. A deep incisional biopsy was performed at the site of the ulcer as was a retrograde urethrogram to assess the patency of his distal urethra, Figure 1a, 1b. Pathology revealed chronic inflammation without evidence of malignancy, Figure 2a. The raw edges of the biopsy were sutured and the patient was advised to pull the skin away from the coronal

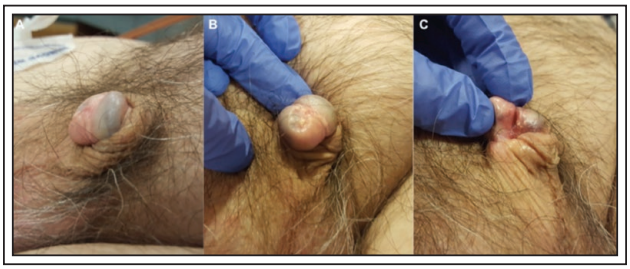

Figure 3. Examination at resolution of active ulceration demonstrating complete loss of phallic length and significant scarring/deformity of the lens.

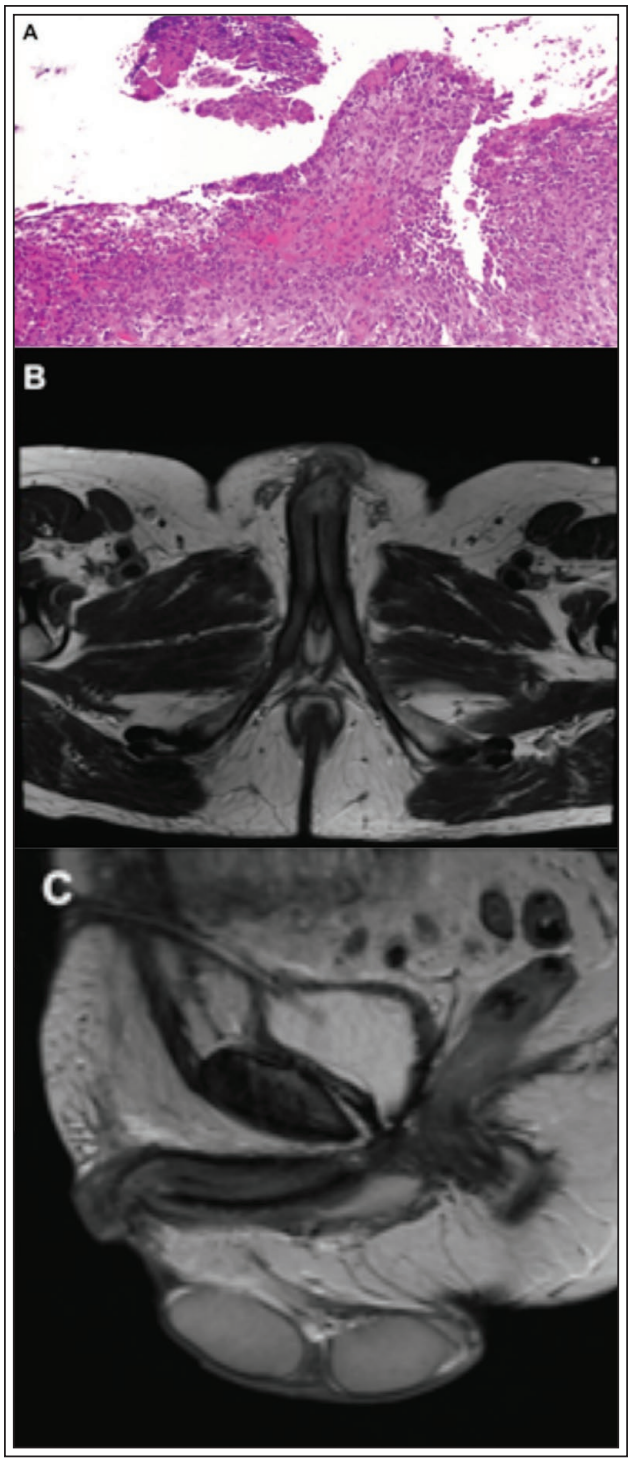

Figure 2. (A) Penile ulcer displaying chronic inflammation with underlying granulation tissue and no evidence of malignancy. **(B)** Axial and **(C)** sagittal MRI highlighting an enhancing lesion extending from the glans to include the distal shaft and corporal bodies with disruption of the tunica albuginea and fascial layers and without evidence of malignancy.

margin daily and apply Bacitracin to prevent penile adhesions from forming. The retrograde urethrogram showed meatal stenosis with a 6 French opening. He subsequently underwent a formal meatotomy. As all testing was negative a 2 week course of Keflex was trialed to reduce any irritation due to possible balantis, however, no improvement was noted.

A month later, the patient reported persistent, unimproved glans ulceration. Examination at follow up revealed ulceration on the underside of the coronal sulcus at the right lateral aspect of the glans consistent with prior exams, Figure 1c. The glans was also noted to have a slightly bluish hue and a smooth shiny appearance, which in combination with the previous meatal stenosis led to an initial presumptive diagnosis of lichen sclerosus. He was started on betamethasone ointment and was referred to an outside dermatologist for evaluation of his nonhealing penile ulcer. The differential diagnosis included Lichen sclerosus atrophicus, Zoon's balanitis, Behcet's disease, cutaneous Crohn's Disease, PG, and Peyronie's disease given the degree of penile scarring. The dermatologist recommended he start daily Calmoseptine ointment (2.5 oz 3x/daily) and Triamcinolone (0.1% 2x/daily) along with trial of triple paste AF for potential yeast involvement. He was also referred to rheumatology, where an autoimmune work up was negative.

Approximately 3 months later, the patient was seen by an outside urologist for a second opinion. Examination at that time revealed an ulcerated linear area where the shaft meets the corona distally and a firm, thickening of the corporal bodies with chronic induration and dramatic scarring of the corporal bodies. Given the persistent ulceration and suspicious thickening, there was concern for urethral carcinoma with infiltration of the corporal bodies. He underwent a core biopsy of the lesion, which once again showed chronic inflammation and ulceration without evidence of malignancy.

As the patient continued to have progressive worsening of his penile ulceration and loss of penile shaft length without a clear etiology, we recommended a third opinion with a specialist at another academic center. At this point he had developed a new deep ulcer on the central dorsal aspect of the glans itself. Upon consultation he was diagnosed with Peyronie's disease, as a broad term for an inflammatory condition of the phallus with resultant scarring. Given the patient's otherwise good health and the delayed presentation of the ulcer 3 years after prostatectomy, the consultant hypothesized that there may be a post-surgical inflammatory process contributing in addition to persistent poor healing and irritation at the distal phallus. Nonetheless, to once again rule out malignancy, he underwent examination under anesthesia with deep excisional biopsy of the ulcerative lesion as well as urethral biopsies, which again were all negative for malignancy. He developed urinary retention postoperatively and transiently had a suprapubic tube placed, which was removed prior to follow up at our home institution. Six months after this third set of biopsies, he developed significantly difficulty urinating and was found to have a pinpoint meatus and near closure of his distal urethra. He underwent formal open suprapubic tube placement for long term management at that point.

In light of the persistent severe induration of the penile shaft with three biopsies negative for carcinoma of any kind, an magnetic resonance imaging (MRI) of the pelvis was ordered. The MRI demonstrated a 3.1 cm x 2.7 cm x 2.4 cm mildly T2 hyperintense enhancing lesion extending from the glans penis into the distal shaft including both corpora cavernosa, and the corpus spongiosum with disruption of the tunica albuginea and fascial layers without lymphadenopathy to suggest malignancy, Figure 2b. The disruption of the normal anatomical planes within the phallus distally clearly demonstrate the destructive process that was evidenced on clinical exam during this patient's course. At follow up, approximately 3 months later the patient continued to note retraction and scarring of the penile shaft along with a persistent non-healing ulcer.

As no urologist had been able to make a successful diagnosis, he was referred to and evaluated by dermatology both at our institution and the outside academic institution in tandem. Our dermatologist evaluated the patient and started him on a Prednisone taper, beginning with a 50 mg PO daily dose. One week later, the outside institution's dermatology team examined the patient and described a deteriorating wound with thickened tissue along the shaft of the penis with significant scarring and ulceration near the glans of unclear etiology. Review of pathology specimens showed granulomas and giant cells which could be from a foreign body, infection, or auto-immune process. He was prescribed a 5-day course of Fluconazole 200 mg PO daily to treat any possible superimposed candidal balanoposthitis and was recommended to continue the calmoseptine/triamcinolone mix as well as the prednisone taper.

The patient was invited to the outside institution's dermatology grand rounds for a clinical pathological consensus, where numerous differential diagnoses were mentioned including ulcerative lichen planus, PG, ulcerative balantis xerotica obliterans, and cutaneous Crohn's disease. His previous biopsy slides were sent

to dermatopathology, with a reading of a foreign body granuloma, mixed inflammatory infiltrate mostly composed of neutrophils, and abscess formation concerning for PG. He was ultimately diagnosed with isolated PG of the penis by a consensus between the local and outside academic dermatologists. Following diagnosis, he underwent an extensive work up to rule out any underlying systemic disease including a colonoscopy, serum protein electrophoresis to rule out irritable bowel disease and urine protein electrophoresis to rule out gammopathy. His penile ulcers began to resolve with the oral Prednisone, which was considered confirmatory of the diagnosis. Dermatology then recommended he stay on a 10 mg oral daily dose of Prednisone with a plan to taper down to 7.5 mg and added oral Methotrexate 12.5 mg weekly with folic acid 1 mg every other day of the week.

At urology follow up 5 weeks later, the patient noted marked improvement in his penile ulcerations, but induration in the penile shaft that was seemingly worsening. Examination revealed a healed scar at the site of prior ulceration on the glans, with significant induration and shortening of the phallus. The urethra was nearly completely closed distally. At his most recent follow up all active ulceration and inflammation has resolved, however, the patient is left with complete loss of phallic length, Figure 3.

He remains on a regimen of Methotrexate and Prednisone taper and undergoes monthly suprapubic tube changes. The long term plan for management of his urinary tract will be decided after a period off steroids without demonstrable disease progression, if this can be achieved.

TABLE 1. **Therapeutic options for Pyoderma gangrenosum (PG) and their respective mechanism of action**

	Mechanism of action
Antimicrobial	
Dapsone	Inhibits DHF synthesis
Minocycline	Protein synthesis inhibitor
Immunosuppressant	
Steroids	Inhibits cytokine production
Cyclosporine	Calcineurin inhibitor
Azathioprine	Inhibits purine synthesis
Infliximab	TNF-alpha inhibitor
Tacrolimus	Calcineurin inhibitor
Other	
Colchicine	Inhibits microtubule polymerization
Imiquinod	Activates TLR7
Thalidomide	Inhibits angiogenesis

Discussion

Correctly diagnosing penile PD may be challenging as it is an extremely rare disease that most urologists will be unfamiliar with. Diagnosis is based on clinical history and exclusion of other disease processes. Consultation with a dermatologist and/or pathologist will be required to make the diagnosis. Although not diagnostic, the main histopathological feature of PG is massive neutrophilic infiltration, and granulomatous inflammation potentially with necrosis. Classically, it affects the legs but may also be found on the hands, arms, and face.[5] It is often perceived as a cutaneous manifestation of a systemic disease such as irritable bowel disease.[6] Thus, in patients who do not display any evidence of systemic disease, it may be lower on the list of differential diagnoses. Other potential diagnoses for a penile ulcer include malignancy, vasculitis, sexually transmitted infection, Behcet's Syndrome, and lichen sclerosus et atrophicus.[7] A hallmark of PG is that the disease can be worsened by surgical intervention, even the biopsy required to make the diagnosis.

A review of the literature shows that PG of the penis is exceptionally rare, with less than 30 cases reported. Although the literature suggests that about 50% of PG cases are associated with systemic disease, in our literature review we found that only a third of the cases of penile PG describe a concomitant systemic disease typically HIV, ulcerative colitis, leukemia, or carcinoma. Despite there being several treatment options, Table 1, first line treatment for the classical form of PG is systemic corticosteroids.[2,3,5] Treatment regimens described varied significantly, demonstrating the lack of uniformity in treatment for this rare entity. The majority of cases were treated with systemic corticosteroids, at times in conjunction with a second immunosuppressant.[9-12] Our case is the first reported to use Methotrexate in combination with systemic steroids in the case of penile PG, and given the patient's full response to treatment, we introduce another potential therapeutic option.

This case represents, by our review of the literature, a particularly destructive form of PG that was difficult to diagnose due to its lack of systemic associations and the rarity of penile PG. Although the ulceration resolved following treatment with steroids and methotrexate, the patient suffered severe penile shortening and obliteration of his urethral meatus. Most practicing urologists will be unfamiliar with this

clinical condition, which highlights the need for further study and information in the medical literature.

As demonstrated, PG can be aggressive, resulting in severe morbidity. In cases that are resistant to local or topical therapy, we recommend a regimen of systemic corticosteroids and an additional immunosuppressive medication. Options include Azathioprine, Cyclosporine and Methotrexate. It is important to first rule out underlying infection and/or malignancy, and then once placed on these medications closely monitor patients for adverse effects as these medications could worsen infection or malignancy.[3,8]

Our case highlights the critical importance of early recognition. His extensive work up, including multiple biopsies and several referrals spanning over more than 2 years, did not reveal any autoimmune or infectious etiology. Local measures did not adequately treat the lesion and as the ulcer progressed, so did his inability to urinate secondary to worsening meatal stenosis. In addition, he experienced significant retraction of the penile shaft, limiting his sexual function. Following diagnosis, his disease progression was successfully halted with systemic therapy in the form of steroids and Methotrexate, however the extent of damage to the patient's distal urethra and penile shaft appear irreversible. Thus, perhaps the most important aspect of the PG disease process to recognize is progression of the disease with each successive surgical procedure or biopsy. Unfortunately, all of these steps were necessary to make the diagnosis in this case, however, with more awareness of the pathognomonic aspects of the disease, it is our hope that the next urologist to encounter this rare disease will be able to make the diagnosis with fewer surgical interventions and less disease progression from initial presentation.

Here we present a case of an isolated penile PG resulting in severe penile scarring and deformity. Urologists should initially rule out infectious and malignant etiologies for ulcerative lesions of the penis. If no evidence of either is found, a work up for concomitant systemic autoimmune disease and referral to dermatology should initiated. If the ulceration appears to worsen with successive biopsies or surgical interventions a diagnosis of PD must be considered. In most cases, the first line treatment consists of a systemic steroid with or without an additional oral immunosuppressant. □

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