Case Report

Successful Treatment of Retroperitoneal Fibrosis with Tamoxifen in a Child

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ABSTRACT. We describe our experience with tamoxifen in a prepubertal girl with retroperitoneal fibrosis who had failed treatment with high dose corticosteroid therapy. Her response was excellent. (J Rheumatol 2001;28:1693–5)

Key Indexing Terms:
CHILD RETROPERITONEAL FIBROSIS TAMOXIFEN

Retroperitoneal fibrosis (RF) is an uncommon disorder of unclear etiology[1]. It is characterized by the development of a fibrotic mass centered around the sacral promontory enveloping the aorta and the ureters and is considered to be a manifestation of multifocal fibrosclerosis, a generalized fibrosing disorder[2].

Although the pathogenesis is poorly understood, the para-aortic location of the lesion and the pathology and characteristics of the infiltrating inflammatory lesions suggest that RF may be an immune response to materials in the vessel wall or a reaction to substances released through the vessel wall[3]. Therefore, antiinflammatory therapy with glucocorticoids has been the primary treatment for this condition[4,5]. Radiation[6] and other immunosuppressant therapies[7,8] have been used. Surgical management of the obstruction of the ureters and the blood vessels is often necessary.

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Recently, Clarke, *et al* introduced the idea of using tamoxifen, a nonsteroidal anti-estrogenic compound, for treatment of RF[9]. Tamoxifen was chosen because both desmoid tumor and RF are characterized by invasive fibroblastic proliferation, and tamoxifen has been effective in the treatment of desmoid tumors[10]. Since that study, there have been several case reports with good results on the use of tamoxifen in the treatment of RF in adults[11-14].

We describe our experience with tamoxifen for successful treatment of a 10-year-old girl with retroperitoneal and mediastinal fibrosis.

CASE REPORT

A 10-year-old girl was evaluated initially for fever, weight loss, neck swelling, and abdominal pain. Examination revealed generalized adenopathy, ascites, and a serpiginous erythematous rash of both legs. Results of initial laboratory studies were as follows: hemoglobin 10.3 g/dl; total white cells 13,100/mm^3 with 81% polymorphs, 5% bands, 8% lymphocytes, 6% monocytes; platelet count 580,000/mm^3; and sedimentation rate 100 mm/h. Examination of the bone marrow showed normal marrow elements with mild myeloid hyperplasia. Multiple blood and urine cultures were negative.

Initial roentgenogram of the chest showed an infiltrate in the right middle and left lower lobes. Ultrasound of the abdomen showed bilateral hydronephrosis. Intravenous urogram showed medial displacement of the ureters, which suggested RF. Computed tomography (CT) of the abdomen showed a mass in the retroperitoneum compressing the right ureter with secondary hydronephrosis. Chest CT showed prominence of the azygos vein and thickening of the retrocrural region of the inferior mediastinum, findings suggestive of mediastinal fibrosis. Biopsy of the retroperitoneal mass showed a diffuse fibroblastic proliferation engulfing surrounding fat and mixed with lymphocytes and plasma cells (Figure 1).

The girl was given pulse dose of methyl prednisolone 30 mg/kg/day for 3 days, followed by oral prednisone 2 mg/kg/day. Initially, she improved with reduction of fever. Ultrasound of the abdomen showed that the hydronephrosis was improving. Thus prednisone dose was tapered and then discontinued 12 months after the diagnosis.

Within 2 months after discontinuation of prednisone, she developed edema of her lower legs, fever, abdominal pain, and tender, subcutaneous nodules in the legs. One of the lesions in the leg, which was probably vasculitic, ulcerated and became chronic because of venous stenosis.

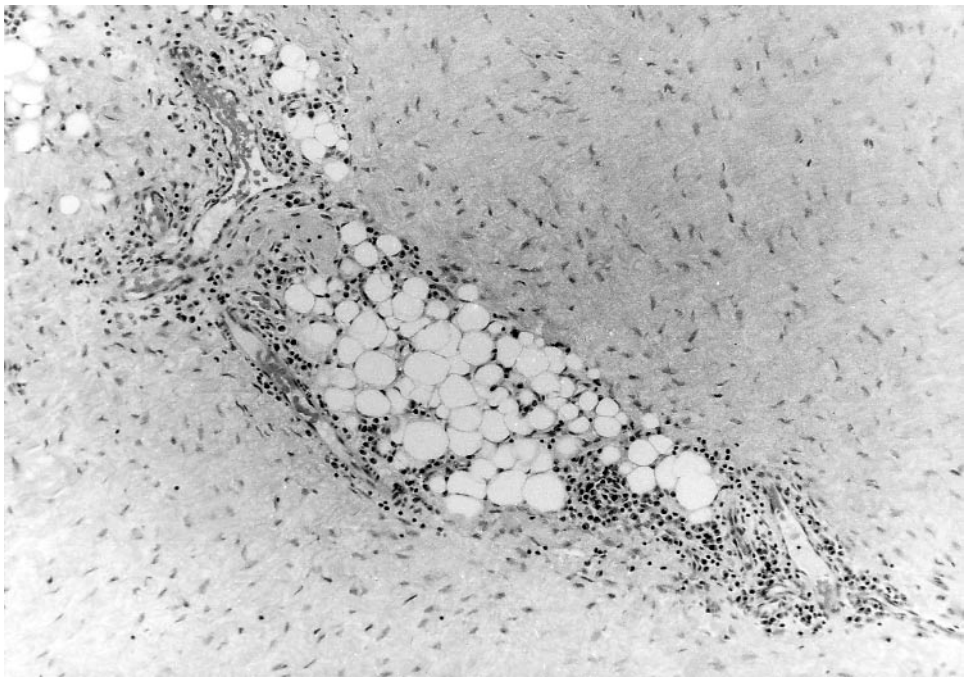

Figure 1. Photomicrograph of retroperitoneal tissue showing fibroblastic proliferation with mixed inflammatory infiltrate (original magnification ×40).

Roentgenogram of the chest showed widening of the superior mediastinum and marked prominence of the azygos vein. Chest CT showed occlusion of the superior vena cava and the brachicephalic vein, fatty infiltration of the mediastinum, and development of collateral vessels, including enlargement of the azygos vein. CT of the abdomen showed increased soft tissue in the retroperitoneum with collateral vessels, occlusion of the inferior vena cava, and bilateral hydronephrosis (Figure 2).

Large doses of prednisone (up to 250 mg/day orally) were initiated. Her fever improved, but the edema, swelling of the legs and the face, and ulcer did not. Hypertension and weight gain became significant management problems.

Tamoxifen was begun 10 mg twice a day. Dose was increased to 10 mg three times a day for a brief period and then reduced again to 10 mg twice a day when her serum levels of aspartate amino transferase and alamine amino transferase were found to be elevated more than twice the normal level. She improved within 3 months, and after a year of treatment, her edema cleared, the abdominal mass decreased, and the ulcer healed completely.

Followup CT of the abdomen showed a decrease in the size of the renal pelvis. Occlusion of the inferior vena cava persisted (Figure 3). Steroid dose was decreased and then discontinued. Treatment with tamoxifen was continued for a total of 2 years. Currently, she has been off tamoxifen for 4 months with recurrence of systemic features, but without evidence of ureteral or venous obstruction.

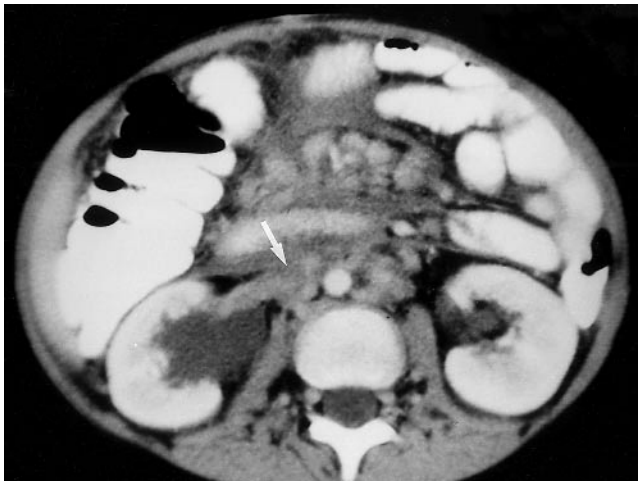

Figure 2. Abdominal CT scan with contrast prior to treatment. Figure shows dilated extrarenal pelvises, occlusion of the inferior vena cava (arrow), and nodularity of the retroperitoneal soft tissues due to collateral vessel formation.

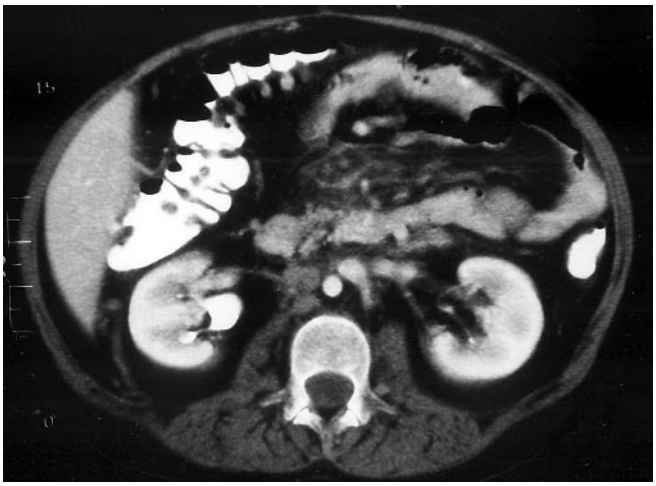

Figure 3. Abdominal CT scan with contrast after treatment showing decreased fullness of the extrarenal pelves. Occlusion of the inferior vena cava and collateral vessels persists.

DISCUSSION

We describe successful treatment of RF using tamoxifen in a 10-year-old girl. To date, there are fewer than 50 children with RF described in the English literature, which includes a report of RF in a 7 month fetus[15].

Treatment of RF is largely empirical because of the relative rarity of the condition and the unclear pathogenesis. Treatment with glucocorticoids seems reasonable given the inflammatory nature of the lesions[1,4,5]. There are no controlled studies documenting the effectiveness of various antiinflamatory and immunosuppressive drugs in the treatment of RF. Radiation therapy[6] and azathioprine[7,8] have been used with inconsistent results.

Before the development of newer surgical techniques, such as internal and percutaneous stent placement, open surgery was the chosen method for biopsy of the tissue and relief of obstruction of the ureters and abdominal vessels[16-18]. Currently, surgery is often individualized and usually is for biopsy to exclude other malignant conditions or for vascular problems.

Tamoxifen has been used in children for the treatment of gynecomastia and desmoid tumors[19,20]. To our knowledge, this is the first report of the use of tamoxifen in a child with retroperitoneal fibrosis. The clinical improvement was dramatic, with reduction in the size of the mass and improvement in symptoms secondary to obstruction such as edema and stasis ulcer. However, the structural changes seemed to persist, as documented by CT of the abdomen.

The mechanism of action of tamoxifen in fibrotic conditions is not clearly understood. One possible mode of action is the drug's ability to increase *de novo* synthesis and secretion of transforming growth factor-ß (TGF-ß), as shown with fetal fibroblasts *in vitro*[21] and in human breast cancer *in vivo*[22]. Although an increased level of TGF-ß may decrease inflammation, it may also increase fibrosis[22]. Also, the effects of tamoxifen are independent of estrogen receptor level in both breast cancer and desmoid tumors[23]. These and other discrepancies in the action of tamoxifen must be clarified before a method of selecting patients with RF for therapy can be developed.

Additionally, concerns exist about the use of tamoxifen in a preadolescent female since this drug is an anti-estrogenic compound. Also, our patient developed a transient elevation of liver enzymes that returned to normal when the dose was reduced. She has also developed ovarian cysts. Other potential longterm effects of tamoxifen are osteoporosis and uterine tumors.

Despite the concerns listed above, our experience and available reports in the literature suggest that tamoxifen should be considered along with glucocorticoids in the initial management of RF in both adults and children.

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