Case Report

Multifocal Idiopathic Fibrosclerosis: Treatment of 2 Cases with Cyclosporine

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ABSTRACT. We describe 2 cases of multifocal idiopathic fibrosclerosis treated successfully with cyclosporine. The first patient presented with chronic abdominal pain and was subsequently found to have retroperitoneal fibrosis with ureteral obstruction. Other findings included cholangiolar fibrosis, retroorbital pseudotumors, submandibular gland enlargement, subcutaneous fibrotic masses, and elevated erythrocyte sedimentation rate (ESR) and serum creatinine. He initially responded well to temporary ureteral stenting followed by combination therapy with steroids and cyclosporine. He relapsed when cyclosporine was stopped, but subsequently remitted completely when cyclosporine was reintroduced. The second patient presented with long-standing abdominal pain with retroperitoneal fibrosis, submandibular gland enlargement, and an enlarged pancreas with a localized mass, all of which improved significantly with 6 months of therapy with cyclosporine. Cyclosporine was well tolerated with no significant side effects in the 2 patients. A review of the literature is presented. (J Rheumatol 2006;33:358–61)

Key Indexing Terms:
MULTIFOCAL IDIOPATHIC FIBROSCLEROSIS CYCLOSPORINE
RETROPERITONEAL FIBROSIS

The idiopathic fibrosclerotic disorders are a group of lesions of unknown etiology characterized by the formation of inflammatory pseudotumors composed predominantly of fibrous tissue associated with chronic inflammation. The most common and best known member of this group is idiopathic retroperitoneal fibrosis. Other examples of idiopathic fibrosclerotic disorders include sclerosing cholangitis, mediastinal fibrosis, sclerosing orbital pseudotumors, Riedel's thyroiditis, sclerosing mesenteritis, and several other related lesions[1]. Their grouping is supported by similar histological appearance and by the occasional occurrence of 2 or more of these entities in the same patient, a disorder known as multifocal fibrosclerosis[2,3]. These disorders have a presumed immunologic pathogenesis[4,5]. We describe 2 cases of multifocal idiopathic fibrosclerosis treated successfully with cyclosporine.

CASE REPORTS

Case 1. A 69-year-old man presented in March 2000 with a 30 year history of chronic intermittent abdominal pain requiring a laparotomy for intestinal pseudoobstruction in the 1970s and a laparotomy and cholecystectomy several years thereafter. At the latter time, cholangiolar fibrosis was detected.

He underwent choledochojujenostomy in 1999 and at that time, 2 right renal masses were detected with associated hydronephrosis. Biopsies showed the presence of marked fibrosis with chronic inflammation, typical of retroperitoneal fibrosis. In January 2000 he developed bilateral edema of the eyes, and diplopia.

Examination revealed bilateral proptosis with restricted extraocular movements. The left submandibular gland was swollen (3 × 3 cm) and firm. There was a small subcutaneous mass over the right scapula. Cardiac, pulmonary, and abdominal examinations were unremarkable, except for abdominal surgical scars. Investigations showed normal complete blood count (CBC), erythrocyte sedimentation rate (ESR) 24 mm/h, C-reactive protein (CRP) 23 mg/l, serum creatinine 151 μmol/l, aspartate transferase (AST) 47 U/l, and alanine transferase (ALT) 62 U/l. Antinuclear antibody (ANA) and rheumatoid factor (RF) tests were negative. Computed tomographic (CT) scan of the head showed retroorbital fibrosis.

The diagnosis of multifocal idiopathic fibrosclerosis was made. Because of ocular involvement he was treated with pulsed intravenous methylprednisolone 1 g daily for 3 days, followed by oral prednisone 40 mg per day tapered slowly over 3 months. Prophylaxis for osteoporosis was initiated (etidronate, calcium, and vitamin D). In addition, he was started on cyclosporine, initially 100 mg BID and then increased to 150 mg BID (our practice after one week of therapy). Cyclosporine trough levels varied between 120 and 150 mg/l (normal range 75–340).

Over 6 months, he had gradual resolution of his abdominal pain, retroorbital fibrosis, and submandibular gland swelling. Acute phase reactants normalized, and serum creatinine decreased to 125 μmol/l. An abdominal ultrasound was normal at 6 months.

After 18 months, cyclosporine was tapered and stopped. Several months later, he developed intermittent abdominal pain, an enlarged left submandibular gland, and a slightly elevated ESR at 22 mm/h. Cyclosporine also was restarted, with complete clinical and radiological remission within 3 months. Acute phase reactants, ultrasound, and serum creatinine normalized. He has continued cyclosporine.

Case 2. A 74-year-old man presented in January 2004 with a 5 year history of

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intermittent left upper quadrant abdominal pain. In May 2000 he had a cholecystectomy that revealed a gangrenous gall bladder. An abdominal CT scan at that time revealed an enlarged pancreas with a localized mass at the junction of head and neck, which had been followed radiologically for 3 years without change in size.

In June 2003 a new pre-aortic mass, detected on CT scan, resulted in an exploratory laparotomy. Biopsy showed dense fibrosis with mild patchy chronic inflammation typical of idiopathic retroperitoneal fibrosis (Figures 1 and 2). This fibrosclerotic process encased the ureter in the region of the ureteropelvic junction (Figure 1).

In August 2003, he was found to have bilateral enlargement of the submandibular glands. Right submandibular gland resection was performed, and microscopic examination revealed dense fibrosis and chronic inflammation replacing the majority of the salivary gland parenchyma, typical of chronic sclerosing sialadenitis (Figure 3).

On examination he was cachectic and had a (3 × 3 cm) firm left submandibular mass. Chest and cardiovascular examinations were normal and there was no lymphadenopathy or splenomegaly. Laboratory investigations showed a normal CBC, ALT, AST, amylase, serum creatinine, ESR, and CRP. ANA and RF tests were negative.

The diagnosis of multifocal idiopathic fibrosclerosis was made. Cyclosporine 50 mg BID as a single agent was initiated and gradually increased to 125 mg BID (as per our protocol). Cyclosporine trough levels varied between 140 and 160 mg/l. Within 6 months he was asymptomatic, the submandibular glands had returned to normal size (at 3 months), and there was a significant reduction in size of the retroperitoneal mass, with disappearance of the pancreatic mass on CT scan at 6 months.

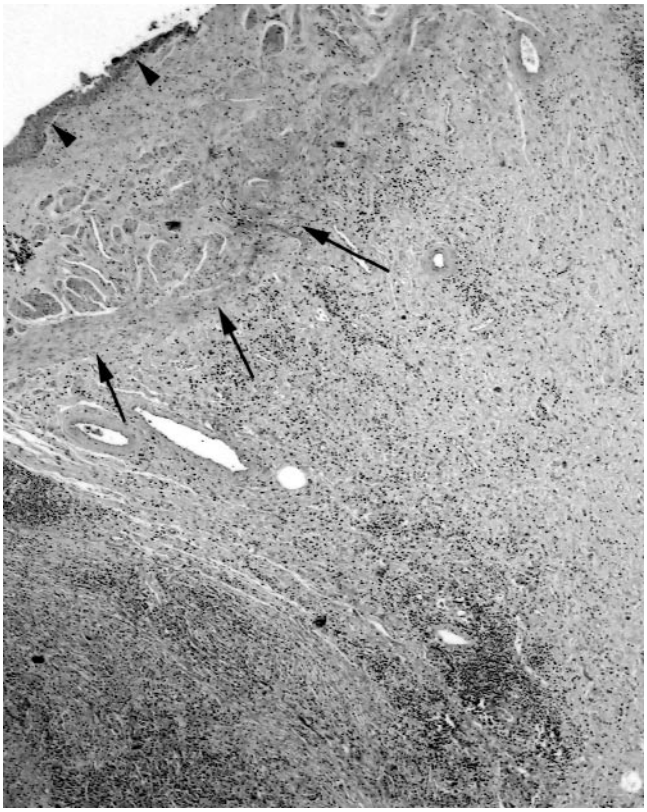

Figure 1. Idiopathic retroperitoneal fibrosis encasing the ureter at the ureteropelvic junction. Note the urothelium in the upper left corner (arrowheads), with smooth muscle of the ureter (arrows) surrounded by fibrosis and patchy chronic inflammation with lymphoid aggregates noted in the upper right and lower portion of the field.

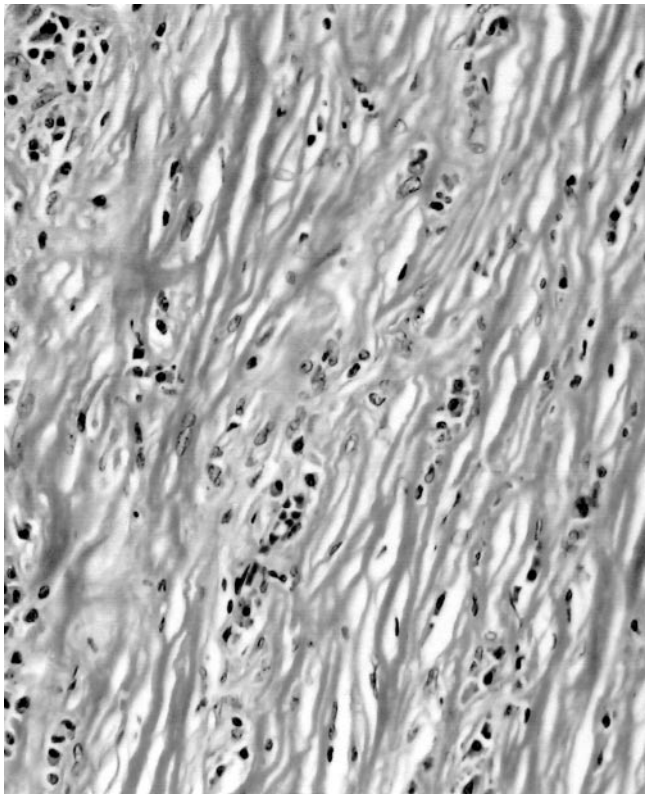

Figure 2. Idiopathic retroperitoneal fibrosis (high power). Collagen fibers with chronic inflammatory cells, predominantly plasma cells.

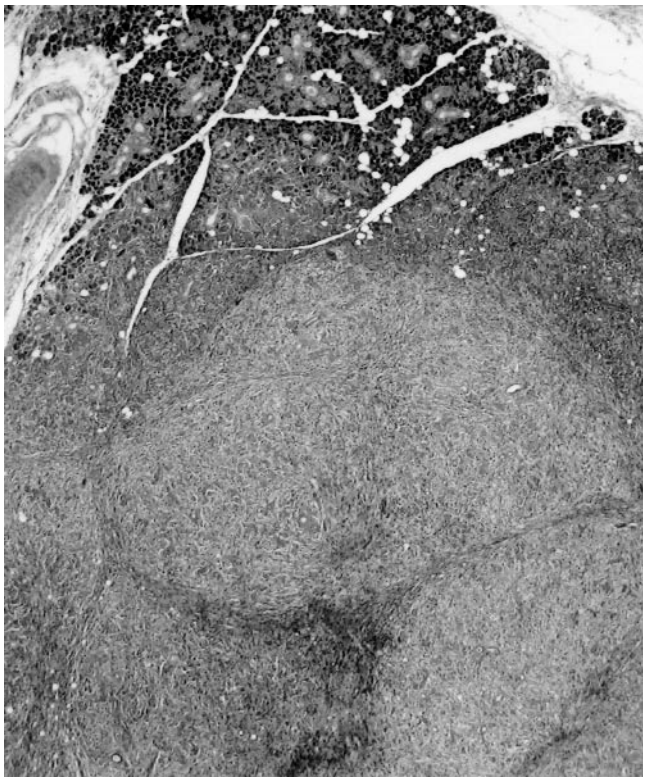

Figure 3. Chronic sclerosing sialadenitis involving the submandibular gland. Relatively uninvolved salivary gland tissue (top) with fibrosis and mild chronic inflammation affecting the lower portion of the field.

DISCUSSION

Multifocal idiopathic fibrosclerosis is a rare connective tissue disease of unknown etiology characterized by the development of fibrotic pseudotumors in multiple sites. Most commonly, patients have retroperitoneal fibrosis combined with Riedel's thyroiditis and/or orbital pseudotumor, but many other sites may also be affected. The pathogenesis of the disease remains unknown. However, immunohistological studies in idiopathic retroperitoneal fibrosis and other associated disorders have shown that T cells are likely responsible for disease progression[4]. T cell receptor gene rearrangement has been reported, but this association has not been proven[5]. On the basis of the T cell abnormalities, cyclosporine was used to treat the 2 cases reported here. The optimal treatment of retroperitoneal fibrosis is still unclear because of the rarity of the disease and the lack of clinical trials.

To our knowledge, only one case of retroperitoneal fibrosis treated with cyclosporine has been described. Marzano, *et al*[6] reported a patient with aggressive retroperitoneal fibrosis and obstructive renal failure who responded initially to corticosteroids. He then improved on cyclosporine, with radiological reduction of tissue deposition, relief of ureteral compression, and reduction in acute phase reactants. Rather than isolated retroperitoneal fibrosis as reported by Marzano, *et al* our 2 cases had biopsy-proven, diffuse, multifocal fibrosclerosis.

Our first patient had retroperitoneal fibrosis with ureteral obstruction, cholangiolar fibrosis, retroorbital pseudotumors, submandibular gland enlargement, and subcutaneous fibrotic masses, with increased acute phase reactants and serum creatinine. He responded well to temporary ureteral stenting followed by combination therapy of corticosteroids and cyclosporine. When cyclosporine was stopped after 18 months he relapsed, but subsequently remitted completely.

The second patient had retroperitoneal fibrosis, chronic sclerosing sialadenitis, and an enlarged pancreas with a mass lesion. Following 6 months of therapy with cyclosporine, he became asymptomatic and the enlargement of the submandibular glands resolved. Retroperitoneal fibrosis as well as the pancreas decreased in size, and the mass lesion disappeared. Cyclosporine was well tolerated and there has been no significant drug related toxicity in the 2 patients.

While surgical debulking of fibrous masses with ureteral stenting to relieve obstruction followed by corticosteroids to avoid recurrence and further progression of fibrosis has been the standard therapy for idiopathic retroperitoneal fibrosis for many years[7], serious corticosteroid induced side effects can occur. Concurrent use of immunosuppressive drugs would likely reduce these side effects.

Wagenknecht and Hardy[7] reported a series of 6 patients with idiopathic retroperitoneal fibrosis in whom treatment with corticosteroids and azathioprine prevented the need for ureteral surgery. Harreby, *et al*[8] described successful treatment in 7 of 11 patients with intravenous methylprednisolone combined with either azathioprine or penicillamine after ureteral stenting.

Cyclophosphamide therapy in combination with corticosteroids was found to be successful by Kohler, *et al*[9] in a patient with multifocal fibrosclerosis with retroperitoneal fibrosis. Grotz, *et al*[10] reported a patient with idiopathic retroperitoneal fibrosis treated successfully with a combination of prednisone and mycophenolate mofetil. Marcolongo, *et al*[11] evaluated the efficacy of different immunosuppressive regimens in a retrospective study of 26 patients with idiopathic retroperitoneal fibrosis. All patients received prednisone (1 to 1.5 mg/kg/day for 3 weeks, then tapered and discontinued within 6 months), as well as ureteral stenting and/or a percutaneous nephrostomy. In 15 patients, prednisone was combined with azathioprine 2.5 mg/kg/day for 6 months, then reduced to 1.5 mg/kg/day and maintained for another 6 months. In the remaining 11 patients, prednisone was administered with either oral cyclophosphamide (2 mg/kg/day for 3 months, then tapered and discontinued within 6 months) or monthly intravenous pulse of 1000 mg/m^2 for 6 months. At a mean followup of 48 months, remission, defined as stable clinical and radiographic disease, was achieved in all patients, except one who died of pneumonia. Seven patients required a second course of treatment.

Tamoxifen has been used as a primary therapy or in combination with surgery with some success, although the exact mechanism of action remains unclear[12]. Ozener, *et al*[13] described good response in one patient with retroperitoneal fibrosis and bilateral hydronephrosis treated with surgery followed by tamoxifen. Clark, *et al*[14] reported successful treatment of 2 patients using tamoxifen; one of the patients relapsed after stopping treatment and then responded once therapy was reintroduced.

In conclusion, the treatment of idiopathic fibrosclerotic disorders can be surgical and/or medical. Immunosuppressive drugs have been shown to modify the natural history of these diseases. We have demonstrated in 2 patients that cyclosporine was effective in the treatment of multifocal idiopathic fibrosclerosis. Controlled studies, although difficult to perform because of the rarity of these disorders, are required to prove their effectiveness.

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