Rapidly resolved IgG4-related retroperitoneal fibrosis after steroid pulse therapy

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Retroperitoneal fibrosis (RF) is a disorder characterized by the presence of a retroperitoneal mass and concurrent systemic inflammation. Some cases of RF are recognized as belonging to the spectrum of immunoglobulin G4-related disease (IgG4-RD). Glucocorticoids are highly effective for treatment of retroperitoneal fibrosis, although the optimal dose and duration of therapy have not been established [1,2]. We report on a 55-year-old man diagnosed with IgG4-related RF and successfully treated with a 3-day course of daily 250 mg (4 mg/kg) intravenous methylprednisolone, which resulted in the prompt resolution of urinary obstruction and systemic symptoms.

Keywords: Glucocorticoids; IgG4-related disease; Retroperitoneal fibrosis; Steroid pulse therapy

INTRODUCTION

Retroperitoneal fibrosis (RF) is a rare disorder characterized by a fibro-inflammatory soft-tissue mass in the retroperitoneal space and concurrent systemic inflammation. The mass frequently encases the ureters, resulting in obstructive uropathy [1,2]. RF is considered to be a manifestation of a systemic autoimmune process and is often associated with other autoimmune conditions [3]. Some cases of RF have recently been recognized as belonging to the spectrum of immunoglobulin G4-related disease (IgG4-RD) [4]. Although glucocorticoids yield a favorable response in most cases of RF, the optimal dose and duration of therapy have not been established [1,2]. Anecdotally, regimens consisting of a daily dose of prednisone 40-60 mg for the initial 1-2 months are widely used, followed by gradual tapering under close monitoring of the response [1]. Steroid pulse therapy has seldom been used for treatment of RF [5,6]. However, it has proven to be effective for inducing the remission of various inflammatory conditions, notably autoimmune diseases [7,8]. We report on a 55-year-old male patient who was diagnosed with RF and successfully treated with intravenous steroid pulse therapy.

CASE

A 55-year-old man was referred to our medical center from a local hospital because of worsening low back pain that had started 2 months earlier. He was previously healthy and had no medication history. In addition to low back pain, he reported fatigue, loss of appetite, and progressive decline of urine output over the previous 2 weeks.

On admission, his blood pressure was 132/80 mmHg, pulse rate 86 beats/min, respiratory rate 18 breaths/min, and temperature 36.0°C. Physical examination revealed bilateral costovertebral angle tenderness, grade 3 pitting edema on both lower extremities, and scrotal swelling. His complete blood cell counts were as follows: leukocytes, 7,000/mm³ (neutrophil 69.2%); hemoglobin, 11.4 g/dL; platelets, 374,000/mm³. Erythrocyte sedimentation rate and C-reactive protein were both elevated, being 112 mm/hr and 5.54 mg/dL, respectively. Blood urea nitrogen was 58 mg/dL and the estimated glomer-
Steroid pulse therapy for IgG4-related retroperitoneal fibrosis

YUJM VOLUME 33, NUMBER 1, JUNE 2016

41

Fig. 1. (A) An initial computed tomography (CT) of the abdomen and pelvis showed a retroperitoneal mass (arrow) surrounding the common iliac arteries (arrowheads). (B) An oblique coronal image showed hydronephrosis on both sides (long arrows) caused by the retroperitoneal mass. (C) Whole-body 18F-fluorodeoxyglucose-positron emission tomography/CT scan showed increased metabolic activity of the retroperitoneal mass (arrow) with a maximum standardized uptake value of 4.2. There were no other significant hypermetabolic lesions, which suggested that the retroperitoneal mass was the only involved tissue. (D) A section of the retroperitoneal mass obtained by CT-guided biopsy was stained with hematoxylin and eosin, which showed abundant lymphoplasmacytic infiltration and concurrent fibrosis (H&E stain, ×200). (E) A characteristic histopathologic finding of storiform fibrosis (arrow) is shown (H&E stain, ×400). (F) A vein is obliterated by inflammation (arrow) which is indicative of obliterative phlebitis (H&E stain, ×400). (G) Immunohistochemical staining for immunoglobulin G4 (IgG4) showed some IgG4-positive plasma cells (immunohistochemical stain for IgG4, ×200). (H) Numerous immunoglobulin G (IgG)-positive plasma cells were detected (immunohistochemical stain for IgG, ×200). (I) A baseline antegrade pyelogram obtained through the nephrostomy tubes showed bilateral hydronephrosis with significant contrast retention at 15 min (arrows). (J) Follow-up antegrade pyelography performed 3 days after initiation of therapy showed improvement in the passage of contrast. There was no contrast remaining in the left ureter at 15 min. However, a delay in the passage of contrast through the right ureter remained (arrow). (K, L) A follow-up CT performed 6 months after steroid therapy showed almost no remaining mass and resolved hydronephrosis.

ular filtration rate was 6 mL/min/1.73 m². Serum creatinine (Cr) level was 9.52 mg/dL, which reflected acute kidney injury, as his Cr level had been 1.18 mg/dL at the initial presentation at his local hospital 2 weeks previously. Urinalysis showed occult blood of 4+, 0 to 2 white blood cells, 0 to 2 red blood cells per high-power field, and a negative result for nitrite. Autoantibodies, including antinuclear antibody, rheumatoid factor, and antineutrophil cytoplasmic antibodies, were all negative. Serum IgG concentration was 15.5 g/L (range, 7-16 g/L), while IgG4 level was 0.72 g/L (range, <1.35 g/L).

Computed tomography (CT) of the abdomen and pelvis obtained 2 weeks previously at the local hospital was thoroughly reviewed. CT showed a soft tissue mass located in the retroperitoneal space. The mass appeared as a homogeneous hypodense lesion on unenhanced CT, and it was enhanced with contrast administration. Both ureters were entrapped by the retroperitoneal mass resulting in bilateral hydronephrosis. The abdominal aorta and iliac vessels that were enveloped by the mass retained their anatomical location. These CT findings were typical for RF (Fig. 1A, 1B).

18F-fluorodeoxyglucose-positron emission tomography/CT revealed heterogeneously increased metabolic activity of the retroperitoneal mass, with a maximum standardized uptake value of 4.2. No other significant hypermetabolic lesions were
observed (Fig. 1C).

For relief of the ureteral obstruction caused by the retroperitoneal mass, bilateral percutaneous nephrostomy tubes were placed on hospital day 2, which was followed by subsequent improvement of the azotemia and prompt resolution of low back pain.

Under the impression of RF, CT-guided core biopsy of the mass was performed to exclude malignant lymphoma, metastatic carcinoma, and other infectious diseases. Microscopically, the tissue was composed of fibroblasts and collagen bundles arranged in a storiform pattern with rich lymphoplasmacytic infiltration (Fig. 1D, 1E). Obliterative phlebitis was also observed (Fig. 1F). There was no evidence of malignant lymphoma. Inflammatory myofibroblastic tumor was excluded by the absence of anaplastic lymphoma kinase 1 immunoreactivity. There were some (20 per high-power field) IgG4-positive plasma cells (Fig. 1G). IgG-positive plasma cells were also detected using immunohistochemical staining (Fig. 1H). The IgG4/IgG ratio was 20%. Overall, these findings supported the diagnosis of IgG4-related RF.

A baseline antegrade pyelogram obtained by administration of contrast agent through bilateral nephrostomy prior to the initiation of glucocorticoid therapy showed a delayed contrast passage through both urinary tracts (Fig. 1I). We initiated a steroid pulse therapy with a 3-day course of daily 250 mg (4 mg/kg) intravenous methylprednisolone, after which the dose was reduced to 60 mg oral prednisolone for the next 5 days. A second antegrade pyelography was performed 3 days after initiation of therapy, which showed improved passage of the contrast medium through both ureters (Fig. 1J).

Bilateral double J ureter stents were inserted via the nephrostomy on day 4 of glucocorticoid therapy, enabling removal of nephrostomy tubes. Both stents were removed 17 days later with no recurrent urinary tract obstruction. Systemic symptoms, such as fatigue and anorexia, swiftly resolved approximately 1 week after initiation of therapy, followed by the normalization of acute-phase reactants 1 week later. Prednisolone was further tapered, reaching physiological steroid dose (prednisolone, 30 mg per day) within 1 month.

A follow-up CT performed 6 months after initiation of glucocorticoid therapy showed a dramatically reduced mass size (Fig. 1K, 1L). Over a period of 15 months, prednisolone was gradually tapered to a dose of 5 mg every other day, with no evidence of relapse.

**DISCUSSION**

IgG4-RD has recently been recognized as a fibro-inflammatory disorder characterized by tumor-like lesions with storiform fibrosis and rich lymphoplasmacytic infiltration, especially IgG4-positive plasma cells [4]. Serum IgG4 levels are usually, but not always, elevated. The disease has been reported to occur in various organs throughout the body. Different medical conditions that have long been described in the medical literature as separate disease entities are now considered to be a part of the spectrum of IgG4-RD. Along with Riedel’s thyroiditis, inflammatory pseudotumor, autoimmune pancreatitis, and periaortitis, some cases of RF are also considered to fall within the spectrum of IgG4-RD [4].

Although our current patient did not show markedly elevated serum IgG4 concentrations, the histopathology of the retroperitoneal mass showed characteristic histopathological findings of lymphoplasmacytic infiltrate organized in a storiform pattern and obliterative phlebitis. In this case, there were 20 IgG4-positive plasma cells per high-power field (cut-off value for IgG4-RD, 10-50 per high-power field). The ratio of IgG4-positive plasma cells to IgG-positive plasma cells was 20%. IgG4/IgG ratio as high as 50% is considered to be strongly suggestive of IgG4-RD. Although our case showed a lower IgG4/IgG ratio, the characteristic histopathologic findings of lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis all supported the diagnosis of IgG4-related RF. Correlation with characteristic histopathological findings is most important for the diagnosis of IgG4-RD, regardless of the serum IgG4 concentration, the number of IgG4-positive plasma cells in tissue, or IgG4/IgG ratio in tissue [4].

Glucocorticoids are often effective in treatment of various forms of IgG4-RD including RF. As a cornerstone of RF treatment, they provide a favorable response in most cases. Unfortunately, there is no universally accepted regimen for glucocorticoid therapy, largely due to a lack of studies comparing efficacy of different doses of glucocorticoids. No randomized trials have been conducted [1,2,9]. In our current case, steroid pulse therapy of daily 250 mg (4 mg/kg) intravenous methylprednisolone for 3 days was introduced instead of anecdotally used regimen of 40-60 mg of oral prednisone, in order to achieve more rapid relief of obstructive uropathy and resolution of systemic symptoms. A higher dose of glucocorticoids led to the rapid resolution of systemic symptoms and
prompted a reduction in mass size. The rapid response to therapy enabled earlier removal of the double J ureter stents compared to the other case series [10] in which the stents were maintained for a median period of 12 months (range, 2-50 months). Earlier removal of stents reduces the risk of a urinary tract infection, encrustation around the stents, and other undesired complications.

Steroid pulse therapy was first established for acute renal allograft rejection. Since lupus nephritis shows histopathological features similar to those of acute renal allograft rejection, the therapy was soon translated to the treatment of lupus nephritis in conjunction with other immunosuppressive agents [11]. It was further employed for treatment of severe manifestations of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease, and numerous other inflammatory diseases [7,12].

The underlying mechanisms of the enhanced effectiveness of steroid pulse therapy over low-dose steroid therapy are not yet fully understood. Steroids, which are derived from cholesterol, are postulated to dissolve in the cell membranes of target cells when administered at extremely high doses. The resulting reduction in membrane fluidity might cause markedly diminished inflammatory cell function. Another possible mechanism is that high plasma levels of glucocorticoids, which are achieved by pulse therapy, can inhibit complement activation [13].

Steroid pulse therapy generally allows for a shorter course of supra-physiologic glucocorticoid dosing, which reduces the unwanted complications of long-term glucocorticoid use, without hampering its effects. Although 1 g intravenous methylprednisolone per day for 3 days has traditionally been employed in treatment of SLE flare-ups, there is a growing consensus that a lower dose of pulse therapy (e.g., 100-300 mg methylprednisolone per day for 3 days) is equally effective for achieving the remission of active SLE or RA. Lower dose therapy is associated with a reduced risk of adverse effects, such as severe infection [7,8]. The regimen of daily 250 mg (4 mg/kg) intravenous methylprednisolone for 3 days, which yielded an excellent response in our patient, falls into this category. Because lower dose of steroid pulse therapy has been used effectively in treatment of various autoimmune diseases, we introduced the therapy to our patient, with RF, which caused postrenal acute kidney injury and relatively severe systemic symptoms of fatigue and loss of appetite. Determination of an appropriate dose of glucocorticoids in different disease entities is important in order to allow for an optimal response with minimal adverse effects.

A few cases of RF treated with steroid pulse therapy have been reported, however immunosuppressive agents were administered concurrently in those cases [5,6]. To the best of our knowledge, this is the first case report of RF treated with steroid pulse therapy in Korea. Further studies comparing efficacy and adverse effects of steroid pulse therapy against conventional oral prednisone therapy are needed in order to establish the optimal dose of glucocorticoids for treatment of RF.

REFERENCES