Long-term outcome of idiopathic retroperitoneal fibrosis treated with surgical and/or medical approaches

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Abstract

Background. Retroperitoneal fibrosis is a severe disease that affects the ureters, causing renal insufficiency in three-quarters of patients. The optimal treatment is far from being established.

Methods. Seventeen patients with idiopathic retroperitoneal fibrosis and ureteral entrapment followed in our unit for at least 1 year were selected for this study. At presentation 13 patients had renal insufficiency. All patients received steroids, associated with ureterolysis in five (group 1), with azathioprine in six (group 2) and with tamoxifen in six (group 3). Four patients of group 2 and five of group 3 received ureteral stenting or nephrostomy. There were no significant differences among the three groups or the clinical and biochemical characteristics at presentation.

Results. All patients of groups 1 and 2 entered remission after therapy. One patient from group 3 did not respond to therapy. During a mean follow-up of 56±41 months, three patients (two from group 1, one from group 2, 18%) had a recurrence of the disease, which fully responded to retreatment in all three cases. At the last observation, all patients were alive; three patients (18%) had renal insufficiency, of them one from group 1 had to start dialysis 6 years after ureterolysis, one patient from group 2 and one from group 3 had serum creatinine of 1.5 mg/dl. Renal survival was 100% at 5 years and 80% at 10 years.

Conclusions. In most patients, each of the three different therapeutic approaches restored renal function and significantly reduced the fibrotic mass in the short-term and maintained stable serum creatinine in the long-term.

Keywords: idiopathic retroperitoneal fibrosis; immunosuppressive therapy; renal long-term survival; ureterolysis

Introduction

Retroperitoneal fibrosis (RF) is an uncommon disease, characterized by a periaortic soft tissue mass of variable thickness that envelops the aorta and the inferior vena cava between the renal hilar and the sacral promontory and extends laterally to entrap one or both ureters [1]. Hydronephrosis, leading to progressive renal failure, is the most frequent and severe complication of the disease, being present at diagnosis in about 75% of patients [1].

RF may be secondary to pelvic neoplasias, asbestos exposure, drugs, abdominal surgery or radiation therapy [1]. However, in about two-thirds of cases the aetiology is unknown and the disease is considered idiopathic (IRF). The clinical presentation of IRF is usually insidious with vague constitutional symptoms and generally low back pain that may be severe and non-responsive to anti-inflammatory drugs. The pathogenesis is still poorly elucidated, but recent evidence supports the hypothesis that the disease may be the result of an inflammatory state triggered by autoimmune responses [2–4]. Parum et al. [2], considering the high correlation of IRF with atheromatous peri-aortitis, postulated that the disease may be due to an immune reaction to some components of atherosclerotic plaques such as low-density lipoprotein (LDL) and ceroid.

Both surgical and medical managements have been used in IRF. Placement of ureteral stents and ureterolysis are often used to relieve ureteral obstruction and hydronephrosis. Steroids may also reverse the ureteral obstruction within a few days and may improve the biological markers of inflammation and the systemic symptoms of the disease [5]. For these
reasons, steroid therapy is often associated with ureterolysis, but uncertainty still exists as to the optimal dosage and duration of steroid therapy. Azathioprine [6–9], cyclophosphamide [9], methotrexate, ciclosporin and mycophenolate mofetil [10] have also been used in association with steroids. Recently, some case reports outlined the efficacy of tamoxifen in the treatment of IRF [11,12].

The aim of this retrospective study was to evaluate the long-term efficacy of three different therapeutic schedules: steroids associated with ureterolysis, steroids plus azathioprine and steroids plus tamoxifen.

Patients and methods

From October 1990 to January 2005, 21 patients with RF were followed by our team. RF was associated with an inflammatory aortic aneurysm in two patients and to a gastric neoplasia in one patient. In the other 18 patients, no aetiological agent was identified and the disease was classified as idiopathic.

To comply with the aims of the study, we selected 17 patients with IRF (in two of them RF was associated with an inflammatory aortic aneurysm) by excluding four patients. Three patients with IRF were excluded because they had a follow-up of <1 year, the fourth patient was excluded for secondary RF due to gastric neoplasia. The clinical presentation of seven patients described in the present article has been partially reported in a previous study [4].

Follow-up

All patients were followed as out-patients in our unit for at least 1 year. Patients were regularly checked every 1–3 months. At each control, patients were submitted to clinical examination and to the following laboratory tests: serum creatinine, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complete blood cell count and urine analysis. Renal echography and computed tomography (CT) were performed every 3 months until the achievement of remission. After remission the same investigations were repeated every year.

Definitions

‘Active disease’ was defined by the presence of a periaortic mass englobing one or both ureters with hydronephrosis at CT scan associated with an increase in CRP or ESR.

‘Inactive disease’ was defined by the regression of hydronephrosis and by a marked reduction of the fibrotic tissue at CT scan in comparison with the basal examination together with the normalization of CRP and ESR.

‘Reactivation of the disease’ was defined by a CT-proven increase of the periortic mass with or without entrapment of one or both ureters associated with a new increase in CRP and/or ESR after at least 1 year of quiescence [4].

Treatments

Therapeutical approaches consisted of unilateral or bilateral ureterolysis associated with steroid therapy in five patients (group 1). Three patients were admitted to our unit immediately after bilateral ureterolysis performed in a Urological Unit, while two other patients were submitted to ureterolysis during hospitalization in our unit due to acute oliguric renal failure. The other 12 patients were treated with medical therapy, namely, steroids and azathioprine (six patients: group 2), or steroids and tamoxifen (six patients: group 3) according to physician preference. For the immediate management of ureteral obstructions, four patients of group 2 and five of group 3 received ureteral stenting or nephrostomy.

Statistical methods

Since the distribution of the variables showed high non-normality distribution, both mean±SD and median plus range were used for descriptive analysis. For the same reasons, t-test and the non-parametric Wilcoxon-test were used to investigate differences between two groups of patients.

Results

Clinical characteristics at presentation

Of the 17 patients, there were 10 men and 7 women. The mean age at diagnosis of RF was 56±8.5 years (range 41–70 years).

The most frequent presenting symptoms were back or abdominal pain, weakness, weight loss, polyuria, oligoanuria, arterial hypertension, leg oedemas and mild fever (Table 1). The duration of symptoms before diagnosis ranged from 1 to 13 months.

At presentation all patients had active disease, 13 patients had renal dysfunction with a median serum creatinine of 3.3 mg/dl (range 1.6–14.4 mg/dl). Four out of these 13 patients had a rapidly progressive...
renal failure with a serum creatinine ≥7 mg/dl and were oliguric or anuric at presentation. CRP was elevated in 78% of the patients (median 2.8 mg/dl, range 0.6–29; normal value <0.5 mg/dl) and ESR was elevated in 87% of patients (median 45 mm/h, range 15–34). The median haematocrit was 32% (range 24–35%).

Two patients had hyperthyroidism and two had hypothyroidism. All of them had positive anti-thyroid microsine and anti-thyroglobulin antibodies. Two patients had anti-nuclear antibodies with speckled pattern. Cryoglobulins, rheumatoid factors, anti-neutrophil cytoplasmic antibodies (ANCA), antibodies to extractable nuclear antigens (ENA) and anti-dsDNA antibodies were negative in all patients.

Diagnosis

The diagnosis of RF was made by CT in all patients and confirmed with a histological evaluation of the fibrotic mass in eight patients. The biopsy of the mass was obtained during ureterolysis in seven patients and with laparoscopy in one patient. At CT scan, 10 out of the 17 patients had atheromatous aortic plaques and all had contrast enhancement of the fibrotic tissue suggesting active IRF. For this reason, none of the patients were considered potentially non-responders.

None of the 17 selected patients was taking any medication known to cause RF nor had clinical or laboratory signs of chronic infection.

Malignancy was excluded on the basis of clinical, laboratory and radiological grounds. In 16 patients, the CT did not show any direct sign of malignancy or indirect signs such as cranial location of the mass, anterior displacement of the aorta, lateral displacement of the ureters and/or bone destruction [13]. In the last patient, the CT scan showed a cranial extension of the mass with massive infiltration of the gastro-spleno-ocolic ligament extending to the retro-pancreatic space with occlusion of splenic vein. The patient was submitted to multiple laparoscopic biopsies. The histological evaluation of the fibrotic tissue excluded a malignancy and confirmed the diagnosis of IRF.

At the time of diagnosis, all patients had ureteral obstruction plus unilateral hydronephrosis in five patients and bilateral hydronephrosis in 12. In the latter group of patients, one of the two kidneys (left kidney in six patients, and right kidney in the other six) had parenchyma retraction at CT and echography and reduced function at radio-isotope scan (sequential renal scintigraphy). Encasement of the vena cava was found in five patients. In another patient, the fibrotic mass enveloped the left renal artery with consequent reduction of the size and the function of the kidney.

Six patients had an associated atherosclerotic vascular disease, namely, femoral artery stenosis with claudicatio in three patients, myocardial infarct in two patients, and carotid artery stenosis in one patient with a previous episode of cerebral thrombosis.

Outcome (Table 2)

Group 1. Five patients received ureterolysis. After surgery, all patients were given prednisone 25 mg/day for 1 month, then progressively tapered to a maintenance of 10–5 mg/day. The median duration of steroid treatment was 6 months (range 4–12 months).

Group 2. Six patients were given steroids associated with azathioprine. Three patients with severe renal failure were treated with intravenous methylprednisolone pulses, 0.5 g/day each, for three consecutive days followed by oral prednisone 0.5 mg/kg/day for 1 month, then gradually tapered to a maintenance of 10–5 mg/day. The other three patients were started with prednisone 1 mg/kg/day for 1 month which was then gradually tapered to a maintenance of 10–5 mg/day. Azathioprine was given at a dose of 1.5 mg/kg/day. Prednisone was administered for a median of 18 months (range 12–24 months), and azathioprine for a median of 16 months (range 8–18 months).

Group 3. Six patients were given steroids associated with tamoxifen. All patients started therapy with oral prednisone at a dose of 1 mg/kg/day for 1 month which was then gradually tapered to a maintenance of 10–5 mg/day associated with tamoxifen 20–40 mg/day. Steroid therapy was continued for a median period of 15 months (range 6–18 months) and tamoxifen for 18 months (range 10–48 months).
in serum creatinine from 1.2 to 2.1 mg/dl and entrapment of the vena cava with deep vein thrombosis of the left leg. Steroid therapy (prednisone 1 mg/kg/day for 1 month then gradually tapered to a maintenance of 5 mg/day) was reinitiated with rapid regression of extra-renal manifestations and a return of serum creatinine to 1.1 mg/dl. At the last follow-up visit, 3 years after the reactivation of the retroperitoneal fibrosis and 2 years after the withdrawal of the therapy, the patient still had inactive disease and normal renal function.

Another patient developed severe respiratory insufficiency due to a lung involvement of the fibrotic process, 5 years after ureterolysis. After lung biopsy, the patient started treatment with steroids (prednisone 1 mg/kg/day for 1 month which was then gradually tapered to a maintenance of 5 mg/day) and mycophenolate mofetil (1.5 g/day) with a rapid improvement of the symptoms and a progressive reduction of the fibrotic tissue at lung CT. The therapy was continued for 2 years. At the last control, 1 year after stopping therapy, the patient is in good general condition with normal renal function. The lung CT scan and spirometry are normal.

One patient developed hyperglycaemia during steroid treatment that reversed after the withdrawal of the therapy.

**Group 2.** Patients were followed for a mean period of 62 ± 81 months (median 48 months; range 12–185). After diagnosis, ureteral stents were placed in three patients, and nephrostomy in one patient. All patients were given steroid and azathioprine therapy. After the beginning of the medical therapy, the constitutional symptoms reversed within a few days and the inflammatory markers normalized within a few weeks. After a reduction of the fibrotic tissue was documented in all patients by CT scan, ureteral stents and nephrostomy were removed 3–9 months after the beginning of the therapy. At the end of the first year of therapy, five patients had normal renal function and one had mild and stable renal dysfunction (serum creatinine 1.5 mg/dl, creatinine clearance 68 ml/min).

After 3 years of inactive disease, one patient with normal renal function had a recurrence of renal obstruction with acute renal failure (serum creatinine 4.4 mg/dl), hydronephrosis and a significant increase in the fibrotic tissue at CT. The patient was treated with methylprednisolone pulses of 0.5 g for three consecutive days followed by oral prednisone (0.5 mg/kg/day). Three months later, when renal function was normal (serum creatinine 1.1 mg/dl), ureterolysis was successfully performed. During the subsequent follow-up, the patient developed a symptomatic autoimmune hyperthyroidism. Clinical signs and symptoms reversed after 4 weeks of treatment with prednisone 20 mg/day.

No patient in this group developed any significant side effects attributable to steroids or azathioprine.

**Group 3.** Patients were followed for a mean period of 39.2 ± 17 months (median 35; range 22–62). After diagnosis, ureteral stents were placed in four patients and nephrostomy in one, while therapy with steroid and tamoxifen was started. The constitutional symptoms receded within a few days and the inflammatory markers normalized within a few weeks. In five patients, RF became inactive within 3–9 months after the beginning of the therapy when ureteral stents and nephrostomy were successfully removed. Renal function normalized in three patients, continued to remain normal in one, while in another patient a mild and stable renal dysfunction (serum creatinine of 1.5 mg/dl, creatinine clearance 52 ml/min) persisted. The clinical conditions and renal function remained stable at the last observation.

In the last patient, who presented with unilateral hydronephrosis and normal renal function, a transient improvement of the disease with regression of the hydronephrosis occurred after the beginning of the therapy. With the progressive reduction of steroids, renal obstruction rapidly recurred involving both kidneys and renal insufficiency developed (serum creatinine from 0.9 to 2.3 mg/dl). The patient was submitted to bilateral ureterolysis. At the last observation, 5 years after ureterolysis, the patient was well with normal renal function (serum creatinine 1.0 mg/dl). One patient developed moderate osteoporosis.

Taking these 17 patients altogether, they were followed for a mean period of 56 ± 41 months (median 58; range 12–185). In all but one patient the disease became inactive after medical therapy.

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**Table 2.** Clinical status at the last observation of patients treated with surgery plus steroids (group 1), with steroids and azathioprine (group 2), with steroids and tamoxifen (Group 3) and in the cumulative group of 17 patients analysed.

<table>
<thead>
<tr>
<th>Follow-up months</th>
<th>Group 1, 5 pts</th>
<th>Group 2, 6 pts</th>
<th>Group 3, 6 pts</th>
<th>All patients, 17 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>69.4 ± 26.4</td>
<td>62 ± 81</td>
<td>39.2 ± 17</td>
<td>56 ± 41</td>
</tr>
<tr>
<td>Median (range)</td>
<td>79 (26–96)</td>
<td>48 (12–185)</td>
<td>35 (22–62)</td>
<td>58 (12–185)</td>
</tr>
<tr>
<td>Response to therapy</td>
<td>5 pts (100%)</td>
<td>6 pts (100%)</td>
<td>5 pts (83%)</td>
<td>16 pts (94%)</td>
</tr>
<tr>
<td>Recurrence after therapy</td>
<td>2 pts (40%)</td>
<td>1 pt (16%)</td>
<td>0</td>
<td>3 pts (18%)</td>
</tr>
<tr>
<td>Normal renal function</td>
<td>4 pts (80%)</td>
<td>5 pts (83%)</td>
<td>5pts (83%)</td>
<td>14 pts (82%)</td>
</tr>
<tr>
<td>Normal serum creatinine (mg/dl), Median (range)</td>
<td>1.05 (1–1.2)</td>
<td>1.1 (1–1.2)</td>
<td>1.1 (1–1.2)</td>
<td>1.1 (1–1.2)</td>
</tr>
<tr>
<td>Mild renal insufficiency</td>
<td>0</td>
<td>1 pt (17%)</td>
<td>1 pt (17%)</td>
<td>2 pts (12%)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>1 pt (20%)</td>
<td>0</td>
<td>0</td>
<td>1 pt (6%)</td>
</tr>
</tbody>
</table>
During the follow-up, three patients (18%) had a reactivation of RF that required surgical and/or medical therapy. At the last observation all patients were alive with inactive disease. As far as renal function was concerned, one patient entered end-stage renal disease and had to undergo chronic haemodialysis 79 months after the diagnosis of RF, two patients had stable mild renal insufficiency (serum creatinine 1.5 mg/dl), while all the other patients had their creatinine clearance higher than 80 ml/min. Patient survival was 100% at 5 and 10 years, renal survival was 100% at 5 years and 80% at 10 years (Figure 1).

Discussion

RF is a severe disease, that may progress until completely blocking the ureters and the blood vessels involved by the process. A prompt diagnosis and an appropriate treatment may prevent the development of these complications. However, an early diagnosis is as difficult as it is important. For a long period of time, the renal function may remain normal and clinical symptoms are vague and non-specific. The diagnosis becomes easier only at a later stage, when both the ureters are affected by fibrosis with the consequent development of symptoms of urinary obstruction or renal failure. In our experience, 75% of the patients had renal failure and an irreversible shrinking of at least one kidney when diagnosis was made. These data confirm that a correct diagnosis is usually made belatedly and show that in many cases the disease first extends laterally to entrap one ureter leading to severe and sometimes irreversible damage of the corresponding kidney.

In the presence of a urinary obstruction, the aim of the initial management should be to restore the patency of the urinary tract and to improve renal function. Placement of stents or nephrostomy may be used as an emergency treatment, followed by ureterolysis that may be performed either by open surgery or by laparoscopy. The advantages of surgery are the relief of obstruction with a recovery of renal function in about 70% of cases [14] and the possibility of taking samples of the invading mass to rule out lymphomas or metastatic cancer. However, obstruction may recur in about 22% of responders [15]. Moreover, surgery does not relieve the systemic manifestations of the disease that affect the majority of patients. Therefore, corticosteroids alone or together with immunosuppressive agents have been used either in association with surgery or to avoid the use of ureterolysis [6,8,9]. In one study, 11 patients with RF were treated with methylprednisolone pulses associated with azathioprine or penicillamine. The results were good in seven patients but only moderately effective in four [7]. There are few data about residual renal insufficiency after surgical or medical treatment. By reviewing some of the most representative articles, we found that 27–50% of patients recovered only partial renal function [5,7,16]. In our series, we were able to obtain or to maintain normal renal function in 14 out of 17 (82%) patients, of whom only five received ureterolysis.

RF may recur, usually within 5 years after the diagnosis, although rare cases of recurrence have been reported even after 10 years of follow-up [15]. In order to prevent the recurrence of obstruction, the use of corticosteroids after ureterolysis has been advocated [14,15], although the optimal dosage and duration of steroid therapy are still poorly defined. The combination of steroids with azathioprine or cyclophosphamide, once again with different duration and dosages, has also been reported to be successful [6–9]. Some case-reports [11,12] outlined the efficacy of tamoxifen in the treatment of IRF. The advantage of tamoxifen on immunosuppressive therapy could be its lower toxicity. However, not all the studies confirmed the efficacy of tamoxifen in RF [1,17].

Regrettably, only a few small-sized series reported follow-ups of 3–5 years. In those studies, urinary obstruction recurred in 14–33% of the patients [9,15,18,19]. In our series, 12% of the patients had a reactivation of urinary tract obstruction during a mean follow-up of 56 months. One patient from group 1 had a retroperitoneal recurrence of RF that fully responded to a new course of therapy with steroids. In group 2, one patient had a retroperitoneal reactivation of RF 3 years after the first remission and successfully underwent surgery followed by a new course of steroids. At present, no patient from group 3 had reactivation of the disease but the mean follow-up was shorter in this group than in the other two. The retroperitoneal space is the most frequent site of recurrence. However, RF being a multisystemic disease, reactivation may also occur in other parts of the body, for example, in the lungs as we observed in a patient from group 1, so that the cumulative rate of recurrence in our series was actually 18%. Also in this patient, lung fibrosis was cured after therapy with steroids and mycophenolate mofetil. It is also important to remember that RF is now thought to be an immune-mediated disorder [1,3,4,10,20].
In this regard, it should be noted that in this series two patients had positive anti-nuclear antibodies at presentation and four other patients developed an autoimmune thyroiditis either before presentation or during the follow-up. Accordingly, any sign or symptom of autoimmune disease in a patient with RF should be considered as a possible warning of activity of the disease.

Little information is available on the long-term outcome of patients with RF, nor is there any study comparing the efficacy of different therapeutic options. In this retrospective study, we found that, apart from the three relapses that responded to therapy, in all patients treated with surgery plus steroids or with steroids plus azathioprine, RF remained inactive and renal function remained normal in the majority of them, while in one out of the six patients treated with steroids plus tamoxifen the disease progressed, involving both kidneys and requiring ureterolysis. Looking at our overall results, the actuarial 10-year renal survival was 80%. A mild but stable renal insufficiency persisted in two patients until the end of an observation of 57 and 64 months, respectively. In another patient, in spite of the regression of the fibrotic mass, the residual renal insufficiency slowly progressed and the patient entered end-stage renal failure 6 years after ureterolysis. None of our patients died during a median follow-up of 56 months in contrast to an actuarial mortality of 22% at 2 years as reported by Baker et al. [15]. It should be noted, however, that most of the deaths in their study were caused by atherosclerosis and not due to RF. In other studies mortality ranged around 9% [21].

In conclusion, this study confirms the possibility of recovering renal function in most patients with IRF in spite of a late diagnosis. As far as the long-term outcome is concerned, we found that all three of the different medical approaches we used allowed good renal and patient long-term survival. It is difficult to give recommendations on the optimal duration of treatment. Previous studies suggested that 3–6 months of steroid therapy [1] were enough to control the disease. Longer treatments may further reduce the rate of recurrence [18] but may render the patient more susceptible to iatrogenic complications. However, as renal insufficiency may persist and local reactivations or other possible complications of the disease may occur, patients with RF should be regularly monitored to promptly diagnose and treat the recurrences of the disease.

Conflict of interest statement. None declared.

Acknowledgements. The study was supported by the grant ‘Project in glomerulonephritis’ in memory of Pippo Neglia.

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Received for publication: 19.3.06
Accepted in revised form: 30.3.06