IgG4-related disease of the ureter mimicking malignant ureter tumor: a case report and experience sharing

Ziyu Fang[1], Yu Sun[2], Shaoxiong Ming[1], Ling Li[1], Xiaofeng Gao[1]

[1]Department of Urology, Shanghai Changhai Hospital, Naval Medical University, Shanghai, China; [2]School of Basic Medicine, Naval Medical University, Shanghai, China

Contributions: (I) Conception and design: L Li; (II) Administrative support: X Gao; (III) Provision of study materials or patients: S Ming; (IV) Collection and assembly of data: Y Sun; (V) Data analysis and interpretation: Z Fang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ling Li, MD. Department of Urology, Shanghai Changhai Hospital, Naval Medical University, 168 Yangpu District, Shanghai 200433, China. Email: ejdll@163.com.

Background: Immunoglobulin G4-related disease (IgG4-RD) is an autoimmune disease that can affect any organ or tissue in the body, and is characterized by intensive infiltration of IgG4-positive plasma cells, and elevated serum IgG4 levels. IgG4-RD causes renal impairment of unknown pathogenesis that may progress to kidney failure. However, few case of IgG4-RD mimicking malignant ureter tumor leading to severe hydronephrosis.

Case Description: This report describes a 38-year-old male patient who was hospitalized for sudden waist pain. Enhanced abdominal computed tomography (CT) revealed a mass involving the right ureter. He presented to the urologist with severe right hydronephrosis. Urinalysis revealed occult blood (3+), and atypical cells were observed in urine cytology, raising the possibility of a ureteral malignancy. After that, the patient underwent diagnostic ureteroscopy instead of direct nephroureterectomy and was found not to have any malignancy. The patient received laparoscopic partial ureteral resection and anastomosis. Histologically, there were observations of IgG4-positive plasma cell infiltration exceeding 10 cells per high-power field, as well as a high ratio of IgG4-positive/IgG-positive cells exceeding 40%. And histopathology revealed ureteral IgG4-related disease, with no evidence of urothelial carcinoma.

Conclusions: IgG4-RD has previously been reported in lesions involving the ureters, but misdiagnosis and subsequent radical nephroureterectomy can cause lifelong regret for the patient in having lost one side of the urinary tract. To avoid such misdiagnoses, clinicians should consider IgG4-RD as a potential condition.

Keywords: Immunoglobulin G4-related disease (IgG4-RD); ureter; hydronephrosis; inflammatory pseudotumor; case report

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently described systemic disorder of unknown etiology. It is characterized by elevated serum IgG4 levels, infiltration of IgG4-positive plasma cell and lymphocytes seen histologically, and affects various organs including the pancreas, liver, lungs, kidneys, prostate and retroperitoneum (1).

In IgG4-related urinary disease (IgG4-RUD), the kidney, renal pelvis, ureter, and bladder were identified as affected areas within the urinary system. Histopathological features of IgG-RUD comprised infiltration of plasma lymphocytes, storiform fibrosis, and the presence of IgG4-positive plasma cells. Additionally, eosinophil infiltration may be observed in the affected tissue. It should be noted that the attention given to the involvement of the ureter in IgG4-RUD has been limited (2).

Table 1 Important timeline in the case

Dates	Events
2022.06	The patient had sudden left waist pain
2022.06	He had enhanced CT and left ureteroscopic lithotripsy in local hospital
2022.07.02	He was admitted to our hospital
2022.07.05	He had right diagnostic ureteroscopy in our department
2022.07.08	He had undergone laparoscopic surgery
2022.07.14	He was discharged

CT, computed tomography.

Here, we present a rare case of IgG4-related disease in which the lesion was identified only within lumen of the upper ureter. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-23-33/rc).

Case presentation

Patient information

A 38-year-old man presented sudden left waist pain two weeks ago, and non-enhanced computed tomography (CT) scan showed left ureteral stone, right ureter obstruction and subsequent hydronephrosis. Further enhanced CT revealed a mass lesion within his right upper ureter with left ureteral stone. He had a history of hypertension. He was then admitted to local hospital and underwent left ureteroscopic lithotripsy. There was no history of stone onset on the right ureteral. Later, he came to Shanghai Changhai Hospital for further treatment. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Highlight box

Key findings

- We presented a case of an adult man presented with a mass involving the right ureter and finally diagnosed with immunoglobulin G4-related disease (IgG4-RD), avoiding direct nephroureterectomy.

What is known and what is new?

- IgG4-RD has previously been reported in lesions involving the ureters, but misdiagnosis and subsequent radical nephroureterectomy can cause lifelong regret for the patient in having lost one side of the urinary tract.
- We report a rare case of ureteral IgG4 disease masquerading as urothelial carcinoma.

What is the implication, and what should change now?

- This case highlights the rare possibility of IgG4-RD mimicking malignant ureter tumor. To avoid such misdiagnosed, urologists should be aware of the possibility that hydronephrosis with ureter obstruction may be involved in IgG4-RD.

Clinical findings

Costovertebral angle percussion pain and bilateral renal percussion pain showed negative. Bilateral ureteral action areas are not tender. There are no positive signs on specialist urological examination.

Timeline of disease progression

The timeline of disease progression is shown in *Table 1*.

Diagnostic assessment

Laboratory testing

Laboratory data of this case on admission to our hospital are shown in *Table 2*.

The urine analysis results were as follows: nitrite (–), protein (±), occult blood (3+), white blood cell (2+), and cast (–). The blood test results were as follows: normal white blood cell (10.33×10^9/L) and neutrophil (7.35×10^9/L) and hemoglobin (HGB) (144 g/L). Renal function [blood urine nitrogen (BUN), 5 mmol/L; creatinine, 85 μmol/L] was noted, with an estimated glomerular filtration rate of 114.67 mL/min/1.73 m^2. Urine cytology revealed slightly atypical cells, prompting further investigations for a mild dysplastic urothelial tumor, benign mass or inflammation.

Imaging

Computerized tomography urogram (CTU) revealed a mass lesion within his right upper ureter, along with severe hydronephrosis of the right kidney (*Figure 1*). The lesion was enhanced during arterial phase. Further inspection of the CTU revealed a thick renal cortex on the right kidney indicating that the kidney was still functioning.

Table 2 Laboratory data of present case on admission to our hospital

Parameter	Value	Normal range
Urinalysis		
Protein	±	–
Occult blood	3+	–
Sugar	2+	–
Nitrite	–	–
White blood cell	2+	–
Cast	–	–
Blood count		
White blood cells ($\times10^9$/L)	10.33	3.5–9.5
Neutrophil ($\times10^9$/L)	7.35	1.8–6.3
Red blood cells ($\times10^{12}$/L)	4.9	4.3–5.8
Hemoglobin (g/L)	144	130–175
Platelets ($\times10^9$/L)	361	125–350
Serum chemistry		
Blood urea nitrogen (mmol/L)	5	3.1–8
Creatinine (μmol/L)	85	57–97
Uric acid (μmol/L)	359	208–428
Sodium (mmol/L)	145	137–147
Potassium (mmol/L)	3.4	3.5–5.3
Chlorine (mmol/L)	107	99–110
Alkaline phosphatase (U/L)	102	45–125
Aspartate aminotransferase (U/L)	19	15–40
Alanine aminotransferase (U/L)	37	9–50
Lactate dehydrogenase (U/L)	102	45–125
Total protein (g/L)	71.1	65–85
Albumin (g/L)	44.3	40–55
Immunological findings (postoperation)		
IgG4 (g/L)	13.7	–

IgG4, immunoglobulin G4.

Diagnostic challenges

The diagnostic challenge presented in this case was the uncertainty of whether or not the mass in the patient's upper ureter was a neoplastic process. The evidence supporting this suspicion was the mass being enhanced during the arterial phase, and the accompanying significant right hydronephrosis. However, the patient did not have a history of hematuria, and urine cytology showed atypical cells, not cancer cells.

Diagnosis

Our initial diagnosis could be right-sided ureteral mass lesion: tumor? polypus? tuberculosis?

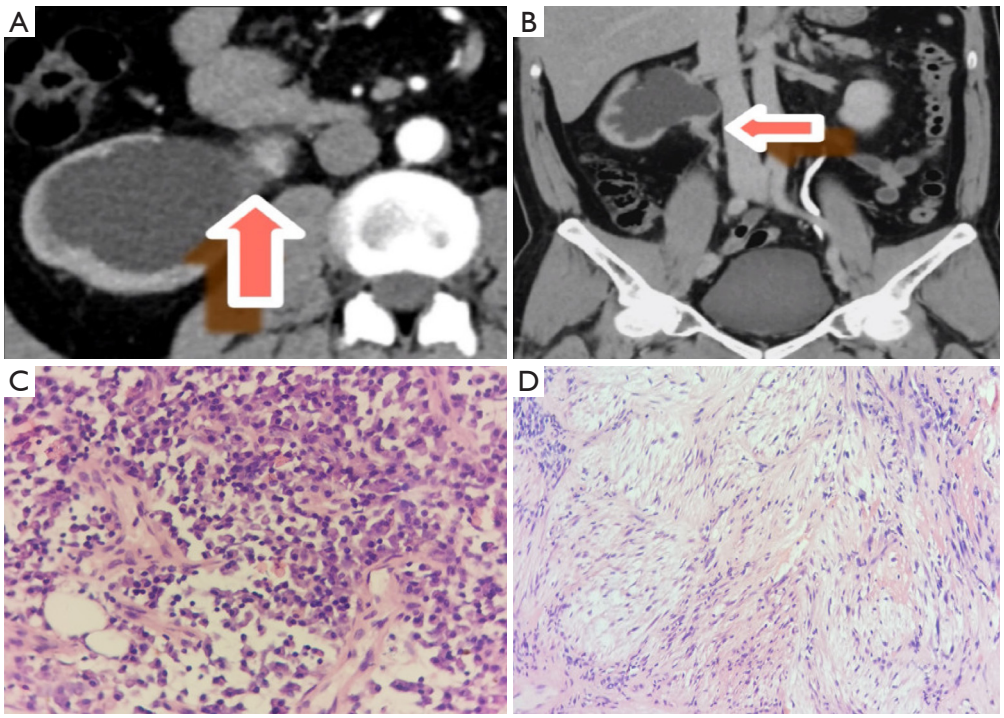

Figure 1 Radiology and histopathology of ureter mass in the ureteropelvic junction. (A) Contrast-enhanced CT showed an abnormal enhanced lesion in the upper right ureter (arrow). (B) Right kidney presented severe hydronephrosis (arrow). (C) HE staining showed abundant infiltration of lymphocytes with lymphoid follicles around the right ureter and peripheral proliferation of collagenous fibers (×200). (D) Storiform fibrosis was observed in HE staining (×200). CT, computed tomography; HE, hematoxylin and eosin.

Prognosis

The diagnostic challenge presented a dilemma in terms of how to provide the best treatment for the patient. If the mass was a tumor, then a right radical nephroureterectomy would be required. However, if it was not cancerous, then this procedure may result in irreversible regret for the patient due to the removal of half of the urinary system. On the other hand, the CT scan suggested the possibility of a carcinoma of the ureter. The patient was also concerned that diagnostic ureteroscopy might delay optimal timing of treatment and increase the risk of tumor implantation and dissemination. After careful consideration, it was decided to perform a diagnostic ureteroscopy firstly. This procedure would provide a more accurate diagnosis and would help ensure that the most appropriate treatment was chosen for the patient.

Therapeutic intervention

Diagnostic ureteroscopy

We performed cystoscopy, and right diagnostic ureteroscopy with tissue biopsy. The cystoscopy showed no stones and no masses in the bladder. And the result showed a neoplasm in the upper right ureter.

During the ureteroscopy procedure, the neoplasm is found with a lesion raised from all sides toward the center of the ureter (*Figure 2A*). The lesion was visualized clearly in the upper section of the right ureter under the endoscopic examination (*Figure 2B*). To perform a biopsy in the ureter, a stone basket was inserted. However, due to the operational challenges encountered, the F8.5 ureteral rigid scope was performed. Subsequently, a biopsy forceps was introduced to obtain a sample of the tissue and renal pelvis urine was retained at the same time. A pile of gray-brown crushed tissue was taken out from the ureter. And the pathological examination of the ureteral biopsy was consistent with ureteral mucosal polyp lesions. As the finding were benign, we decided to perform a laparoscopic lesion biopsy procedure.

Changes in therapeutic intervention

The patient underwent laparoscopic surgery under general

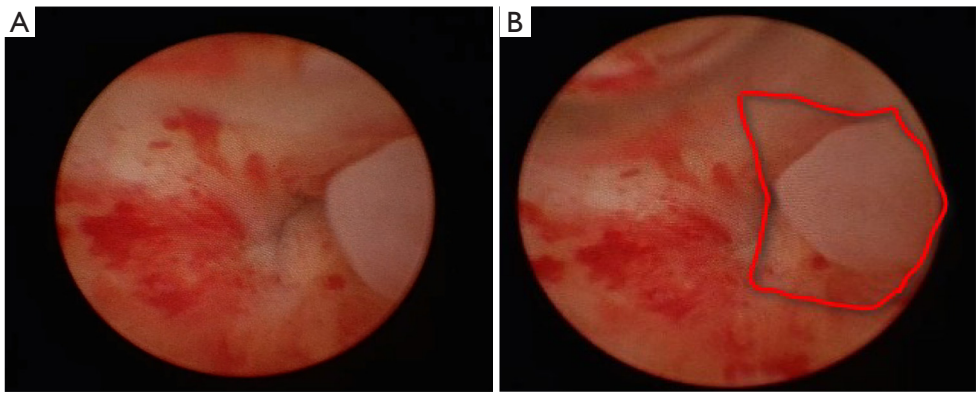

Figure 2 Images of ureteroscopy. (A) Image of diagnostic ureteroscopy. (B) Diagnostic ureteroscopy showed a polypoid lesion in the right upper ureter. Red circle indicates the polypoid lesion.

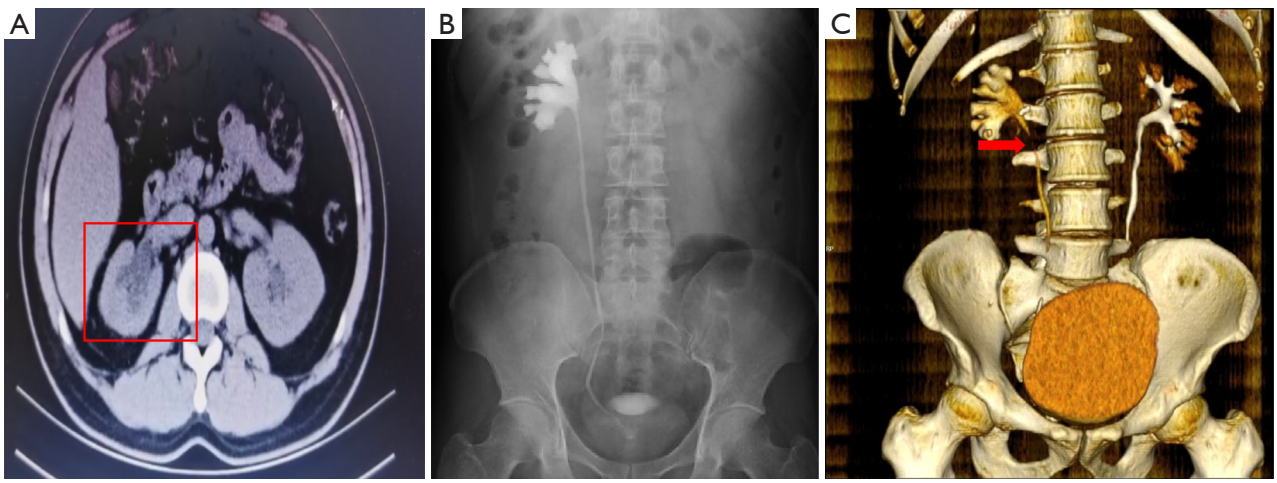

Figure 3 Images after surgery. (A) CTU showed significantly reduced right hydronephrosis. Red box indicates the hydronephrosis. (B) Right retrograde pyelography two months after surgery showed unobstructed spontaneous excretion. (C) CTU showed unobstructed spontaneous excretion in right ureter 5 months after surgery (arrow). CTU, computed tomography urography.

anesthesia. During the procedure, the lesion showed severe adhesions to the surrounding tissues, including to the inferior vena cava and lower part of the kidney. The lesion was not able to be isolated from the lower part of the kidney, and we proceeded with a surgical removal of ureteral masses and partial nephrectomy. The intraoperative frozen pathology suggested that the lumen of the ureters was filled with spindle cell tumor-like tissue. The pathological results could not be determined as benign or malignant. After fully discussing this situation with family members, the patient underwent laparoscopic right ureter resection for the lesion and end-to-end ureter anastomosis.

Follow-up and outcomes

Follow-up diagnostic and test results

Following the surgical intervention, the patient recovered well and was discharged six days later. A double J stent was removed under ureteroscopy six weeks post-op. CTU showed significantly two months after discharge showed significantly reduced right hydronephrosis (*Figure 3A*). In addition, right retrograde pyelography showed unobstructed spontaneous excretion demonstrating the significant improvement of renal function (*Figure 3B*). Five months after the operation, CTU scans proved that the right kidney

function recovered well again (*Figure 3C*). There was no relapse or organ involvement, and the postoperative serum IgG4 level was 1.27 g/L. Postoperative histopathologic results revealed abundant lymphoplasmacytic infiltration with an increased number of IgG4-positive plasma cells (+, 50–100/HPF and a >40% ratio of IgG4-positive/IgG-positive cells). The diagnosis of IgG4-RD of the Ureter was confirmed. The mass contained hyperplasia of massive fibrous tissue and lymphoid hyperplasia in the ureteral wall, as well as atypical lymphatic follicles, extensive plasma cell infiltration and storiform fibrosis (*Figure 1C*,*1D*). Cell differentiation was relatively mature. The right paraureteral adipose tissue was also affected. Immunohistochemistry showed Vim (+), SMA (+), Desmin (+), CD117 (–), Dog-1 (–), S100 (–), CK20 (–), CK7 (–), P63 (+), CK5/6 (+), GATA3 (–), HMB45 (–), CD34 (blood vessels+), CD20 (B cells+), CD3 (T cells+), CD5 (T cells+), CD23 (FDC+), CD21 (FDC+), Ki-67 (+, 10%). Plasma cells showed CD38 (+), CD138 (+), IgG (+), IgG4 (+, 50–100/HPF), IgG4/IgG >40%.

Patient perspective

I am happy that doctors all over the world are learning from my case and do not mind my condition being discussed. I hope the doctors all over the world have learnt something from reading my case.

Discussion

Clinically, the management of suspicious ureteral masses varies among physicians. Some opt for diagnostic ureteroscopy as the initial step, and subsequent treatment is based on the pathological results. Alternatively, some favor direct nephroureterectomy. Each method has its own advantages and disadvantages. Endoscopic biopsy allows for more reliable results from which treatment is based on, however, this can lead to delayed treatment and increased risk of tumor implantation, as well as increased hospitalization costs for patients due to the staged process. Direct nephroureterectomy, on the other hand, shortens the treatment time, reduces costs, and minimizes the risk of tumor implantation. However, if the pathology report shows benignity, it could result in a lifetime of regret for the patient who lost one side of the urinary tract. Additionally, this can also lead to medical disputes.

IgG4-RD is an autoimmune disorder which involves multiple organs and tissues, and is characterized by elevated serum IgG4 concentrations and IgG4 positive plasma cell infiltration in different tissues. The diagnosis of IgG4-RD is mainly based on pathological examination, and the standards proposed by Umehara *et al.* (3) are currently used: (I) one or multiple organs have diffused or localized masses; (II) serum IgG4 concentrations are ≥1.35 g/L; (III) pathological results demonstrate significant lymphocyte/plasma cell infiltration and fibrosis, IgG4 positive plasma cell infiltration, IgG4/IgG positive cells >40%, and IgG4 positive plasma cells >10/HPF. A patient can be confidently diagnosed with IgG4-RD upon meeting these three criteria. The pathogenesis of IgG4-RD is not yet fully understood. Its key pathological feature is the infiltration of IgG4-positive plasma cells in various organs and tissues, resulting in calcifications and fibrosis and a transition from the inflammatory phase to the fibrotic phase (4).

In this case, the ureteral mass was observed to have severe adhesions to the surrounding tissues, including the inferior vena cava and lower part of the kidney. The inflammatory reaction was consistent with a diagnosis of IgG4-RD. IgG4-RD is more common in men and is usually seen in patients over the age of 60. It is frequently found in salivary glands, pancreas, bile duct, retroperitoneum, lymph nodes and breasts (5). Involvement of the urinary system is rare.

To our knowledge, published literatures concerning ureteral IgG4-RD are rare. The initial documentation of ureteral IgG4-RD can be traced back to a study conducted by Kim *et al.* in 2011 (6). Interestingly, this discovery suggests that a considerable proportion of ureteral IgG4-RD cases may have previously been misidentified as conventional pseudotumor. IgG4-RD is a systemic condition that can potentially affect various urologic sites, making it challenging to diagnose accurately due to its uncommon nature. This disease can sometimes imitate urologic disorders, including cancers. Consequently, it is crucial for urologists to conduct preliminary assessments to prevent inappropriate urologic treatments. By doing so, proper management and care can be provided to patients with IgG4-RD (7).

Radiographic evaluation of urothelial carcinoma and ureteral IgG4-RD can present with similar appearances, making it very probably to undergo nephroureterectomy in order to avoid a missed diagnosis of urothelial carcinoma. However, in our clinical practice, we opt to perform a diagnostic ureteroscopy firstly, thereby avoiding misdiagnosis. Lesions involving the ureter have been previously reported; however, most of these cases were mistakenly thought to be tumors and radical

Table 3 Summary of IgG4-related disease in the ureter

Case	Author	Age	Sex	Clinical diagnosis	Hydronephrosis	Operation
1	Kim *et al.* (6)	45	M	Cancer	–	Nephroureterectomy
2	Hamano *et al.* (8)	60	M	Cancer	+	Nephroureterectomy
3	Nomura *et al.* (9)	79	F	Cancer	+	Nephroureterectomy
4	Lei *et al.* (10)	66	M	Cancer	+	Laparoscopic nephroureterectomy
5	Zhong *et al.* (11)	64	M	Cancer	+	Nephroureterectomy
6	Miyanaga *et al.* (12)	72	M	Cancer	+	Nephroureterectomy
7	Joo *et al.* (13)	53	M	Cancer	+	Nephroureterectomy
8	Marando *et al.* (14)	82	F	Cancer	+	Nephroureterectomy
9	Our case	38	M	Cancer	+	Laparoscopic partial ureteral resection + anastomosis

IgG4, immunoglobulin G4; M, male; F, female.

nephroureterectomy was performed (6,8-14) (*Table 3*). This report details our successful laparoscopic partial ureteral resection and anastomosis for IgG4-related disease of the ureter.

Conclusions

IgG4-RD is a chronic and inflammatory condition that affects single or multiple organs and can often be mistaken for a tumor. In clinical practice, there are patients whose imaging examinations or urine tests are atypical. Therefore, diagnostic ureteroscopy is essential for these patients in order to prevent misdiagnosis. In our clinical experience, we should consider IgG4-RD when faced with a lesion that does not match the typical cases. For examples, a mass with rough edges, poorly-defined boundaries, inflammation, and infiltration in imaging should prompt us to think of IgG4-RD. To confirm the diagnosis, a biopsy may be necessary. Only in this way can we ensure an accurate diagnosis while avoiding misdiagnosis.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-23-33/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-23-33/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-23-33/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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