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Review

Urologic and genital manifestations of granulomatosis with polyangiitis☆

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is a systemic necrotizing granulomatous vasculitis, which predominantly affects small-sized blood vessels. Major organ involvement includes the upper/lower respiratory tract and kidneys. In contrast, genitourinary disease is rare in GPA patients, reported in <1% of cases in large cohorts. Manifestations at this level include prostatitis, destructive urethritis, genital ulcers, orchitis and renal masses. Also, high-dose cyclophosphamide, one of the main immunosuppressive drugs used for GPA treatment, is associated with bladder toxicity, i.e., hemorrhagic cystitis and cancer. In this review we describe the main urogenital symptoms associated with this ANCA-associated vasculitis. In addition, cyclophosphamide-induced urologic complications are detailed.

Contents

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1. Introduction

Granulomatosis with polyangiitis (Wegener's, GPA) is an anti-neutrophil cytoplasmic antibody (ANCA) associated multisystemic disease characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract and necrotizing vasculitis affecting predominantly small vessels [1,2].

Worldwide, GPA is considered an uncommon disease, with annual incidence of 3–12 new cases per million inhabitants and prevalence of 22–157 cases per million [2,3]. Mean age at diagnosis is between 45 and 60 years, but children can also be affected [3,4].

Although GPA can virtually affect all body organs, urogenital involvement is rare. Large series of patients with this condition have reported <1% of cases with evident signs at this level [5–10]. In this sense, information regarding the urologic and genital manifestations of GPA is derived from case reports and in particular, from three small series [9,11,12].

The objectives of this review are: 1) to describe the main urological manifestations associated with GPA, 2) to detail bladder complications arising from cyclophosphamide exposure, the most widely used remission induction treatment for severe forms of ANCA-vasculitis and 3) to summarize current therapeutic options for GPA patients suffering from urogenital disease. Search in *MEDLINE* database for English language articles published between January 1970 and December 2014 was performed. Terms included were *ANCA-associated vasculitis, small vessel vasculitis, granulomatosis with polyangiitis* and *Wegener's granulomatosis*, in combination with keywords *prostate, prostatitis, urethra, ureter, urethritis, hydronephrosis, epididymis, epididymitis, seminal vesicles, bladder, cystitis, renal mass, testis, orchitis, perineum, penis, cyclophosphamide, treatment adverse effects, treatment toxicity* and *cancer*. Full text of relevant articles were retrieved and reviewed by all authors. In addition, late-breaking communications from international Rheumatology and Urology meetings celebrated during the past five years were reviewed.

2. General characteristics

Mean age of cases reported in the three larger studies detailing the characteristics of urogenital involvement in GPA was 56 years (range 21–77) [9,11,12]. These data are similar to that reported in general GPA cohorts [8,10,13]. With regard to gender, urogenital abnormalities appeared predominantly in males (n = 23/27, 85% of all cases in the referred series [9,11,12]), which clearly contrasts with the usual men to women ratio (1.5:1.0) observed in this disorder [6,10,13–15].

Regarding clinical characteristics, when urogenital involvement was present, it was usually observed early, at disease onset (80%, as described in one series [9]). In GPA, urogenital tract symptoms are usually observed as part of generalized systemic disease, with constitutional symptoms, pulmonary (81–87%), kidney (45–60%) and upper respiratory tract (90–100%) tract involvement [9,11,12]. Laboratory findings include elevated acute phase reactants, with increased levels of erythrocyte sedimentation rate and C-reactive protein, as in general GPA cohorts. Remarkably, ANCA were present in 75–87.5% of patients; of these, 90% were directed against proteinase 3 and the remaining against myeloperoxidase [9,11,12].

In the aforementioned series (6, 7), isolated urogenital symptoms preceded GPA diagnosis in 12–18% of cases. In these cases, vasculitis or granulomatous inflammation was an incidental finding on biopsied tissues, mostly performed for suspected malignancy. Most of these patients later showed signs of generalized disease. Only few cases with limited involvement of the urogenital tract have been reported [12].

Recurrences are frequent in GPA [2,10]. In this sense, urogenital involvement has been reported not only at disease onset but also during relapses, with symptoms occurring as a new manifestation [9,11]. Of relevance, recurrences are common at this level, observed in 36–50% of patients [9,11,12]. Half of these episodes are characterized by isolated genitourinary disease, which usually have a good response to immunosuppressive therapy [9,11].

It should be noted that a small percentage of cases have asymptomatic involvement of the urogenital system, as has been evidenced in autopsy studies of GPA patients with severe vasculitis [16]. Furthermore, it is likely that some cases with insidious onset and mild manifestations go unnoticed because genital examination is not performed routinely as part of the management of this disorder [17].

3. GPA manifestations in specific organs

3.1. Penis

Approximately 20 cases of patients with GPA involvement of the penis have been reported [18–23]. In the series addressing urogenital involvement [9,12], this organ was affected in 9–25% of patients. Ulceration was the presenting symptom in almost all cases, either at disease onset or during flares [11,12]. These ulcers were usually painless, recurrent and in some cases accompanied by local edema and regional lymphadenopathy [9,12,18–23], simulating a neoplasm. In Behçet's disease (in contrast to GPA), genital ulcers are often painful and mainly located in the scrotum [24].

3.2. Urethra

We found eight case reports of GPA patients with destructive urethritis [25] and two more described in a specialized series of 8 patients [12]. Presenting symptoms included urinary urgency, dysuria and in one patient, obstructive symptoms caused by segmental stenosis that required repeated dilations for relief [12]. In most of these cases, symptoms resolved with immunosuppressive treatment [11,12].

3.3. Prostate

Prostatitis is the most common presentation of GPA urogenital involvement, being reported in 12–37% of cases [9,11,12]. It is also the urological manifestation with the highest number of reported cases, with approximately forty [26–40]. However, prostatitis secondary to GPA is very uncommon, as demonstrated in a study that included approximately 25,000 biopsies, of which only 200 were histologically classified as granulomatous prostatitis, and only 2 were secondary to GPA [41].

In most cases prostate involvement is part of the initial GPA symptoms, presenting as dysuria, urgency, macroscopic hematuria (17% of cases), obstructive symptoms (70%) and occasionally acute urinary retention (18%) or purulent discharge [9,11,12,26–40]. This manifestation exhibits high recurrence rate (up to 25%) [11,27–40]. Also, prostatic inflammation can be demonstrated histologically in the absence of

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symptoms, as described in *postmortem* studies in 7% of patients with severe generalized GPA [16].

Physical examination can reveal a normal (40%), enlarged (50%) or indurated (10%) gland, while imaging studies may show calcifications or findings that resemble an abscess or neoplasm [9,11,29,36,42]. Total prostate antigen may be slightly elevated, but the free fraction is usually normal [27,31]. Differential diagnosis of granulomatous prostatitis due to GPA includes infections caused by *Mycobacterium tuberculosis*, *Blastomyces dermatitidis*, *Brucella* sp and spirochetes in addition to sarcoidosis and allergic reactions [9].

3.4. Bladder

Twenty-five percent of patients reported in two of the specialized series had bladder involvement directly related to active GPA [11,12]. All patients presented urinary urgency and dysuria [11]. Uncommon manifestations include urinary incontinence, and obstructive signs with ureter dilatation and hydronephrosis secondary to inflammatory pseudotumours [11,43–45] or blockage of the ureteral orifices by necrotic tissue residues [11,12]. Cystoscopy usually reveals a diffusely thickened bladder, with ulcerations and fibrosis [11], while computed tomography images may show wall thickening or polyps [46].

Importantly, some of these patients presented with micro or macroscopic hematuria [11]. In these cases it must be accurately investigated whether this is part of active vasculitis, chronic renal damage [47] or bladder toxicity secondary to cyclophosphamide (*see below, complications associated with treatment*). Among the rarest manifestations of GPA in this organ we found the case of a woman with a vesico-vaginal fistula [12] and one case with isolated bladder neuropathy [48].

3.5. Ureter

There are about 20 published reports of patients with ureteral stenosis associated to GPA [9,11,31,49–56]. This organ was affected in 12.5–25% of cases reported in two previous series [11,12]. The most common clinical findings were hematuria, pain and hydronephrosis [9,11,49]. Anuria and acute renal failure developed in a patient with bilateral stenosis [9,11,49]. The most frequent stenosed segment was the lower third, in the iliac region (60% of cases) [11,49]. Most of the time there was a single ureteral reduction of the lumen, although multiple stenosis affecting several segments simultaneously can also be observed.

Ureters may be affected due to retroperitoneal inflammation that directly damages the ureter itself or the periureteral tissue with subsequent development of fibrosis [9,31,49] or by segmental thickening of surrounding vessels, such as the iliac artery [57,58].

3.6. Testicles

Testicular vasculitis could be observed in 12.5–36% of GPA patients with urogenital disease [9,12]. The main symptom was pain, although edema, scrotal hyperemia, necrotic ulcers, inflammatory masses, infarction and necrosis have also been reported [9,11,12,59–61]. Similarly to other organs of the urogenital tract, testicular involvement was part of a systemic disease in most cases, although limited disease has also been described [62]. As in the case of bladder involvement, testicular vasculitis can be asymptomatic and discovered incidentally [11,16]. In contrast to germinal tumors, alpha-fetoprotein and chorionic gonadotropin levels are usually in normal range [59].

3.7. Epididymis

Epididymitis was described in 1 of 11 patients in one series [9] and in three case reports, where it presented as the initial manifestation of GPA [59,63,64]. These patients suffered testicular pain and edema. In one case, recurrent episodes of epididymitis were described in addition to an inflammatory mass of 2 cm in the head of the right epididymis [9]. Of relevance, in half of these patients, the initially isolated urogenital involvement evolved into a systemic disease with constitutional symptoms, pulmonary nodules, peripheral neuropathy or cutaneous manifestations [9,64].

3.8. Renal masses

We found 18 cases of patients with renal fibro-inflammatory masses associated with GPA [9,29,42,65–70]. These granulomatous pseudotumors were usually asymptomatic and discovered incidentally on imaging studies. One case highlighted an interesting histological combination: the removal of a perirenal mass of 6.5 cm showed granulomatous inflammation with vasculitis and fibrinoid necrosis while in the surrounding renal tissue evidence of pauci-immune focal segmental glomerulonephritis was observed [9].

Differential diagnosis of renal inflammatory mass is primarily kidney cancer. In this regard, a previous study reported that GPA itself, independently of cyclophosphamide effect, conferred a higher risk (8.7 times) of developing renal carcinomas when compared with other autoimmune diseases [71]. However, this finding has not been demonstrated in other studies [72].

4. Urologic complications associated with cyclophosphamide treatment

Cyclophosphamide (in combination of glucocorticoids, GC) has classically been the cornerstone of treatment of severe forms of ANCA-associated vasculitis (AAV) [73]. Before the routine use of this drug, GPA caused the death of 90% of affected patients [16]. Now, this therapy induces remission in 75–90% of patients [7,8,74]. Unfortunately, chronic use of cyclophosphamide is associated with a number of side effects, some of which related to the urinary tract.

In particular, there is a clear relationship between high dose oral cyclophosphamide and hemorrhagic cystitis and bladder cancer. The incidence of these complications is associated with both, length of drug exposure and cumulative dose [75–77]. Acrolein, a cyclophosphamide metabolite excreted by the kidneys, is supposed to be responsible for bladder toxicity [77,78].

4.1. Hemorrhagic cystitis

Based on data of three of the largest cohorts of GPA patients, incidence of cyclophosphamide-associated cystitis (diagnosed by cystoscopy) ranged between 12% and 41% [15,79,80]. In these studies, patients received a daily oral dose of 100–150 mg (2 mg/kg/day) during a period higher of 12 months [8,79]. Mean cumulative dose related with the development of hemorrhagic cystitis was between 57 and 100 g [15,75,79,80], with an exposure lapse of approximately 30 months [15,79,80].

Regarding clinical presentation, this complication is asymptomatic in 50% of cases, while in the other half is manifested as dysuria and/or nonglomerular hematuria (40% of cases presenting with gross hematuria) [8,79,81]. In a minority of these cases (2–4%), hemorrhage was so intense that transfusions and intravesical treatment with formalin or silver nitrate were required [15,80–82]. In hemorrhagic cystitis characteristic cystoscopic bladder changes include patchy areas of neovascularity and telangiectasia, multiple tortuous thin-walled veins and small areas of hemorrhage [79]. Although 75% of cystitis episodes developed during cyclophosphamide treatment, almost a quarter occurred after drug discontinuation [83,84].

4.2. Bladder carcinoma

Several studies have found an association between chronic administration of oral cyclophosphamide (2 mg/kg/d) with high-cumulated doses and the development of bladder cancer [8,79,83]. Frequency of

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this particular type of cancer in GPA cohorts has been reported between 2 and 5% [8,15,75,79]. Based on these studies, it is estimated that GPA patients exposed to high cyclophosphamide doses had a 31 times greater risk of developing bladder cancer than the general population [8,79,83]. This factor is increased even more (51 times) for patients <65 years [8,79]. In fact, the standardized incidence ratio (SIR) calculated for this malignant neoplasia is between 3.6 and 4.8 [83–85].

The reported time elapsed for the development of this complication varies from 7 months to 15 years after the start of cyclophosphamide [8,75,79,83] or between 0 and 14 years after the last dose received [8,79]. In one series, the diagnosis of cancer was performed at a mean of 2 years and 7 months after the initiation of cytotoxic treatment [76].

In these studies, the risk of developing bladder carcinoma was higher in patients with cumulative doses >25–36 g (more than 5–9 times the risk when compared to the general population) or an exposure period >12 months. It was particularly high with doses that exceeded 72–100 g [83], which are usually achieved after prolonged treatment >2.5 years [79]. Based on these data, it was estimated that each 10 g increment in cumulative dose of cyclophosphamide was associated with a doubled risk of bladder cancer. Likewise, exposure to this drug >13 months confers an eightfold increased risk when compared to general population [76]. Other major risk factor for the development of this complication is the presence of previous episodes of hemorrhagic cystitis and tobacco exposure [8,15,77,79,80].

The vast majority of bladder neoplasms reported in these patients were transitional cell carcinomas, detected as superficial tumors not involving the muscular layer in 65–80% of cases [76,86]. Treatment of these superficial tumors is performed by transurethral resection with or without intravesical chemoimmune therapy. Invasive tumors are treated with radical cystectomy and/or radiation, which portend a 5-year survival of 50–60% [76,86,8,76,79]. Bladder sarcomas and squamous cell carcinomas have been rarely associated with cyclophosphamide exposure [87,88].

4.3. Detection and prevention of bladder complications related to cyclophosphamide

4.3.1. Recommendations to reduce cyclophosphamide-associated toxicity

1) *Limiting treatment duration and reduction of initial dose*. As mentioned, development of the above complications depends on the cumulative dose and length of cyclophosphamide exposure. Based on this observation, oral cyclophosphamide is currently recommended to be used for remission induction in ANCA-vasculitis for a maximum of 3–6 months with doses not exceeding 1.5–2 mg/kg/d [73]. Following this regimen, a recent series reported that only 2.2% of 180 GPA patients developed chemical cystitis [89]. In the same line, substitution of oral cyclophosphamide by intermittent intravenous (i.v.) pulses allows a reduction in the cumulative dose and reduction in adverse effects [90,91]. In this sense, the reported incidence of hemorrhagic cystitis in patients treated with i.v. cyclophosphamide has been 2.6% only [91].
2) *Reduction of acrolein-related toxicity*. In order to avoid prolonged contact of this toxic metabolite with bladder tissue, it is recommended that patients treated with oral cyclophosphamide receive their full dose early in the morning and drink at least 2 l of water daily to force diuresis. In addition, concurrent administration of mesna (sodium 2-mercaptoethane sulfonate) should be done with cyclophosphamide pulses, as it inactivates acrolein in the urine, protecting the bladder from its toxic effects [73,92,93]. In GPA patients, incidence of hemorrhagic cystitis decreased from 43% reported in series where mesna was not used routinely [8,79] to 12% when this drug was included in treatment protocols [15]. In other words, the relative risk for this complication is 0.41 (CI 0.25–0.69) with no mesna administration and 0.28 (CI 0.17–0.45) when the drug is applied [94]. Similarly, mesna may also be protective with respect to bladder carcinoma. Incidence of this neoplasia was 3–5% in two series [8,79] where mesna was not administered compared to <1% in a cohort where its use was protocolized ($p = 0.034$) [94].

4.3.2. Recommendations for the detection of bladder toxicity

To timely diagnose both hemorrhagic cystitis and bladder cancer it is recommended to screen for hematuria with urinalysis initially every 4 weeks and then every 3–6 months, even when cyclophosphamide therapy has been discontinued [79,90]. In addition, some centers perform urine cytology every 6–12 months. This last technique is highly sensitivity for detecting high-grade tumors [79,86]. Patients with new-onset nonglomerular hematuria should undergo cystoscopy [79,90]. Also, patients with previous episodes of hemorrhagic cystitis should be evaluated with cystoscopy every 1–2 years [79]. It is important to remark that surveillance of urological complications associated with cyclophosphamide therapy should be continued throughout patient's life [79].

5. Treatment of urogenital involvement

Therapeutic approach of GPA urogenital disease can be divided into medical and surgical (interventional). According to data from specialized series [9,11,12], most patients have an excellent response to immunosuppressive therapy, with complete resolution of symptoms and low residual chronic morbidity. Surgical treatment is then reserved for acute situations requiring prompt solution, as in the case of acute urinary retention or for those patients with significant functional impairment, i.e., fistulas or stenosis.

5.1. Medical therapy

Given the rarity of urogenital involvement, there are no controlled studies that set the tone of optimal treatment for these patients. Therefore, we consider that general principles of GPA therapy are applicable in these patients [73]. In this sense, selection of the induction regimen depends on the severity of the vasculitis [73]. If the disease is extensive or threatening organ function, the combination of GC and cyclophosphamide (or rituximab) will be considered the treatment of choice [73,95]. In limited disease, methotrexate could be a valid option [74]. In prime studies related to this topic [9,11], combination of prednisone and cyclophosphamide resulted in improvement of all patients and complete remission in approximately 80%. It should be emphasized that most of the reported cases had generalized GPA.

Cyclophosphamide is administered every two to three weeks (15 mg/kg) until remission, which occurs approximately after 6–9 i.v. pulses [91]. The initial GC dose is 1 mg/kg/day for the first month, with gradual tapering in 12–18 months. After 3–6 months, cyclophosphamide is replaced by methotrexate, azathioprine or rituximab for maintenance phase [14,96–98]. Cyclophosphamide dose should be adjusted depending on age, renal function and leukocyte count [91]. In addition, these patients should receive prophylaxis for *Pneumocystis jirovecii* and bone protection measures with calcium, vitamin D and eventually bisphosphonates.

5.2. Surgical treatment (interventional)

This comprises placing ureteral catheters as a temporary measure for relief obstruction symptoms [9,11]. One of the reported cases with ureteral stenosis required resection of the affected segment and anastomosis [9]. In the case of urethral stricture, dilation may be frequently required [12].

Published series also described the performance of a suprapubic cystotomy in a case of acute urinary retention secondary to prostatic inflammation and gland resection as part of the treatment for abscess formation due to extensive necrosis [9,11,12]. The repair of a vesicovaginal fistula was necessary in a patient [12]. Finally, some patients underwent surgical procedures (orchiectomy, prostatectomy and

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nephrectomy) as part of the diagnostic protocol for suspected malignant neoplasms [9].

6. Conclusions

Clinically evident genitourinary involvement is rare in GPA, although it can be the first manifestation of this disease. Differential diagnosis of these manifestations includes, in addition of disease activity, treatment-related adverse effects, infections and chronic damage, which should be accurately identified and treated. Combination of cyclophosphamide and glucocorticoids usually results in complete remission of vasculitis-related urogenital disease.

Conflict of interest statement

The authors declare no conflicts of interest.

Take-home messages

- Urogenital involvement is uncommon in GPA. Manifestations can include orchitis, cystitis, bladder fibrosis, urethral and ureteral stenosis, prostatitis, genital ulcers and kidney masses.
- High-cumulated cyclophosphamide doses are associated with an increased risk of bladder cancer and hemorrhagic cystitis.
- Genitourinary symptoms seem to be highly sensitive to glucocorticoids in combination with immunosuppressive drugs. Surgical procedures are rarely necessary.

References

[1] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1–11.
[2] Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. Autoimmun Rev 2014;13:1121–5.
[3] Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suarez LF. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrol Dial Transplant 2015;30(Suppl. 1):i14–22.
[4] Cooper A, Rakheja D, Punaro M. A 14-year-old boy with sore throat and tea-colored urine. Pediatrics 2014;133:e1377–80.
[5] Holle JU, Gross WL, Latza U, Nolle B, Ambrosch P, Heller M, et al. Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. Arthritis Rheum 2011;63:257–66.
[6] Anderson G, Coles ET, Crane M, Douglas AC, Gibbs AR, Geddes DM, et al. Wegener's granuloma. A series of 265 British cases seen between 1975 and 1985. A report by a sub-committee of the British Thoracic Society Research Committee. Q J Med 1992; 83:427–38.
[7] Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983; 98:76–85.
[8] Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116: 488–98.
[9] Dufour JF, Le Gallou T, Cordier JF, Aumaitre O, Pinede L, Aslangul E, et al. Urogenital manifestations in Wegener granulomatosis: a study of 11 cases and review of the literature. Medicine (Baltimore) 2012;91:67–74.
[10] Thai LH, Charles P, Resche-Rigon M, Desseaux K, Guillevin L. Are anti-proteinase-3 ANCA a useful marker of granulomatosis with polyangiitis (Wegener's) relapses? Results of a retrospective study on 126 patients. Autoimmun Rev 2014;13:313–8.
[11] Huong DL, Papo T, Piette JC, Wechsler B, Bletry O, Richard F, et al. Urogenital manifestations of Wegener granulomatosis. Medicine (Baltimore) 1995;74:152–61.
[12] Davenport A, Downey SE, Goel S, Maciver AG. Wegener's granulomatosis involving the urogenital tract. Br J Urol 1996;78:354–7.
[13] Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. Arthritis Rheum 2001;44:1149–54.
[14] Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36–44.
[15] Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nolle B, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum 2000;43:1021–32.
[16] Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). Br Med J 1958;2:265–70.
[17] Agraharkar M, Gokhale S, Gupta R. Wegener's granulomatosis diagnosed by testicular biopsy. Int Urol Nephrol 2002;34:559–64.
[18] Bories N, Becuwe C, Marcilly MC, Wolf F, Balme B, Thomas L. Glans penis ulceration revealing Wegener's granulomatosis. Dermatology 2007;214:187–9.
[19] Al Rajabi W, Venturini M, Sala R, Calzavara-Pinton P. Wegener's granulomatosis of the penis: genital presentation of systemic disease. Dermatology 2006;212:370–2.
[20] Adam R, Katz S, Lee K, Jewett M, Kodama R. Wegener's granulomatosis of the penis: diagnosis and management. Can J Urol 2004;11:2341–3.
[21] Ebo DG, Mertens AV, De Clerck LS, Gentens P, Daelemans R. Relapse of Wegener's granulomatosis presenting as a destructive urethritis and penile ulceration. Clin Rheumatol 1998;17:239–41.
[22] Fowler M, Martin SA, Bowles WT, Packman R, Katzenstein AL. Wegener granulomatosis. Unusual cause of necrotizing urethritis. Urology 1979;14:66–9.
[23] Matsuda S, Mitsukawa S, Ishii N, Shirai M. A case of Wegener's granulomatosis with necrosis of the penis. Tohoku J Exp Med 1976;118:145–51.
[24] Stone JH. Vasculitis: a collection of pearls and myths. Rheum Dis Clin North Am 2007;33:691–739.
[25] Dore B, Duriez P, Grange P, Aubert J. Wegener's granulomatosis with urethral-penile location. Apropos of a case. Ann Urol (Paris) 1990;24:256–8.
[26] Lamarche JA, Peguero AM, Rosario JO, Patel A, Courville C. Anti-MPO small-vessel vasculitis causing prostatis and nephritis. Clin Exp Nephrol 2007;11:180–3.
[27] Gunnarsson R, Omdal R, Kjellevold KH, Ellingsen CL. Wegener's granulomatosis of the prostate gland. Rheumatol Int 2004;24:120–2.
[28] Davies CW, Wathen CG. Wegener's granulomatosis presenting as prostate and submandibular gland disease. Sarcoidosis Vasc Diffuse Lung Dis 1997;14:190–1.
[29] Yalowitz PA, Greene LF, Sheps SG, Carlin MR. Wegener's granulomatosis involving the prostate gland: report of a case. J Urol 1966;96:801–4.
[30] Murty GE, Powell PH. Wegener's granulomatosis presenting as prostatitis. Br J Urol 1991;67:107–8.
[31] Middleton G, Karp D, Lee E, Cush J. Wegener's granulomatosis presenting as lower back pain with prostatitis and ureteral obstruction. J Rheumatol 1994;21:566–9.
[32] Sozer IT. Wegener's granulomatosis with infiltration of the prostate. Br J Urol 1986; 58:335.
[33] Khattak AQ, Nair M, Haqqani MT, Williamson EP. Wegener's granulomatosis: prostatic involvement and recurrent urinary tract infections. BJU Int 1999;84:531–2.
[34] Tousignant J, Truong TT. Wegener's granulomatosis with prostatic involvement. Ann Dermatol Venereol 1992;119:131–3.
[35] Bray VJ, Hasbargen JA. Prostatic involvement in Wegener's granulomatosis. Am J Kidney Dis 1991;17:578–80.
[36] Stillwell TJ, DeRemee RA, McDonald TJ, Weiland LH, Engen DE. Prostatic involvement in Wegener's granulomatosis. J Urol 1987;138:1251–3.
[37] de Celis G, Vidaller A, Pac MV, Bolao F, Nolla M. Wegener's granulomatosis: initial form of prostatic involvement. Rev Clin Esp 1987;180:518–9.
[38] Tung KT, Woolf A, Falzon M. Prostatic involvement in Wegener's granulomatosis. Postgrad Med J 1987;63:53–4.
[39] Gaber KA, Ryley NG, Macdermott JP, Goldman JM. Wegener's granulomatosis involving prostate. Urology 2005;66:195.
[40] Brunner A, Tzankov A, Akkad T, Lhotta K, Bartsch G, Mikuz G. Wegener's granulomatosis presenting with gross hematuria due to prostatitis. Virchows Arch 2004;444: 92–4.
[41] Stillwell TJ, Engen DE, Farrow GM. The clinical spectrum of granulomatous prostatitis: a report of 200 cases. J Urol 1987;138:320–3.
[42] Vaught WW, Wilson TM, Raife MJ, Horne DW. Wegener granulomatosis: prostatic involvement and bladder outlet obstruction. Urology 1989;34:43–5.
[43] Fienberg R. Necrotizing granulomatosis and angiitis of the lungs with massive splenic necrosis and focal thrombotic granulomatous glomerulonephritis. Am J Clin Pathol 1953;23:413–28.
[44] Hooda D, Parsons J, Hooda S, Nuss M, Layne R. Isolated bladder vasculitis: a rare presentation of Wegener's granulomatosis. W V Med J 2011;107:24–5.
[45] Hansen BJ, Horby J, Hansen HJ. Wegener's granulomatosis in the bladder. Br J Urol 1990;65:108–9.
[46] Katz DJ, Sengupta S, Snow RM. Isolated vasculitis of the bladder. Urology 2005;65: 797.
[47] Magrey MN, Villa-Forte A, Koening CL, Myles JL, Hoffman GS. Persistent hematuria after induction of remission in Wegener granulomatosis: a therapeutic dilemma. Medicine (Baltimore) 2009;88:315–21.
[48] Hazzan M, Bridoux F, Verier A, Gobert P, Vanhille P. Urologic manifestations in Wegener's disease. Ann Med Interne (Paris) 1991;142:319–20.
[49] Lillaz J, Bernardini S, Algros MP, Bittard H, Kleinclauss F. Wegener's granulomatosis: a rare cause of hydronephrosis. Case Rep Med 2011;2011:814794.
[50] Sataa S, Ben Rhouma S, Tanguour M, Rebai S, Cherif K, Kchir N, et al. Ureteral stenosis due to Wegener's granulomatosis. Tunis Med 2011;89:725–6.
[51] Ben Ghorbel I, Chebbi W, Zouari M, Hentati F, Miled M, Houman MH. Ureteral stenosis in Wegener's granulomatosis. Case report. Presse Med 2006;35:1659–63.
[52] Kamar N, Malavaud B, Alric L, le Mao G, Mazerolles C, Duffaut M, et al. Ureteral stenosis as the sole manifestation of Wegener's granulomatosis. Urology 2003; 62:352.
[53] Plaisier EM, Mougenot B, Khayat R, Gattegno B, Mignon F, Ronco PM. Ureteral stenosis in Wegener's granulomatosis. Nephrol Dial Transplant 1997;12:1759–61.
[54] Rich LM, Piering WF. Ureteral stenosis due to recurrent Wegener's granulomatosis after kidney transplantation. J Am Soc Nephrol 1994;4:1516–21.
[55] Le Thi Huong D, De Gennes C, Wechsler B, Etienne SD, Godeau P. Anuria caused by bilateral ureteral stenosis in Wegener's granulomatosis. Presse Med 1988;17:870.
[56] Ronco P, Mignon F, Laneo Y, Roland J, Morel-Maroger L, Gattegno B. Ureteral stenosis in Wegener's granulomatosis. Report of a case. Nephron 1982;30:201–4.

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[57] Farpour F, Abrudescu A. A case of granulomatosis with polyangiitis causing hydroureter and hydronephrosis. Case Rep Rheumatol 2014;2014:713957.
[58] Umemoto A, Ikeuchi H, Hiromura K, Hamatani H, Sakurai N, Sakairi T, et al. Hydronephrosis caused by a relapse of granulomatosis with polyangiitis (Wegener's). Mod Rheumatol 2012;22:616–20.
[59] Lee SS, Tang SH, Sun GH, Yu CP, Jin JS, Chang SY. Limited Wegener's granulomatosis of the epididymis and testis. Asian J Androl 2006;8:737–9.
[60] Barber TD, Al-Omar O, Poulik J, McLorie GA. Testicular infarction in a 12-year-old boy with Wegener's granulomatosis. Urology 2006;67(846):e9-10.
[61] Paik ML, MacLennan GT, Seftel AD. Embolic testicular infarction secondary to non-bacterial thrombotic endocarditis in Wegener's granulomatosis. J Urol 1999;161: 919–20.
[62] Hernandez-Rodriguez J, Tan CD, Koening CL, Khasnis A, Rodriguez ER, Hoffman GS. Testicular vasculitis: findings differentiating isolated disease from systemic disease in 72 patients. Medicine (Baltimore) 2012;91:75–85.
[63] Al-Arfaj A. Limited Wegener's granulomatosis of the epididymis. Int J Urol 2001;8: 333–5.
[64] Miller DC, Koss MN. Wegener granulomatosis presenting as epididymitis. Urology 2009;73:1225–6.
[65] Roussou M, Dimopoulos SK, Dimopoulos MA, Anastasiou-Nana MI. Wegener's granulomatosis presenting as a renal mass. Urology 2008;71(547):e1–2.
[66] Ruiz Carazo E, Medina Benitez A, Lopez Milena G, Rabaza Espigares J, Leon L, Marquez B. Multiple renal masses as initial manifestation of Wegener's granulomatosis. AJR Am J Roentgenol 2001;176:116–8.
[67] Schydlowsky P, Rosenkilde P, Skriver E, Helin P, Braendstrup O. Wegener's granulomatosis presenting with a tumor-like lesion in the kidney. Scand J Rheumatol 1992; 21:204–5.
[68] Smith DJ, Milroy CM, Chapple CR. An unusual renal mass:? Wegener's granulomatosis. Br J Urol 1993;72:980–1.
[69] Villa-Forte A, Hoffman GS. Wegener's granulomatosis presenting with a renal mass. J Rheumatol 1999;26:457–8.
[70] Ward A, Konya C, Mark EJ, Rosen S. Granulomatosis with polyangiitis presenting as a renal tumor. Am J Surg Pathol 2014;38:1444–8.
[71] Tatsis E, Reinhold-Keller E, Steindorf K, Feller AC, Gross WL. Wegener's granulomatosis associated with renal cell carcinoma. Arthritis Rheum 1999;42:751–6.
[72] Stone JH, Holbrook JT, Marriott MA, Tibbs AK, Sejismundo LP, Min YI, et al. Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial. Arthritis Rheum 2006;54:1608–18.
[73] Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310–7.
[74] De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461–9.
[75] Stillwell TJ, Benson Jr RC. Cyclophosphamide-induced hemorrhagic cystitis. A review of 100 patients. Cancer 1988;61:451–7.
[76] Knight A, Askling J, Granath F, Sparen P, Ekbom A. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Ann Rheum Dis 2004;63:1307–11.
[77] Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. Arthritis Rheum 2010;62:9–21.
[78] Cox PJ. Cyclophosphamide cystitis—identification of acrolein as the causative agent. Biochem Pharmacol 1979;28:2045–9.
[79] Talar-Williams C, Hijazi YM, Walther MM, Linehan WM, Hallahan CW, Lubensky I, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med 1996;124:477–84.
[80] Stillwell TJ, Benson Jr RC, DeRemee RA, McDonald TJ, Weiland LH. Cyclophosphamide-induced bladder toxicity in Wegener's granulomatosis. Arthritis Rheum 1988;31: 465–70.
[81] Johnson WW, Meadows DC. Urinary-bladder fibrosis and telangiectasia associated with long-term cyclophosphamide therapy. N Engl J Med 1971;284:290–4.
[82] Aptekar RG, Atkinson JP, Decker JL, Wolff SM, Chu EW. Bladder toxicity with chronic oral cyclophosphamide therapy in nonmalignant disease. Arthritis Rheum 1973;16: 461–7.
[83] Knight A, Askling J, Ekbom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. Int J Cancer 2002;100:82–5.
[84] Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. J Am Soc Nephrol 1998;9:842–52.
[85] Faurschou M, Sorensen IJ, Mellemkjaer L, Loft AG, Thomsen BS, Tvede N, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 2008;35:100–5.
[86] Hellmich B, Kausch I, Doehn C, Jocham D, Holl-Ulrich K, Gross WL. Urinary bladder cancer in Wegener's granulomatosis: is it more than cyclophosphamide? Ann Rheum Dis 2004;63:1183–5.
[87] Sigal SH, Tomaszewski JE, Brooks JJ, Wein A, LiVolsi VA. Carcinosarcoma of bladder following long-term cyclophosphamide therapy. Arch Pathol Lab Med 1991;115: 1049–51.
[88] Stein JP, Skinner EC, Boyd SD, Skinner DG. Squamous cell carcinoma of the bladder associated with cyclophosphamide therapy for Wegener's granulomatosis: a report of 2 cases. J Urol 1993;149:588–9.
[89] Seo P, Min YI, Holbrook JT, Hoffman GS, Merkel PA, Spiera R, et al. Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET). Arthritis Rheum 2005;52:2168–78.
[90] Langford CA. Cyclophosphamide as induction therapy for Wegener's granulomatosis and microscopic polyangiitis. Clin Exp Immunol 2011;164(Suppl. 1):31–4.
[91] de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670–80.
[92] Hows JM, Mehta A, Ward L, Woods K, Perez R, Gordon MY, et al. Comparison of mesna with forced diuresis to prevent cyclophosphamide induced haemorrhagic cystitis in marrow transplantation: a prospective randomised study. Br J Cancer 1984;50:753–6.
[93] Lapraik C, Watts R, Bacon P, Carruthers D, Chakravarty K, D'Cruz D, et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology (Oxford) 2007;46:1615–6.
[94] Sneller MC. Cystitis, bladder cancer, and myelodysplasia in patients with Wegener's granulomatosis: comment on the article by Reinhold-Keller et al. Arthritis Rheum 2000;43:2853–5.
[95] Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363: 221–32.
[96] Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008; 359:2790–803.
[97] Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener's granulomatosis: induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. Arthritis Rheum 1999;42:2666–73.
[98] Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.

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