Wegener's granulomatosis and retroperitoneal fibrosis: a case report and review of the literature

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ABSTRACT

Granulomatosis with polyangiitis (GPA), also known as Wegener's granulomatosis (WG), is a rare systemic auto-inflammatory disease characterized by necrotizing granulomatous inflammation and antineutrophil cytoplasmic antibodies-associated small vessel vasculitis. Retroperitoneal fibrosis (RPF) is an uncommon collagen vascular disease of unclear etiology, characterized by a chronic non-specific inflammation of the retroperitoneum, which can entrap and obstruct retroperitoneal structures, notably abdominal aorta, iliac arteries and ureters. RPF is mostly idiopathic, but an association with vasculitis has been shown. However, only few cases of retroperitoneal fibrosis with ureterohydronephrosis secondary to GPA have been described in literature. The outcome seems to be better when compared to the idiopathic form, and immunosuppressive treatment demonstrated to be effective, with low need in surgery. We provide the case report of a 57-year-old patient, affected by GPA, referred to our Division for massive vein thrombosis and ureteral stenosis secondary to retroperitoneal fibrosis. We also provide a review of the literature currently available on this topic.

Introduction

Granulomatosis with polyangiitis (GPA) is a rare systemic auto-inflammatory disease characterized by necrotizing granulomatous inflammation and antineutrophil cytoplasmic antibodies (ANCA)-associated small vessel vasculitis.[1] GPA affects both genders equally, and the mean age at onset is within the fourth decade. Its worldwide prevalence is estimated to be 23.7-156.5 per million, with an estimated annual incidence of 3.0-14.4 per million.[2,3] The etiology remains unknown although a number of exogenous factors, such as exposure to infectious agents or environmental factors have been supposed to be relevant in the pathogenesis of the disease. Diagnosis might be challenging because of the broad spectrum of clinical characteristics that ranges from predominantly granulomatous manifestations restricted to the respiratory tract (localized disease) to severe, life-threatening necrotizing vasculitis affecting many organs, with a predilection for lung and kidney involvement (alveolar hemorrhage and crescentic glomerulonephritis).[1] It may also impact other organs like skin or peripheral nerves, but it rarely involves the urological area. Nevertheless, GPA may affect large blood vessels such as the aorta or vena cava. Ureters may also be compressed by the large inflammatory mass. In GPA, ANCA are mainly directed against proteinase 3 (PR3); there is strong evidence from *in vitro* studies that ANCA play a crucial role in the mediation of small-vessel vasculitis.[4] The consensus classification of GPA by the American College of Rheumatology requires at least two of the following four criteria: abnormal urinary sediment (microscopic hematuria or proteinuria), abnormal findings on chest radiography, oral ulcers or nasal discharge, and granulomatous inflammation on biopsy.[5] In that respect, our case qualified for a diagnosis of GPA. Despite the large amount of new potential therapies, cyclophosphamide and corticosteroids remain the most recognized and effective means of inducing and sustaining remission of GPA.[6]

Chronic periaortitis is an umbrella term used to de-

scribe a group of nosologically allied conditions that include idiopathic retroperitoneal fibrosis (Ormond's disease), inflammatory abdominal aortic aneurysm, and perianeurysmal retroperitoneal fibrosis.[7] Retroperitoneal fibrosis (RPF) is an uncommon collagen vascular disease of unclear etiology. It is characterized by a chronic non-specific inflammation of the retroperitoneum, which can entrap and obstruct retroperitoneal structures, notably abdominal aorta, iliac arteries and ureters. The idiopathic form accounts for over 70% of cases of retroperitoneal fibrosis. According to a Finnish study, the estimated incidence of idiopathic retroperitoneal fibrosis is 0.1 per 100,000 person-years. Men are affected twice to three times more often than women and the mean age at presentation is 50-60 years, although reports on the condition in children and older adults are not uncommon.[8] Retroperitoneal fibrosis is generally idiopathic, but can also be secondary to the use of certain drugs, malignant diseases, auto-inflammatory diseases, infections, and surgery. Irrespective of its cause, most cases of non-malignant RPF - if in the active *cellular* stage - will respond to treatment with corticosteroids, with no need for surgical treatment. Accumulating data suggest alternative treatment strategies for steroid-resistant cases (*i.e.* intensive immunosuppression) or when steroids are not feasible (*i.e.* other forms of immunosuppression or hormonal treatment, particularly tamoxifen). Although early diagnosis and treatment provide excellent renal and patient outcome, long-term follow-up is mandatory in all cases.[9]

Little is known about the association between GPA and RPF. Only few cases of retroperitoneal fibrosis with ureterohydronephrosis secondary to GPA have been described in literature. Neither the diagnostic algorithm nor the therapeutic approach is standardized. Thus, we provide the case report of a 57-year-old patient, affected by GPA, referred to our Division for massive vein thrombosis and ureteral stenosis secondary to retroperitoneal fibrosis. We also provide a systematic review of the literature on this topic.

Case Report

A 57-year-old Caucasian woman was referred to our Division in April 2016 for right upper leg inflammation. Medical history was positive for arterial hypertension, type 2 diabetes. Four years before, the patient was also diagnosed with Wegener's granulomatosis, with pulmonary infiltration, oral ulcers and granulomatous inflammation on skin biopsy, currently treated with low dose corticosteroids and methotrexate (15 mg/week). Physical examination showed right leg edema and flushing, and no other relevant clinical findings. Familiar history was positive for ischemic cardiomyopathy and type 2 diabetes.

Laboratory tests indicated modest neutrophilia, elevation of inflammatory markers (erythrocyte sedimentation rate: 33 mm/h, fibrinogen: 664 mg/dL) and D-dimer (2006 ng/mL). Serum concentration of urea, creatinine, and electrolytes were within normal limits. Anti-neutrophil cytoplasmic antibodies (c-ANCA) were markedly increased (86 U.A./mL, reference range <20 U.A./mL).

An ultrasound was performed and showed deep vein thrombosis of the common and superficial femoral vein and popliteal vein. A computed tomography angiography excluded pulmonary embolism, revealing extensive thrombosis involving superficial and deep femoral vein, iliac vein and inferior vena cava; the exam showed the presence of retroperitoneal solid tissue around abdominal aorta, inferior vena cava, sheathing left ureter and causing alithiasic ureterohydronephrosis. A positron emission tomography scan showed weak and patchy tracer uptake of the retroperitoneal tissue (Figures 1-3).
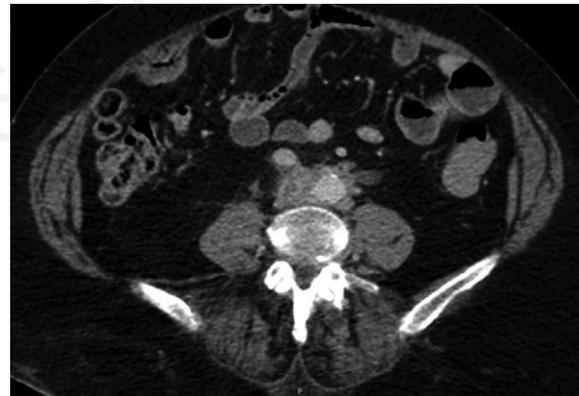
IgG4 levels were within normal range. Urine cy-

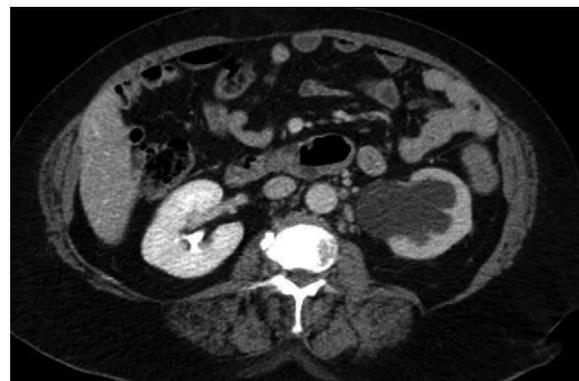**Figure 1. Abdomen computed tomographic scan showing retroperitoneal fibrosis.**

Figure 2. Abdomen computed tomographic scan showing hydroureteronephrosis.

tology showed nonspecific inflammatory and dystrophic cells and was not suggestive of a transitional cell carcinoma. Thrombophilia screen was performed: lupus anticoagulant ratio was 1 and antiphospholipid screen revealed IgG levels 3.3 U/mL and IgM levels 1.4 U/mL; prothrombin (FII), factor V Leiden and methylene tetrahydrofolate reductase mutation tests showed wild-type homozygosis; protein C and protein S activity determination were within normal range respectively (117% and 58%).

A retroperitoneal fibrosis secondary to GPA complicated by ureterohydronephrosis and deep vein thrombosis was diagnosed. A urinary diversion was performed using a double J endoureteral stent. High-dose intravenous corticosteroids (prednisone 1 mg/kg QD), tamoxifen (10 mg BID) and oral anticoagulant therapy with apixaban (10 mg QD) were started. At the time of GPA diagnosis, the patient was started on cyclophosphamide, but she experimented hematological

Figure 3. Positron emission tomography-computed tomographic scan showing retroperitoneal F18-fluorodeoxyglucose uptake.

side effects. The ongoing therapy with methotrexate was then continued. The patient gradually improved.

Because of the necessity of anticoagulant therapy, and seen the rapid improvement in clinical conditions, a biopsy of the retroperitoneal mass was not performed.

A new computed tomographic (CT) scan was performed after two months, in order to evaluate the evolution of the abdominal situation. It revealed regression of ureterohydronephrosis, complete recanalization of deep vein thrombosis and persistence of retroperitoneal fibrosis (to reassess with long-term follow-up).

Discussion

Little is known about the association between GPA and retroperitoneal fibrosis. Indeed, the relation between retroperitoneal fibrosis and vasculitis is intriguing and complex. Systemic vasculitis may present as a tumor-like mass, miming fibrotic tissue. In 2000 Kariv *et al.* reviewed this association in 83 patients.[10] The most common vasculitis presenting as tumor-like lesions were Wegener's granulomatosis (35%) and giant cell arteritis (21%). GPA was distinct for the diversity of tumor-like locations, affecting 12 different sites, with a prevalence of breast, pulmonary, mediastinal, and renal masses; only 1 case presented with GPA and retroperitoneal mass. Conversely, although RPF pathogenesis is unknown, it has often been suggested that immunological mechanisms play a role.[8] A possible link between RPF, ANCA and small-vessel vasculitis is not surprising when we consider that about 10% of RPF masses contain overt vasculitic lesions with fibrinoid necrosis in the small vessels.[11] Furthermore, recent case reports have described isolated RPF associated with positive C- or P-ANCA[12,13] and RPF associated with defined systemic vasculitis, including Takayasu arteritis[14] and c-ANCA or p-ANCA-positive vasculitis, such as periarteritis nodosa,[15] Churg-Strauss syndrome[16] and Wegener's granulomatosis.[17] Before the availability of ANCA-testing, other cases of RPF associated with vasculitis were reported in which vasculitis involved the small vessels.[18] The possibility that a vasculitic process may play a role in the pathogenesis of RPF therefore cannot be excluded. Vasculitis could involve the aortic vasa vasorum and retroperitoneal vessels, and thus lead to different pathological pictures, bringing about an aortic aneurysm with marked adventitial inflammation (the pathological hallmark of *inflammatory aneurysms*) or extending into the retroperitoneum and eliciting a fibrogenic response surrounding other structures (*e.g.* the ureters or duodenum). The appearance of periaortitis with aortic aneurysm as a consequence of GPA is a very rare complication, likely due to an ANCA-mediated vasculitis of vasa vasorum in
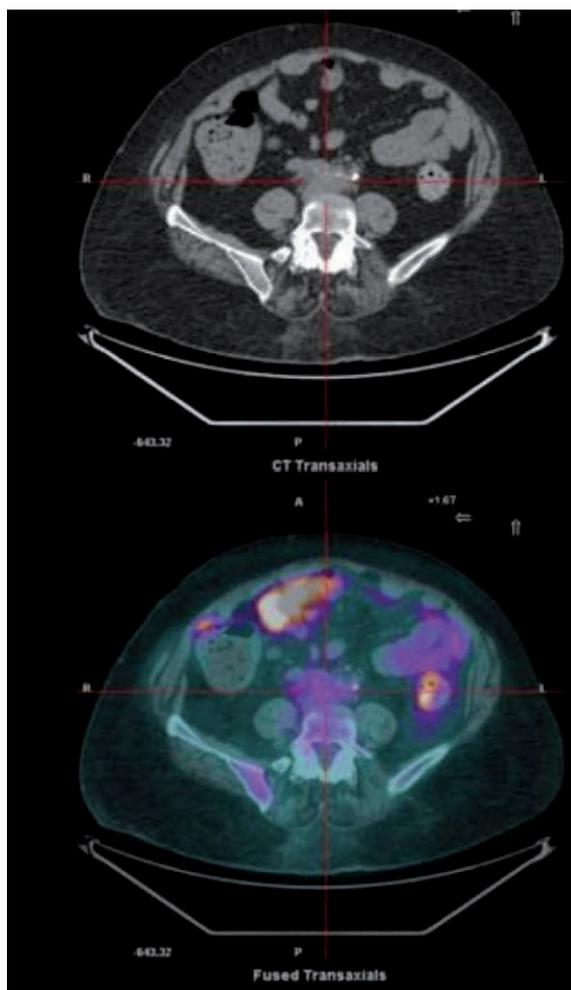
the aortic wall. Reports in literature have described only few cases of large-vessel aneurysms associated with GPA.[19] Histology is only available for the cases in which surgical treatment was required, and biopsies of the aortic tissue revealed vasculitis suggestive of GPA.[20-24] While renal involvement is a cornerstone in GPA presentation and diagnosis, urogenital manifestation in patients with GPA, including prostatitis, orchitis, epididymitis, renal pseudotumor, penile ulceration and ureteral stenosis, are extremely rare.[25,26] Furthermore, to our knowledge, only 22 documented cases regarding retroperitoneal fibrosis with ureteral stenosis secondary to GPA were found in literature.

As reported in 12 out of the 22 cases described in this report, retroperitoneal fibrosis with ureteral narrowing may appear as the sole preliminary symptom of GPA.[18,27,28] Vaglio *et al.* described two cases of RPF associated with ANCA-mediated vasculitis, presenting with ureteral stenosis. In both cases immunosuppressive treatment led to favorable clinical course and improvement in laboratory tests.[18] Izzedine *et al.* reported the case of a 51-year-old man with abdominal pain, urinary symptoms and a constitutional syndrome. Imaging studies revealed retroperitoneal fibrosis. Necrotizing granulomas, giant cells and a lymphoepithelioid cellular infiltrate were observed in biopsy of the retroperitoneal tissue. The patient responded poorly to antituberculous treatment. Finally, a renal biopsy was performed, which revealed pauci-immune rapidly progressive glomerulonephritis with necrotizing vasculitis. Alveolar hemorrhages were observed on thoracic CT and a diagnosis of GPA was made. The patient presented a significant improvement after treatment with immunosuppressive agents and corticosteroids.[28] Gonzales Revilla *et al.* reported a case of GPA onset with pulmonary and periaortic involvement, associated with retroperitoneal fibrosis causing left-sided ureterohydronephrosis; treatment with corticosteroids and methotrexate led to clinical and radiological improvement after 1 month.[27] We should be aware of the fact that the unique involvement of rarely reported GPA locations may hamper the diagnosis in the absence of classic granulomatous locations such as sinus, lungs and kidneys. Usually ureteral stenosis was reported at the level of iliac artery, however, multilevel or bilateral lesions have also been reported, leading to acute renal failure and anuria.[18,25,26] Le Thi Huong *et al.* reported 80 cases with urogenital involvement due to GPA; only 2 cases with ureteral stenosis were found and only one of them had bilateral ureteral involvement. Ureteral double-J stents were inserted for bilateral ureteral obstruction. The treatment was followed by high dose corticosteroid and cyclophosphamide, with complete recovery.[25] ANCA, mainly PR3, were almost always positive.

No data emerged on the IgG4 profile of these pa-

tients, mainly because the current immunoglobulin G4 (IgG4)-testing was not available when most of the cases were described. IgG4-related disease (IgG4-RD) is a newly recognized systemic disorder characterized by a lymphoplasmacytic cell infiltrate abundant in IgG4-positive plasma cells, storiform tissue fibrosis, and variably elevated IgG4 levels in serum. The disease mainly affects kidneys, pancreas, salivary glands, mediastinum and retroperitoneum. A differential diagnosis between ANCA-mediated vasculitis and IgG4-RD is often challenging. Lomborg *et al.* described the case of a patient, previously diagnosed with GPA (with no granulomas at the biopsy) that secondarily developed a retroperitoneal fibrosis with ureteral stenosis. A biopsy of the tissue was performed, showing abundant infiltration of plasma cells positive for IgG4.[29] In a recent study on patients with idiopathic retroperitoneal fibrosis, 57% had morphological and immuno-histochemical stainings compatible with IgG4-RD.[30] We also have to remark that in most of the reported cases a mass biopsy has not been performed. However, referring to our patient, the previous histological finding of a granulomatous lesion (uncommon in IgG4-RD) and the negativity of IgG4 serum levels strengthened the GPA diagnosis (Table 1[18,25-28,31-44]).

Urogenital complications of Wegener's granulomatosis have been shown to be sensitive to corticosteroid and cyclophosphamide therapy.[31,32] Because of the toxicity associated with the long-term administration of cyclophosphamide, a number of alternative regimens have been investigated as initial therapy, though none has displaced the regimen of intravenous cyclophosphamide plus oral glucocorticoids. The treatment of choice for patients who cannot receive or who decline cyclophosphamide is rituximab. However, low weekly doses of oral methotrexate have also been used for the initial therapy in patients who do not have renal alterations or severe disease.[27,33,34] Also tamoxifen (TMX) has shown to be a suitable alternative in idiopathic retroperitoneal fibrosis (iRPF). A recent retrospective trial compared the efficacy of corticosteroids and tamoxifen in monotherapy, concluding that corticosteroids are superior to TMX in treating iRPF disease. However, among patients with initial primary treatment success, recurrence rate was lower in TMX-treated patients. No data are available on the use of tamoxifen in retroperitoneal fibrosis secondary to small vessel vasculitis. However, the impossibility to treat our patient with cyclophosphamide, induced us to use the hormonal therapy with TMX, aiming to block another potential mechanism of the disease. Since a good improvement was rapidly seen, this choice gave us the chance to avoid surgical treatment. In some of these cases, unfortunately, immunosuppressive management was not started right after diagnosis of ureteral obstruction, instead surgery was performed. In most of the cases obstruction com-

Table 1. Current literature on granulomatosis with polyangiitis.

Gender	Age	Ureteral stenosis as first symptom	Clinical presentation	Medical treatment	Surgical treatment	Outcome	References
M	65	No	Lower back pain, intermittent fever, weight loss, urinary hesitancy, dribbling	CYC	Balloon dilatation, ureteral stent	Resolution of obstructive syndrome within 4 weeks; symptom free after 11 months without therapy	Middleton, 1994[36]
M	50	Yes	Abdominal pain	Cortic/CYC	No	Improvement of renal function, hemodialysis discontinued after 4 months	Metselaar, 1985[31]
M	30	Yes	Leg pain, nausea, weight loss, intermittent fever, fatigue	Cortic/CYC	No	-	Adelizzi, 1986[37]
F	37	Yes	Anuria, intermittent fever, abdominal pain, fatigue	Cortic/CYC	No	Remission	Leche, 1985[38]
M	49	Yes	Persistent pain in the groin	Cortic/CYC	Ureterolysis	After 7 years, renal function deteriorated and chronic dialysis was started	Ter Maaten, 1993[39]
F	60	No	Fatigue, weakness, intermittent fever, sweats and chills	Cortic/CYC	Transureteroureterostomy	Remission	Baker, 1978[40]
M	56	No	Renal colic, hematuria	Cortic/CYC	No	Remission for 60 months, residual asymptomatic ureteral stenosis	Le Thi Huong, 1996[25]
F	72	No	Anuria	Cortic/CYC	Surgical therapy double-J stent	Stent removed after 2 months, 36 months later death for acute espiratory failure	Le Thi Huong, 1996[25]
M	51	Yes	Abdominal pain, urinary symptoms, weight loss, intermittent fever	Cortic/CYC	Double-J stent	After 12 months light improvement in renal function	Izzedine, 2002[28]
M	67	No Under Cortic/MTX	Abdominal pain	Cortic/CYC	Double-J stent	After 18 months complete remission	Umemoto, 2012[32]
M	53	No Under MTX	Asymptomatic		Double-J stent Resection of the ureteral stricture	After 106 months death due to metastatic carcinoma of the upper airways	Dufour, 2012[26]
F	71	Yes	Right renal colic, anorexia, loss of weight, asthenia	Cortic/CYC	Double-J stent Resection of the ureteral stricture	After 6 months improved renal function	Lillaz, 2011[41]
-	-	No	-	Cortic/CYC		Death for sepsis	Davenport, 1996[35]
M	44	No	Severe right abdominal pain	Cortic/MTX	No	After 24 months asymptomatic	Farpour, 2014[33]
M	47	Yes	Fever, livedo and skin necrosis of lower limbs	Cortic/AZA then Cortic/CYC	No	After 24 months asymptomatic	de Roux-Serratrice, 2002[42]
M	21	Yes	Fever, fatigue, diffuse arthralgias, and myalgias	Cortic/CYC	Double-J stent Resection of the ureteral stricture	After 6 months no evidence of recurrence	Kamar, 2003[34]
F	59	Yes	Fatigue and severe lower back pain	TMP/SMX	Double-J stent Resection of the ureteral stricture	After 12 months asymptomatic	Kamar, 2003[34]

Table 1. Continued from previous page.

Gender	Age	Ureteral stenosis as first symptom	Clinical presentation	Medical treatment	Surgical treatment	Outcome	References
-	-	No	-	Cortic/CYC	Surgical intervention	-	Hensle, 1978[43]
F	24	-	-	Cortic/AZA Cortic/CYC		-	Rich[44]
M	74	Yes	Continuous pain over the right renal angle, associated with dark urine	Cortic/MTX	Retroperitoneal mass biopsy	Radiological and clinical improvement after 1 month	Gonzales-Revilla, 2016[27]
F	74	Yes	Fever, oliguria, asthenia and anorexia	Cortic/CYC	Double-J stent	Radiological and clinical improvement after 18 months	Vaglio, 2002[18]
M	57	Yes	Asthenia, abdominal pain and dyspnea Acute renal failure	Hemodialysis Cortic/CYC	Right percutaneous pyelostomy, ureteral stenting renal biopsy	50% reduction in the retroperitoneal mass after 6 months	Vaglio, 2002[18]

CYC, cyclophosphamide; MTX, methotrexate; AZA, azathioprine; TMP/SMX, trimethoprim/sulfamethoxazole.

pletely resolved after immunosuppressive therapy except one case.[35] Davenport *et al.* reported 8 GPA cases with urogenital involvement, one of them with retroperitoneal involvement and ureteral obstruction; the patient was started on immunosuppressive therapy but unfortunately died of sepsis.[35] Only one case ended up with surgery while on immunosuppressive therapy. Dufour *et al.* evaluated 11 patients with urogenital manifestation of GPA; only one patient presented ureteral obstruction. Immunosuppressive therapy with prednisone and methotrexate was maintained. A double-J ureteral stent was inserted. However, after 6 months the resection of the stricture with end-to-end anastomosis was done due to persistence of ureteral obstruction.[26] However, in this case, no change in immunosuppressive therapy was made prior to surgery, and surgical treatment could have been possibly avoided by a change in immunosuppressive management.

Conclusions

To summarize, we presented a case of GPA with retroperitoneal fibrosis that led to hydronephrosis and deep vein thrombosis. We also reviewed the current literature on this topic. Ureteral obstruction usually resolves with stenting and immunosuppressive therapy. Although data on follow up are often missing or incomplete, a low recurrence rate of ureteral stenosis after treatment was observed in the cases reported. It seems logical to consider medical management as a first line therapy in any urologic involvement of GPA, although in patients with persistent symptoms surgical procedures should be regarded. However, further investigations are required to confirm this consideration. Furthermore, we always suggest evaluating the possible diagnosis of IgG4-RD, as clinical features of this disease often overlap with RFP and GPA.

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