



IgG4 Related Disease of Epididymis, Mimicking Testicular Malignancy – A Rare Entity

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Abstract Immunoglobulin G4 related disease (IgG4-RD) is a systemic fibro inflammatory condition that usually presents with multiorgan involvement. We present a rare case of 54 year old male with an isolated IgG4-RD of epididymis. The patient presented with a progressive swelling of the left testicle. A clinical diagnosis of tuberculosis was made. Ultrasound scrotum showed a relatively hetero-echoic mass lesion involving the left epididymis in close proximity to the left testis. There was a focal spindle cell proliferation and an increase in number of plasma cells and keloid like collagen. Immunohistochemistry was positive for vimentin and IgG4 and negative for CD34. Serum level of IgG4 was elevated (165 mg per dL). Computed tomography of abdomen and thorax did not show any systemic involvement. HE was posted for excision of the epididymal mass. Intraoperatively, the mass was found to be densely adherent to left testicle and inseparable from it, necessitating left total orchiectomy. Histopathology and immunohistochemistry with elevated serum IgG4 levels confirmed the diagnosis of IgG4-RD of the epididymis. To the best of our knowledge, this condition is an extremely rare entity, with only very few cases of isolated IgG4-RD of epididymis reported in medical literature, with no other systemic manifestations.

Key words IgG4, epididymal mass, tuberculosis, orchiectomy, plasma cell

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Introduction

IgG4-related disease (IgG4-RD) is a rare fibrous and inflammatory disease that comprises of a dense lymphocytic and plasma cell infiltrate with abundance of IgG4 positive plasma cells [1]. A dense fibrosis with focal storiform pattern is characteristic of this entity. This condition typically produces a mass lesion that affects various parts of the body with multiorgan involvement. Serum IgG4 levels are found to be elevated in this condition [2].

IgG4-RD was originally reported to occur in the pancreas, as part of auto-immune pancreatitis. Various literature evidences mention about the disease involving multiple organs in the body. The organ systems include salivary glands, periorbital tissues, biliary system, lymph nodes, kidneys, aorta, mesenteric soft tissue, thyroid gland, lungs, meninges, breast, prostate, and skin [3]. The genitourinary system comprising of the kidneys, ureters, urinary bladder, urethra, prostate gland, testes and penis is one of the multiple organ systems to be affected by IgG4-RD [4]. Involvement of epididymis is uncommon compared to kidney, ureter, bladder and prostate [5]. We report one such entity, where an isolated epididymal IgG4 disease was treated with total orchiectomy.

Case report

A 54 year old male presented with painless mass over the lower aspect of left hemiscrotum for the past one month. The mass was distinctly separate from the left testis, but was densely adherent to it, with a granulomatous discharging sinus at the bottom of scrotum. A clinical diagnosis of left epididymal mass was made (**Figure 1A**). He also had a low grade fever, more in the late evenings along with loss of weight. He had lost about 8 kg in the past two months. On evaluation, there was moderate leukocytosis with a total leucocyte count of 14,500 cells/mL with predominant lymphocytosis. The scrotal skin over the site of swelling was normal. A clinical diagnosis of left epididymal tuberculosis was made. The ultrasound of scrotum showed a heteroechoic lesion involving the left epididymis and the mass was seen in close proximity to left testis.

A wide local excision of the epididymal mass was planned. Intraoperatively, the mass was found to be densely adherent to the testis and inseparable from it, necessitating left total orchiectomy (**Figure 1B**). The histopathological report was suggestive of extensive atrophy with infarction of epididymal tissue (**Figure 1C**). Focal spindle cell proliferation and increase in number of plasma cells and keloid like collagen (**Figure 2A & Figure 2B**) were the hallmark findings. In Immunohistochemistry (IHC), the inflammatory cells were positive for vimentin and IgG4 (**Figure 3A & Figure 3B**). CD34 was negative (**Figure 3C**). IHC demonstrated 55 IgG4 positive plasma cells per high power

field. Serum level of IgG4 was elevated to 165 mg/dL (normal range: 8 – 140 mg/dL). Contrast enhanced computed tomography (CT) of thorax, abdomen and pelvis did not show any systemic involvement.

Discussion

IgG4-RD is a newly diagnosed fibro inflammatory, immune mediated condition with unknown etiology. It is predominantly a systemic disorder with multiorgan involvement but also present with isolated organ involvement. This entity links many conditions that were once regarded as isolated single organ diseases, without any systemic involvement, and often compared to a “black crow flying through the dark night” [6]. This disease closely simulates sarcoidosis and various forms of vasculitis. This condition has now been described in virtually every organ system: the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium and skin [7]. The two features considered to be hallmark of the disease include the characteristic histopathological appearance and an elevated number of IgG4 plasma cells in the tissue. The serum IgG4 concentration is elevated in many patients but may be normal in up to 40% of patients with biopsy-proven IgG4-related disease [8].

The three major histopathological features associated with IgG4-related disease are dense lymphoplasmacytic infiltrate, fibrosis arranged at least focally in a storiform pattern and obliterative phlebitis. The other histopathological features associated with IgG4-RD are phlebitis without obliteration of the lumen and increased numbers of eosinophil count [9]. A pathological diagnosis of IgG4-related disease requires the presence of two of the three major histological features. In the majority of cases, these include a dense lymphoplasmacytic infiltrate and storiform-type fibrosis [10]. It is characterized by organ enlargement or nodular/hyperplastic lesions in multiple organs synchronously or metachronously due to marked infiltration of lymphocytes and IgG4 positive plasma cells and fibrosis [11-14]. This disease most commonly seen in middle aged men and elderly individuals. In the genitourinary tract, there has only been one previous case of isolated primary testicular IgG4-RD ever reported [15].

The gold standard for diagnosis of IgG4-RD regardless of the organ involved is by the histological features such as rich lymphoplasmacytic infiltration, storiform fibrosis with significant IgG4 plasma cell infiltrate & obliterative phlebitis, elevated serum IgG4 (> 135 mg/dL), IgG4/IgG ratio > 0.4 and more than 50 IgG4 cells per HPF. Normal IgG concentrations in many patients are nowadays reported, even in the setting of biopsy proven disease [16]. The clinical significance of the IgG4 antibody in pathogenesis of the disease however remains unclear [17].

The optimal treatment for IgG4-RD is not being established.



Figure 1. Gross and micro photograph of the left testicular mass and the excised specimen. **A:** Gross photograph left epididymal mass; **B:** Orchidectomy specimen with removal of epididymal mass with left testicle; **C:** Epididymis (red arrow) surrounded by dense lymphoplasmacytic in filtration. H & E stain, 100 X.

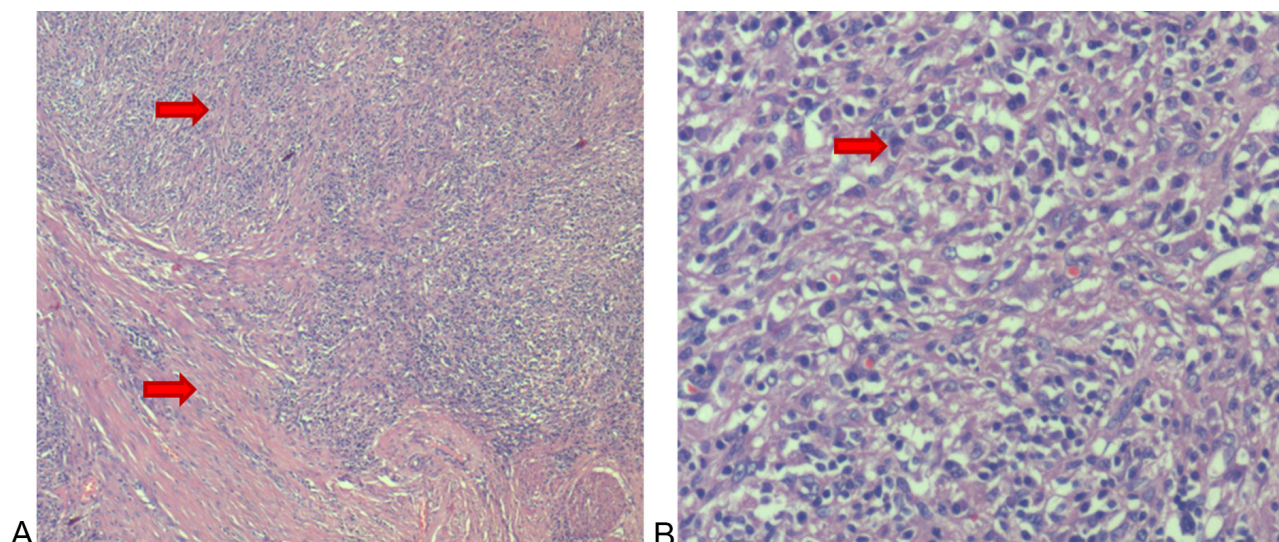


Figure 2. Hallmark histological findings in H&E stain in IgG4 disease of Epididymis. **A:** Keloid like dense collagen (lower arrow) & plasma cells (upper arrow). H & E stain 100 X; **B:** Plasma cells(arrow) with eccentric nuclei and peri-nuclear halo. H & E stain, 400 X.

Prednisone 40 mg per day for 2 - 4 weeks is the first line agent for IgG4-RD. A few retrospective case series on use of azathioprine, methotrexate and mycophenolate mofetil as second line agents are available, but until more effective and safer therapies are tested in clinical trials, glucocorticoids should remain the first-line therapy for patients with IgG4-RD [18]. Risk of malignancy increased in organs involved by IgG4-RD requiring further study.

Conclusions

IgG4-RD is an emerging clinical condition that consists of various pathological features that affect various organs in the body. As the condition is a potentially treatable one, an awareness of this rare entity would enable the clinicians diagnose the condition at an earlier stage and treat it appropriately. Since elevated serum and tissue levels of IgG4 are not specific for the disease, the diagnosis of such rarer condition would require an effective communication between the pathologist and the treating physician. The diagnosis of IgG4-RD rests on the combined presence of the characteristic histopathological appearance with increased numbers of IgG4 positive plasma cells.

A greater cognizance of this rare disease in the medical fraternity largely helps in an earlier detection of IgG4-RD. Furthermore, it

is necessary to identify more reliable biomarkers than the existing serum IgG4 levels for an effective diagnosis of this rare condition.

The spectrum of this disease continues to expand. There is a growing need for encouraging strict use of criteria for including newer entities as components of this relatively newer and often under reported IgG4-RD spectrum. Awareness and knowledge of the immune dysregulation associated with IgG4-RD helps us to understand and treat the disease better.

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Ethics approval and consent to participate

Written informed consent was obtained from patients for the use of their biological samples for research purposes. This case report has been performed in accordance with the Declaration of Helsinki.

Author contributions

All authors have contributed to the article, including writing the manuscript, preparing the microphotographs, preparing immune

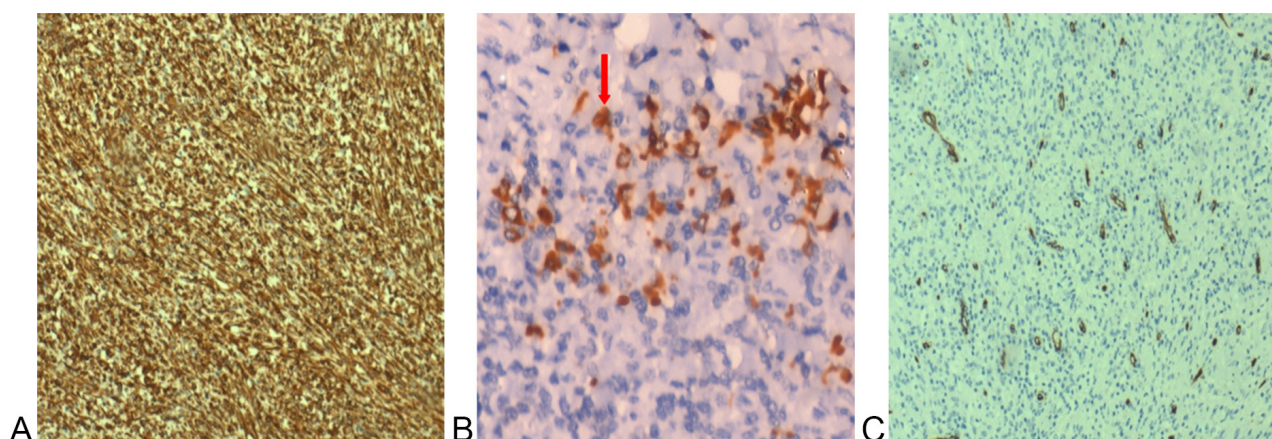


Figure 3. Immuno histo-chemistry findings of IgG4 disease of Epididymis. **A:** Lesional cells are diffusely positive for vimentin. Vimentin IHC, 100 X; **B:** Many plasma cells are stained with IgG4 immunostain (red arrow). > 50 IgG4 positive plasma cells/HPF and IgG4/IgG ratio > 40%. IgG4 IHC, 400 X; **C:** Lesional cells are negative for CD 34 with background blood vessels staining positive. CD34 IHC, 100 X.

histo-chemistry and final proof reading.

Competing interests

The authors declare no conflict of interest with the work.

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