Case Report

Rare case of immunoglobulin G4-related disease arising in gonadal glands with long-term remission without steroid treatment: Discussion and literature review

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Abbreviations & Acronyms
AIP = autoimmune pancreatitis
IgG4-RD = immunoglobulin G4-related disease
MRI = magnetic resonance imaging
RPF = retroperitoneal fibrosis
TURP = transurethral resection of the prostate

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Introduction: Immunoglobulin G4-related disease embraces a wide range of extra-pancreatic manifestations. However, localized pathogenesis in gonadal glands, including testes or seminal vesicles, is rare. The clinical course and therapeutic strategy for this disease have not been clearly characterized.

Case presentation: A 61-year-old Asian male had a left orchiectomy and right seminal vesicle biopsy because of a mass in the left testis and right seminal vesicle. Histological findings showed an infiltration of immunoglobulin G4-positive plasma cells in the respective tissues and met immunoglobulin G4-related disease diagnostic criteria. No recurrence and exacerbation have been observed after 12 years' follow-up without any clinical intervention. To date, immunoglobulin G4-related disease in gonadal tissue is rare. This is the first case with mass-forming lesions in both the testis and seminal vesicle.

Conclusion: Based on the clinical course of our case and the literature, for patients with accurately diagnosed inactive gonadal immunoglobulin G4-related disease, watchful waiting is a feasible clinical treatment option.

Key words: IgG4-related disease, malignant lymphoma, scrotal mass, seminal vesicle, testis.

Keynote message

IgG4-RD localized in gonadal glands involving simultaneously the testis and contralateral seminal vesicle is rare. Watchful waiting after an accurate diagnosis is an alternative option in cases with slight symptoms or without dysfunctional organs.

Introduction

IgG4-RD is a systemic fibroinflammatory autoimmune disorder involving invasion by IgG4-positive plasma cells of various organs. Single-organ manifestations of IgG4-RD mainly localize to the pancreas and salivary glands. Gonadal gland cases are rare. Information on clinical course and imaging characteristics is limited, with no established strategy for remnant disease after a pathological diagnosis. Herein, we describe an IgG4-RD case with a mass-forming lesion and suspected malignant disease in the left testis and right seminal vesicle.

This study was approved by the Nagoya City University Graduate School of Medical Sciences Institutional Review Board (#60-20-0040). Written informed consent was obtained from the patient for publication of this article and accompanying images.

Case presentation

A 61-year-old Asian male presented to our department with painful left scrotal swelling and pain on urination. He had no medical history and was not taking medication. On physical examination, he had a tender, egg-sized left scrotum but no fever. Blood examination revealed

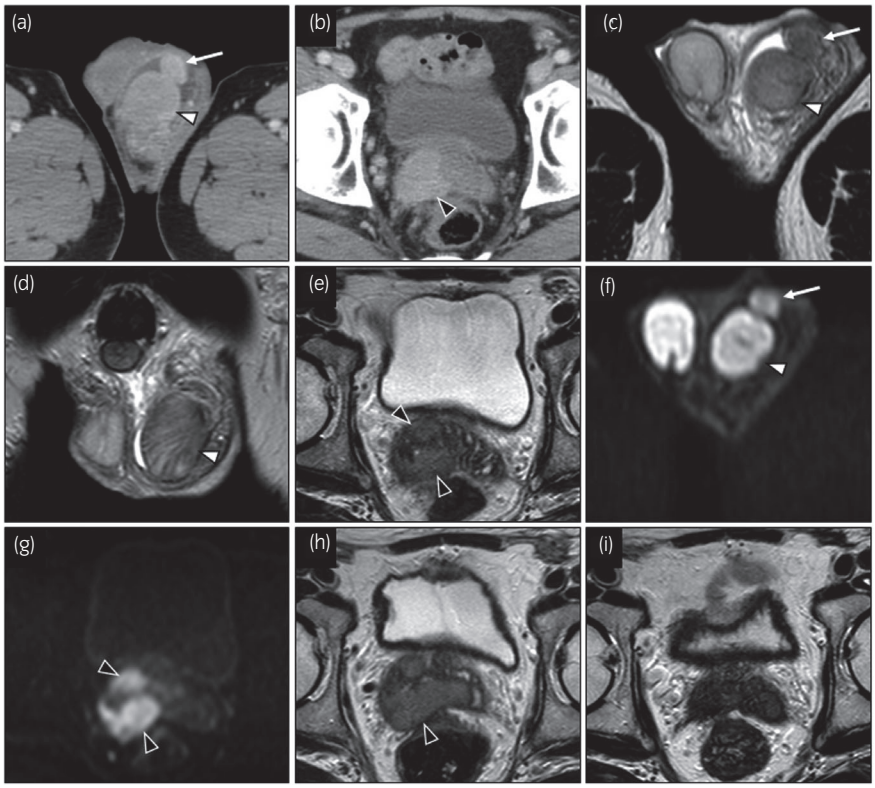

Fig. 1 Contrast-enhanced computed tomography showed swelling of the left testis (a) (white arrowhead), epididymis (a) (white arrow), and the right seminal vesicle (b) (black arrowhead) with an increase in the contrast enhancement. There was fluid collection in the scrotal mass. MRI showed a diffuse signal reduction in the left testis with multiple linear hypointense structures. Hypointense nodules in the left epididymis (c,d) and an intermediate-intensity mass in the right seminal vesicle (e,h) on T2-weighted images were found. The mass in the left epididymis (f) and right seminal vesicle (g) demonstrated diffusion restriction. The mass in the seminal vesicle disappeared after a left orchiectomy (i).

high levels of white blood cells (14 300/μL; normal range 3300–8500) and C-reactive protein (15.50 mg/dL; normal range <0.5). Urine analysis revealed pyuria and bacteriuria. Contrast-enhanced computed tomography showed swelling of the left testis, epididymis, and right seminal vesicle with an increase in contrast enhancement (Fig. 1a,b). Fluid had collected around the scrotal mass. MRI showed a diffuse signal reduction in the left testis with multiple linear hypointense structures, hypointense nodules in the left epididymis, and an intermediate-intensity mass in the right seminal vesicle on T2-weighted images (Fig. 1c–e). The mass in the left epididymis and right seminal vesicle demonstrated diffusion restriction (Fig. 1f,g). An acute bacterial infection in the epididymis was diagnosed and oral antibiotics (levofloxacin 500 mg/day) administered. Urine culture was positive for *Escherichia coli*. After 7 days' treatment, the patient's general condition and inflammatory status improved. Serum tumor markers, including lactate dehydrogenase, α-fetoprotein, human chorionic gonadotropin β subunit, and prostate-specific antigen, the erythrocyte sedimentation rate, and soluble interleukin-2 level, were within normal levels. However, since the scrotal swelling was persistent, MRI was repeated 11 days after the initial examination. Compared with the prior image, the right seminal vesicle mass was enlarged. The signal intensities of the testis and epididymis remained unchanged (Fig. 1h). Therefore, in spite of negative testicular tumor markers, we suspected a malignant testicular tumor, specifically, seminoma or malignant lymphoma. A histopathological examination was consequently suggested to the patient. After informed consent, an immediate left orchidectomy and right seminal vesicle biopsy were performed (Fig. 2a). Histopathological examination revealed infiltrating inflammatory cells of extensive lymphocytes and plasma cells, as well as diffuse fibrosis with a focal storiform pattern in the testis (Fig. 2b–d). Due to severe inflammation and fibrosis, seminiferous tubules were atrophied and degenerated; atypical cells were not found. Immunohistochemical examination detected abundant CD^{138+} and CD^{3-}, CD^{20-} plasma cells (Fig. 2e–g). IgG4 and IgG immunostaining revealed IgG4-positive cells among IgG-positive plasma cells. IgG4-positive/IgG-positive plasma cells were over 50% in both the left testis and right seminal vesicle (Fig. 2h,i). After surgery, high levels of serum IgG (1940 mg/dL) and IgG4 (142 mg/dL) were observed, although rheumatoid factor and antinuclear antibody were within normal range. The final diagnosis was IgG4-RD arising in the gonadal gland. Slight discomfort in pelvis persisted after surgical treatment; however, the symptom was gradually improved as time advances. When the patient's symptoms completely resolved, serum IgG and IgG4 levels became normal (Fig. 3). MRI revealed the mass in the right seminal vesicle became reduced after surgical treatment without further medication (Fig. 1i). The patient has now been in remission for over 10 years.

Discussion

IgG4-RD is an immune-mediated systematic fibroinflammatory disease, most frequently localizing to the pancreas and salivary glands that shows multi-organ involvement in the middle-aged to the elderly people. Inoue *et al.* reported data on 235 consecutive patients with IgG4-RD from eight general hospitals in Japan: of 486 total cases, 60% presented with pancreatitis, 34% with sialadenitis, 23% with tubulointerstitial nephritis, 23% with dacryoadenitis, and 20% with

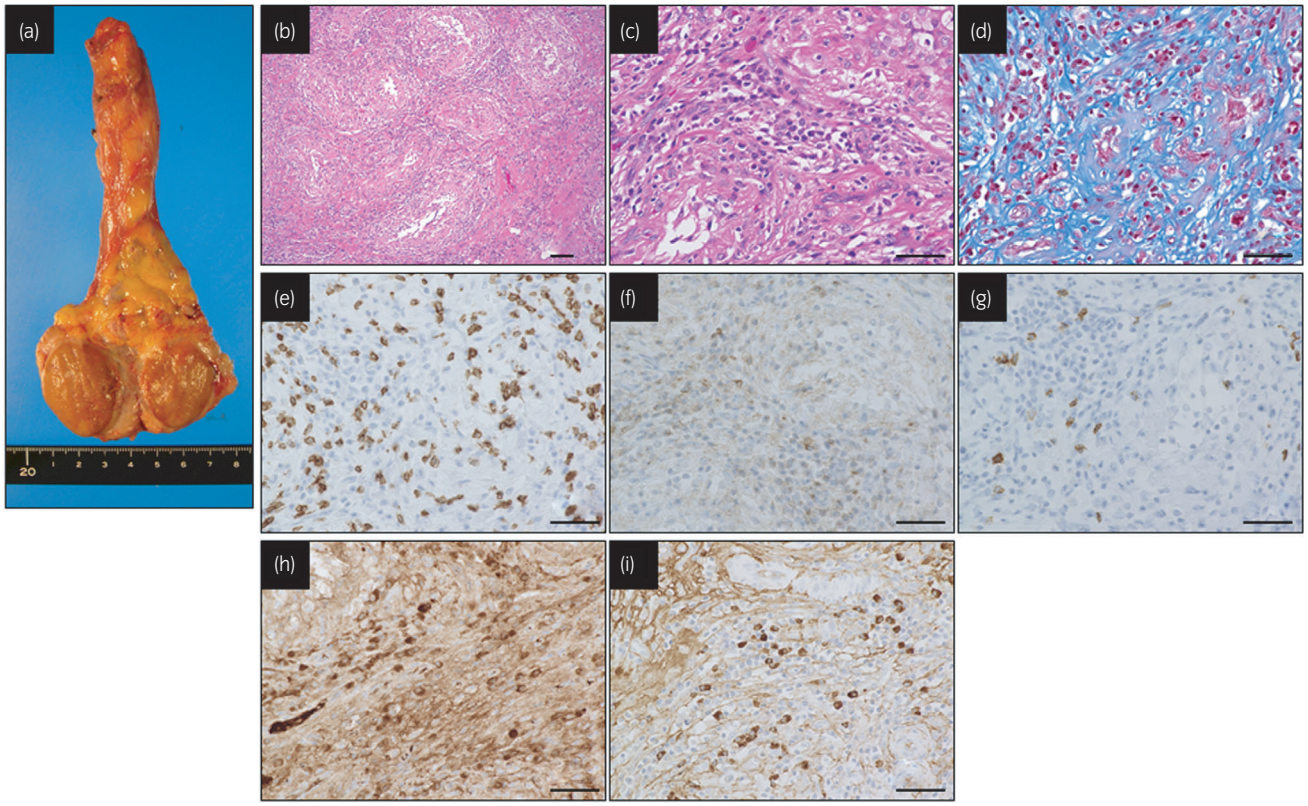

Fig. 2 Macroscopic findings of a left orchidectomy specimen (a). A yellowish mass-like lesion was seen in the left epididymis and testis. Hematoxylin–eosin staining of the specimen (b,c) revealed an infiltration of inflammatory cells that consisted of an extensive number of lymphocytes and plasma cells, as well as diffuse fibrosis with a focal storiform pattern in the testis. Masson's trichrome staining (d) showed a storiform fibrosis and infiltration of plasma cells and lymphocytes. Immunohistochemical examination detected abundant plasma cells that were CD^{138+} (e), and CD^{3-} (f) and CD^{20-} (g). Immunostaining for IgG (h) and IgG4 (i) showed IgG4-positive cells among IgG-positive plasma cells. The ratio of IgG4-positive to IgG-positive plasma cells was over 50% in both the left testis and right seminal vesicle.

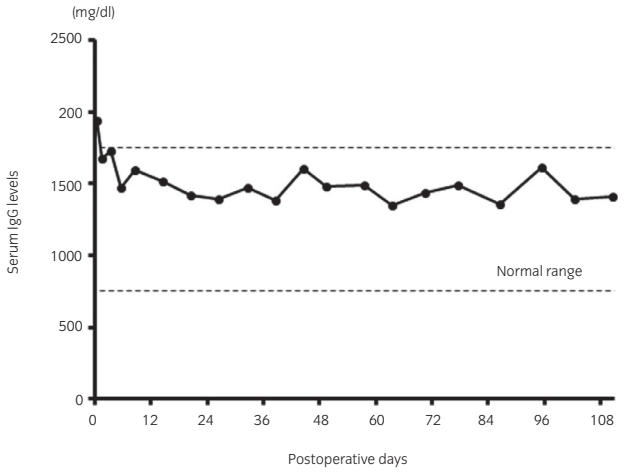

Fig. 3 Transition of serum IgG levels after orchidectomy. Post-surgery, the serum IgG level immediately decreased to normal range and no exacerbation has been observed to date.

periaortitis.[1] Most patients had at least one of the five common disease characteristics. Therefore, disease localization to the gonadal glands, including the testis, seminal vesicle, and prostate, is rare. Only two IgG4-RD cases with testicular involvement, and one case of seminal vesicle involvement, have been described.[2–4] This is the first report of IgG4-RD in gonadal glands involving a testis and contralateral seminal vesicle simultaneously.

An accurate diagnosis of IgG4-RD requires histopathological proof. Several reports outline how patients with IgG4-RD tend to have increased malignancies.[5] Because in our case the patient was elderly and testicular tumors are common at over 60 years of age, a testicular germ cell tumor or malignant lymphoma involving the testis should have been suspected.[6] Distinguishing IgG4-RD with testicular involvement from malignant lymphoma localized only in the testis as extranodal involvement is difficult using imaging tests. In MRI, used to diagnose testicular malignancies, both such tumors might show iso-intensity on T1-weighted images and low-intensity on T2-weighted images. We have summarized the reports of IgG4-RD involvement in gonadal glands in Table 1. In all cases involving the testis or tunica vaginalis, as in our case, orchiectomy was performed according to the definition for pathological findings. Considering the concomitant of malignancy, a pathological diagnosis by orchiectomy should be performed for an accurate diagnosis.

IgG4-RD in vital organs, such as the pancreas and kidney, can cause irreversible damage within months, even in asymptomatic cases. Immediate induction treatments have been recommended, with glucocorticoids widely recognized as the

Table 1 Summary and characteristics of previous cases of IgG4-RD arising in gonadal tissues

No.	Age	Involved site of IgG4-RD	Past medical history related to IgG4-RD	Lower urinary tract symptoms	Elevation of serum IgG4	Method used for histopathological findings	Steroid treatment
1	57	Bilateral testis	AIP, RPF	No	Not tested	Bilateral orchiectomy	Not treated
2	35	Right testis	None	No	No	Right orchiectomy	Not treated
3	73	Right tunica vaginalis	AIP, RPF	No	Yes	Right orchiectomy	Not treated
4	72	Right tunica vaginalis	RPF	No	Yes	Right orchiectomy	Not treated
5	41	Right tunica vaginalis	None	No	Not tested	Right orchiectomy	Not treated
6	28	Right spermatic cord	None	No	Not tested	Local excision	Not treated
7	19	Right spermatic cord	None	No	Not tested	Local excision	Not treated
8	69	Prostate	AIP	Yes	No	TURP	Yes
9	39	Prostate	AIP	Yes	Yes	Not obtained	Yes
10	67	Prostate	AIP	Yes	Yes	Not obtained	Yes
11	69	Prostate	AIP	Yes	No	TURP	Not treated
12	64	Prostate	AIP	Yes	Yes	TURP	Not treated
13	74	Prostate	AIP	Yes	Yes	Prostatectomy	Not treated
14	67	Prostate	AIP	Yes	Yes	TURP	Not treated
15	63	Prostate	AIP	Yes	No	Needle biopsy	Not treated
16	74	Prostate	AIP	Yes	Yes	TURP	Not treated
17	72	Prostate	AIP	Yes	Yes	Needle biopsy	Not treated
18	64	Prostate	AIP	No	Yes	Needle biopsy	Yes
19	67	Prostate	None	Yes	Yes	TURP	Not treated
20	71	Prostate	None	Yes	Yes	Needle biopsy	Not treated
21	74	Prostate	AIP	Yes	Yes	Needle biopsy	Yes
22	61	Prostate	AIP	Yes	No	TURP	Not treated

first-line of systemic therapy. However, watchful waiting with prudent follow-up is an alternative option to be considered in patients with slight symptoms or no vital organ dysfunction, as in our case.[7]

The patient's initial antibiotic treatment was administered for left epididymitis; however, a mass-like lesion in the left testis and right seminal vesicle remained. A left orchiectomy and right seminal vesicle biopsy were conducted to rule out malignancy. Post-surgery, the patient had no symptoms, and serum IgG and IgG4 levels returned to normal. An MRI revealed a reduction of the mass in the right seminal vesicle without any further treatment. Novel lesions were not found. As shown in Table 1, most of the previous cases with gonadal gland involvement and slight or no symptoms did not use steroids even without the resectioning of a mass-like lesion. Considering the high incidence of adverse events induced by steroids, watchful waiting might be preferable for asymptomatic patients with IgG4-RD localized in gonadal glands. However, further investigation of this rare disease is required.

Conclusion

IgG4-RD localized in gonadal glands simultaneously involving the testis and contralateral seminal vesicle is rare. Watchful waiting after an accurate diagnosis might be preferable in cases with slight symptoms or without organ dysfunction.

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Conflict of interest

The authors declare no conflict of interest.

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