Unexpected discovery of renal mass in a patient with granulomatosis with polyangiitis: accidental or inevitable?

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is an uncommon disorder that mainly involves the upper and lower respiratory tract and kidney, presenting as sinusitis, saddle nose, otitis media, pulmonary nodule and cavity, rapidly progressive glomerulonephritis. It also affects skin, eye, heart, joint and nervous system. Renal involvement in GPA is commonly manifested as necrotising glomerulonephritis, while renal mass is very rare. We herein present two hospitalised cases with fever, pulmonary cavity and renal mass. Clinical course and examinations of the cases, from symptoms to diagnosis, will be discussed in detail, along with a relevant literature review of this unusual renal manifestation.

Introduction

Granulomatosis with polyangiitis (GPA) is classified as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which is a systemic vasculitis of small vessels, including microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and GPA. It is characterised by lesions in the upper and lower respiratory tract, kidney, and other sites including skin, eyes, heart, joints and nervous system (1-4). Pathological changes of GPA include arteriolitis and venulitis infiltrated by inflammatory cells, resulting in necrotising granulomatous inflammation and necrotising glomerulonephritis. In 1990, the American College of Rheumatology (ACR) published criteria for the classification of Wegener's granulomatosis (presently named GPA) (5), which was effective and widely accepted. In 2011, it was proposed to change the name 'Wegener's granulomatosis' to 'granulomatosis with polyangiitis'(6), and the nomenclature was clarified in 2012 (7). In 2022, ACR published the revised criteria for the classification of GPA based on real-world cases enrolled in the Diagnostic and Classification Criteria for Vasculitis (DCVAS) study and validated on a separate set of patients, with a higher sensitivity of 93% (95% confidence interval [95% CI] 87–96%) and a specificity of 94% (95% CI 89–97%) (8). The final criteria moved from the 'number of criteria' rule, as used in the ACR 1990 criteria, toward weighted criteria with threshold scores, because certain items within a criteria list may be more discriminative. The final criteria and their weights were as follows: (1) bloody nasal discharge, nasal crusting, or sinonasal congestion (+3); (2) cartilaginous involvement (+2); (3) conductive or sensorineural hearing loss (+1); (4) cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) or anti-proteinase 3(PR3) ANCA positivity (+5); (5) pulmonary nodules, mass, or cavitation on chest imaging (+2); (6) granuloma or giant cells on biopsy (+2); (7) inflammation or consolidation of the nasal/paranasal sinuses on imaging (+1); (8) pauci-immune glomerulonephritis (+1); (9) perinuclear ANCA(p-ANCA) or anti-myeloperoxidase (MPO) ANCA positivity (-1); (10) eosinophil count ≥1×109/litre (-4). After excluding mimics of vasculitis, a patient with a diagnosis of small- or medium-vessel vasculitis could be classified as having GPA if the cumulative score was ≥5 points (9). Among the final criteria, the renal involvement commonly manifests as necrotising glomerulonephritis, while renal mass is very rare. We herein present two hospitalised cases with fever, pulmonary cavity and renal mass, one with right renal mass and the other with bilateral renal masses. After combined therapy with glucocorticoid (GC) and cyclophosphamide (CYC), the renal masses remained unchanged or shrunk.

Case reports

Patient A

A 51-year-old man presented with fever, cough and sputum for two months, with aggravating chest pain one month prior to admission. He denied haematuria, foam in urine, oedema or discomfort in renal region. Chest computed tomography (CT) revealed high-density patches and masses with coarse margin and cavity in posterior segment of upper lobe and basal segment of lower lobe of right lung. A bronchoscopy biopsy of lung tissue revealed neutrophilic infiltration and focal necrosis. The patient with suspected pulmonary

abscess received a complete course of broad-spectrum antibiotics (meropenem 1g ivgtt q8h and vancomycin 1g ivgtt q12h were given for one week) in the local hospital, but the symptoms aggravated with increased temperature (Tmax 38→39.8°C), newly onset chest pain and enlarged high-density shadow of upper and lower lobe of right lung on CT image. The unsatisfactory treatment response and the negative microbiological test results without evidence of opportunistic infection did not support the earlier diagnosis of bacterial pulmonary abscess. The patient then underwent wedge resection of upper and lower lobes of the right lung. The diagnosis of carcinoma was temporarily excluded since intraoperative frozen section examination revealed no tumour cells. Then the patient was further transferred to our hospital.

Upon admission, the patient reported bilateral hearing loss (particular on the left) since 2005 and left ear pyorrhoea without tinnitus. Physical examination showed hearing loss in the left ear and mild percussive pain in the right renal region. Laboratory tests showed elevated erythrocyte sedimentation rate (ESR, 114 mm/h) and hypersensitive C-reactive protein (hsCRP, 44.7 mg/L), along with c-ANCA positivity at the titer of 1:10 and elevated PR3 ANCA levels (59 RU/ml). The tumour markers were negative. Serum creatinine, urine routine and urinary sediment microscopy results were within normal range. Ear, nose and throat (ENT) examination showed mild conductive hearing loss in the left ear and moderate conductive hearing loss in the right ear, indicating chronic suppurative otitis media. Nasal CT showed paranasal sinusitis. The histopathological examination of the specimen obtained on the wedge resection of the lung showed characteristic features of GPA, including massive necrosis of lung tissue, multiple suppurative granulomas and focal vasculitis.

Suspecting AAV, the patient was thoroughly evaluated, and an ultrasound of urinary system accidentally revealed a mass in the central portion of the right kidney, measuring 3.3×2.9 cm, with a regular shape, clear boundaries, hypoechoic rim and surrounding blood flow.

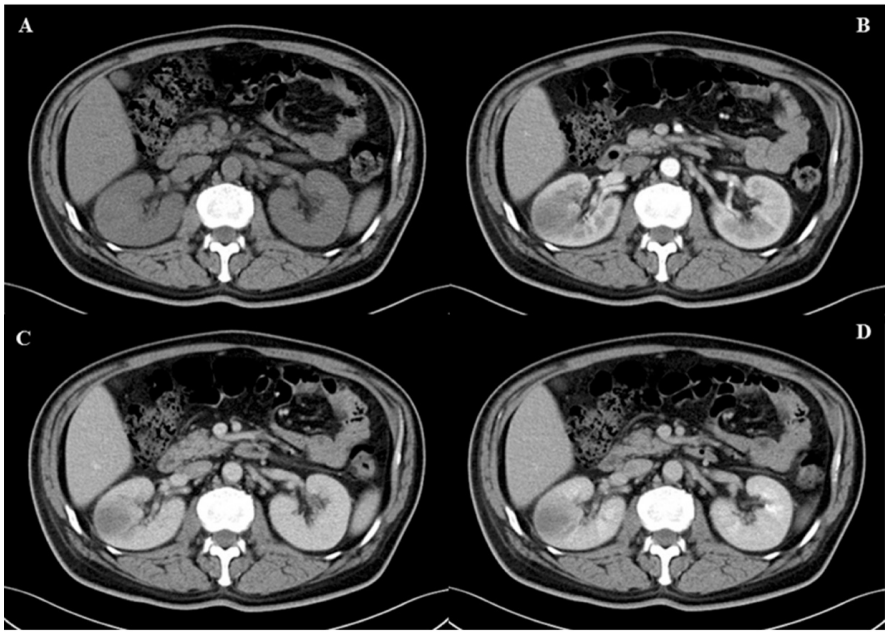

Fig. 1. Abdominal contrast-enhanced CT of patient A.
(A) Flat scan phase; **(B)** Arterial phase; **(C)** Venous phase; **(D)** Delayed phase.
The renal mass presented as an ill-defined, iso- and low-density area about 3.0×3.2cm in size with necrosis without obvious enhancement in right kidney.

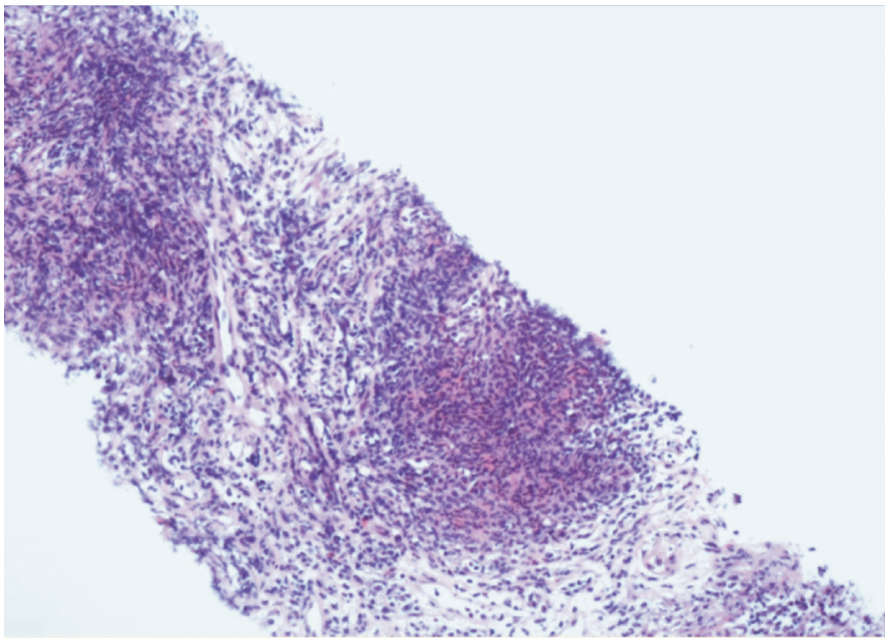

Fig. 2. Histopathologic specimen of renal tissue obtained from renal biopsy: chronic granulomatous inflammation and focal vasculitis, glomerular atrophy, supporting the diagnosis of GPA.

Contrast-enhanced CT of abdomen showed an ill-defined, equal and slightly low-density mass measuring 3.0×3.2 cm with necrosis and no apparent enhancement in the right kidney (Fig. 1).

With systemic involvement (ear, nasal sinus, lung), elevated inflammatory markers (ESR and hsCRP), ANCA (c-ANCA and PR3-ANCA) positivity, exclusion of infection and tumour, and pathological evidence, the cumulative score according to the 2022 ACR classification criteria for GPA (9) was 11, and he was diagnosed with AAV, classified as GPA.

GPA can be characterised as either systemic or localised, depending on the presence or lack of renal involvement,

which typically manifests as necrotising glomerulonephritis. Renal mass with normal urinalysis and serum creatinine, as our patient displayed, is extremely uncommon. CT-guided renal mass biopsy was performed to determine whether it was renal cancer or inflammatory pseudotumour. Histopathological examination of the biopsy-obtained renal tissue showed chronic granulomatous inflammation and focal vasculitis, supporting the diagnosis of GPA (Fig. 2).

Following the diagnosis of GPA, remission induction therapy with high-dose glucocorticoid (methylprednisolone 80mg qd ivgtt) and immunosuppressant (CYC 0.8 g qw ivgtt) was initiated. During the course of treatment, clinical symptoms, inflammatory biomarkers, and radiologic changes of the lung and kidney were carefully monitored. The size of the renal mass did not alter much. However, other monitoring index, including body temperature, respiratory symptoms and inflammatory biomarkers (ESR 114 mm/h→40 mm/h, hsCRP 44.7 mg/L→16.26 mg/L) improved significantly. Chest CT also showed that the cavity and nodules of right lung were significantly absorbed. Considering effective treatment, the dose of glucocorticoid was reduced to prednisolone 60 mg qd po and the dose of CYC was adjusted to 150 mg qd po. The patient was discharged and the dose of glucocorticoid was reduced regularly during the outpatient follow-up in the subsequent six months. Re-examination of CT showed that the pulmonary cavity and nodules had shrunk, and the pleural fluid had been absorbed. The renal mass, however, remained almost the same size during follow-up.

Patient B

A 29-year-old woman experienced hearing loss for 7 months, fever and facial paralysis for 6 months, cough and sputum for 20 days before hospitalisation. The inflammatory markers were elevated (hsCRP 110mg/L, ESR 94mm/h). The haematological results for infection-related parameters were negative. Immunological tests revealed elevated anti-nuclear antibodies (ANA) with a titer of 1:100 and elevated PR3-ANCA (111.98U/ml). The urinary analysis revealed haematuresis with 100% of aberrant RBC. The urinary protein test showed a 24h urinary protein level of 0.01g/24h. Serum creatinine then was unknown, Magnetic Resonance Imaging (MRI) of the brain showed bilateral ethmoid and sphenoid sinusitis as well as mastoiditis. Chest CT showed bilateral, multiple nodules with bilateral pleural effusion. The patient didn't take radiologic examination of abdomen so the situation of the kidney was unknown. Lung tissue obtained through CT-guided biopsy of the lung nodules revealed chronic inflammation, fibrous hyperplasia and localised multinucleated giant cell reaction. Suspected with GPA, immunosuppressive therapy with glucocorticoid (dexamethasone 10 mg qd iv for 16 days followed by prednisone 20 mg tid for 1 month, then reduced 5 mg every 2 weeks to 40mg qd, and reduced 5 mg every month to 30mg qd) was initiated. The therapeutic regimen of the immunosuppressant was unknown. The body temperature returned to normal in two weeks and hearing loss was temporarily alleviated. However, as the dose of glucocorticoid was decreased, the patient developed bilateral palpebral conjunctiva congestion, oedema and left temporal para-eyelid pustule, along with impaired left eyesight, followed by cough and sputum with occasional blood streaks for 20 days before admission. Orbital MRI showed oval and lengthy aberrant signal alternations between lateral walls of orbits and rectus lateralis on the T1-weighted imaging (T1WI), and cystoid hyperintensity within the left eye lesion on fat suppression T2-weighted imaging (FS-T2WI). The patient was subsequently admitted to our hospital.

On admission, she still had cough and yellow sputum with occasional blood streaks, but denied haematuria, foam in urine, oedema or discomfort in renal region, and she was taking prednisone (30mg qd po), CYC (100mg qd po) and compound sulfamethoxazole (2 tablets bid). The physical examination showed skin ulceration and crust with a 1cm-diameter on the temporal side of left eye, bilateral palpebral oedema, bilateral palpebral conjunctiva congestion. Solid lumps were palpable in the bilateral lacrimal gland regions. There were multiple ulcerations on the lingual and maxillary mucosa. Lung auscultation revealed reduced breath sounds in bilateral lower lung fields, particular the left lung filed. Diplopia was induced by looking upwards, downwards and leftwards. Flattening of forehead, poor eyelid closure, weakness of orbicularis oris were seen on the left. The haematological examinations revealed elevated ESR (68mm/h) and hsCRP (15.31mg/L), along with C-ANCA positivity at the titer of 1:40 and elevated PR3 ANCA levels (>200 RU/ml). Examinations of extractable nuclear antigen (ENA) antibodies were negative. The haematological results for infection-related parameters revealed HBsAg positivity, indicating that the patient was an HBV carrier. Serum creatinine, urine routine and urinary sediment microscopy results were within normal range. ENT examination showed severe conductive hearing loss in the left ear and mild conductive hearing loss in the right ear. A contrast-enhanced MRI combined with diffusion weighted imaging (DWI) revealed bilateral mastoiditis. Chest high-resolution CT (HRCT) revealed multiple nodular masses with cavities, hilar and mediastinal lymph nodes enlargement, consistent with clinical features of GPA.

These findings met the 2022 ACR classification criteria (9) for GPA based on bilateral conductive hearing loss (symptoms, +1), c-ANCA/PR3-ANCA positivity (serological findings, +5), the multiple pulmonary nodular masses and inflammation of paranasal sinuses (imaging findings,+3) and granulomatous lesions (histological findings,+2). With a total score of 11, the patient was diagnosed with AAV, classified as GPA. Although the patient denied renal symptoms, ultrasound of urinary system was taken and detected multiple cystic masses in both kidneys. Contrast-enhanced abdominal CT showed bilateral multiple cystic renal masses (Bosniak class II) (Fig. 3-1). Percutaneous renal biopsy was not performed since the patient had multiple cystic renal masses without renal function impairment, haematuria or proteinuria.

Following the diagnosis of GPA and exclusion of active infection, remission

induction therapy with high-dose glucocorticoid (methylprednisolone 160 mg qd ivgtt for 3 days, then reduced to 80 mg qd ivgtt for 2 weeks) and immunosuppressant (CYC 0.8g qw ivgtt) was started. Meanwhile, antiviral treatment for hepatitis B (lamivudine 0.1g qd po) was administered according to the patient's positive HBsAg status. During the course of treatment, clinical symptoms, inflammatory biomarkers, and radiologic changes of eyes, lung and kidney were carefully monitored. The cystic renal masses were significantly absorbed (Fig. 3-2). Additionally, other monitoring index, including body temperature, visual, hearing and respiratory symptoms, inflammatory biomarkers (ESR 68 mm/h→5 mm/h, hsCRP 15.31 mg/L→0.97 mg/L) and titre of c-ANCA (1:40→1:20) improved significantly. Masses of bilateral lacrimal glands and lungs were also significant reduced just as the renal masses did, indicating that the renal masses were inflammatory pseudotumours resulting from GPA. The dose of glucocorticoid was reduced to prednisolone 55 mg qd po and the dose of CYC was reduced to 1g q3w ivgtt. The patient was discharged and the dose of glucocorticoid was lowered on a regular basis during outpatient follow-up.

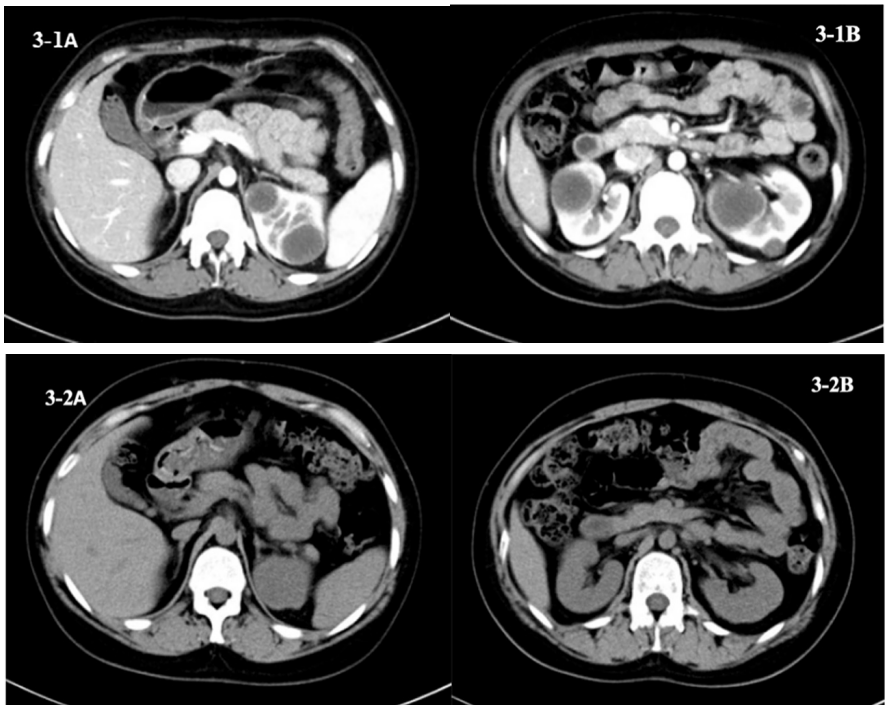

Fig. 3. Abdominal CT of patient B before and 2 weeks after initiation of treatment.
3-1A and B: Abdominal contrast-enhanced CT before treatment; **3-2A and B**: Abdominal CT 2 weeks after initiation of treatment.
Cystic renal masses were significantly absorbed.

Discussion

Granulomatosis with polyangiitis (GPA), formerly named Wegener's granulomatosis (6, 7), is a multisystemic vasculitis. GPA is an uncommon disorder, with the prevalence ranging from 2.3 to 146.0 cases per million persons, and an incidence of 0.4 to 11.9 cases per million person-years (4). It is most prevalent among the elderly and uncommon among children, although it has been reported at all ages, with no significant difference of incidence between males and females (4). GPA mainly affects the population predominantly of European ancestry and is rarely observed in East Asia (10, 11). Clinically, GPA has varied presentations ranging from nonspecific symptoms such as fever, fatigue, myalgias, arthralgias, anorexia and weight loss, which may overshadow other symptoms, leading to suspicion of carcinoma, to life-threatening complications, including pulmonary haemorrhage and rapidly progressive renal failure. Among the clinical presentations, involvement of upper and lower respiratory tracts, and kidneys are the most common, other involved sites include skin, eye, heart, joint and nervous system (4).

The typical clinical presentation of renal involvement is glomerulonephritis (GN), in which rapidly progressive glomerulonephritis (RPGN) may be life-threatening. Evident GN may present in only eighteen percent of patients at presentation, but subsequently developed in 77 to 85 percent of patients, usually within the first two years of disease onset (12, 13). RPGN usually presents as rapidly rising serum creatinine with haematuria and proteinuria, while the imaging findings are non-specific, including increased echogenicity of the kidneys as the early sign, and scarred and shrunken appearance in chronic renal failure at ultrasound examination (14).

Renal mass is a very rare manifestation. In the thirty-five cases reported so far (including the two cases in our case report), GPA has been reported to present with solitary (26/35), or multiple unilateral (2/35), multiple bilateral (7/35) renal masses and very rarely, restricted to renal mass without systemic involvement (5/35). Among those case reports, thirty-one cases were diagnosed as inflammatory pesudotumour(s), three cases were renal cell carcinoma with possible association with long-term immunosuppressive treatment, and one case reported the coexistence of renal cell carcinoma and GPA without medication history of immunosuppressant. Summaries of the case reports are shown in Table I.

Renal masses associated with GPA commonly present with systemic involvement. Most of the published case reports presented with similar presentation with systemic involvement. Among them, ENT involvement is the most common (28/35), followed by pulmonary (14/35) and ophthalmic involvement (6/35) (15-19), respectively. Other sites including CNS (20, 21), pituitary (22), peripheral nervous system (PNS) (21-23), skin (24), spleen (25), prostate (26) and musculoskeletal involvement (21) are also reported to be involved. Cases with solitary renal mass without systemic involvement are

Table I. Summary of the published case reports of GPA with renal mass.

Author	Age /Sex	Systemic involvement	Urinalysis Creatinine	ANCA	Histology (GN-1, Granuloma-2, Vasculitis-3, Fibrosis-4)	Diagnostic approach	Renal mass	Initial treatment
Higashi-hara (27)	75/F	Kidney	Haematuria, proteinuria, Renal failure	Negative	1,2,3,4	Nephrectomy	Inflammatory pseudotumour (solitary)	GC, dialysis
Tiwari (15)	60/F	ENT, eye, kidney (renal mass)	Normal	P-ANCA Anti-MPO	2	Renal biopsy	Inflammatory pseudotumour (solitary)	GC + MTX
Yama-moto(28)	60/M	Kidney (renal mass)	Normal	Anti-MPO	2,3,4	Nephrectomy	Inflammatory pseudotumour (solitary)	GC
Boncoraglio (26)	47/M	ENT, kidney, prostate	Haematuria, proteinuria, renal failure	ANCA Anti-PR3	1,2,4 **IgG4/IgG ratio >40%**	Partial nephrectomy	Inflammatory pseudotumour (overlap of IgG4-RD and GPA, solitary)	GC+RTX
Dai (43)	32/M	ENT, lung, kidney (renal mass)	Normal	C-ANCA Anti-PR3	2,4	Renal biopsy	Inflammatory pseudotumour (solitary)	GC+ CYC
Vandergheynst (22)	23/F	ENT, pituitary, kidney (renal mass)	Normal	P-ANCA Anti-MPO	1,2	Renal biopsy	Inflammatory pseudotumour (multiple, bilateral)	GC + RTX
Xu (30)	55/M	Kidney (renal mass)	Haematuria	Anti-PR3	1	Radical nephrectomy	Inflammatory pseudotumour (solitary)	NM
Ward (20)	48/F	ENT, CNS, kidney (renal mass)	NM	C-ANCA	2	Radical nephrectomy	Inflammatory pseudotumour (solitary)	GC+CYC
Lo Gullo (42)	38/M	ENT, lung, kidney (renal mass)	Normal	ANCA Anti-PR3	2 (not well-formed)	Renal biopsy	Inflammatory pseudotumour (solitary)	GC+RTX
Mohammadi (41)	22/F	ENT, kidney	Microscopic haematuria, proteinuria	NM	2,3,4	Renal biopsy	Inflammatory pseudotumour (solitary)	No (death before treatment initiation)
Dufour (21)	70/M	ENT, lung, kidney, PNS	Increased serum creatinine	P-ANCA Anti-MPO	1,2,3,4	Radical nephrectomy	Inflammatory pseudotumour (solitary)	GC+CYC
Dufour (21)	67/M	Musculoskeletal, CNS, lung, kidney	Normal	Anti-PR3	NM	NM	Inflammatory pseudotumour (solitary)	GC+CYC
D'Hauwe (35)	14/F	ENT, kidney (renal mass)	Massive sterile pyuria	Negative	2	Renal biopsy	Inflammatory pseudotumour (solitary)	GC+RTX+ MTX
Ahmed (39)	28/F	Lung, kidney	Microscopic haematuria	Anti-PR3	1,2,4	Renal biopsy	Inflammatory pseudotumour (solitary)	GC+CYC
Frigui (16)	59/M	ENT, eye, kidney (renal mass)	Proteinuria	C-ANCA Anti-PR3	2,3,4	Renal biopsy	Inflammatory pseudotumour (multiple, bilateral)	GC+CYC
Schydlowsky (40)	47/M	ENT, lung, kidney (renal mass)	Normal	NM	2,3,4	Radical nephrectomy	Inflammatory pseudotumour (solitary)	GC+CYC
Roussou (32)	72/F	ENT, kidney (renal mass)	Normal	P-ANCA	2	Radical nephrectomy	Inflammatory pseudotumours (multiple, unilateral)	GC+CYC
Negi(50)	40/M	ENT, kidney (renal mass)	Renal failure	C-ANCA Anti-PR3	NA	Medication	Inflammatory pseudotumour (multiple, bilateral)[§]	Treatment regimen NM
Vandergheynst (23)	32M	ENT, kidney, PNS	Proteinuria	Anti-PR3	2,4	Renal biopsy	Inflammatory pseudotumour (solitary)	GC+CYC
Kra-mbeck (36)	61/M	ENT, kidney (renal mass)	Normal	Negative	2	Partial nephrectomy	Inflammatory pseudotumour (solitary)	GC + AZA
Leung (33)	66/M	ENT, kidney (renal mass)	Normal	P-ANCA Anti-MPO	2	Renal biopsy	Inflammatory pseudotumour (multiple, bilateral)	GC + MTX
Kapoor (29)	22/M	Kidney	Haematuria, proteinuria, renal failure	C-ANCA Anti-PR3	1,3	Renal biopsy	Inflammatory pseudotumour (multiple, bilateral)	Dialysis
Carazo (17)	29/M	Eye, kidney (renal mass)	Normal	C-ANCA	1,2,3	Radical nephrectomy	Inflammatory pseudotumour (multiple, bilateral)	GC+CYC
Vers-wijve (25)	24/M	ENT, spleen, kidney	Microscopic haematuria, Renal failure	C-ANCA Anti-PR3	**1**,2	Renal biopsy	Inflammatory pseudotumour (solitary)	GC+CYC

Author	Age/Sex	Systemic involvement	Urinalysis Creatinine	ANCA	Histology (GN-1, Granuloma-2, Vasculitis-3, Fibrosis-4)	Diagnostic approach	Renal mass	Initial treatment
Fairbanks (34)	68/M	ENT, lung, kidney (renal mass)	Normal	P-ANCA	2,3,4	Renal biopsy	Inflammatory pseudotumours (multiple, unilateral)	GC+ MTX
Boubenider (31)	45/F	Kidney	Haematuria, proteinuria, renal failure	C-ANCA	2,3,4	Nephrectomy	Inflammatory pseudotumour (solitary)	Dialysis
Smith (18)	52/F	ENT, eye, kidney	Sterile pyuria	NM	2	Nephrectomy	Inflammatory pseudotumour (solitary)	GC + AZA
Schapira (51)	45/M	ENT, lung, kidney	proteinuria	NM	1,2,3	Partial nephrectomy	Inflammatory pseudotumour (solitary)	GC+CYC
Maguire (52)	27/F	ENT, lung, kidney	NM	PR3-ANCA	1,2	Partial nephrectomy	Inflammatory pseudotumour (solitary)	CYC
Bumbasirevic (24)	55/M*	ENT, lung, kidney, skin	Normal (Proteinuria, microscopic haematuria when diagnosed as GPA)	C-ANCA (negative when finding the renal mass)	RCC (clear cell type)	Radical nephrectomy	RCC	GC+CYC 150g¶
Deger (48)	46/F*	ENT, kidney	Normal (Haematuria, renal failure when diagnosed as GPA)	C-ANCA	RCC (chromo-phobe cell type)	Partial nephrectomy	RCC	GC+CYC 120g¶+ AZA 64.5g¶
Villa-Forte (53)	NM	ENT, lung, kidney (renal mass)	NM	NM	RCC	Renal biopsy	RCC	No
Odeh (19)	72/M*	ENT, lung, kidney, eye	Normal (Renal failure when diagnosed as GPA)	C-ANCA (negative when finding the renal mass)	RCC (clear cell type)	Renal biopsy	RCC	GC+CYC 70g¶
Present case A	51/M	ENT, lung, kidney (renal mass)	Normal	C-ANCA Anti-PR3	2,3	Renal biopsy	Inflammatory pseudotumour (solitary)	GC+CYC
Present case B	29/F	ENT, lung, kidney, eye (renal mass)	Normal	C-ANCA Anti-PR3	NA	Medication	Inflammatory pseudotumour (multiple, bilateral)§	GC+CYC

ENT: ear, nose and throat; CNS: central nervous system; PNS: peripheral nervous system; Anti-PR3: anti-proteinase 3; Anti-MPO: anti-myeloperoxidase; GN: glomerulonephritis; IgG4-RD: IgG4-related disease; GC: glucocorticoid; RTX: rituximab; MTX: methotrexate; CYC: cyclophosphamide; AZA: azathioprine; RCC: renal cell carcinoma; NA: not applicable; NM: not mentioned;
*The patient developed renal cell carcinoma after long-term immunosuppressive treatment;
§The diagnosis was based on improvement after immunosuppressive treatment;
¶The immunosuppressive treatment was given before the renal mass occurred.

rare (5/35) (27-31), which bring great difficulty to differentiate between GPA and carcinoma. Urinalysis and renal function were commonly within normal range (17/35) when renal masses were incidentally found on imaging. However, some patients presented as renal mass may develop renal insufficiency (7/35), haematuria (8/35) and proteinuria (8/35), and renal failure may progress rapidly, demanding renal biopsy and prompt treatment.

Testing for ANCA should be performed in patients suspected to be GPA and presented with renal mass. Indirect immunofluorescence (IIF) assay or antigen-specific enzyme-linked immunosorbent assays (ELISAs) for PR3 and MPO are the commonly used techniques and are recommended to work as a combined testing system. GPA is primarily associated with C-ANCA and PR3-ANCA positivity, while some patients with clinical GPA have the alternative ANCA, even negative. In our review of literature, seven cases (7/35) (15, 21, 22, 28, 32-34) were associated with P-ANCA/MPO-ANCA, three cases (3/35) (35, 36) remained negative. It is reported that GPA patients with ancestry of Europe mostly have PR3-ANCA positivity, while approximately half of GPA patients in east Asia may have MPO-ANCA positivity (10, 11).

Differential diagnosis mainly includes GPA and malignancies, such as renal cell carcinoma and malignant lymphoma (37, 38). Radiologic examinations and histopathology are needed to evaluate the renal masses.

Renal masses can be evaluated by ultrasound (US) examination, CT with or without contrast-enhancement, MRI and positron emission tomography CT(PET-CT). As a result of our review of literature, twenty cases (20/35) had US examination, twenty-eight cases (28/35) had CT examination, five patients (5/35) had MRI examination, and four patients (4/35) went through PET-CT. Among the thirty-two patients diagnosed as GPA-associated inflammatory pseudotumour, nineteen patients (19/32) had US examination, and five cases (5/19) presented as hypoechoic area (15, 25, 26, 35); twenty-eight patients (28/32) had CT examination, with fourteen cases (14/28) (15-17, 26, 28, 30, 31, 34-36, 39-42) presented as typical ill-defined, hypovascular area; five patients (5/32) had MRI examinations and four cases (4/5) presented as iso-intense mass on T1-weighted image

and hypo-intense mass on T2-weighted image (25, 28, 29, 43); four patients (4/32) went through PET-CT, and all of them had hypermetabolic lesions (15, 22, 42, 43). However, these imaging findings are not specific and have been found in many other malignancies, such as renal cell carcinoma and malignant lymphoma, so it is important to perform renal biopsy in order to prevent unnecessary surgery (37, 38).

Most (29/33) of the renal masses with GPA in the published case reports turned out to be inflammatory pseudotumours, with eleven cases (11/29) also had characteristics of GN (25, 26), four of which clinically presented with renal failure (25-27, 29). It is worth mentioning that IgG4-RD may be overlapped with GPA, and the histopathology of the renal mass tissue had both the features of GPA and IgG4-RD (26). Further exploration of the relationship between the two spectrum of diseases is needed.

Therapy for inflammatory pseudotumours associated with GPA follows the same principle of GPA composed of induction of remission with immunosuppressive therapy and maintenance of remission with immunosuppressive therapy for a variable period to prevent relapse. Initial choice of immunosuppressant depends largely upon the severity of disease and the organ systems involved. Considering inflammatory pseudotumour commonly present with systemic involvement of important organs, it is recommended that GC in combination with either rituximab (RTX) (44, 45) or CYC rather than monotherapy with GC should be given promptly. Recently new management guidelines endorsed by the ACR recommend the use of a reduced-dose GC regimen for remission induction of severe disease. Remarkably, for the first time RTX treatment has been recommended over CYC for induction of remission of severe disease in light of the similar efficacy and lower toxicity burden (9, 45, 46). However, the COVID-19 pandemic has pinpointed the risk of increasing adverse effect (AE) numbers and severity with new biological drugs that have demonstrated efficacy against AAVs thus opening important questions on how to optimise AAV therapeutic management (8). In most patients who achieve remission after induction immunosuppressive therapy, we suggest treatment with rituximab for maintenance of remission. Azathioprine, methotrexate, and mycophenolate(MMF) are reasonable alternatives and may be preferred based on other patient-specific factors (45), among which MMF may be the potential alternative to CYC for AAV remission induction and maintenance, finding similar rates of remission at six months and relapse rates, especially in renal-limited disease (46).

However, it has been reported that CYC is associated with a significantly increased risk of urinary bladder cancer development, which is directly related to the duration of therapy and the total dosage (more than 50g) (47).There were three cases of solitary renal mass turned out to be renal cell carcinoma. All of them were diagnosed with GPA and underwent long-term treatment of immunosuppressant (19, 24, 48). It is worth mentioning that GPA can emerge as a paraneoplastic syndrome, most frequently in renal cell carcinoma (49), and anti-programmed cell death protein 1 (anti-PD-1) immunotherapy is reported to induce flare of GPA. Therefore, it is important to monitor the symptoms and radiologic changes of patients with long-term GPA or presented as GPA, particularly presented as renal mass. Renal biopsy is warranted when necessary.

In our case report, both of our patients presented with the typical manifestation of GPA, including fever, pulmonary involvement, paranasal sinusitis, conductive hearing loss, c-ANCA and/or PR3-ANCA positivity, characteristic histopathologic features (granulomatous necrosis and focal vasculitis) of GPA seen in lung tissue, one patient had involvement of central nervous system and eyes. Both our patients incidentally found renal masses (one patient had unilateral solitary renal mass, the other had bilateral multiple renal masses) in the systemic evaluation with normal urinalysis and serum creatinine. Both patients went through US and abdominal contrast-enhanced CT, and the imaging of the renal masses shared the characteristic feature of hypoechoic area in US and ill-defined, hypodense without obvious enhancement in CT imaging, indicating that the lesions were hypovascular. Percutaneous CT-guided renal biopsy was performed in one patient and the histopathologic examination showed chronic granulomatous inflammation and focal vasculitis, supporting the diagnosis of GPA. Remission induction therapy with high-dose glucocorticoid and CYC were initiated in both patients, and successfully achieved remission, and the clinical situation improved as the cystic renal masses were significantly absorbed, indicating that the multiple renal masses were associated with GPA.

Conclusion

GPA presented as renal mass is a very rare but known presentation, which is usually discovered by accident. Differentiation diagnosis between GPA and carcinoma is very important, and renal biopsy as well as careful continuous monitoring are warranted.

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