

MRI diagnosis of tumor-like IgG4 masses in bilateral distal ureters: A case report

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Abstract. IgG4 masses in the bilateral distal ureters are rare and frequently misdiagnosed. The present study reported the case of a 55-year-old male patient with IgG4-related disease (IgG4-RD) who had symmetrical soft tissue masses of the bilateral distal ureters found on magnetic resonance imaging (MRI) with a significant increase in the serum levels of IL-6, IgG4 and IgE. Regarding treatment, this patient received prednisone acetate tablets (40 mg/day) and mycophenolate mofetil dispersible tablets (1 g/day). During the follow-up, significant reductions in the levels of IgG4 and IgE were found after 30 days. MRI after 6 months indicated complete disappearance of the masses. The prognosis has been good so far. In clinical practice, it is necessary to consider the possibility of IgG4-RD in cases with soft tissue masses surrounding both ureters and elevated levels of serum IgG4.

Introduction

IgG4-related disease (IgG4-RD) is a chronic inflammatory disease related to fibrosis that is mediated by the immune system. The characteristic features of IgG4-RD include elevated serum IgG4 levels, infiltration of abundant IgG4+ plasma cells and lymphocytes and fibrosis in affected

organs (1). This disease may occur in various parts of the body, with the pancreas being the most commonly involved organ, followed by the hepatobiliary system, salivary glands, lacrimal glands, lungs, posterior peritoneum, kidneys and prostate (1,2). Furthermore, IgG4-RD is a disease characterized by involvement of multiple organs and systems. Due to the limited knowledge and understanding of IgG4-RD, it is common for doctors to misdiagnose IgG4-RD as malignant or infectious lesions, resulting in certain patients undergoing unnecessary surgical interventions. However, as an immune-mediated systemic disease, IgG4-RD was indicated to show excellent responses to glucocorticoid therapy (2,3). Thus, early diagnosis and accurate treatment are crucial for patients to acquire more benefits. Imaging examinations are effective methods to find the lesions of IgG4-RD. Furthermore, they may be used to describe the scope of lesions and evaluate the efficiency of hormone therapy (2,4). The present study reported a case of IgG4-RD of the bilateral distal ureters, which are rarely involved in IgG4-RD, and the magnetic resonance imaging (MRI) features were analyzed to improve the understanding and diagnosis of the disease.

Case report

In September 2021, a 55-year-old male patient sought medical attention at Xiangyang No. 1 People's Hospital (Xiangyang, China) due to complaints of 'lower back pain for one week', without any symptoms such as painful urination, gross hematuria, frequent urination and urgency of urination. The medical record indicated a history of oral medication therapy for hypertension and hypothyroidism. Physical examination on admission found no obvious abnormality. MRI showed symmetrical soft tissue masses around the bilateral distal ureters, with equal signal on T1-weighted imaging (T1WI) (Fig. 1A), slightly higher signal on T2WI (Fig. 1B) and significant enhancement (Fig. 1C and D). In the diffusion-weighted imaging sequence (DWI), the lesions had a high signal (Fig. 1E), while they had a low signal in the apparent diffusion coefficient (ADC) image (Fig. 1F). The size of the larger mass was 25x23x35 mm and the smaller one was 18x21x23 mm(right). Magnetic resonance urography indicated stenoses of bilateral distal ureters and proximal hydronephrosis (Fig. 2). The serological results revealed that the IgG4 level was 8.690 g/l (0.03-2.01, for

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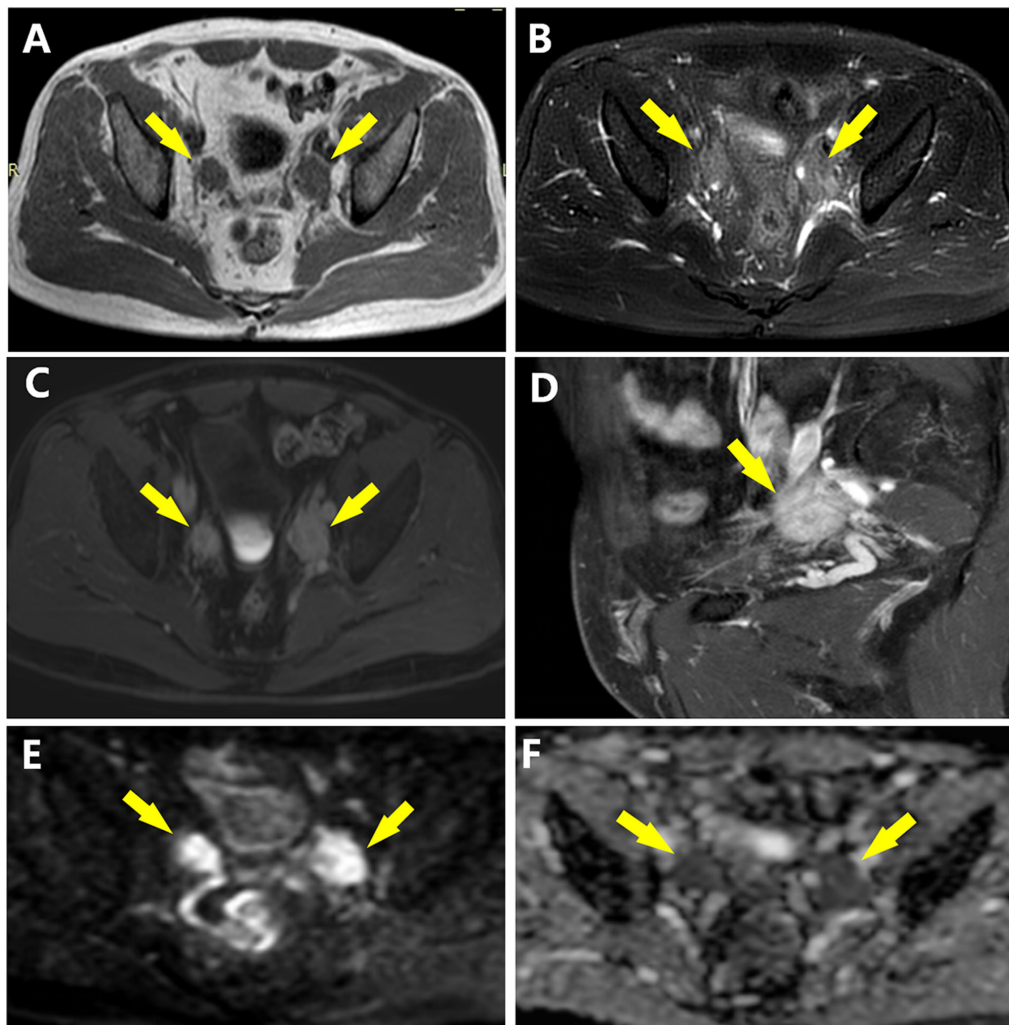


Figure 1. Imaging presentation of a 55-year-old male patient with IgG4-related retroperitoneal disease. In the axial (A) T1WI and (B) T2WI magnetic resonance imaging, bilateral lumpy soft tissue masses around the lower ureter are visible, the border is clear, the contour is not polished, T1WI has equal signal intensity and T2WI has equal or slightly higher signal intensity. On (C) T1WI axial enhanced and (D) T1WI sagittal enhanced, the masses display as significantly enhanced. (E) On diffusion-weighted imaging, the masses were displayed with a high signal. (F) In the apparent diffusion coefficient image, the masses had a low signal. T1WI, T1-weighted imaging. Yellow arrows indicate the soft tissue masses.

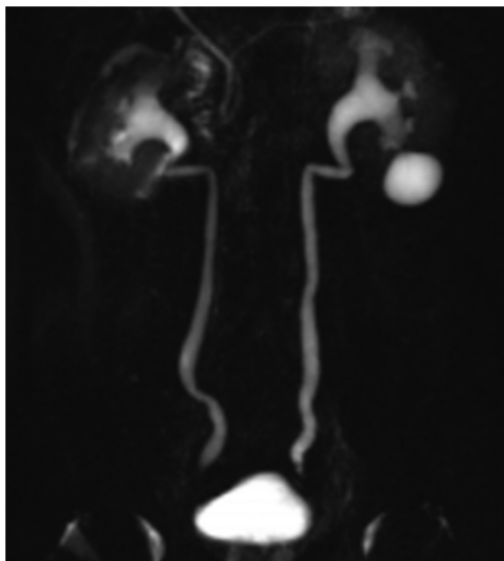


Figure 2. Magnetic resonance urography indicates that the local ureter is compressed and narrowed with hydronephrosis. Yellow arrows indicate local ureter compressed.

IgG4-RD cutoff, >1.35 g/l), IL-6 level was 7.1 pg/ml (normal range: 0.1-2.9 pg/ml) and IgE level was 255.10 IU/ml (normal, ≤100 IU/ml). Due to consideration of IgG4-RD, prednisone acetate tablets (40 mg/day) and mycophenolate mofetil dispersible tablets (1 g/day) were administered. After 30 days, the IgG4 level had dropped to 4.610 g/l and the IgE level had decreased to 130.60 IU/ml. After 6 months, the masses had disappeared completely in the follow-up MRI (Fig. 3A and B). In May 2022, laboratory examination at another hospital indicated that IgE and IL-6 had dropped to normal. The patient continued to take mesalazine dispersible tablets (0.5 g/day) to prevent relapse. According to an MRI scan conducted in April 2023, there was no significant recurrence of the lesions observed at the distal ends of both ureters.

Discussion

Patients with IgG4-RD usually undergo a two-stage progression, including an inflammatory phase and a fibrotic phase. The inflammatory lesions of IgG4-RD may be related to immune disorders, environmental pollution or drug abuse (5).

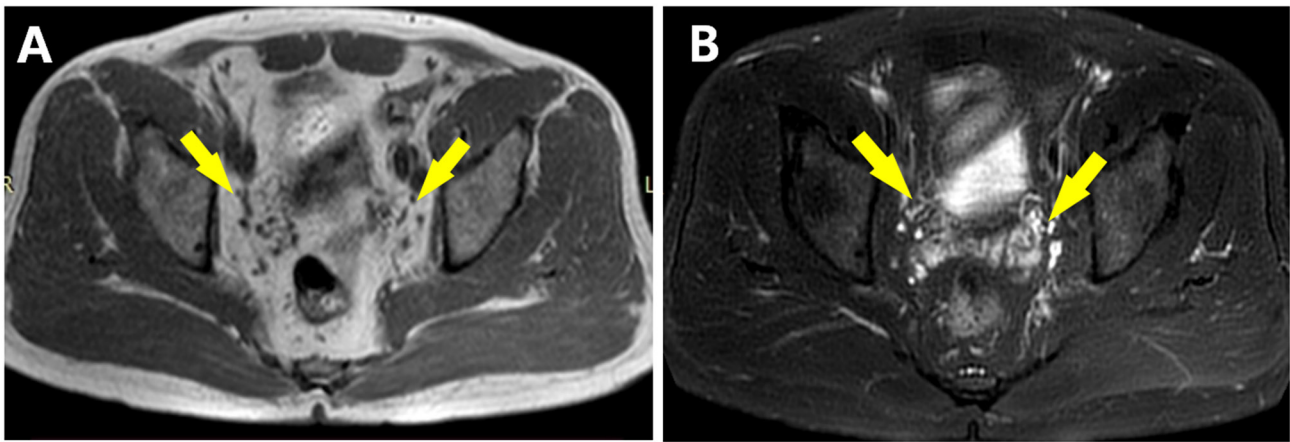


Figure 3. Follow-up. (A) T1WI and (B) T2WI magnetic resonance imaging after 6 months of treatment, indicating that the masses had completely disappeared. T1WI, T1-weighted imaging. Yellow arrows indicate the previous location of the soft tissue masses.

According to a study conducted in Japan, there has been an increase in the incidence rate of IgG4-RD over a period of 10 years, from 0.8 cases per 100,000 individuals to 3.1 cases per 100,000 individuals. This may be attributed to the improvement in the diagnosis of IgG4-RD (6). Of note, IgG4-RDs more commonly occur in middle-aged and elderly individuals (with an average age of 56 years) and males (7). An important characteristic of IgG4-RD is its ability to affect multiple organs. Several previous studies have provided insight into the prevalence of multi organ involvement, reporting that it ranges from 51 to 92% (7-10). Furthermore, the symptoms of IgG4-RD are usually nonspecific and vary according to the organs involved. For patients with retroperitoneal IgG4-RD, the initial symptoms are milder and more undetectable than those with other organs involved. As a result, the diagnosis of retroperitoneal IgG4-RD may be delayed (11). Ureteral IgG4-RD is a fairly uncommon condition that is predominantly reported as an individual case with symptoms including lower back pain, loss of appetite and renal dysfunction (12,13). In the case of the present study, the patient only had lower back pain.

Thus far, there are no unified diagnostic criteria for IgG4-RD. Elevated serum IgG4 is an important indicator for the diagnosis and evaluation of IgG4-RD. It can be found in 55-97% of cases, particularly in Asian patients, and it is correlated with the number of organs involved (14). Serum IgG4 levels of >1.35 g/l are considered strong evidence for the diagnosis of IgG4-RD (15). However, elevated serum IgG4 is not a specific biomarker for IgG4-RD, as it may be found in numerous other diseases, such as tumors, infections, connective tissue diseases, hematological diseases and allergic conditions. In addition, not all patients with IgG4-RD have elevated serum IgG4 levels. Thus, higher serum IgG4 is neither sufficient nor necessary for the diagnosis of IgG4-RD. Higher serum IL-6 is a marker to reflect acute phase response (16). The IgG4 and IL-6 levels in the present case were significantly elevated, which may support the diagnosis and suggest that the disease is in an active phase.

The pathogenesis of IgG4-RD has remained to be elucidated; however, it is thought to be mainly mediated by immunological imbalance. Its main pathological features are lymphocyte and plasma cell infiltration and fibrosis within the affected tissues

or organs, and the histopathological presentation remains the gold standard for diagnosis (17). The pathological changes of IgG4-RD provide an important basis for characteristic radiological manifestations, particularly MRI signal changes and enhancement patterns (7). Although the international diagnostic criteria for IgG4-RD are different, they all emphasize that imaging findings are the main basis for the diagnosis of IgG4-RD (2), particularly CT and MRI (18), which may display the location, scope and shape and size of the lesion. MRI is slightly superior to CT in determining the nature of the lesion involving retroperitoneal organs. MRI may show a patchy soft tissue signal shadow surrounding the anterolateral abdominal aorta and the common iliac artery, which is similar to the psoas major muscle signal, frequently causing medial displacement or obstruction of the lower ureter (11). The imaging findings of retroperitoneal IgG4-RD are mostly isodense on plain CT scan. MRI shows an equal or slightly lower signal on T1WI and T2WI, and mild to moderate delayed enhancement after enhancement (19). The characteristic imaging features may be related to intrafocal fibrosis and more infiltration of lymphocytes and plasma cells. When the lesion stays in the active phase, T2WI shows high signal intensity (19). DWI is conducive to identifying whether IgG4-RD is in the active phase and presenting similar retroperitoneal malignancies (20). The ADC value of nonactive lesions is higher than that of active lesions and retroperitoneal malignant tumors. When a patient is clinically suspected to have IgG4-RD with a retroperitoneal mass, a puncture biopsy of the retroperitoneal lesion is often necessary. However, Raglianti *et al* (19) suggested that when clinical suspicion of retroperitoneal mass associated with IgG4-RD is confirmed by serological examinations, and there are typical imaging manifestations as described above, hormone treatment may be directly initiated to avoid the potential risk of retroperitoneal vascular injury caused by biopsy. IgG4-RD occurring in the ureter is relatively rare and the imaging manifestation is often segmental thickening of the ureter wall or the formation of local masses, accompanied by mild to moderate hydronephrosis (13,21). It may affect any part of the ureter, but unilateral involvement is more common, with the left side being more frequently affected than the right side (13). When the ureter is affected unilaterally, it is difficult to differentiate

from ureteral malignancy. According to previous reports, it has been frequently misdiagnosed as an ureteral malignancy prior to surgery and surgical resection was performed (12,13,21). However, in patients with ureteral IgG4-RD, the degree of hydronephrosis is relatively mild compared to that with malignant tumors (21). This may be because the ureteral stenosis in this disease is mostly due to compression by wall or peripheral inflammatory lesions, rather than direct obstruction by intraluminal soft tissue masses (21). In cases where no malignant tumor cells are found in cytological and ureteroscopic brush specimens, particularly when the mass involves the bilateral ureters, consideration should be given to the possibility of ureteral IgG4-RD and further related serological immunological tests may be performed to assist in the diagnosis. The imaging manifestation of the case of the present study is relatively special, with the main features being symmetrical, round, soft tissue signal masses at the bilateral distal ureters, accompanied by limited lesions and irregular morphology. The T2WI signal is higher than that of the surrounding muscle and soft tissue, with significant enhancement, diffusion limitation and a significant decrease in ADC value, suggesting that the patient may be in the active stage, which is prone to be misdiagnosed as a neoplastic lesion. The reasons for the relatively accurate imaging diagnosis at initial MRI may include the following: i) The lesion simultaneously involves the bilateral ureters and symmetry development may be an important basis for excluding other malignant tumors; ii) the signal of the lesion is relatively uniform, without obvious cystic changes, necrosis and bleeding; iii) the boundary of the lesion is relatively vague with surrounding adipose tissue, while other tumors at this site generally have clear boundaries or exhibit aggressive growth patterns and peripheral tissue traction; iv) bilateral hydronephrocalyces are not serious. Most malignant tumors feature severe hydronephrosis, frequently accompanied by hematuria (21).

IgG4-RD retroperitoneal lesions may be divided into three subtypes based on the anatomical location and their involvement (22): i) Surrounding the abdominal aorta or iliac artery; ii) surrounding the renal pelvis and ureter; iii) no clear correlation with any pelvic cavity organ and only distributed behind the pelvic peritoneum. The first subtype is the most common. When the lesion is localized around the bilateral ureters, it is mainly differentiated from the following malignant tumors in the ureter: A) Primary tumors of the ureter: Clinically rare, most are transitional cell carcinoma. The major clinical manifestation is recurrent gross hematuria. MRI often shows a mass in the ureter or invade its surroundings, with T1WI and T2WI signals higher and lower than those in urine, respectively, and frequently uneven signals involving the outside of the lumen. Symmetrical involvement of bilateral ureters is rare and it is difficult to differentiate from unilateral ureteral involvement of IgG4-RD. However, when urinary cytology examination and ureteroscopic biopsy are inconclusive regarding malignant tumors, IgG4-RD should be considered and further relevant serum immunological tests should be performed (13,23). B) Lymphoma: Lymphoma has a wide range, with common retroperitoneal enlarged lymph nodes appearing from the peripancreatic level, and some of them can be fused; 'when the lymph nodes behind the abdominal aorta are gradually enlarged, the abdominal aorta can be pushed forward and obscure display, resulting in an aortic submersion

sign. However, the lymphoma is soft and rarely causes bilateral ureteral stenosis' (24). C) Periureteral metastatic tumor: It can appear as a parenchymal mass or enlarged lymph nodes adjacent to the ureter, the former having no obvious characteristics, while the latter often presents as a single or multiple discontinuous nodular lesions with a clear boundary. Most patients have a history of primary malignant tumors.

Glucocorticoids are generally effective for IgG4-RD and immunosuppressants are also necessary as drugs to induce remission. The responsiveness of glucocorticoids to treatment is also one of the diagnostic inclusion criteria for IgG4-RD (25). When IgG4-RD is suspected, timely serum immunologic testing and hormone impact treatment may spare patients from having to undergo surgery, radiotherapy and chemotherapy. Biological targeted therapy, particularly the anti-CD20 monoclonal antibody rituximab, has achieved good results in the treatment of IgG4-RD (26). Rituximab may be considered for patients who have failed traditional treatment, experienced relapse during steroid tapering, or have steroid resistance or intolerance. However, precautions should be taken to prevent infection after using this medication. In urgent situations where specific sites affected by IgG4-RD cause organ dysfunction due to compression, if medication fails to rapidly control the condition, surgical or interventional treatments may be considered. IgG4-RD is a disease prone to relapse. Different studies have reported risk factors for relapse, including male gender, younger age, history of allergies, elevated baseline serum IgG4 levels, low maintenance steroid dosage and previous relapse history (27,28). Furthermore, a subsequent increase in serum IgG4 levels during follow-up is also a risk factor for disease relapse (29). In this case, the patient's IgG4 and IgE levels significantly decreased after one month of combined treatment with glucocorticoids and immunosuppressive agents. Six months later, a follow-up MRI showed the disappearance of the retroperitoneal mass, and thus, no further treatment with targeted biological drugs or surgery was considered. The patient continued to take mesalazine dispersible tablets (0.5 g/day) to prevent relapse. In April 2023, the patient came to our hospital for re-examination and pelvic MRI showed no obvious recurrence of bilateral ureteral terminal masses. The prognosis has been good so far. The patient has shown sensitivity and effectiveness to hormone and immunosuppressive therapy, which provides strong evidence for the diagnosis of IgG4-RD in this case.

Therefore, when clinically encountering patients with subacute onset, only presenting with lower back pain and retroperitoneal soft tissue masses surrounding the bilateral ureters, the possibility of IgG4-RD should be considered and a comprehensive diagnosis should be made in combination with serological examination, imaging characteristics and treatment response to avoid misdiagnosis.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JC, YW and PG contributed to the conceptualization and design of the study and drafting of the manuscript. AG, PA, HC and RC collected the patient's clinical information and images and assisted with the drafting of the manuscript. YW and PG contributed to critical revisions of the intellectual content and confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Xiangyang No.1 People's Hospital, Hubei University of Medicine (approval no. 2023KY037), complied with the Health Insurance Portability and Accountability Act, and followed the guidelines of the Declaration of Helsinki.

Patient consent for publication

Written informed consent was provided by the patient for publication of data and images.

Competing interests

The authors have no competing interests to declare.

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