MEDICAL MANAGEMENT OF RETROPERITONEAL FIBROSIS

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ABSTRACT

Background: Small series and case reports suggest that a combination of mycophenolate mofetil and prednisone is an efficacious and safe treatment for patients with retroperitoneal fibrosis.

Objective: To describe the outcomes of patients with retroperitoneal fibrosis treated with a combination of prednisone and mycophenolate mofetil.

Design: Prospective, case series.

Patients: 31 patients with retroperitoneal fibrosis.

Setting: Single-center tertiary care facility.

Intervention: Prednisone 40 mg administered daily and tapered over 6 months and mycophenolate mofetil 1,000 mg given twice daily.

Measurement: Clinical course, laboratory assessment, measurement of periaortic mass.

Results: Systemic symptoms resolved in all patients. Eighty-nine percent of patients had a 25% or greater reduction in periaortic mass. Eighteen patients had 32 obstructed ureters. Thirty of these ureters were free of obstruction after an average of 513 days of therapy. Laboratory abnormalities of elevated erythrocyte sedimentation rate and serum creatinine and decreased hemoglobin levels normalized in all patients. Recurrent disease occurred in 2 of 28 patients.

Conclusion: Combined prednisone and mycophenolate mofetil appears to be an effective therapeutic option for patients with retroperitoneal fibrosis.

INTRODUCTION

Retroperitoneal fibrosis (RPF) is a condition characterized by inflammation and fibrosis surrounding the infrarenal aorta and other retroperitoneal structures (1). Historically, treatment has focused on
relieving the patient’s ureteral obstruction with double “J” stents or percutaneous nephrostomy tubes followed by more definitive resolution by surgical ureterolysis. In the last several years, case reports and small series have documented successful nonsurgical management with various immunosuppressive agents (2–5). In this prospective case series, we describe the clinical outcomes of 31 patients treated with medical therapy for RPF.

METHODS

Patient Population

Between April 1, 2005, and October 1, 2011, 90 patients were referred to the nephrology clinic for management of RPF. Patients were considered to have RPF if they fulfilled the following criteria: 1) had soft tissue density surrounding the infrarenal aorta or iliac vessels by contrast-enhanced computerized tomography (CT); 2) had an absence of aneurysmal dilation of the infrarenal aorta; 3) had an absence of intra-abdominal or pelvic mass by imaging aside from periaortitis; 4) had a lack of clinical suspicion of malignancy from history and physical examination; and 5) had a negative up-to-date, age- and gender-appropriate cancer screening. Any patient who did not meet these requirements underwent biopsy.

Nine patients elected for surgical intervention, 6 patients were excluded because CT was consistent with perianuerysmal fibrosis, 6 patients were excluded because they had Erdheim Chester disease (non–Langerhans-cell histiocytosis), 18 patients elected not to be enrolled in our trial, and 51 patients agreed to medical therapy, 31 of whom have completed therapy, whereas 20 remain under active management.

Baseline laboratory screening included chemistry panel, complete blood count (CBC), erythrocyte sedimentation rate (ESR), Hepatitis B surface antigen, and Hepatitis C antibody.

Treatment

Chemotherapy consisted of 1,000 mg of mycophenolate mofetil (MMF) administered orally twice daily until 6 months after resolution of systemic symptoms and extubation of affected ureters. If patients did not have ureteral obstruction, the MMF was continued for 6 months after resolution of symptoms, normalization of lab values, and a 25% or greater reduction in periaortic mass. All patients were ini-
tially started on prednisone 40 mg administered daily for 30 days, with tapering of daily dose by 10 mg each month until the patient had been on 10 mg daily for 30 days. Prednisone was subsequently reduced to 5 mg each day for 30 days, and subsequently 5 mg every other day, and then off.

Follow-up

All patients were seen at least every 6 months. Laboratory follow-up was obtained monthly and included CBC, ESR, and serum creatinine levels. Radiologic follow-up with CT scanning was obtained every 6 months. Decisions to remove ureteral stents were made based on improvement in laboratory parameters and radiographic evidence that the periaortic mass no longer encased the affected ureter. For patients with bilateral obstruction, ureteral stents were removed several weeks apart. After each stent removal, the patient underwent a nuclear medicine flow scan with delayed images to insure that there was no evidence of obstruction.

Radiographic Review

CT scans were reviewed by a single observer. The extent of disease was determined at the first visit before treatment using a classification previously described by Scheel (6). The temporal change in disease was determined by measuring the thickness of the soft tissue relative to the aorta.

Statistical Analysis

Descriptive statistics were used to summarize and compare laboratory and radiographic measurements before and after medical therapy. The mean values of measures before and after medical therapy were compared using paired \( t \) tests. Absolute \( P \) values for the differences are reported. Statistical analysis was performed using Stata SE, Version 10.1 (College Station, TX).

RESULTS

The demographic and clinical characteristics of the group of patients are presented in Table 1. The average time on study drugs was 23.28 months with a range of 6 months to 63 months. Three patients had prior attempts at ureterolysis (1 bilateral and 2 unilateral) and were referred for contralateral involvement or recurrent disease.
Table 2 shows the laboratory data at baseline and follow-up. Eighteen patients (58%) had ureteral obstruction requiring stenting of the ureter(s). Fourteen of these were bilateral and 4 were unilateral for a total of 29 obstructed ureters. Thirty (93%) of the 32 ureters were successfully extubated. The average time to extubation was 513 days (range, 60 days to 2,558 days). One patient developed a focal ureteral stricture that has required continued stenting; 1 patient who had prior unilateral ureterolysis had the contralateral ureter extubated, but since his initial ureterolysis, has been unable to extubate the ureter.

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Presentation Mean (+ SD)</th>
<th>Follow-up Mean (± SD)</th>
<th>P</th>
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<tbody>
<tr>
<td>Hgb (g/dL)</td>
<td>11.6 (2.1)</td>
<td>13.2 (1.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>48.7 (41.1)</td>
<td>9.9 (9.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.52 (2.39)</td>
<td>1.07 (0.39)</td>
<td>0.0015</td>
</tr>
</tbody>
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which had been lysed, despite no radiographic evidence of disease. One patient with bilateral obstruction did not respond to therapy.

Table 3 shows the radiographic classification of the patient population at presentation. With treatment, 28 of 31 patients had a 25% reduction in the periaortic mass. The average percent reduction was 52.42%. Of the three patients with a poor response, two had no detectable reduction at 24 months of therapy, and one patient had a 19% reduction at 47 months of therapy. No patient showed radiographic progression during treatment. Figure 1 shows a representative baseline and follow up CT scan of this study population.

No patient had complaints of pain or ongoing fatigue after completion of therapy, and all were restored to baseline self-reported body weight before the onset of illness.

Three patients experienced single dermatone-limited Herpes zoster during therapy that required temporary discontinuation of MMF. One patient who had diabetes controlled with oral medication required insulin during the prednisone arm of therapy. Three patients (9.6%) experienced recurrence of disease once MMF had been discontinued, 1 at 2 months, and 1 at 4 months, and 1 at 7 months after MMF withdrawal. Two presented with unilateral obstruction and 1 with increasing periaortic mass by follow-up CT scan. All 3 were treated with recycling of treatment regimen, and no patient required stenting.

**DISCUSSION**

This report adds to an expanding body of literature that RPF is a disease that can be successfully treated with medical therapy. This report is the largest series using MMF and prednisone, performed prospectively, from a single center using a standardized definition of

**TABLE 3**

*Radiographic Classification at Initial Visit for 28 Patients With RPF*

<table>
<thead>
<tr>
<th>Radiographic Class</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>4 (13)</td>
</tr>
<tr>
<td>I + II</td>
<td>5 (16)</td>
</tr>
<tr>
<td>I + III</td>
<td>2 (6)</td>
</tr>
<tr>
<td>I,II,III</td>
<td>10 (32)</td>
</tr>
<tr>
<td>I,II,IV</td>
<td>1 (3)</td>
</tr>
<tr>
<td>I,II,III,IV</td>
<td>9 (29)</td>
</tr>
</tbody>
</table>

*Class I: Soft-tissue density surrounding the infrarenal aorta and/or iliac vessels; Class II: Soft-tissue density surrounding the infrarenal vena cava; Class III: Lateral extension of the inflammation/fibrosis with compression of one or both ureters; Class IV: Extension of inflammation/fibrosis to include the renal hilum with compression of the renal artery and/or renal vein.
RPF. Although the ideal agents have yet to be defined, this report confirms and expands on our initial observations that a combination of prednisone and MMF can alleviate the symptoms (weight loss, pain, fatigue) and correct the laboratory abnormalities (ESR, Hgb, serum creatinine) associated with RPF (7). Additionally, this pharmacologic combination can result in a measurable decrease in the periaortic mass characteristic of this disease and allows for the eventual discontinuation of ureteral stents in those patients with associated ureteric obstruction.

Our decision to use a combination of prednisone and MMF was based on the available literature of the pathophysiology of this disease. RPF begins histopathologically as an aggregation of round mononuclear cells composed of B and T lymphocytes. As the disease progresses, there is capillary proliferation and an eosinophilic infiltrate. This active inflammatory infiltrate changes in appearance with time to appear as a dense fibrous mass (8).

Corticosteroids are known to inhibit the cellular cascade of inflammation and the immune response at all levels. The overall effect of corticosteroids is inhibition of the recruitment of cells to the inflammatory site, and blockade of the production and effects of pro-inflammatory mediators. Limited data has shown that high-dose corticosteroids prescribed for 12 months or greater is quite effective for correcting the inflammation of RPF and is associated with mass regression. This regime is, however, associated with significant morbidity and has a high rate of recurrence once the steroids are withdrawn (9).
Mycophenolic acid, the active metabolite of MMF, inhibits T and B lymphocyte proliferation and antibody production (10). Additionally, MMF has been shown to have antifibrotic properties in non-immune experimental models of acute and chronic kidney disease, as well as pulmonary fibrosis (11–14). Small series and case reports have suggested that the addition of MMF to corticosteroids for RPF decreases the duration of steroid use without affecting efficacy and decreases the disease recurrence rate (15–19). The disease recurrence rate in our report of 9.6% is significantly less than the 72% that has been reported with steroid use alone (9).

Three patients in our report did not show significant regression of the periaortic mass. All 3 of these patients were African American men. Although the exact reason for this failure is unknown, one possible explanation is the rapid metabolism of MMF that has been reported in some African Americans. In patients who are receiving MMF for solid organ transplantation, the dose of MMF is frequently increased to 1,500 mg twice daily, and the treatment failures in our report may represent under-dosing (20). Because we did not perform pill counts or measure mycophenolic acid levels, we cannot exclude non-adherence as a reason for treatment failure.

We acknowledge the limitations inherent in this report. The results are not those of a controlled clinical trial with randomization. Patients were treated with corticosteroids and MMF, and we cannot exclude the possibility that a similar outcome would have been achieved with MMF or corticosteroids alone. As with all novel treatment strategies, the proper role for a combination of MMF and prednisone in the management of RPF can only be determined by prospective, well-designed clinical trials in appropriately stratified, large patient cohorts.

REFERENCES

6. Scheel PJ, Feeley N: Retroperitoneal fibrosis: the clinical, laboratory and radio-


**DISCUSSION**

*Paget, New York:* Wonderful paper. As a rheumatologist, I loved it. So, the whole concept of retroperitoneal fibrosis as with interstitial lung disease or pulmonary fibrosis, I think, in most situations is a misnomer. The usual inflammatory process is: they eventuate in cicatricial changes, but it’s the inflammatory process, and in this illness, we see it in lupus patients, we see it in Wegener’s granulomatosis, and we’ve seen increasing number in IgG4 disease, and they respond well to steroids and particularly well to rituximab. Any thoughts about the concept of using rituximab or the plus or minus of
using your regimen plus that one? And then, have you looked to see whether they had IgG4 disease in their blood or in the tissue?

**Scheel, Baltimore:** In keeping with previous speakers, I will answer your last question first. For our initial patients, we biopsied all of them, and so we were able to do IgG4 staining on all of the tissue. They were IgG4-positive in 41% of the specimens. From a serologic perspective, we only saw that 30% of patients had elevated IgG4 levels. Clinically, I haven’t found the right place for monitoring IgG4 levels. I do know that if you have very high IgG4 levels when you start therapy, you can use those levels as a marker of disease activity and tailor your treatment accordingly. As far as the use of rituximab, we do have a group of physicians from around the world who have established a research consortium for the purpose of conducting clinical trials. That group is very interested in studying rituximab as possible treatment for RPF. It is difficult to justify the use of such an expensive and unproven drug when you have treatment which has very few complications, is relatively inexpensive, and has such a success rate in treating this disease.

**Zeidel, Boston:** Wonderful paper. It’s interesting that we have a lot of fibrotic illnesses. In the past we were taught that once the fibrosis sets in, for instance in rapidly progressive glomerulonephritis and among other things, the game is over, and what this shows really strikingly is the fact that it would appear that fibrosis is a process where you are laying it down and you are taking it up. Somehow when you are giving this combination of drugs, you are lowering the rate of laying it down and perhaps increasing the rate of taking it up and this offers a good deal of promise for a lot of other fibrotic illnesses. I understand that there is a lot of inflammation, but the game isn’t up when fibrosis occurs.

**Scheel, Baltimore:** One of the papers that I did look at prior to prescribing this regimen was a paper where they took pulmonary fibroblasts and cultured them with mycophenolate mofetil. Those pulmonary fibroblast cultured in the presence of mycophenolate mofetil had an increase in the production of collagenase 1 as compared to controls, and so there is a potential mechanism whereby mycophenolate may actually have antifibrotic properties. The second piece of evidence is a model for inflammatory kidney disease where they use unilateral ureteral obstruction, which is a classic model for inflammation and fibrosis, and in that model, mycophenolate also interrupts that fibrotic process, and so the potential benefit of mycophenolate appears to broader than just retroperitoneal fibrosis. It appears to be the same in the lung and also the parenchyma of the kidney.