Refractory bilateral scrotal ulcers with numerous IgG4-positive plasma cells: Another skin location for IgG4-related sclerosing disease

Jaclyn L Jerz, Jae Y Ro, Alberto G Ayala

ABSTRACT

Introduction: Immunoglobulin G4-related sclerosing disease (IgG4-RSD) is an emerging diagnosis characterized by mass-forming inflammation which responds to corticosteroids. Cases have been reported in virtually every organ, however, skin cases are rare and tend to involve the head and neck region.

Case Report: An 85-year-old male presented with painful, bilateral, non-healing scrotal ulcers refractory to treatment with antibiotics and creams. On examination, he was found to have multiple large, purulent, stage three scrotal ulcers. He was admitted for administration of broad-spectrum antibiotics, but the cultures of the ulcer discharge grew normal, non-pathogenic skin flora. Dermatology was consulted for evaluation of other non-infectious etiologies for the ulcers’ failure to heal. A shave biopsy showed 50% IgG4-positive plasma cells, and light-chain in situ hybridization studies demonstrated polyclonality. The patient's serum IgG4 was elevated to 115 mg/dL (reference range 7–89 mg/dL), and he had an unclear remote history of Whipple surgery. The patient was discharged home with topical clobetasol (a synthetic corticosteroid) and required no follow-up for the ulcers.

Conclusion: IgG4-RSD includes a variety of disease entities and may manifest as diffuse or solitary inflammatory mass lesions. Older males are affected most often overall. The diagnosis is made on histopathology with >40% IgG4-positive plasma cells, fibrosclerosis, and obliterative phlebitis, regardless of organ. Elevated serum levels of IgG4 are markers of disease, but not required for diagnosis. Given the patient's histologic findings and laboratory results, this case is likely the first report of IgG4-RSD in scrotal skin.
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Keywords: IgG4, Sclerosing disease, Pseudolymphoma, Corticosteroids

INTRODUCTION

Immunoglobulin G4-related sclerosing disease (IgG4-RSD) is a systemic autoimmune inflammatory process. The characteristic tumorous lesions may be solitary or diffuse. The diagnosis is made based on the morphologic findings. The major histologic features are a dense...
lymphoplasmacytic infiltrate, fibrosclerosis (storiform pattern), and obliterative phlebitis; the first two features are seen more frequently. An increased number of IgG4-positive plasma cells is also required, however, the reported numeric cutoffs vary by organ and degree of fibrosis [1].

IgG4-RSD has been reported in virtually every organ, but skin lesions are rare. Since a scrotal presentation has not been reported, our purpose is to describe the clinicopathologic aspects of this case.

CASE REPORT

An 85-year-old male was presented to the emergency department from his nursing home with a two-month history of bilateral, painful scrotal ulcers. His wife reported mild mental status changes during this time, but there were no other associated localized or systemic symptoms. He had been treating the ulcers at home with an unknown antibiotic and topical ointment.

The patient had multiple medical problems including hypertension, diabetes, peripheral vascular disease, and prior cerebrovascular accidents. He had undergone a below-knee amputation for gangrene and recent hip surgery after a fall, which rendered him bedridden. He was incontinent of urine and wore a diaper, which was often wet. He was taking lisinopril 40 mg, acetaminophen 325 mg, furosemide 80 mg, naproxen 375 mg, amlodipine 10 mg, citalopram 40 mg, aspirin 81 mg, and potassium-chloride 8 mg daily, metoprolol 50 mg twice daily, and pancrelipase three times daily with meals. The patient was also taking doxycycline 100 mg daily for chronic lung disease.

Physical examination showed a normal white blood cell count of 10.9x10^4/µL, with a normal differential. The patient’s creatinine was elevated to 2.0 mg/dL. Urine analysis showed 1+ protein, 10 to 15 white blood cells per microliter, and large leukocyte esterase. The patient received a dose of levofloxacin in the emergency department for his presumed urinary tract infection, and he was admitted for more aggressive treatment of his ulcers and further work-up.

The patient began receiving broad-spectrum intravenous antibiotics (vancomycin and cefepime), and the wound care specialty team was consulted for assistance. Dermatology was consulted on hospital day 1 for evaluation of other possible etiologies for the non-healing scrotal ulcers. The dermatologist’s differential diagnosis included infectious (bacterial, viral, fungal, mycobacterial, and sexually-transmitted), malignant (squamous cell carcinoma), and systemic-disease related (pyoderma gangrenosum) causes, however, she felt that the most likely explanation was ongoing skin irritation and maceration from soiled diapers. She sent ulcer tissue for culture (negative), ordered tests for sexually transmitted infections (negative), and performed a shave biopsy to rule-out malignancy (Figure 1). Formalin-fixed, paraffin-embedded tissue sections stained with hematoxylin and eosin were examined and showed full-thickness loss of epidermis, with dermal fibrosis and a band-like inflammatory infiltrate. The inflammation was composed almost entirely of plasma cells (Figure 2). Special periodic acid-Schiff (PAS) staining was negative for micro-organisms. Immunohistochemistry showed numerous IgG4-positive plasma cells (approximately 50% of total plasma cells seen) (Figure 3). In situ hybridization studies for kappa and lambda light-chains demonstrated a polyclonal phenotype.

The patient’s initial urine culture grew low-titers of Proteus mirabilis and Enterococcus. The culture of the drainage from the patient’s scrotal ulcers grew Proteus mirabilis, Enterococcus, and multi-drug resistant Acinetobacter baumannii or Acinetobacter calcoaceticus complex management is discussed below. The patient’s initial broad-spectrum antibiotics regimen was tapered, and many of the remaining medicines were switched to

Figure 1: Biopsy of a scrotal skin ulcer with underlying, band-like chronic inflammation (H&E stain, x400).
oral equivalents. An infectious disease (ID) consultation was requested for assistance with managing the patient’s multiple infections with multiple multidrug-resistant organisms. The specialist saw the patient on hospital day 6. He noted that the Proteus and Acinetobacter in the scrotal ulcers was normal, non-pathogenic skin flora and did not require antibiotics. Based on his experience with similar wounds, the ulcers would require topical wound care and significant time. The consultant also felt that the sample sent for urine culture which grew Proteus and Enterococcus was contaminated. It had been a voided specimen, and there was only a low-titer of organism growth. The ID consultant recommended discontinuation of all antibiotics, except doxycycline for the patient’s chronic MRSA.

The patient’s scrotal ulcers remained stable after the antibiotics were discontinued. Around the time of discharge, the pathologist interpreting the skin biopsy discussed the possibility of IgG4-RSD with the dermatologist, and serum total IgG and IgG1-4 subclass levels were ordered; both were elevated. The total IgG was 1530 mg/dL (reference range 696–1488 mg/dL) and IgG4 was 115 mg/dL (reference range 7–89 mg/dL). The remaining three IgG subclass levels were within normal limits. Based on the combined results, the dermatologist recommended two-weeks of 0.05% Temovate® (clobetasol propionate) ointment, a synthetic corticosteroid with high glucocorticoid activity and some mineralocorticoid activity.

On hospital day 8, the ulcers had no drainage, and were subjectively less painful. The patient was able to be discharged to a skilled nursing facility with wound care instructions and Temovate®. He was told to follow-up with dermatology if the ulcers had not healed within two weeks, and has never made a follow-up appointment.

DISCUSSION

The patient’s histologic and immunohistochemical findings, combined with his elevated serum total IgG and IgG4 levels, support a diagnosis of IgG4-related sclerosing disease. To our knowledge, this case is the first report of IgG4-RSD in scrotal skin.

IgG4-RSD was first described by Hamano et al. in 2001, and was initially recognized as a cause of autoimmune pancreatitis in the presence of elevated levels of serum IgG4 [2]. The characteristic lesions of IgG4-RSD encompass a wide range of diagnoses: chronic sclerosing sialadenitis [3], Mikulicz’s disease in the lacrimal gland [4], retroperitoneal fibrosis [5], and tubulointerstitial nephritis [6]. There are far fewer reports of IgG4-RSD in skin, and cases tend to involve the head and neck region [7]. The skin lesions present clinically as plaques or nodules and can be seen in isolation or in the context of systemic disease [8]. Differentiating IgG4-RSD of the skin from other causes of pseudolymphoma-type lesions, such as Rosai Dorfman and angiolymphoid hyperplasia with eosinophilia, is important for treatment reasons, as IgG4-RSD responds dramatically to corticosteroids [1].

The diagnosis of IgG4-RSD requires a dense, IgG4-positive lymphoplasmacytic infiltrate on histology. The inflammation is often accompanied by storiform fibrosis and obliterator phlebitis. The number of Ig4-positive plasma cells specific for IgG4-RSD has been studied for type 1 autoimmune pancreatitis, and ranges from >10/high-power field (HPF) on biopsies to >50/HPF in resection specimens. However, cutoffs are thought to depend on the organ and degree of fibrosis. A more powerful quantitative measure is the IgG4+:IgG+ plasma cell ratio; >40% has been proposed as a comprehensive cutoff value for any organ. Serum IgG4 levels are often,
but not always, elevated, and abnormal serology is not required for the diagnosis. If the histology shows possible, but not definitive, IgG4-RSD, then additional clinical, serologic, or radiologic evidence is needed to confirm the diagnosis. A serum level of IgG4 >135 mg/dL supports the diagnosis of IgG4-RSD [1].

CONCLUSION

This case represents the first report of IgG4-RSD in scrotal skin, and it is likely that the ulcers are a localized set of IgG4-positive lesions, without underlying systemic disease. Although the reason for the patient’s remote Whipple procedure is not clear, the surgery does not seem to have been performed for autoimmune pancreatitis. The patient’s left hip surgical wound is known to be chronically infected with methicillin-resistant Staphylococcus aureus (MRSA), and his sacral decubitus ulcers are unlikely to be IgG4-positive, given his bedridden condition.

Author Contributions

Jaclyn L Jerz – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Jae Y Ro – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Alberto G Ayala – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.
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