Bilateral Ureteral Stenosis with Hydronephrosis as First Manifestation of Granulomatosis with Polyangiitis (Wegener’s Granulomatosis): A Case Report and Review of the Literature

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Received 18 February 2020; Revised 17 November 2020; Accepted 8 December 2020; Published 23 December 2020

Hindawi
Case Reports in Nephrology
Volume 2020, Article ID 7189497, 6 pages
https://doi.org/10.1155/2020/7189497

Case Report

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Received 18 February 2020; Revised 17 November 2020; Accepted 8 December 2020; Published 23 December 2020

Academic Editor: Phuong Chi Pham

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Ureteral stenosis is a rare manifestation of granulomatosis with polyangiitis (formerly known as Wegener’s granulomatosis). We report the case of a 76-year-old woman with progressive renal failure in which bilateral hydronephrosis due to ureteral stenosis was the first manifestation of the disease. Our patient also had renal involvement with pauci-immune crescentic glomerulonephritis associated with high titers of anti-proteinase 3 c-ANCAs, but no involvement of the upper or lower respiratory tract. The hydronephrosis and renal function rapidly improved under immunosuppressive therapy with high-dose corticosteroids and intravenous pulse cyclophosphamide. We reviewed the literature and found only ten other reported cases of granulomatosis with polyangiitis/Wegener’s granulomatosis and intrinsic ureteral stenosis: in two cases, the presenting clinical manifestation was unilateral hydronephrosis and in only two others was the hydronephrosis bilateral, but this complication developed during a relapse of the disease. This case emphasizes the importance of including ANCA-related vasculitis in the differential diagnosis of unusual cases of unilateral or bilateral ureteral stenosis.

1. Introduction

Granulomatosis with polyangiitis (GPA) (formerly known as Wegener’s granulomatosis) is a necrotizing vasculitis of the small to medium vessels, according to the revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [1]. Its classic triad consists of necrotizing granulomatous vasculitis of the upper and lower respiratory tract in association with pauci-immune crescentic glomerulonephritis [2]. It is often associated with antineutrophilic cytoplasmic antibodies (ANCA) against proteinase 3 (anti-PR3), but occasionally also against myeloperoxidase (anti-MPO) [2]. GPA is an uncommon disease, with an annual incidence of about 10 cases per million inhabitants, a prevalence of 22–157 cases per million [3] and a peak incidence in the fourth and fifth decades of life [4]. Men and women are affected at a similar frequency. GPA was a fatal disease before the introduction of effective immunosuppressive treatments. The use of high-dose corticosteroids associated with cyclophosphamide has markedly improved survival as well as renal survival of patients with ANCA-associated vasculitis [3].

GPA can affect all organs of the body. Although rare, urogenital manifestation can occur during the course of the disease and may be asymptomatic [5]. Granulomatous inflammation of the prostate, bladder, penis, testes, seminal vesicles, ureters, urethra and epididymis have already been reported.

We are reporting on a case in which bilateral hydronephrosis due to bilateral ureteral stenosis was the first clinical manifestation of GPA. Ureteral stenosis is a rare complication of GPA: only 11 cases (including ours) have been reported in the literature to date and, to our knowledge, our case is the first one in which bilateral hydronephrosis was the presenting manifestation of the disease.
2. Case Report

A 76-year-old woman was transferred to our hospital after a 6-month history of progressive renal failure with bilateral hydronephrosis of unclear origin and normal cystoscopy.

At admission the patient complained of fatigue, bilateral leg oedema and a 10 kg weight loss. The patient denied any episode of macroscopic hematuria. Clinical examination found a patient in poor general condition with bilateral pitting edema of the legs. Temperature was 36.5°C, blood pressure 135/70 mmHg. The laboratory findings were as follows: serum creatinine was 60 l μmol/l, urea 39.5 mmol/l, total protein 57.5 g/l, serum albumin 28 g/l, sodium 143 mmol/l, potassium 4.8 mmol/l. The sedimentation rate was 81 mm/h, C-reactive protein (CRP) 33 mg/l, hemoglobin 107 g/l, leukocyte count 7.2 G/l and platelets 333 G/l. Urinalysis showed microscopic hematuria with mild leukocyturia. Urine culture was sterile. Creatinine clearance was 4 ml/min. Proteinuria was present at 1.9 g/24 h, without paraproteins.

A native abdominal CT scan was performed showing bilateral uretero-nephrosis with massive dilatation of the upper ureters and of the renal pelvis (Figure 1(a)). The CT scan showed no signs of an obstructive abdomino-pelvic mass, of retroperitoneal fibrosis, or retroperitoneal obstruction. However, the differential diagnosis also includes other rare etiologies. Table 1 summarizes the causes of bilateral, or potentially bilateral, ureteral obstruction according to the mechanism of obstruction and shows that different inflammatory or systemic diseases, including small and medium vessel vasculitis, can cause bilateral hydro-uretero-nephrosis. As we will discuss further below, sometimes, unilateral or bilateral ureteral stenosis with hydronephrosis may be due to ANCA-associated vasculitis. To our knowledge, we are reporting on the first patient with bilateral hydronephrosis as the presenting manifestation of ANCA-associated vasculitis.

Urogenital involvement is rare in GPA. Large series of GPA patients have reported between 1% and 10% of cases with urogenital involvement [6, 24]. Cases of asymptomatic urogenital involvement have also been reported in autopsy studies of patients with GPA, and urological manifestation may be underestimated because complete urological investigations are not routinely performed [5]. The main locations of the urogenital manifestations of GPA are summarized in Table 2. Prostatitis is the most common, followed by bladder involvement, orchitis, and penile ulcerations [5]. When urological involvement is present, it is usually observed as part of a generalized systemic disease associated with upper respiratory involvement in 90–100% of the cases, pulmonary lesions in 80%, and glomerulonephritis in 45–60% [5]. Isolated urological manifestations can precede GPA diagnosis in 12–18% of the cases having urological involvement [6, 24]. Intrinsic ureteral stenosis is a rare manifestation of GPA as only 11 cases (including ours) have been reported in the literature to date [6, 24–30]. Huong et al. [6] and Kamar et al. [27] each described two cases. One case was reported twice by the same author [6, 31]. Two other cases were published twice [26, 29, 32, 33] and another case three times [25, 34, 35]. It should be noted that cases of patients with GPA in which hydronephrosis was due to extrinsic ureteral obstruction caused by retroperitoneal inflammation, pseudotumors, or vascular compression as well as prostatic obstruction as a consequence of GPA-related inflammation have also been reported [36–44].

Table 3 summarizes the main clinical features of the 11 cases of ureteral stenosis reported in the literature. In most cases (8/11 = 73%), the ureteral involvement occurred during a relapse of GPA and in only two cases was the involvement bilateral [6, 26]. In the two remaining cases, the ureteral stenosis was, as in our patient, the initial manifestation of GPA, but in these two patients, the hydronephrosis was unilateral [27, 30]. Davenport et al. briefly described a case of initial manifestation of GPA with bilateral ureteral obstruction, but this was due to necrotic debris in the bladder and in the two ureters [43]. Interestingly, a case of ureteral stenosis has also been reported in a kidney transplant due to the recurrence of GPA after transplantation [28].

In 6 of these 11 cases, open ureteral surgery was performed as part of the diagnostic and/or therapeutic workup and granulomatous/vasculitic inflammation was found in all [24, 27–30]. In the other four cases that underwent only an endoscopic workup, no ureteral biopsy was performed [6, 25, 26]. Hence, our case is in fact the only one where a small
endoscopic biopsy was performed in order to rule out malignancy. This biopsy showed only nonspecific inflammation, and we consider that our biopsy was too small and superficial to allow the detection of a granulomatous or vasculitic inflammation. However, one may question if the bilateral ureteric stenosis in our patient may eventually be unrelated to the ANCA-associated vasculitis. In this respect,

Figure 1: Native CT scan (a) at admission showing massive bilateral hydronephrosis and (b) at 3 months showing a complete regression of the hydronephrosis on the left side and a partial regression on the right side.

Figure 2: Retrograde pyelography showing bilateral hydro-uretero-nephrosis with a complete ureteral stenosis on the right and a partial ureteral stenosis on the left.

Figure 3: Renal biopsy showing extracapillary crescentic glomerulonephritis involving almost all glomeruli (HE, 100x).

Table 1: Causes of bilateral or potentially bilateral ureteral obstruction*.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract malformations</td>
<td>Several mainly congenital pediatric diseases</td>
</tr>
<tr>
<td>Urolithiasis and endoluminal obstruction</td>
<td>Calculi, papillary necrosis with sloughed papilla, blood clots, fungus balls</td>
</tr>
<tr>
<td>Intrinsic ureteral obstruction</td>
<td>Transitional cell carcinoma and other malignant neoplasms fibroepithelial polyps, ureteritis cystica</td>
</tr>
<tr>
<td>Extrinsic ureteral obstruction</td>
<td>Abdominopelvic tumors, lymphoma, retroperitoneal fibrosis endometriosis, sarcoidosis</td>
</tr>
<tr>
<td>Systemic and inflammatory diseases**</td>
<td>Small-vessel vasculitis, periarthritis nodosa, Churg–Strauss, Henoch–Schönlein purpura, eosinophilic ureteritis, RA</td>
</tr>
<tr>
<td>Ureteral localization of infections</td>
<td>Fungal (actinomycosis), tuberculosi, bacterial, viral (immunocompromised host)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Pregnancy, slowed peristalsis, obstructed stent, postoperative</td>
</tr>
</tbody>
</table>

*Adapted from references [6–23]. **Some can cause either intrinsic or extrinsic obstruction. RA = rheumatoid arthritis.

Table 2: Relative frequency of the different urogenital manifestations of granulomatosis with polyangiitis.

<table>
<thead>
<tr>
<th>Site</th>
<th>Clinical manifestations</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Prostatitis, urinary retention, asymptomatic</td>
<td>++++++</td>
</tr>
<tr>
<td>Bladder</td>
<td>Cystitis, pseudotumor</td>
<td>+++</td>
</tr>
<tr>
<td>Penis</td>
<td>Ulcerations</td>
<td>+++</td>
</tr>
<tr>
<td>Testicles</td>
<td>Orchitis</td>
<td>+++</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Pseudotumors, asymptomatic</td>
<td>+++</td>
</tr>
<tr>
<td>Urethra</td>
<td>Urethritis</td>
<td>++</td>
</tr>
<tr>
<td>Ureter</td>
<td>Stenosis, hydronephrosis</td>
<td>++</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Epididymitis</td>
<td>+</td>
</tr>
</tbody>
</table>

Data adapted from Alba et al. [5].
we consider that the accurate initial diagnostic workup, the follow-up exams performed at 3 months, and the favourable response with the regression of the hydro-uretero-nephrosis under immunosuppressive therapy allow to reasonably rule out the alternative diagnosis listed in Table 1.

Concerning ANCAs, ANCA determinations were not performed on the oldest cases reported in the literature as this diagnostic test was not yet available at the time. Except for the two cases reported by Kamar et al., ANCA was positive in all other cases, with anti-PR3 positivity in three patients and anti-MPO positivity in one. The two ANCA-negative cases reported by Kamar et al. are unique since these two patients had isolated 2 and 3 cm long unilateral ureteral stenoses with granulomatous inflammation at surgical resection as the sole manifestation of the disease [27].

The treatment of GPA with a combination of glucocorticoids and immunosuppressants, mainly cyclophosphamide, has been well established. All but three of the reported patients received this treatment and responded well to it (Table 3). To the best of our knowledge, the recurrence of ureteral stenosis upon medical treatment has never been reported. Endoscopic placement of double J catheters was performed in our case, as well as in five others [6, 24, 26], followed by open surgery in two cases [27]. Open surgery was initially performed in four cases [28–30, 35]. The last case underwent no urological therapy as the patient

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Ureteral stenosis</th>
<th>ANCA Type</th>
<th>Treatment</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>2003</td>
<td>59</td>
<td>F</td>
<td>Inaugural Left hydronephrosis with a 3 cm-long iliac ureteral stenosis</td>
<td>Negative</td>
<td>Double J stent, resection of the stenosis by open surgery</td>
<td>No</td>
</tr>
<tr>
<td>30</td>
<td>2011</td>
<td>71</td>
<td>F</td>
<td>Inaugural Right hydronephrosis related to a ureteral stenosis</td>
<td>Positive</td>
<td>exploration and resection of the stenosis</td>
<td>PRED + CYC</td>
</tr>
<tr>
<td>Our case</td>
<td>76</td>
<td>F</td>
<td>Inaugural Bilateral hydronephrosis related to ureteral stenosis</td>
<td>Positive PR3</td>
<td>Bilateral ureteral double J stents</td>
<td>PRED + CYC</td>
<td>Remission at 3 months</td>
</tr>
<tr>
<td>6, 31*</td>
<td>1988</td>
<td>69</td>
<td>F</td>
<td>Inaugural Bilateral hydronephrosis related to pelvic bilateral ureteral stenosis</td>
<td>Negative</td>
<td>Bilateral ureteral double J stents</td>
<td>PRED + CYC, and plasma exchanges</td>
</tr>
<tr>
<td>26, 32*</td>
<td>2006</td>
<td>38</td>
<td>F</td>
<td>Relapse Bilateral dilatation of both collecting systems with bilateral ureteral stenosis</td>
<td>Positive MPO</td>
<td>Endoscopic dilatation and double J stent on the left side</td>
<td>PRED + CYC</td>
</tr>
<tr>
<td>25, 34*, 35*</td>
<td>1977</td>
<td>60</td>
<td>F</td>
<td>Relapse Left ureteral obstruction at the pelvic brim Moderate dilatation on the right urinary tract</td>
<td>NA</td>
<td>Transureteral ureterostomy</td>
<td>PRED + CYC</td>
</tr>
<tr>
<td>29, 33*</td>
<td>1982</td>
<td>50</td>
<td>M</td>
<td>Relapse Hydro nephrosis in a transplanted kidney by ureteral obstruction at the ureterovesical junction</td>
<td>NA</td>
<td>Ureteral resection</td>
<td>PRED + CYC</td>
</tr>
<tr>
<td>28</td>
<td>1994</td>
<td>25</td>
<td>F</td>
<td>Relapse</td>
<td>Positive NA</td>
<td>Ureteral resection</td>
<td>PRED + CYC + AZA</td>
</tr>
<tr>
<td>6</td>
<td>1995</td>
<td>55</td>
<td>M</td>
<td>Relapse Right-sided ureteral stenosis Isolated right hydronephrosis with a 2 cm-long stenosis of the iliac ureter</td>
<td>Positive NA</td>
<td>None</td>
<td>PRED</td>
</tr>
<tr>
<td>27</td>
<td>2003</td>
<td>21</td>
<td>M</td>
<td>Relapse Isolated right hydronephrosis with a 2 cm-long stenosis of the iliac ureter</td>
<td>Negative</td>
<td>Double J stent followed by open surgery excision</td>
<td>PRED + CYC</td>
</tr>
<tr>
<td>24</td>
<td>2012</td>
<td>53</td>
<td>M</td>
<td>Relapse Right-sided hydronephrosis with ureteral stenosis</td>
<td>Positive PR3</td>
<td>Ureteral catheter</td>
<td>PRED and MTX</td>
</tr>
</tbody>
</table>

responded rapidly to immunosuppression [6]. In general, surgical repair of the ureters is unnecessary because urological symptoms improve quickly on medical treatment. Consequently, all authors advocate that surgery should only be considered in patients who do not rapidly and effectively respond to the combination of corticoids and immunosuppressants.

In summary, the present review indicates that unilateral or bilateral ureteral stenosis can be the first clinical manifestation of GPA or may occur during a relapse of the disease. Since the clinical presentation may mimic cancer, the right diagnosis can avoid unnecessarily invasive procedures. Therefore, ANCA-related vasculitides should be considered in the differential diagnosis of unusual cases of unilateral or bilateral ureteral stenosis and ANCA testing should be performed in patients in whom a diagnosis is not readily apparent. The data from the reviewed literature suggest that ureteral stenosis responds well and rapidly to glucocorticoids and immunosuppressants.

**Conflicts of Interest**

All authors declare no conflicts of interest.

**References**


