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CASE REPORT Open Access

IgG4-related tubulointerstitial nephritis accompanied with cystic formation

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Abstract

Background: An immunoglobulin G4 (IgG4)-related disease is important disease in differential diagnosis of tumors in kidney, pancreas, lung and other organs. The imaging findings of IgG4-related kidney diseases are usually expressed as defect contrast region, while cystic formation in kidney is extremely rare. Here, we report a case of IgG4-related tubulointerstitial nephritis with renal cystic change caused by the narrowing or obstruction of collecting duct in renal medulla.

Case presentation: Abdominal contrasted CT scan showed a 31 × 24 mm cystic tumor at the upper pole of the right kidney and multiple low-attenuation areas in the left kidney. ^{18}F-fluorodeoxyglucose (FDG)-PET/CT scan showed moderate FDG accumulation of cystic tumor in marginal lesion. In addition, FDG-PET/CT scan also showed moderate FDG accumulation in the pancreatic body. Laparoscopic right nephrectomy was performed. Histological examination was revealed lymphoplasmacytic infiltrate with focal fibrosis and severe narrowing or obstruction of lumen of collecting duct in renal medulla. Furthermore, the IgG4 positive plasma cells infiltrated exceeding 10 cells per one high-power field in renal medulla. The ratio of IgG4-plasma cells to IgG-positive plasma cells was about 50%. The serum level of IgG4 was also elevated (218 mg/dl). Based on these findings, we finally diagnosed IgG4-related tubulointerstitial nephritis with renal cystic change.

Conclusion: IgG4-related kidney disease might cause cystic formation by severe narrowing and obstruction of collecting duct.

Keywords: IgG4-related tubulointerstitial nephritis, Renal cyst change, Collecting duct

Background

An immunoglobulin G4 (IgG4)-related disease is a newly-proposed clinical disease entity characterized by elevated serum IgG4 and IgG4 positive plasma cell infiltration in various organs. IgG4-related disease was first described as autoimmune pancreatitis (AIP) and has subsequently been described in other organs [1-3]. The affected common site is considered to be pancreas, liver, salivary gland, lung, breast, prostate and kidney. The histological characteristics are lymphoplasmacytic infiltrate, IgG4 plasma cell and fibrosis [4]. Imaging feature is often described as an interstitial lesion [5]. However, we sometimes encounter pseudotumor formation which is not easy to distinguish from malignant tumor [6,7]. Herein, we report a case of IgG4-related tubulointerstitial nephritis with renal cystic change caused by the narrowing or obstruction of collecting duct in renal medulla.

Case presentation

A 63-year-old woman was referred to Kochi University Hospital with a renal tumor discovered by medical examination, incidentally discovered on a computed tomography (CT) scan. There was no previous medical history and family history of kidney disease. Her vital signs were normal value. Blood electrolytes, proteinogram, renal function and hepatic enzymes showed all normal value. Soluble IL-2 receptor was slightly elevated (703 U/ml (normal, 145–519)). The other tumor markers were all within the normal range. Abdominal contrasted CT scan showed a 31 × 24 mm cystic tumor at the upper pole of the right kidney and multiple low-attenuation areas in the left kidney (Figure 1a).

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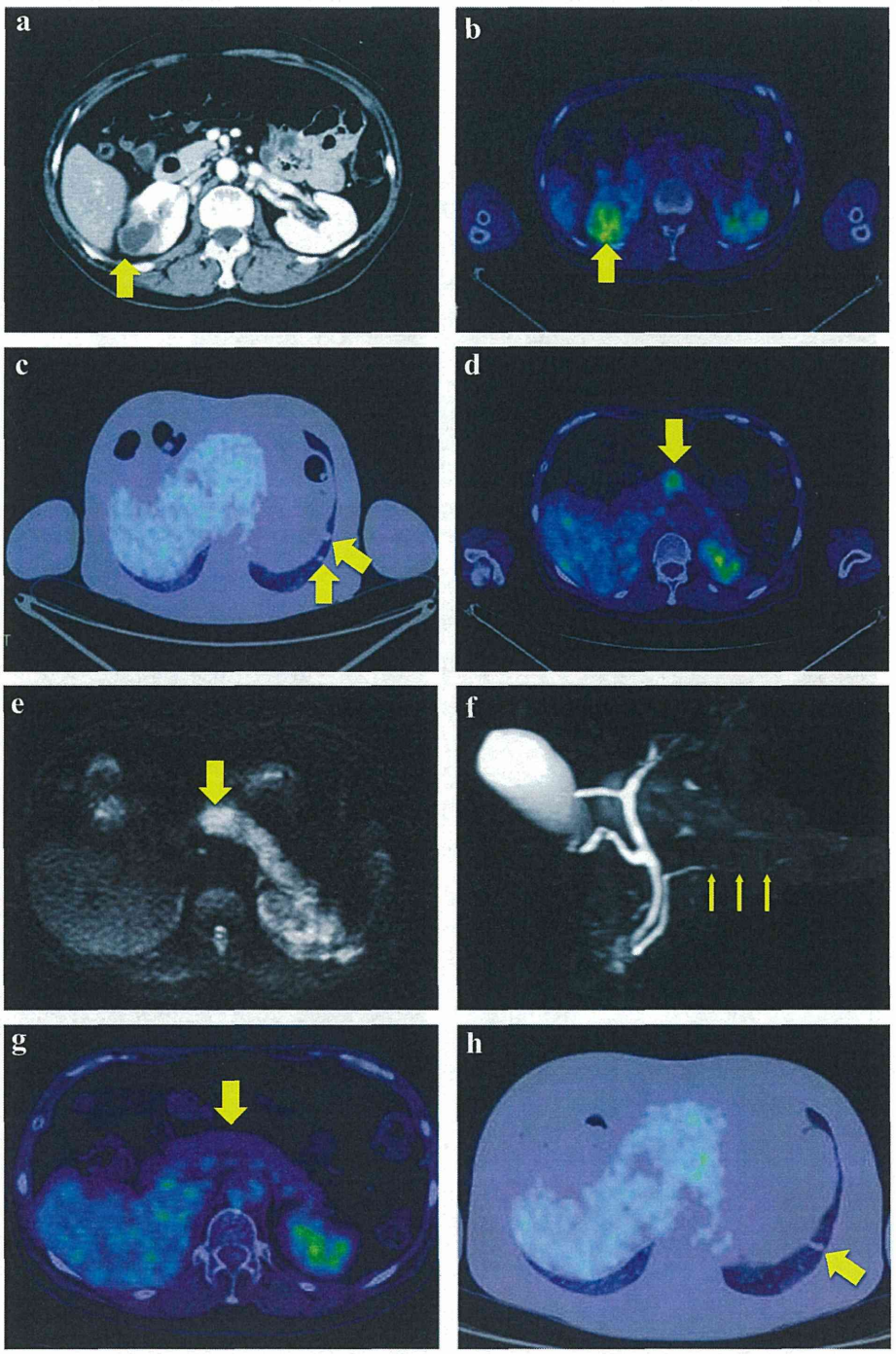

Figure 1 Imaging findings. a. Abdominal computed tomography scan shows 31×24 mm cystic lesion in right kidney (arrows). **b.** PET/CT scan showed moderate FDG accumulation of cystic lesion in right kidney (arrows). **c.** PET/CT scan showed moderate FDG accumulation of lung tumor (arrows). **d.** PET/CT scan showed moderate FDG accumulation of pancreatic body (arrows). **e.** Diffusion-weighted MRI showed high intensity area in pancreatic body (arrows). **f.** MRCP showed irregular narrowing in main pancreatic duct (arrows). **g.** PET/CT scan demonstrated a decrease of FDG accumulation in pancreatic body (arrows). **h.** PET/CT scan demonstrated a decrease of FDG accumulation in lung tumor (arrows).

^{18}F-fluorodeoxyglucose (FDG)-Positron Emission Tomography/Computed Tomography (PET/CT) scan showed moderate FDG accumulation of cystic tumor in marginal lesion (Figure 1b). In addition, FDG-PET/CT scan also showed moderate FDG accumulation in the pancreatic body and small lung mass (Figure 1c, d). Diffusion-weighted magnetic resonance images (MRI) showed high intensity area and focal enlargement on pancreatic body.

Furthermore, main pancreatic duct showed irregular narrowing on magnetic resonance cholangio pancreatography (MRCP) (Figure 1e and f), indicating autoimmune pancreatitis.

Multiple low-attenuation area in left kidney fitted the imaging findings of tubulointerstitial nephritis. However, right renal cystic tumor had diffuse wall thickening and weak enhancement of the cystic wall on CT scan and renal

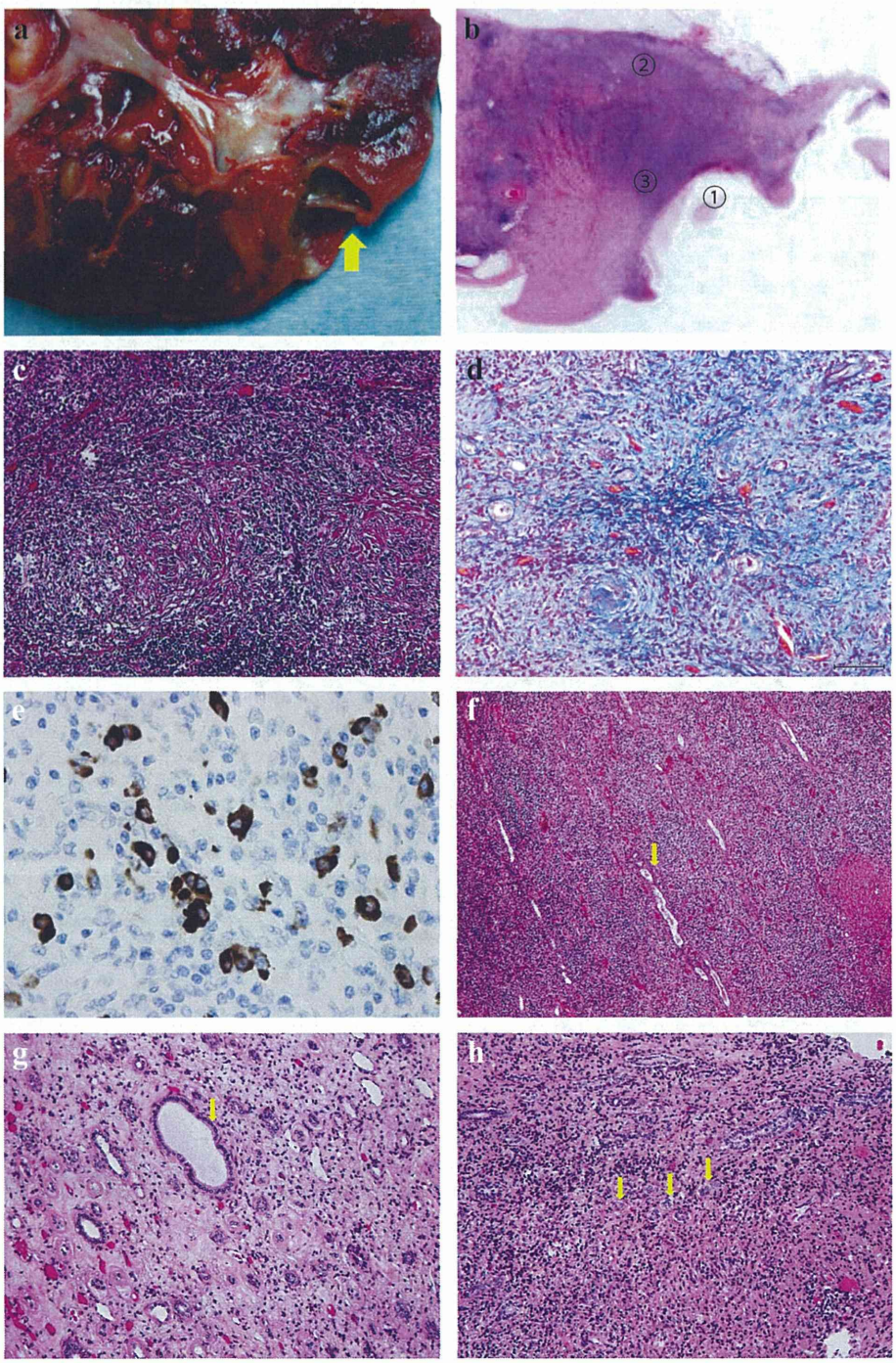

Figure 2 Macroscopic and microscopic findings. a. The macroscopic findings of renal cystic tumor (arrows). **b.** low power loupe images of 3 parts (①; cystic cavity, ②; renal cortex, ③; renal medulla). **c.** H&E stain. Marked lymphoplasmacytic infiltrate and storiform fibrosis. **d.** Storiform fibrosis with Azan staining **e.** Immunohistochemical result. A significant amount of IgG4-positive plasma cells infiltrates in renal medulla. **f.** Collecting duct was compressed longitudinary in renal cortex (arows). **g.** Collecting duct was dilated in renal in renal medulla (arrows). **h.** Collecting duct became narrowed and obstructed in renal medulla (arrows).

cell carcinoma with cystic change was suspected. In imaging test, it was very difficult to distinguish from tubulointerstitial nephritis and malignant renal cystic tumor. Ultimately, we made a preoperative diagnosis as suspicious of renal cell carcinoma with cystic change and then performed laparoscopic right nephrectomy. The macroscopic findings of cystic wall were gray white color and no hemorrhage was observed inside (Figure 2a and b). Histological examination was revealed lymphoplasmacytic infiltrate with storiform fibrosis in renal cortex (Azan staining positive) (Figure 2c and d).

Immunohistochemically, the IgG4 positive plasma cells infiltrated exceeding 10 cells per one high-power field (Figure 2e). The ratio of IgG4-plasma cells to IgG-positive plasma cells was about 50%.

Collecting duct was compressed longitudinally by severe inflammation and fibrosis in renal cortex around cyst (Figure 2f). In contrast, collecting duct had a tendency to dilate in renal medulla adjacent to renal cortex and obstruct in renal medulla away from renal cortex (Figure 2g and h). In additional immunohistochemical analysis of cyst wall showing collecting duct markers, epithelial membrane antigen (EMA), the paired box (PAX) 2 and PAX8, were positive in the lining cell of the cyst wall (Figure 3a and b). While proximal tubule markers, CD10 and renal cell carcinoma marker antigen (RCC-Ma), were negative (Figure 3c and d). Also, cystic wall had no significant malignant components.

Based on pathological results after surgery, then we analyzed stored preoperative serum retrospectively. As a result, the patients had hypocomplementemia and polyclonal gammopathy with elevated levels of serum IgG (1934 mg/dl) and IgE (1061 IU/ml). The serum level of IgG4 was also elevated (218 mg/dl). Finally, we diagnosed IgG4-related tubulointerstitial nephritis with renal cystic change according to a diagnostic algorithm of the Japan Society of Nephrology. After the operation, the patient receives steroidal therapy. Oral prednisolone at initial dose of 30 mg/day was administrated after surgery. Six month after therapy, serum level of IgG4 returns to normal level (28.1 mg/dl) and FDG-PET/CT scan showed disappearance of FDG accumulation in pancreatic body and lung mass (Figure 1g and h).

Discussion

To our knowledge, renal cystic formation of IgG4-related disease in our case is the first reported case in English literatures. The imaging findings of IgG4-related kidney diseases are usually expressed as defect contrast region based mainly on interstitial lesion. While, the mass formation is also found in some cases [6,7]. These cases are difficult to distinguish from renal cell carcinoma by imaging findings. The imaging findings of IgG4-related kidney diseases have some variations. In the representative imaging study by Takahashi et al., they categorized IgG4-related kidney

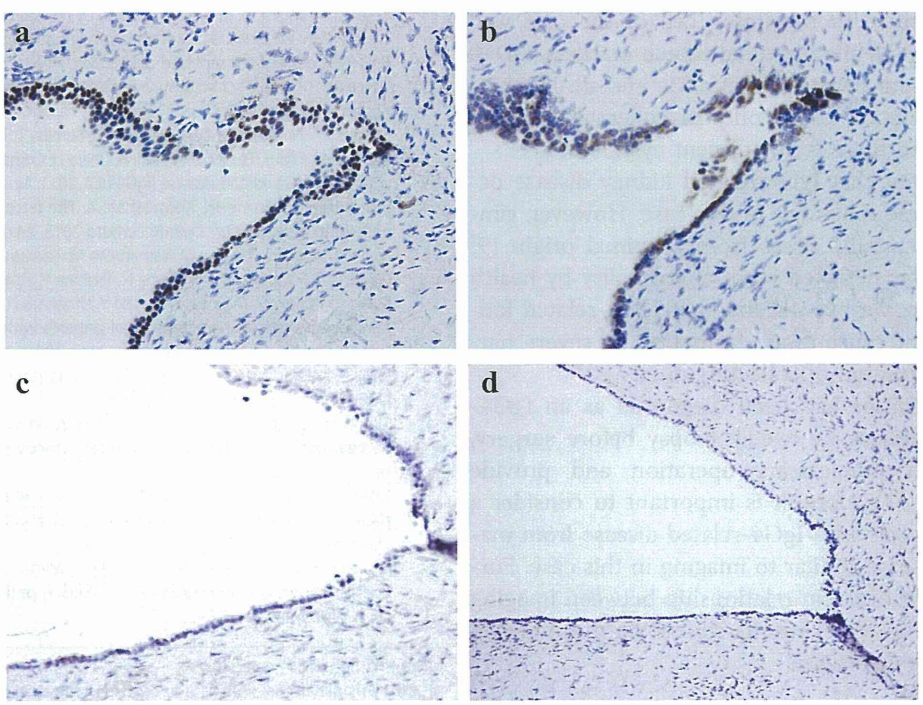

Figure 3 Immunostaining findings. a. Immunohistochemical result. PAX2 highlights cells lining in the cyst wall (collecting duct maker). **b.** EMA highlights cells lining in the cyst wall (collecting duct maker). **c.** RCC-Ma negative cells lining in the cyst wall (proximal duct maker). **d.** CD10 negative cells lining in the cyst wall (proximal duct marker).

disease into four types (1. mass or nodule; 2. diffuse patchy; 3. kidney swelling; 4. pelvic wall thickening) [8]. This case demonstrated cystic formation and did not correspond to any four types in imaging inspection. Then, cystic type of IgG4-related kidney disease is extremely rare.

We assume the mechanism of cystic formation in this case according to pathological examination: lymphoplasmacytic lesion and storiform fibrosis in IgG4-related kidney disease tends to occur in renal cortex. But if inflammation and fibrosis spread to renal medulla, we must consider about affect on collecting duct. In this case, the inflammation and fibrosis in renal cortex spread to renal medulla and induced severe narrowing or obstruction of lumen of collecting duct in renal medulla (Figure 2h). Collecting duct in renal medulla adjacent to renal cortex had a tendency to dilate due to mild inflammation and fibrosis (Figure 2g), whereas collecting duct in renal cortex around cyst was compressed longitudinally by sever inflammation and fibrosis and did not show dilation (Figure 2f).

Thus, spread of inflammation and fibrosis from renal cortex induced atrophy and narrowing or obstruction of lumens of collecting duct in renal medulla (Figure 2h). These findings provide that the severe narrowing and obstruction of collecting duct in renal medulla followed by the dilation of proximal site of collecting duct system and finally led to cystic formation in renal cortex. In immunohistochemical analysis of cyst wall showing the cystic change, collecting duct markers, EMA, PAX2 and PAX8, were positive in the lining cell of the cyst wall (Figure 3a and b). While proximal tubule markers, CD10 and RCC-Ma, were negative (Figure 3c and d). Furthermore, the obstruction exists only in collecting duct of renal medulla and there is no adjacent cystic lesion.

One might point that IgG4-related kidney disease occurred with simple renal cyst in this case. However, simple renal cyst generally arises from proximal origin [9] and she has never detected renal abnormality by health check. Therefore, we hypothesize that IgG4-related kidney disease might cause cystic formation by severe narrowing and obstruction of collecting duct.

If this cystic tumor had been diagnosed as an IgG4-related kidney disease by needle biopsy before surgery, we could avoid unnecessary operation and provide steroid therapy. Therefore, it is important to consider a differential diagnosis with IgG4-related disease from malignant cystic disease similar to imaging in this case. Further case investigations on relationship between imaging findings and pathological results should be examined in IgG4-related kidney disease.

Conclusion

IgG4-related kidney disease might cause cystic formation by severe narrowing and obstruction of collecting duct.

Consent

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations

IgG4: Immunoglobulin G4; AIP: Autoimmune pancreatitis; PAX: Paired box; EMA: Epithelial membrane antigen; RCC-Ma: Renal cell carcinoma marker antigen.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HF drafted the report. YT, SF, KI, SF, YT and TS cared for patient and approved the final version of the manuscript. MM and NK performed histopathological examinations. All authors reviewed the report and approved final version of the manuscript.

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RAPID COMMUNICATION

Spondylodiscitis and Achilles tendonitis due to gout

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Abstract

The patient, a 62-year-old man with a 3-year history of hyperuricemia, presented with severe neck pain, Achilles enthesopathy and polyarthralgia. He consumed alcohol heavily. The biochemical profile was normal except for elevated levels of CRP (3.6 mg/dl; normal < 0.3), uric acid (UA) (10.9 mg/dl; normal 2.5–7.5) and creatinine (1.7 mg/dl; normal 0.5–1.0). Bone scintigraphy showed polyarthritis at the right elbow, wrist and bilateral first MTP joints. Notably, bone scintigraphy with computed tomography also revealed spondylodiscitis of C5-C6, which was confirmed by MRI, and left Achilles tendonitis. Moreover, left Achilles tendonitis was also confirmed by ultrasonography, indicating enthesitis with low-echoic lesion and calcification. Needle aspiration yielded a white viscous liquid, with numerous urate crystals identified on polarized light microscopy. He was diagnosed with gouty arthritis associated with spondylodiscitis and Achilles tendonitis. After the treatment with allopurinol, colchicine and predonisolone, his symptoms were improved, and serum CRP and UA levels were normalized. The cervical spine and Achilles tendon are rare and notable sites of involvements in gout, and differential diagnosis of gouty arthritis from spondyloarthritis, rheumatoid arthritis, tumor, pseudogout, and infection is necessary. When the patient was noted to have neck pain and Achilles enthesopathy, we should always recognize gouty arthritis.

Keywords:

Achilles tendonitis, gout, scintigraphy, spondylodiscitis, ultrasonography

History

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Inflammatory arthritis is caused by several disorders including rheumatoid arthritis, spondyloarthritis, gout, pseudogout, infection, and connective tissue diseases. Of these, gout is the most common cause. The prevalence of gout is rapidly increasing in the general population [1,2]. New diagnostic imaging methods for gouty arthritis have been investigated. Recently, several reports have demonstrated the safe and accurate identification of multiple sites of involvement in patients with gout using ultrasonography (US), magnetic resonance imaging (MRI), and computed tomography (CT) [3,4]. Here, we report a rare and informative case of gout associated with spondylodiscitis and Achilles tendonitis.

A 62-year-old man, with a 3-year history of hyperuricemia, presented with severe neck pain, Achilles enthesitis, and polyarthralgia. He was a heavy drinker, consuming two to three alcoholic beverages per day. His biochemical profile was normal except for elevated levels of C-reactive protein (3.6 mg/dl; normal < 0.3), uric acid (10.9 mg/dl; normal 2.5–7.0), and creatinine (1.7 mg/dl; normal 0.5–1.0). Plain X-ray showed no calcification in each joint. Bone scintigraphy (Figure 1A) showed polyarthritis at the right elbow and wrist, and bilateral first metatarsophalangeal (MTP) joint. Notably, bone scintigraphy with CT also revealed spondylodiscitis with bone erosion of C5-C6 (Figure 1A and B), which was confirmed by MRI (Figure 1C). Bone scintigraphy with CT also revealed left Achilles tendonitis (Figure 1A). This was confirmed by US, which indicated enthesitis with a low-echoic lesion and calcification (Figure 1D). Needle aspiration yielded a white viscous liquid, with numerous urate crystals detected by polarized light microscopy (Figure 1E). The patient was diagnosed with gouty arthritis associated with spondylodiscitis and Achilles tendonitis/enthesitis. Treatment with daily oral prednisolone (PSL) (15 mg) and colchicine (0.5 mg) was initiated, and after acute attack was followed by daily oral febuxostat (10 mg). PSL was tapered and stopped after 3 weeks. Following treatment, the patient's symptoms improved and serum C-reactive protein and uric acid levels normalized, and he was discharged without further complications.

Recent report demonstrated that tendons are commonly affected by monosodium urate crystal deposition in patients with tophaceous gout, and that the Achilles tendon is the most commonly involved tendon/ligament site (39.1% of all Achilles tendons) by dual-energy CT study [5]. Another US-controlled study showed that Achilles enthesitis was more frequent in hyperuricemic than normouricemic individuals (15% vs. 1.9%) [6]. However, spinal gout is not as rare as previously thought. Recent reports demonstrated that lesions of the spine, including the discs, vertebral bodies, and facet joints, were present in 35% of gout cases [7,8].

Consistent with this report, spondylodiscitis and Achilles tendonitis due to gout often mimic heterogeneous spinal conditions and peripheral enthesitis such as spondyloarthritis. The cervical spine and Achilles tendon are informative and notable sites of involvement in gout, and this possibility indicates the need to diagnose gouty arthritis from spondyloarthritis, rheumatoid arthritis, tumor, pseudogout, and infection. In addition, bone scintigraphy with CT helps in evaluating the extent of gouty arthritis. Gouty arthritis should always be considered in patients with neck pain and Achilles enthesitis.

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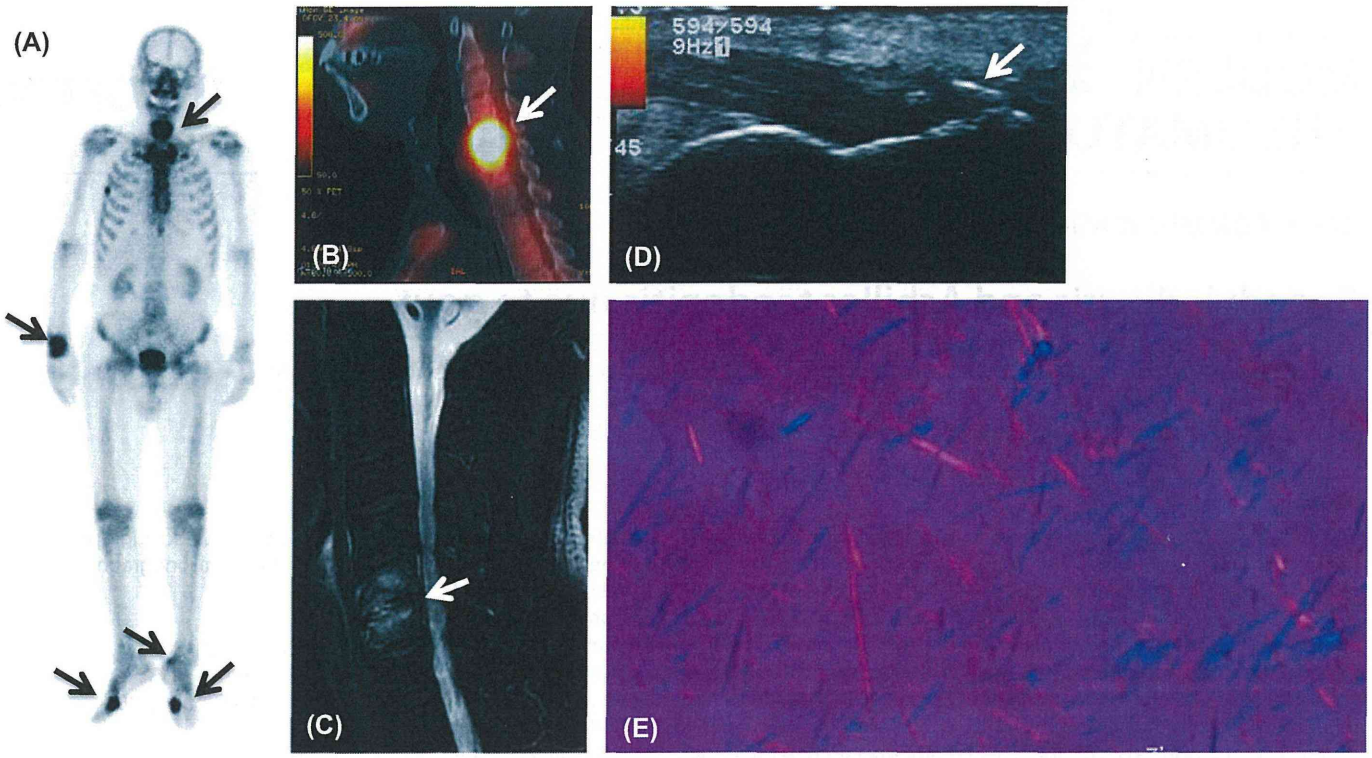

Figure 1. (A) Evaluation of widespread inflammatory sites of involvement by bone scintigraphy; (B) C5-C6 spondylodiscitis detected using bone scintigraphy with CT; (C) C5-C6 spondylodiscitis detected by MRI (fat-suppressed T2 weighted imaging) of the cervical spine; (D) Achilles enthesitis with low-echoic lesion and calcification detected by US; (E) Spiked rods of numerous monosodium urate crystals detected by polarized light microscopy from synovial fluid and tissue.

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Conflict of interest

None.

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RAPID COMMUNICATION

Clinical characteristics of Japanese patients with reactive arthritis following intravesical BCG therapy for bladder cancer

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Keywords

Bacillus Calmette-Guerin, Reactive arthritis, Bladder cancer, Enthesitis

History

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Intravesical instillation of Bacillus Calmette-Guerin (BCG), a live attenuated vaccine prepared from attenuated strains of *Mycobacterium bovis*, is an effective immunotherapy for bladder cancer, especially, superficial bladder cancer. Intravesical therapy is commonly used as a prophylactic treatment to prevent recurrence of the disease, and as a therapeutic treatment to eliminate residual small volume disease and carcinoma in situ, and therefore to prevent the progression of the tumor. However, the exact mechanism of action is not fully understood. BCG acts by stimulating the inflammatory response and the local cytokine production rather than directly killing the neoplastic cells. Reactive arthritis (ReA) is an adverse event of BCG therapy with a reported incidence of 0.5–1% in Western countries [1,2], while approximately 90% of patients who received BCG immunotherapy have cystitis [3]. The incidence and clinical characteristics of ReA caused by intravesical BCG therapy (iBCG) in Japanese patients are not well known. In the present study, we examined the incidence and clinical characteristics of ReA caused by iBCG for bladder cancer in Japanese patients.

Of the 1054 Japanese patients with bladder cancer who were treated at our hospital from March 1997 to October 2012, we retrospectively reviewed the clinical features, and laboratory and imaging findings of 134 patients who received iBCG. We also examined the incidence of specific iBCG complications including ReA, uveitis, conjunctivitis and hepatic dysfunction, and performed human leukocyte antigen (HLA) typing. This study was approved by the Ethics Committee of Kochi University Hospital and conducted in accordance with the Declaration of Helsinki. Data are presented as mean ± SD.

Of the 134 patients who received iBCG, 95 were male and 39 were female, with a mean age of 71 ± 10 years. Presenting symptoms were fever, hematuria, and dysuria in 40 (30%), 41 (31%), and 59 (44%) patients, respectively. ReA developed in 3 (2.2%) patients (age, 67 ± 9 years; all males), while uveitis occurred in 3 (2.2%; age, 64 ± 5 years; 2 males and 1 female; 2 patients also had ReA) and conjunctivitis in 12 (8.9%; age, 67 ± 8 years; 9 males and 3 females) patients. Of the three patients with ReA, two also had uveitis and two developed hepatic dysfuntion. All cases of ReA developed after three or more instillations of iBCG at 40–80 mg/dose (Immunobladder®) (Table 1). Clinical findings including those of ultrasonography and Positron Emission Tomography/Computed Tomography with [18F] fluorodeoxyglucose (FDG-PET/CT) showed asymmetric polyenthesitis and polyarthritis involving the shoulder (% of patients, 66.6%), sternoclavicular joint (33.3%), spinous process (33.3%), sacroiliac joint (33.3%), ischial tuberosity (66.6%), hip (100%), knee (100%), and ankle (100%), and signs were predominately in the lower extremities (Figures 1 and 2). Laboratory tests showed high elevated levels of C-reactive protein (CRP) (14.8 ± 3.6 mg/dl), erythrocyte sedimentation rate (ESR) (135 ± 8 mm/1 h) and matrix metalloproteinase-3 (MMP-3) (169.5 ± 10.1 ng/ml) in all three cases, while HLA-B27 was positive in only one case (33%) (Table 1). ReA improved after treatment with oral prednisolone (10–15 mg/day) in all cases, isoniazid in 1/3 cases and celecoxib in 2/3 cases combined with iBCG cessation. The treatment of isoniazid is not always necessary, and should be reserved for patients who fail to respond by nonsteroidal anti-inflammatory drugs. Uveitis and conjunctivitis were treated with corticosteroid eye drop.

In the present study, the incidence of iBCG-induced complications of ReA, uveitis and conjunctivitis, was higher than expected. The distribution pattern of arthritis and enthesitis indicated an asymmetric polyarthritis and polyenthesitis (Figure 2), consistent with that observed in Western countries [2]. Interestingly, in the present study, the rate of patients affected spinous process, sacroiliac joint and ischial tuberosity was higher than the report from Western country [2]. Furthermore, in Japanese iBCG-induced ReA and uveitis patients, the development of hepatic dysfunction is a notable finding. However, the relationship between ReA and hepatic dysfunction observed in the present study is unclear, and following study is expected.

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Table 1. Characteristics of patients with reactive arthritis, uveitis, and conjunctivitis caused by intravesical BCG therapy.

	iBCG-induced ReA	Uveitis	Conjunctivitis
Age (mean ± SD)	67 ± 9	64 ± 5	67 ± 8
Number of male/femal	3/0	2/1	9/3
No. of doses before complication	5 ± 2	5 ± 1	6 ± 2
CRP (mg/dl)	14.8 ± 3.6	ND	ND
ESR (mm/hour)	135 ± 8	ND	ND
MMP-3 (ng/ml)	169.5 ± 10.1	ND	ND
HLA-B27 positive (%)	33.3 (1/3 cases)	0	0

ND not done, *ReA* reactive arthritis.
Patients characteristics are shown. Data are expressed as mean ± SD.

It is important to clarify the epidemiology of iBCG-induced ReA in the Japanese population, and it might help to elucidate the pathomechanism. The pathomechanism of ReA caused by iBCG might involve enhancement of the BCG-induced cytotoxic immune response due to cross-reactivity with endogenous heat shock protein presented by HLA-B27 [4]. The reported prevalence of HLA-B27 in cases of iBCG-induced ReA in Western countries is 50.9–53% [2,5], whereas HLA-B27 positivity was 33% in the present study and was not detected in other reported cases in Japan [6]. This suggests that a common HLA genotype and genetic predisposition to iBCG-induced ReA may be absent in Japanese patients. The incidence of ReA in Japanese patients treated with iBCG in the present study was 2.2%, which is similar to the 0.5–1% reported in Western countries [1,2]. However, the

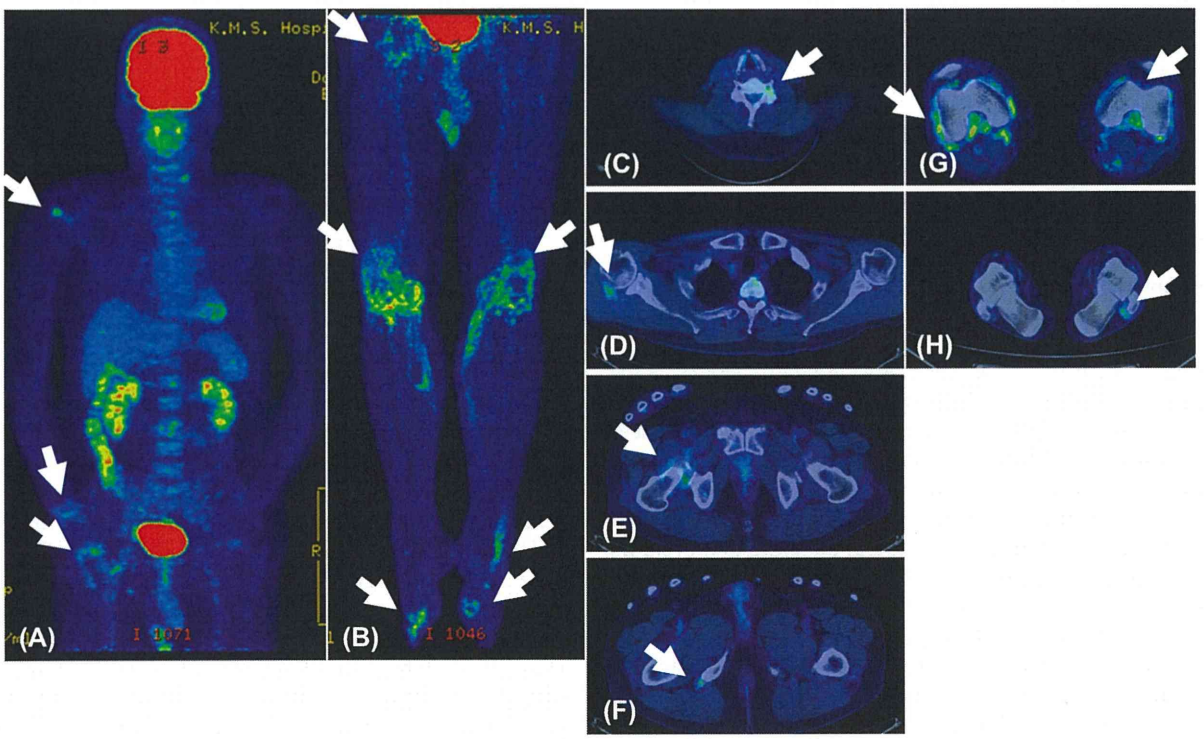

Figure 1. FDG-PET/CT findings of Case 1. Evidence of polyenthesitis and polyarthritis (A and B) was observed in the spinous process (C), shoulder (D), hip (E), ischial tuberosity (F), knee (G) and ankle (H) (*arrows*).

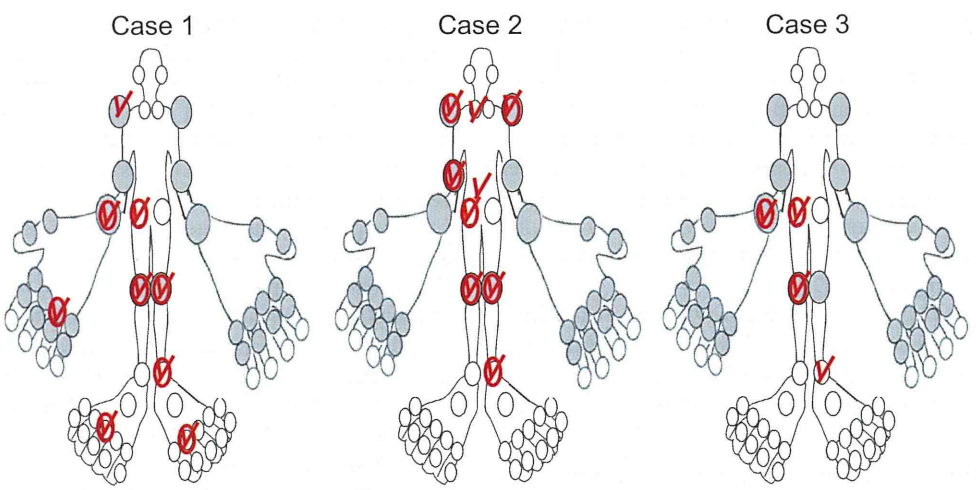

Figure 2. Distribution of enthesitis and arthritis in the three ReA cases. The distribution pattern of polyenthesitis and polyarthritis was asymmetric (v, tenderness; o, swelling).

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proportion of healthy Japanese individuals positive for HLA-B27 is reported to be 0.5% [7]. Therefore, in addition to the HLA genotype of Japanese patients, a cross-reaction between a mycobacterium epitope and joint cartilage antigen might also contribute to the pathogenesis of iBCG-related ReA. Further studies of iBCG-induced ReA are needed to determine its incidence, pathogenesis, and pathophysiology in the Japanese population.

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Conflict of interest

None.

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