Treatment of hyper-IgG₄ disease with sequential corticosteroids and tamoxifen – case report and review of the literature


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Abstract. We report a patient with multifocal fibrosclerosis presenting as salivaryitis, hepatic fibrosis, and retroperitoneal fibrosis with renal failure. His medical management consisted of prednisone (4 months at 40 mg daily, then tapered down to 5 mg daily for another 14 months) and 18 months of tamoxifen. He responded clinically and radiographically to this regimen, and remains in clinical remission 10 months after discontinuing medical therapy. Subsequent histologic examination of submandibular gland tissue revealed strong staining for IgG₄-positive plasma cells. To our knowledge, this is the first case of confirmed multifocal hyper-IgG₄ disease to be successfully treated with sequential corticosteroids and tamoxifen.

Introduction

Hyper-IgG₄ disease is a recently described entity characterized histologically by infiltration of any one of a number of different organs by IgG₄-positive lymphoplasmacytic cells. Originally described in cases of sclerosing pancreatitis, IgG₄-positive inflammatory infiltrates have since been reported in a variety of patients with fibrosclerosing conditions, including all of a series of 12 patients previously diagnosed with idiopathic retroperitoneal fibrosis [Nielid et al. 2006]. Idiopathic multifocal fibrosclerosis (IMF) is a rare syndrome characterized by fibrosclerosis in two or more organ systems, one of which is almost always the retroperitoneum [Cankurtaran et al. 2004]. It is therefore likely that at least some cases of IMF occur as a result of hyper-IgG₄ disease. Given its rarity, there is no consensus on the optimal treatment of this condition. Treatment options are informed entirely by case reports and by the literature pertaining to idiopathic retroperitoneal fibrosis (IRF). Corticosteroids are the mainstay of therapy in IMF, and information on adjuvant therapy with other immunomodulating agents is especially limited [Al-Harthy et al. 2006]. Scattered case reports and a case series highlight the successful use of tamoxifen in the treatment of IRF [van Bommel et al. 2006]. We report a patient with hyper-IgG₄ disease with multifocal fibrosclerosis – presenting as retroperitoneal fibrosis, portal fibrosis, and submandibular fibrosclerosis – who has had a complete response to sequential corticosteroid and tamoxifen therapy.

Case report

A previously well 57-year-old male of Japanese origin developed nontender, bilateral submandibular swelling in October 2005. An ultrasound revealed bilaterally enlarged submandibular glands. The right measured 4.1 × 3.7 × 2.6 cm and the left 4.7 × 1.9 × 3.9 cm. Two courses of antibiotics were prescribed without effect, and he was referred to a rheumatologist. In the rheumatology clinic,
his blood pressure was 160/90, and blood work disclosed a serum creatinine of 196 μmol/l, erythrocyte sediment rate of 105 mm/h, and C-reactive protein 8.8 mg/l (reference range less than 8 mg/l). Antineutrophil antibodies, C- and P-ANCA antibodies, rheumatoid factor, complements, and angiotensin-converting enzyme levels were all normal. Serum protein electrophoresis with immunofixation disclosed a polyclonal immunoglobulin fraction increase that was not further characterized. A urinalysis by dipstick was negative for blood or protein. He was started on amlodipine and referred to a nephrologist.

In the renal clinic in May 2006 he complained of frequent urination and denied pain, fevers, or weight loss. An abdominal ultrasound revealed bilaterally enlarged kidneys, each 13.5 cm in maximal length. There was mild-to-moderate hydronephrosis of both kidneys, and mild bilateral distension of the renal pelvis and proximal ureters. There was fatty infiltration of the liver, and the aorta appeared normal. He was referred to a urologist and in June underwent a cystoscopy that showed mild prostatic enlargement with inflammation consistent with prostatitis. Prostate specific antigen level was normal. Computed tomography of abdomen and pelvis performed with intravenous contrast showed mild-to-moderate hydronephrosis with enlargement and thickening of proximal ureters. No adenopathy or discrete masses were seen.

In July 2006 left flank pain and symptoms of uremia ensued. His serum creatinine was 411 μmol/l and he was admitted to hospital. A pelvic and abdominal MRI with gadolinium enhancement (total dose 15 ml gadopentetate dimeglumine (Magnevist®) showed an extensive infiltrative process encasing the upper ureters and extending into the renal pelvis bilaterally (Figure 1A). There was also infiltration along the left portal vein extending into the intersegmental fissure between the medial and lateral segments of left lobe of the liver (Figure 1B). Liver function tests and transaminases were normal. Biopsy of the submandibular glands showed numerous plasma cells, lymphocytes, and germinal cell formation with marked fibrosis and parenchymal atrophy consistent with chronic sialadenitis (Figures 2A,B). Brucella and HIV serologies were negative as were urine cultures for tuberculosis mycobacterium and schistosoma.

He was diagnosed with idiopathic multifocal fibrosclerosis and treated with bilateral ureteric stents and prednisone 40 mg daily. He was discharged in late July 2006 at which point his serum creatinine was 204 μmol/l, and his neck swelling had started to recede. Tamoxifen was added 1 month later, initially at 20 mg daily for 2 weeks, and then 40 mg daily. CT scan of the neck in September demonstrated no focal masses, and his prednisone was tapered over 2 months down to 5 mg daily. In October his serum creatinine was 146 μmol/l and a repeat pelvic and abdominal CT scan performed without intravenous contrast showed intact stents, no evidence of hydronephrosis and an infiltrative process in the renal pelvis bilaterally extending into the ureters. The ureteric stents were removed after 6 months in January 2007. C-reactive protein was normal in March 2007. A repeat pelvic and abdominal MRI performed with gadolinium enhancement in June 2007 reported significant improvement in soft tissue
IMF is much rarer than idiopathic retroperitoneal fibrosis (IRF), which itself is a rare condition with an estimated incidence of only 1 : 200,000 to 1 : 500,000 per year [Vaglio et al. 2006]. Retroperitoneal fibrosis is deemed idiopathic approximately two-thirds of the time, with the remainder of cases being secondary to conditions such as abdominal aortic aneurysm, neoplasm, infection, trauma, amyloidosis, radiotherapy, surgery and the use of certain drugs (methylsergide, β-blockers, hydralazine, methyldopa and bromocriptine) [Vaglio et al. 2006].

Clinical presentations of IMF vary with distribution and degree of fibrosclerosis and often include nonspecific features such as weight loss, fevers, and biochemical evidence of an acute phase response. Fibrosclerosis has been reported in the retroperitoneum, retroorbital, thyroid, pancreas, pituitary, submandibular, mediastinum, mesentery, portal and biliary tract, and in lung tissue (bronchiolitis obliterans with organizing pneumonia) [Cankurtaran et al. 2004, Duvic et al. 2004, Neild et al. 2006].

Histologically, fibrosclerosis is characterized by chronic mononuclear inflammatory cells, fibroblasts, and a variable degree of sclerosis. The mononuclear cells include plasma cells, lymphocytes (CD20+ B cells and CD4+ T cells), macrophages, and eosinophils [Vaglio et al. 2006]. In October 2006 Neild et al. [2006] reported finding IgG4-positive lymphoplasmacytic cells in 9 of 9 archived retroperitoneal tissue specimens, and in kidney, omentum, and liver tissue specimens of another 3 patients. All 12 patients had a clinical diagnosis of IRF. Further characterization of serum from one of these patients (which had demonstrated a polyclonal IgG increase) revealed elevated serum IgG4 levels. Two patients who were clinically successfully treated with prednisone no longer demonstrated any IgG4-positive lymphoplasmacytes on repeat retroperitoneal biopsies. The authors proposed the term hyper-IgG4 disease be used to describe these patients, and suggested the use of histology and serum tests looking for abnormal IgG4 levels to confirm this diagnosis.

Most reports of the management of fibrosclerosing conditions have focused on IRF. Surgical management of IRF is indicated to relieve obstructive uropathy, while medical
therapy aims to prevent recurrence of obstructive complications, and to relieve systemic features. Glucocorticoids are the mainstay of medical management, but often require long-term treatment and only rarely result in sustained clinical and radiographic resolution of retroperitoneal fibrosis when used alone [Bourroum et al. 1997, Vaglio et al. 2006, van Bommel et al. 2006, 2007]. In their series of 24 patients with IRF treated with prednisone alone, van Bommel et al. [2007] reported a clinical and radiographic response rate of 75% at 1 year, with 13 of the 18 responders relapsing a mean of 10 months following discontinuation of prednisone. Other options for adjunctive and steroid-sparing medical therapy include methotrexate, cyclophosphamide, cyclosporine, azathiprine, and tamoxifen. Al-Harthy et al. [2006] reported the successful use of cyclosporine in 2 patients with IMF, 1 of whom also received corticosteroids for the first 3 months of treatment. The immunosuppressive agents have significant side effect profiles, however, and recent reports have examined the use of tamoxifen as an alternative adjunctive agent. Van Bommel et al. [2006] reported a prospective trial in which 14 of 19 IRF patients treated with tamoxifen alone had an improvement in symptoms and signs of inflammation. The rationale stems from its successful use in the treatment of desmoid tumors as described by Benson and Baum [1993]. Although its mechanism of action remains unclear, tamoxifen is believed to regulate tissue growth factor-β secretion by mesenchymal fibroblasts [van Bommel et al. 2006]. Tamoxifen is generally well tolerated, with reported side effects that include flushing, mood changes, hypertension, peripheral edema, weight loss, and thromboembolic events [van Bommel et al. 2006].

References


Conclusion

Given its rarity and the lack of understanding regarding the underlying pathophysiology of IMF, the literature regarding treatment is sparse. Most is limited to case reports in which corticosteroids is the only medical therapy. Corticosteroids alone rarely result in sustained cure of retroperitoneal fibrosis, one of the most important and common sites of involvement in IMF. Our report confirms that the newly described condition hyper-IgG4 disease is one cause of multifocal fibrosclerosis. Our patient with multifocal hyper-IgG4 disease experienced a radiographic and sustained clinical remission after treatment with tamoxifen and low-dose prednisone.