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Case Report

IgG4-related prostatitis progressed from localized IgG4-related lymphadenopathy

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Abstract: Immunoglobulin G4-related disease (IgG4-RD) is a recently described inflammatory disease involving multiple organs. Prostate involvement with IgG4-RD is very rare. In this report, we describe a case of IgG4-related prostatitis progressed from localized IgG4-related lymphadenopathy. This patient was present with urine retention symptoms. MRI and CT examination revealed the prostatic enlargement and the multiple lymphadenopathy. Serum IgG4 levels were elevated. Prostatic tissue samples resected both this time and less than 1 year earlier showed the same histological type of prostatitis with histopathologic and immunohistochemical findings characteristic of IgG4-RD. The right submandibular lymph nodes excised 2 years earlier were eventually proven to be follicular hyperplasia-type IgG4-related lymphadenopathy. This is the first case of IgG4-RD that began as localized IgG4-related lymphadenopathy and progressed into a systemic disease involving prostate and multiple lymph nodes. This patient showed a good response to steroid therapy. This leads us to advocate a novel pathogenesis of prostatitis, and a novel therapeutic approach against prostatitis. Pathologists and urologists should consider this disease entity in the patients with elevated serum IgG4 levels and the symptoms of prostatic hyperplasia to avoid ineffective medical or unnecessary surgical treatment.

Keywords: Prostatitis, IgG4, IgG4-related disease, IgG4-related prostatitis, IgG4-related lymphadenopathy

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently described spectrum of systemic diseases that is characterized by mass-forming lesions in affected organs with extensive lymphoplasmacytic infiltration, fibrosis or sclerosis, an increase of IgG4 positive plasma cells in the tissues involved, an elevated IgG4 serum level and a good response to steroid therapy. Currently, reported sites of involvement and disease associations are diverse and include sclerosing sialadenitis, lacrimal gland, ocular adnexa, pancreatitis, thyroid gland, pulmonary lesions, breast, liver, idiopathic retroperitoneal fibrosis, inflammatory aortic aneurysm, central nervous system, kidney, skin and lymph node [1, 2]. The lymph node involvement of IgG4-RD is a common finding. The histologic patterns may be subdivided into at least 5 histological subtypes, including multicentric Castleman disease-like morphology (type I), follicular hyperplasia (type II), interfollicular expansion (type III), progressive transformation of germinal center-like morphology (type IV), and inflammatory pseudotumor-like morphology (type V). IgG4-related lymphadenopathy may coexist with or follow, but also precede extranodal manifestations of the disease [3]. The latter is also recognized as primary IgG4-related lymphadenopathy, and it may progress to extranodal lesions or systemic disease during the clinical course. Recently, a few papers have described involvement of prostate in IgG4-RD.

We present a case of IgG4-related prostatitis progressed from localized IgG4-related lymphadenopathy, and this patient underwent the transurethral prostate resection for 2 times due to being misdiagnosed. Thus, it is important to recognize this new disease entity to avoid ineffective medical or unnecessary surgical treatment.

Case report

A 69-year-old man was admitted to the urological department of our hospital because of the

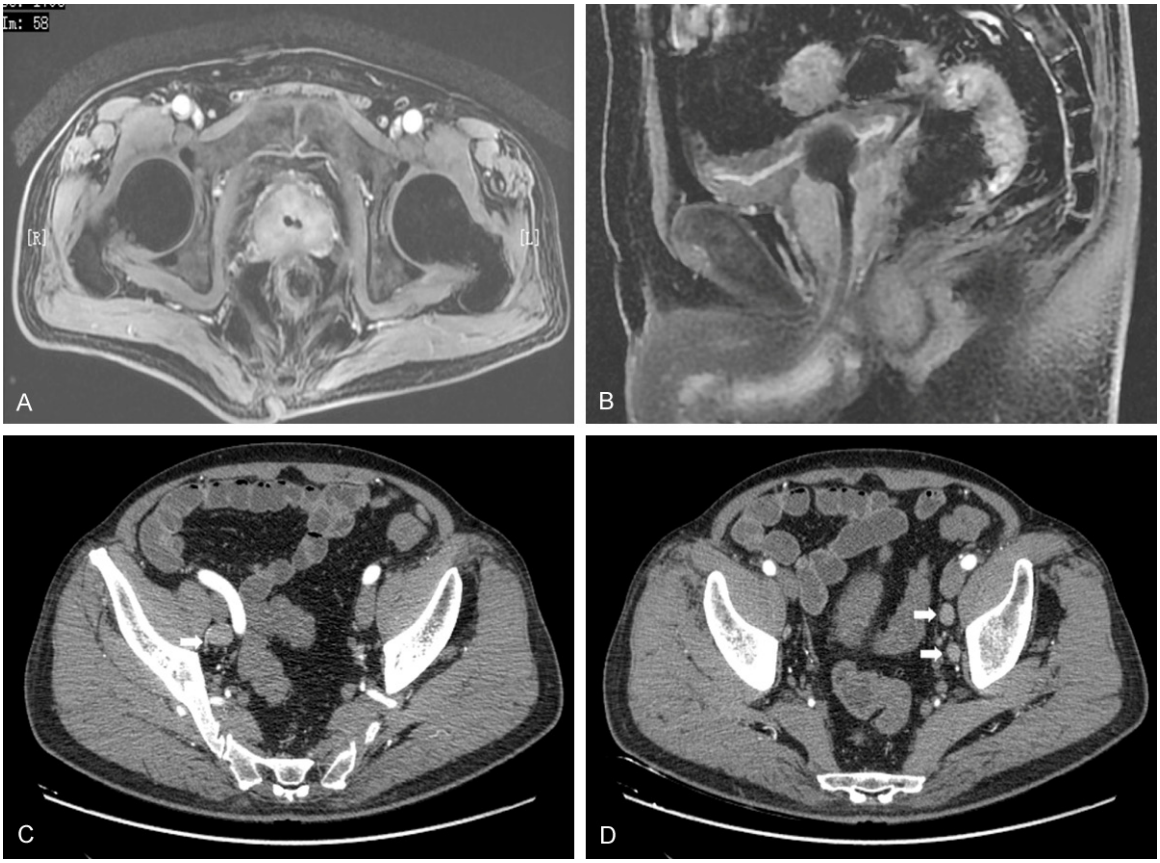

Figure 1. Abdominal magnetic resonance imaging revealed an enlarged prostate and the heterogenous enhancement on fat-suppressed contrast-enhanced T1-weighted imaging (A, B). Abdominal computed tomography showed multiple lymphadenopathy (arrow) whose sizes were approximately 1.2-1.8 cm (C, D).

urinary symptoms of urinary frequency, nocturia and urinary hesitancy for two months, with urgent urine retention for 24 hours. The digital rectal examination revealed an asymmetrically enlarged and firm prostate with no tenderness. Abdominal magnetic resonance imaging (MRI) revealed an enlarged prostate (**Figure 1A**, **1B**), and abdominal computed tomography (CT) showed multiple para-aortic, retroperitoneal and pelvic lymphadenopathy whose sizes were approximately 1.2~1.8 cm (**Figure 1C**, **1D**). Less than one year ago, he underwent the first transurethral prostate resection on a diagnosis of benign prostatic hypertrophy. Pathological results showed benign proliferative lesions with chronic inflammation. Two years ago, he was presented with right submandibular masses accompanied by no regional pain or fever. The patient underwent the excision of right submandibular masses. Two swelling lymph nodes approximately 2.6 cm and 4 cm in diameter were seen. He was pathologically diagnosed as the reactive follicular hyperplasia of lymph nodes.

On suspicion of the recurrence of prostatic hyperplasia, this patient underwent the second transurethral prostate resection during the current admission. The histopathology of the prostate samples revealed the patchy infiltration of dense lymphocytes and plasma cells with increased number of eosinophils, conspicuous lymphoid follicle formation with hyperplastic germinal centers, accompanying severe atrophy of exocrine glands and dense fibrosis focally in a storiform pattern (**Figure 2A-D**). No findings were suggestive of prostatic carcinoma. Immunohistochemical examination showed a large number of IgG4-positive plasma cells (an average of 195/HPF) (**Figure 2E**) and the IgG4/IgG ratio was more than 80%. In addition, increased IgG4-positive cells were visible within the intra-germinal center (**Figure 2F**). As a result, there were typically pathological characteristics of IgG4-RD.

During the current admission, laboratory findings revealed that serum IgG levels (4879 mg/dL) and IgG4 levels (1550 mg/dL) were elevat-

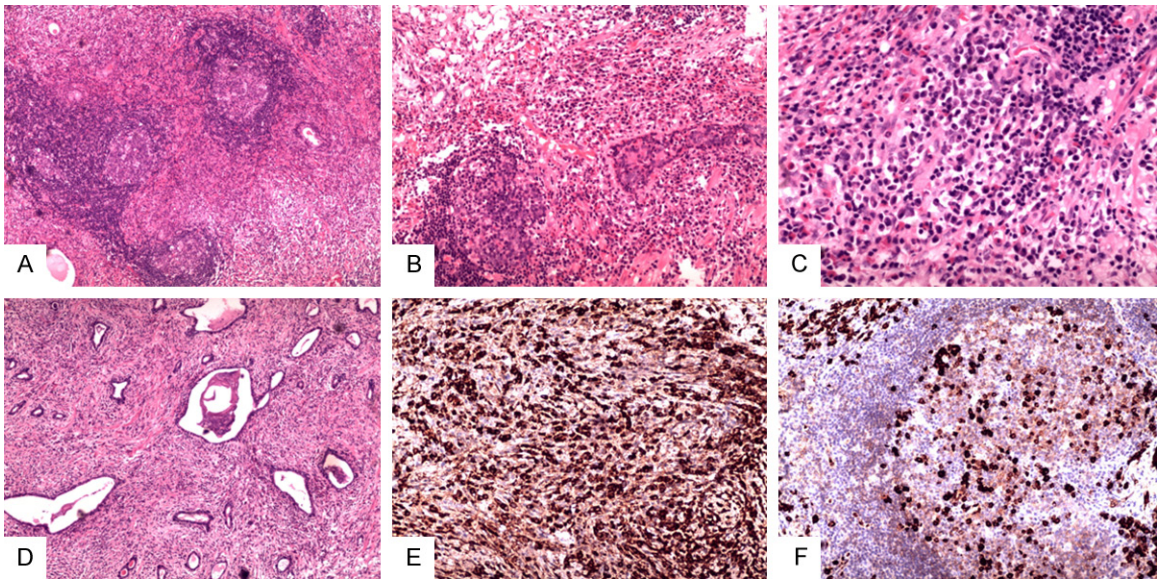

Figure 2. Tissue samples of transurethral prostate resection both this time and less than 1 year earlier showed the IgG4-related prostatitis. The histopathology of the prostate samples showed the patchy infiltration of dense lymphocytes and plasma cells with increased eosinophils, conspicuous lymphoid follicle formation with hyperplastic germinal center (A-C), accompanying severe atrophy of exocrine glands and dense fibrosis focally in a storiform pattern (D) (original magnification (A) ×40; (B) ×100; (C) ×200; (D) ×40). Immunostaining for IgG4 (E) showed abundant IgG4-positive cells (195/HPF) (original magnification ×200). Increased IgG4-positive cells were visible within the intra-germinal center (F) (original magnification ×200).

ed. The eosinophils in the blood were increased. Serum IgA, IgM, lactate dehydrogenase (LDH), and C-reactive protein (CRP) levels were all within normal limits. The tests for anti-DNA antibodies, antinuclear antibodies and rheumatoid factor were also negative. Serum prostate-specific antigen level was normal. Urine sediment and culture did not reveal any abnormalities. No remarkable abnormality of the pancreas was detected by CT and MRI examination.

Prostate samples first resected less than 1 year earlier were reevaluated. The histopathologic and immunohistochemical analysis showed the same pattern as obtained from the prostate samples of the second resection, and also confirmed to be typically IgG4-related prostatitis. The specimens of the right submandibular masses resected 2 years earlier were reviewed again. The enlarged lymph nodes demonstrated numerous lymphoid follicles with hyperplastic germinal centers and a distinct mantle zone, and no significant expansion of the interfollicular area (**Figure 3A**). The interfollicular area showed increased numbers of mature plasma cells and eosinophils (**Figure 3B**). Furthermore, the intra-germinal center showed conspicuous infiltration of mature plasma cells (**Figure 3C**). Follicular dendritic cell networks showed a normal or reactive pattern. Immunohistochemically, abundant IgG4-positive cells (an average of 130/HPF) were present in the interfollicular areas and the intra-germinal center, and the IgG4/IgG-positive cells ratio was more than 70% (**Figure 3D-F**). The lymph node by previously published criteria was consistent with follicular hyperplasia-type IgG4-related lymphadenopathy (type II) [3].

The patient was additionally treated with oral prednisolone after the second transurethral prostate resection. Two months later, we documented the substantial reductions in levels of serum IgG (2756 mg/dL) and IgG4 (578 mg/dL). In the following 14 months, his medical condition remained stable, and he was free of urinary or other complaints.

Discussion

We present a case of IgG4-related prostatitis progressed from localized IgG4-related lymphadenopathy. The clinicopathological features summarized as follows: this patient was present with urine retention symptoms; MRI and CT

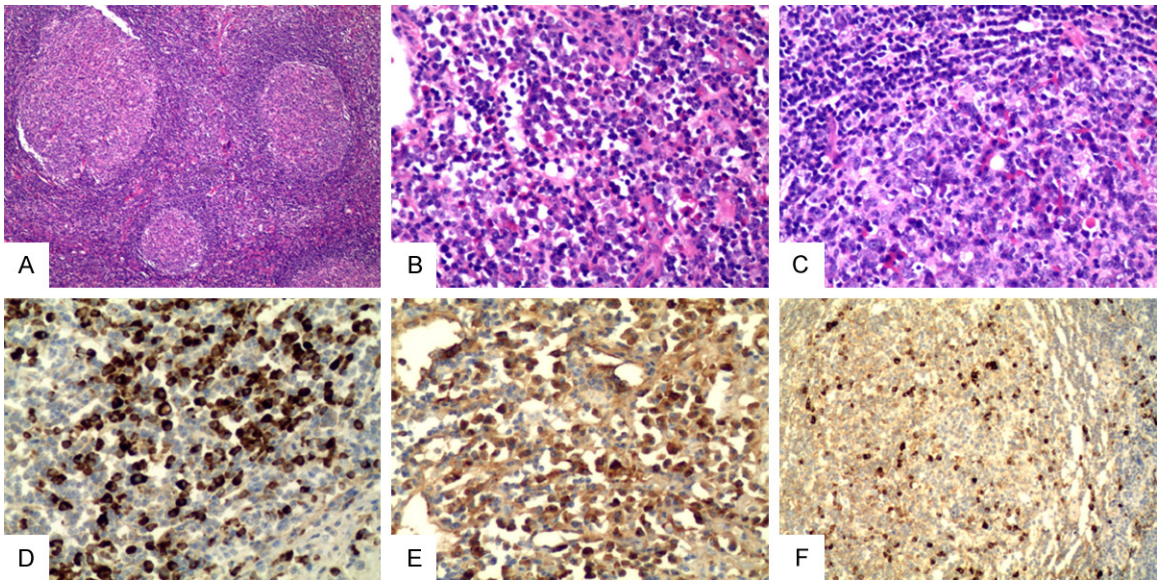

Figure 3. The right submandibular enlarged lymph nodes showed follicular hyperplasia-type IgG4-related lymphadenopathy. (A) Numerous reactive lymphoid follicles were evident (original magnification ×40). (B) The interfollicular area showed increased eosinophils and mature plasma cells (original magnification ×200). (C) The intra-germinal center showed conspicuous infiltration with mature plasma cells (original magnification ×200). Immunostaining for IgG4 (D) and IgG (E) showed abundant IgG4-positive cells (130/HPF and more than IgG4/IgG ratio of 70%) (original magnification ×200). (F) Increased IgG4-positive cells were present the intra-germinal center (original magnification ×200).

examination revealed the prostatic enlargement and the multiple lymphadenopathy. Serum IgG4 levels were elevated. Prostatic tissue samples resected both this time and less than one year earlier showed the same histological type of prostatitis, characterized by more lymphoplasmacytic and eosinophilic infiltration, severe atrophy of exocrine glands and dense fibrosis accompanying infiltration of abundant IgG4-positive cells. In addition, the right submandibular lymph nodes excised 2 years earlier were eventually proven to be follicular hyperplasia-type IgG4-related lymphadenopathy. Based on these findings, this is a case of IgG4-RD that began as localized IgG4-related lymphadenopathy and progressed into a systemic disease involving prostate and multiple lymph nodes.

IgG4-RD is a recently described inflammatory disease involving multiple organs, which has been reported in almost all organ systems, including the genitourinary tract. IgG4-related kidney disease is the best described, including tubulointerstitial nephritis, low-density cortical lesions and hypovascular renal masses. The involvement of the other genitourinary organs is relatively uncommon. A small number of paratesticular or ureteral pseudotumors have been reported to be IgG4-related [4, 5]. The periurethral involvement of IgG4-RD in an elderly woman has been reported [6]. The involvement of prostate, currently referred to as IgG4-related prostatitis, is one of the newly described manifestations of IgG4-RD. To our knowledge, only 19 cases with IgG4-related prostatitis have been reported in the English literature [7-11], including 18 cases complicated with AIP or IgG4-associated cholangitis, 1 case with chronic hypothyroiditis. Our present case is the first report of IgG4-related prostatitis progressed from localized IgG4-related lymphadenopathy.

Prostatitis is classified into four groups: (I) acute bacterial prostatitis, (II) chronic bacterial prostatitis, (III) chronic-prostatitis/chronic pelvic pain syndrome (CP/CPPS), and (IV) asymptomatic inflammatory prostatitis. Our case should be classified as the category III prostatitis. Various noninfectious etiologies including autoimmunity may be involved in this pathological condition for this category. Yoshimura et al first reported that a patient with CP/CPPS showed the characteristic findings of IgG4-related prostatitis [10]. Recently, a few authors

have proposed that a proportion of patients currently diagnosed with CP/CPPS might in fact suffer from a monosymptomatic disease manifestation of IgG4-related prostatitis [11].

Recent consensus on IgG4-RD advocates the following criteria: (1) histopathologic findings with increased IgG4-positive plasma cells in the involved organs, (2) high serum IgG4 concentration, (3) favorable response to glucocorticoid therapy, and (4) involvement of multiple organs [1]. Up to now, serum IgG4 is the best single test to diagnose IgG4-RD. However, sensitivity and specificity are limited. The diagnosis of IgG4-related disease rests on the combined presence of the characteristic histopathologic appearance and increased numbers of IgG4 plasma cells. The critical histopathological features are a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis and obliterative phlebitis. In addition, if the number of IgG4-positive plasma cells is greater than 50/HFP, the diagnostic possibility of IgG4-RD is generally high, but there are also many non-IgG4-related diseases such as multicentric Castleman's disease, rheumatoid arthritis, or other autoimmune diseases that need to be included in the differential diagnosis [1, 12, 13].

Little is known on the histopathological features of IgG4-related prostatitis. We observed that the prostate lesions of this patient showed increased numbers of IgG4-positive plasma cells, lymphocytes and eosinophils with severe atrophy of exocrine glands and dense fibrosis focally in a storiform pattern, in line with the earlier descriptions reported in other organs affected by IgG4-RD. In addition, conspicuous lymphoid follicle formation with visible plasma cells in the intra-germinal centers was observed, which might be related to being progressed from localized follicular hyperplasia-type IgG4-related lymphadenopathy. Obliterative phlebitis, once considered one of the hallmarks of IgG4-RD, was not significantly present in our case. The difference in the IgG4-related prostatitis was also observed by Buijs et al [11]. In fact, fibrosis and phlebitis may not be present in all sites of involvement especially at the early stage of the disease. It has earlier been reported that storiform fibrosis or phlebitis in most cases are notably absent in the lacrimal gland, lung and lymph node, indicating the variability across the different organs. Therefore, pathologists should be aware of IgG4-RD in the prostate when conspicuous infiltration of lymphocytes and plasma cells, together with eosinophils, is observed, even in absence of storiform fibrosis and phlebitis. In addition, patchy or uneven distribution of IgG4-positive plasma cells was seen in our case. Given this finding, it should be noted that negative staining evaluations of IgG4 on needle core biopsies might not be sufficient to exclude IgG4-related prostatitis.

The 18 patients with IgG4-related prostatitis reported in the literature were aged 63-74 years, and only 1 patient aged 39 years. Serum IgG4 levels were all markedly elevated. Notably, a clinicopathological series by Uehara et al showed that 2 of 6 patients with elevated PSA levels and the histopathological features of IgG4-related prostatitis had synchronous prostate cancer [9]. Thus, prostate cancer may occur in patients with IgG4-related prostatitis. In addition, 1 of 6 patients had elevated PSA levels without histological evidence of cancer, indicating that IgG4-related prostatitis might cause the increase of PSA levels, mimicking prostate cancer.

The recurring nature of IgG4-RD, combined with the diversity of possible sites of involvement, may mean multiple resections and potential loss of exocrine gland function. On the contrary, steroids and rituximab have been used for successful treatment of this disease [14]. Thus, it is imperative to make this an important entity to diagnose promptly and correctly. We here present the first case of IgG4-related prostatitis progressed from localized IgG4-related lymphadenopathy, and the prostate symptoms relapsed within less than 1 year after the transurethral prostate resection. Instead, the patient showed a good response to steroid therapy. This leads us to advocate a novel pathogenesis of prostatitis, and a novel therapeutic approach against prostatitis. Furthermore, this case highlights a potential diagnostic pitfall with therapeutic consequences. Prostatic involvement might not be rare in patients with IgG4-RD, even without the distinct features of pancreatic or biliary involvement. Therefore, pathologists and urologists should consider this disease entity in the patients with elevated serum IgG4 levels and the symptoms of prostatic hyperplasia, and

particularly those with the fast recurrence of the prostate symptoms after transurethral prostate resection, to avoid ineffective medical or unnecessary surgical treatment.

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Disclosure of conflict of interest

None.

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References

[1] Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, Kloppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H and Stone JH. Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012; 25: 1181-1192.

[2] Stone JH, Zen Y and Deshpande V. IgG4-related disease. N Engl J Med 2012; 366: 539-551.

[3] Cheuk W, Yuen HK, Chu SY, Chiu EK, Lam LK and Chan JK. Lymphadenopathy of IgG4-related sclerosing disease. Am J Surg Pathol 2008; 32: 671-681.

[4] Kim SA, Lee SR, Huh J, Shen SS and Ro JY. IgG4-associated inflammatory pseudotumor of ureter: clinicopathologic and immunohistochemical study of 3 cases. Hum Pathol 2011; 42: 1178-1184.

[5] Hart PA, Moyer AM, Yi ES, Hogan MC, Pearson RK and Chari ST. IgG4-related paratesticular pseudotumor in a patient with autoimmune pancreatitis and retroperitoneal fibrosis: an extrapancreatic manifestation of IgG4-related disease. Hum Pathol 2012; 43: 2084-2087.

[6] Yamamoto H, Fukushima T, Yokoyama H, Yoshizawa A and Hamano H. Periurethral involvement of IgG4-related disease in an elderly woman mimicking an enlarged prostate in man. Ann Intern Med 2012; 157: 78-79.

[7] Hart PA, Smyrk TC and Chari ST. IgG4-related prostatitis: a rare cause of steroid-responsive obstructive urinary symptoms. Int J Urol 2013; 20: 132-134.

[8] Nishimori I, Kohsaki T, Onishi S, Shuin T, Kohsaki S, Ogawa Y, Matsumoto M, Hiroi M, Hamano H and Kawa S. IgG4-related autoimmune prostatitis: two cases with or without autoimmune pancreatitis. Intern Med 2007; 46: 1983-1989.

[9] Uehara T, Hamano H, Kawakami M, Koyama M, Kawa S, Sano K, Honda T, Oki K and Ota H. Autoimmune pancreatitis-associated prostatitis: distinct clinicopathological entity. Pathol Int 2008; 58: 118-125.

[10] Yoshimura Y, Takeda S, Ieki Y, Takazakura E, Koizumi H and Takagawa K. IgG4-associated prostatitis complicating autoimmune pancreatitis. Intern Med 2006; 45: 897-901.

[11] Buijs J, Maillette de Buy Wenniger L, van Leenders G, Verheij J, van Onna I, Hansen B, van Heerde M, Krak N, Beuers U, Bruno M and van Buuren H. Immunoglobulin G4-related prostatitis: a case-control study focusing on clinical and pathologic characteristics. Urology 2014; 83: 521-526.

[12] Sato Y, Notohara K, Kojima M, Takata K, Masaki Y and Yoshino T. IgG4-related disease: historical overview and pathology of hematological disorders. Pathol Int 2010; 60: 247-258.

[13] Sato Y and Yoshino T. IgG4-Related Lymphadenopathy. Int J Rheumatol 2012; 2012: 572539.

[14] Khosroshahi A, Carruthers MN, Deshpande V, Unizony S, Bloch DB and Stone JH. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine (Baltimore) 2012; 91: 57-66.