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Urethral involvement in granulomatosis with polyangiitis: a case-based review

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Abstract

Granulomatosis with polyangiitis (GPA) commonly presents with glomerulonephritis and inflammation of upper and lower respiratory tracts. It can also involve other organs including those of the urinary tract. The involvement of the urethra is very rarely reported. We present a case of GPA in a patient who had recurrent urinary tract infections and an acute bladder outlet obstruction due to a urethral thickening by GPA. In this report, we discuss urethral involvement with GPA. The incidence of such involvement, as with other urinary tract organs, might be underestimated. It can affect both sexes, with male predominance, and can occur at any age. It responds to standard GPA medical treatment but may require surgical intervention. Rheumatologists should be aware of this limited form of GPA as early recognition and treatment can decrease the risk of complications.

Keywords Granulomatosis with polyangiitis · GPA · Wegener's · Urogenital · Urethra · Limited form

Introduction

Granulomatosis with polyangiitis (GPA) is a type of vasculitis that affects the small and medium vessels that were first described in the late 1930s [1]. It affects both sexes and is more prevalent in white elderly population [2]. It is characterized by the presence of necrotizing granulomas and is commonly associated with anti-neutrophil cytoplasmic antibodies (ANCA). Common organs involved with GPA include the upper and lower respiratory tracts and the kidneys in the form of a pauci-immune glomerulonephritis. Other organs that can be involved include the peripheral nervous system, mucous membranes, skin, and eyes. Urogenital involvement is rarely described [3, 4]. We present a case of a patient with localized GPA in the urethra and review of the literature related to the topic.

Search strategy

We reviewed the literature, from the last 50 years, using "Pubmed," "MEDLINE," "Scopus," and "Google Scholar" online search engines using a different combination of the following keywords: "Wegner's," "Granulomatosis with polyangiitis," "urinary tract," "urogenital," and "urethra." All types of studies, case series, case reports and review articles

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were included in the search. All abstracts were reviewed and relevant articles were further studied. We excluded articles written in languages other than English and French.

Case presentation

A 64-year-old Caucasian woman with a medical history of hypertension, presented to the emergency department with worsening recurrent frontal headache with cheeks, periorbital and behind ears pain. She was diagnosed with sinusitis 6 months prior, but symptoms did not resolve after multiple courses of antibiotics and over-the-counter medications. On examination, she was found to have tenderness over paranasal sinuses and there was evidence of left otitis media. Her initial laboratory workup, including complete blood picture and liver and kidney function tests, did not reveal abnormalities. A computerized tomography (CT) scan of the sinuses showed mucoperiosteal thickening and near complete opacification of the frontal, maxillary, sphenoid, and mastoid sinuses along with a lesion in the left external auditory canal. She had bilateral endoscopic total ethmoidectomy, maxillary antrostomy, sphenoidectomy, and frontal sinusotomies. Biopsies from the sinuses revealed marked acute inflammation suggestive of abscess, necrotic polypoid tissue and giant cell histiocytic reaction. Excisional biopsy of the ear lesion showed extensive chronic inflammation and necrosis with acute inflammatory cells.

Few weeks after surgery, symptoms persisted and a repeat sinus CT showed recurrence of mucoperiosteal thickening in some of the sinuses with acute sinusitis. Infection work-up was again negative. Further laboratory workup was pertinent for elevated erythrocyte sedimentation rate (124 mm/h), low titer rheumatoid factor (35), positive C-ANCA (anti-neutrophil cytoplasmic antibody) with a titer of 1:80 and negative ANA (anti-nuclear antibody). A diagnosis of GPA was made by exclusion. Pulmonary and renal involvement was ruled out by laboratory and imaging studies. She was started on oral prednisone 1 mg/kg/day and oral methotrexate 15 mg/week. Her clinical symptoms and inflammatory markers improved, and prednisone was tapered down till it was stopped after 6 months.

2 years later, she complained of recurrent lower abdominal pain and dysuria. Urine analysis and culture showed urinary tract infection. Antibiotics were given, but the dysuria persisted and symptoms eventually progressed to urinary hesitancy. She was found to have supra-pubic fullness due to a distended urinary bladder, with relief on urinary catheterization. Complete blood count, comprehensive metabolic panel, C-reactive protein, and erythrocyte sedimentation rate were unremarkable. A CT of the abdomen and pelvis showed non-specific irregular thickening of the urinary bladder. Cystoscopy showed a narrowed urethra with friable, ulcerated, markedly inflamed, and necrotic appearing proximal urethra. The urinary bladder wall was trabeculated with no masses. Biopsies of the urethra and bladder neck revealed necrotizing granulomatous inflammation (Fig. 1). She was treated initially with intravenous methylprednisolone 1 mg/kg/day and intravenous cyclophosphamide 500 mg. Steroids were transitioned to a slow prednisone taper and intravenous cyclophosphamide was continued for 3 months. Her symptoms improved and azathioprine 100 mg/d was used as maintenance therapy. There has been no evidence of disease progression throughout 7 years of follow-up.

Discussion

According to the number and type of organs involved, GPA can be classified into systemic and limited forms [5, 6]. In the systemic form, there is involvement of the "vital organs" mainly the kidneys (glomerulonephritis), and/or the lungs. The limited form usually refers to a non-renal single organ involvement (localized) with an indolent course and no immediate threat to a vital organ or the patient's life. The localized form has a higher tendency toward chronicity and recurrence. A major subset of patients with the limited form can eventually progress to involve the vital organs. The distinction between both forms is significant for treatment guidance and prognostic expectations [7]. It is important to remember that the terms "limited" and "systemic" do not describe the degree of the severity of a single disease flare.

The diagnostic efficacy of non-renal biopsies in GPA is variable as classic findings of GPA are evident in 30–90% of the cases. However, these biopsies are usually important to rule out infection and malignancy etiologies. Thus, in

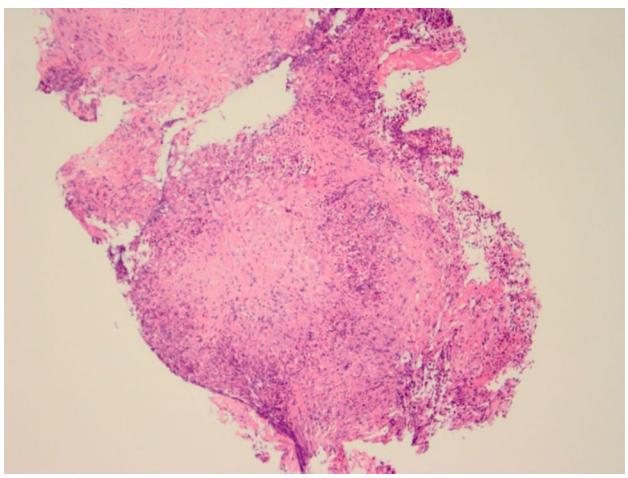

Fig. 1 Microscopic picture of urethral biopsy showing necrotizing granuloma with tissue necrosis and infiltration with inflammatory cells with some evidence of inflammation surrounding blood vessels (vasculitis)

selected cases, repeating biopsies may be reasonable to establish the diagnosis of GPA [8, 9]. The initial diagnosis of GPA in this patient was based on her clinical presentation and laboratory findings (elevated erythrocyte sedimentation rate and weakly positive C-ANCA), and after exclusion of possible malignant and infectious etiologies of such extensive sinusitis. Despite the extensive sinuses involvement, she had the limited form of GPA due to lack of renal and lung disease. Thus, she was treated with steroids and maintained on methotrexate which is a moderate potent immunosuppressant medication. With the involvement of urethra, she continued to have a limited GPA form. The significant complications were related to site of GPA involvement and not to GPA itself. Laboratory results, including inflammatory markers, during the second disease flare, were not suggestive of disease activity. Although, she was treated with an initial more potent immunosuppressant medication regimen in the second time, both flares responded well to medical treatment, and the disease did not progress to the severe form.

It is estimated that urogenital involvement occurs in < 1 to 2% of patients with GPA [10, 11]; however, a higher prevalence, of up to 10%, was reported in one cohort [12]. The most frequently involved organ in the urogenital tract is the prostate followed by the urinary bladder [11–14].

In our review of literature, we identified a total of fourteen patients reported to have urethral involvement secondary to GPA [14–25]. These patients along with the patient presented in this report are summarized in Table 1. One case was excluded as it was written in Danish [26].

The actual incidence of GPA in the urethra may be higher than what is reported. One reason could be that it might not be clinically evident due to its small size similar to GPA in the prostate. Postmortem prostatic involvement was found in around 7% of patients who had systemic form of GPA [27]. Another possible reason is that such small organ involvement may regress in response to systemic therapy, given for treatment of GPA in other sites, before it becomes clinically evident.

The literature shows an age range at the time of diagnosis with urethral involvement from 25 to 73 years. Half of these patients had their disease before age of 50 years which is the average age for GPA diagnosis [1, 3]. While GPA in general affects males and females equally, a male predominance noted in urethral GPA with a male–female ratio of 9:5. In six patients, the involvement of the urethra was detected at the time of GPA diagnosis. Isolated urogenital involvement (urethra and other organs), as the first presentation of GPA, occurred in four of these patients. In only one of case, the urethra was the only affected organ. In the rest of them, symptoms of urethral involvement occurred between 2 and 10 years after the diagnosis of GPA.

Symptoms of urethral involvement included hematuria, urethral discharge, dysuria, acute urinary retention, and chronic urinary obstruction symptoms. Most of these symptoms were initially thought to be related to a urinary tract infection. Acute urinary retention occurred mainly in patients with younger age. None of these patients complained of any pain related to the GPA lesion itself. One patient had an extensive lesion that progressed to the outer surface and manifested as a penile ulcer. Otherwise, all patients had a benign course and outcome. Practically, most of these symptoms could be misdiagnosed as a urinary tract infection which is commonly suspected in patients who are immunosuppressed. Also, hematuria could be misdiagnosed as hemorrhagic cystitis in patients who are receiving cyclophosphamide. Thus, GPA involving the lower urinary tract should be part of the differential diagnosis for unexplained recurrent urinary tract infections and/or hematuria in patients with GPA.

It is suggested that the rise in ANCA titers may predict flares of GPA [28]. However, this could be applicable more to patients with renal involvement [29]. In all patients, the diagnosis was made through the biopsies taken directly from the urethra and other parts of the urogenital tracts. It is noted that in four patients, ANCA antibodies were not checked. In patients whom ANCA antibodies were checked, all of them had C-ANCA antibody except for only one who had P-ANCA. Most of the patients had relatively low titers ≤ 1:80 except for two patients who had a titer of 1:160. This finding suggests that urogenital involvement may not correlate with high ANCA titers and may occur at times during which the disease activity is quiet. With advancement of ANCA assays, the significance of titers may not be the same from times when those cases were reported.

In half of these patients, medical treatment alone was enough to manage the disease. Surgical treatment was combined with medical treatment in four patients and was used alone in two others. Steroids were the most used medical treatment (eleven patients). They were combined with cyclophosphamide in eight patients and with methotrexate in two patients. The outcomes were not explicitly reported in most of the cases; however, it is speculated that most patients had good outcomes. Death was reported in two patients (14%). The first one died from surgical complications after developing multiple recurrences requiring multiple surgeries. The second patient developed a severe GPA attack with pulmonary–renal involvement.

Conclusion

Limited forms of GPA can involve different organs including the urogenital tract. Although urethral involvement is rarely reported, the actual incidence may not be well known. In reported cases, non-specific symptoms suggestive of urinary tract infection and obstructive uropathy were reported.

Table 1 Reported patients with urethral involvement with granulomatosis with polyangiitis (GPA)

No.	References	Age (years) at GPA diagnosis	Time between GPA diagnosis and urethral involvement	Presenting symptom	Urogenital organs involved (other than urethra)	Other organs[a]	ANCA test	Treatment and outcomes
1	Fowler [15]	56/F	2 years	Dysuria, urethral discharge	Bladder	Sinuses, lung	Not done	Prednisone and cyclophosphamide Responded to treatment
2	Jensen [16]	25/F	0 (presentation)	Dysuria, bloody discharge, urinary incontinence	Urethro-vaginal fistula		Not done	Prednisone and surgery Responded to treatment
3	Dore [17]	44/M	0 (presentation)	Dysuria, urethral discharge			Not done	Prednisone, cyclophosphamide and multiple surgical debridement Died after few months from surgical complications
4	Weiss [18]	73/M	10 years	Hematuria	Bladder neck	Lung	Not done	Surgical treatment (no report on outcomes)
5	Maaten [19]	49/M	10 years	Acute urine retention	Prostate	Lung, sinuses, retroperitoneal fibrosis, glomerulonephritis	C-ANCA	Immunosuppression (no details)
6	Zielonka [20]	33/M	5 years	Acute urinary retention		Lungs, sinuses, nasal septum, subglottic stenosis, parotid gland	Not reported	Prednisone and cyclophosphamide Responded to treatment
7	Linehan [21]	73/M	0 (presentation)	Difficulty micturition	Penis	Lung, sinuses (After)	C-ANCA (1/160)	Steroids and cyclophosphamide Responded to treatment
8	Davenport [14]	73/M	Not reported	Penile discharge, urinary frequency and retention	Prostate	Lung (before)	P-ANCA, 1/10	TURP Responded to treatment
9	Davenport [14]	67/M	0 (presentation)	Urinary frequency	Penis	Sinuses, foot drop	C-ANCA, 1/160	Repeated dilatation Recurrence treated with cyclophosphamide and prednisone
10	Ebo [22]	48/M	7 years	Recurrent cystitis, phimosis, balanitis, penile ulceration	Penis		C-ANCA (1/80)	Prednisone and cyclophosphamide
11	Sharma [23]	40/M	0 (presentation)	Acute urinary retention	Prostate	Lung, skin, glomerulonephritis	C-ANCA, PR3	Methylprednisolone and cyclophosphamide Died from pulmonary renal syndrome
12	Marin [24]	62/F	0 (presentation)	Vaginal bleeding, bladder tenesmus	Vagina, vesico-vaginal fistula		C-ANCA (1/80)	Prednisone and methotrexate

Table 1 (continued)

No.	References	Age (years) at GPA diagnosis	Time between GPA diagnosis and urethral involvement	Presenting symptom	Urogenital organs involved (other than urethra)	Other organs[a]	ANCA test	Treatment and outcomes
13	Anderson [25]	36/F	6 years	Acute urinary retention		Lungs, sinuses	PR-3	Prednisone and methotrexate
14	Present case	64/F	2 years	Difficulty micturition, urinary retention	Bladder neck	Nose and sinuses	C-ANCA, 1/80	Surgical dilatation, prednisone and cyclophosphamide

F female, *M* male, *TURP* trans-urethral resection of prostate

[a]Other organs involved at time of diagnosis unless otherwise specified

Rheumatologists should be aware of such limited forms of GPA as early treatment may help to avoid surgical treatment and its risks.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

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