Obstructive Nephropathy as a Result of Retroperitoneal Fibrosis: A Review of Its Pathogenesis and Associations

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Abstract. Retroperitoneal fibrosis is a rare disease, typically with an insidious clinical course. It is thought that this disease process is perhaps an exaggerated reaction to an inciting inflammatory event. In this study, a case of retroperitoneal fibrosis is reported, in which the patient presented with typical symptoms of retroperitoneal fibrosis, along with some atypical vasculitic symptomatology. Retroperitoneal fibrosis is a disease process with an unknown etiology, which has been observed to be associated with a number of different possible inciting factors. Two factors that have been documented in the literature as being associated with retroperitoneal fibrosis include the use of beta-blocking agents, and connective tissue disease processes such as systemic lupus erythematosus. The patient discussed was using beta-blocker medication and also had signs and symptoms suggestive of a lupus syndrome. There are no reported cases of the combined association of beta-blocker usage, lupus, and retroperitoneal fibrosis. (J Am Soc Nephrol 8: 684–688, 1997)

We describe a patient with retroperitoneal fibrosis, who presented with hypertension and progressive renal insufficiency. Retroperitoneal fibrosis is an unusual cause of renal insufficiency that presents as an insidious process. The initial symptoms are often as vague as a poorly localized pain over the flank, low back, and abdomen (1). Typically, patients that are found to have retroperitoneal fibrosis have already progressed to bilateral urinary tract obstruction by the time of diagnosis (2). The etiology of this disorder has been postulated to be secondary to either a local or systemic inflammatory process. Often this disease is discovered in coexistence with other systemic inflammatory processes such as mediastinitis, Reidel’s thyroiditis, sclerosing cholangitis, and orbital pseudotumor (3). Some studies have also shown an association of retroperitoneal fibrosis with a local inflammatory process involving retroperitoneal structures, including the aorta, bowel, and lymph nodes (1). The patient we describe had symptoms and signs suggestive of a systemic inflammatory process associated with a positive antinuclear antibody titer.

Her serum creatinine concentration was 3.1 mg/dl in August of 1995, after having been measured at 1.2 mg/dl 2 months earlier.

Recent history was significant for erythema nodosum involving both lower extremities, complaints of an inflammatory arthritis, and Raynaud’s phenomenon. Her antinuclear antibody titer in May of 1995 was 1:2560 (homogeneous pattern). Additional workup at an outside center included a normal angiotensin-converting enzyme level, negative tuberculin skin test, and a chest x-ray, which was noteworthy for only mild bilateral apical thickening.

Repeat urinalyses over the past 2 yr were significant for microhematuria (three to five red blood cells per high-powered field). Renal workup previously included a normal intravenous pyelogram and renal ultrasound in November of 1993; however, a radionuclide renogram with and without enalaprilat in August 1995 showed a nonfunctioning left kidney, with rapid perfusion of the right kidney and slight prolongation of excretion after treatment with enalaprilat.

Because of the worsening renal function, hypertension, and abnormal radionuclide renogram, the patient was referred for further diagnostic evaluation.

Past medical history included reflux and migraine headaches. A complete abdominal hysterectomy was performed in 1992. The patient’s medications at the time of admission included nadolol 40 mg daily, and indapamide 1.25 mg daily. Upon repeated questioning, the patient denied any prior medication history involving use of ergot medications. Family history was significant for adult onset diabetes mellitus. Social history was positive for tobacco use, which had ceased 3 months prior to the evaluation date.

Physical examination at the time of hospital admission revealed a blood pressure of 132/96 in both arms, with a heart rate of 60 beats per min. Examination of the head, neck, chest, and heart were normal. Abdominal examination revealed no
palpable viscera or masses, and there was no costovertebral angle tenderness. Examination of extremities revealed two mildly erythematous, tender, 0.5 cm by 1 cm nodules over each anterior tibial area. Neurologic examination was intact.

Laboratory studies on admission revealed the following measurements: sodium, 136 mEq/l; potassium, 3.3 mEq/l; chloride, 97 mEq/l; carbon dioxide, 27 mEq/l; blood urea nitrogen, 49 mg/dl; serum creatinine, 2.7 mg/dl; white blood cell count, 8.2, with a normal differential; hemoglobin, 11 mg/dl; and platelet count, 269 thousand. Urinalysis showed three RBC's per high power field without protein, casts or white blood cells.

Inpatient studies included a renal ultrasound with Doppler ultrasound renal vascular studies. The right kidney was 11.9 cm in pole-to-pole length, with moderate hydronephrosis, and the left kidney was 7.9 cm in pole-to-pole length, with cortical thinning. There was no renal artery stenosis or renal vein thrombosis.

Retrograde pyelography was performed, confirming the moderate right hydronephrosis and mild left hydronephrosis in association with a filling defect in the right mid-ureter, as well as medial deviation of the ureters (Figure 1). Bilateral ureteral stents were inserted.

Computer-assisted tomography (CAT) of the abdomen and pelvis (with contrast) showed extensive soft tissue infiltration concentrically around the aorta, inferior vena cava, and both ureters. No adenopathy or tumor was noted. Further serologic workup included negative anti-ribonucleoprotein, anti-Smith, antinuclear, and anti-double-stranded DNA antibodies. Complement levels were normal. Urine cytology was benign, and urine acid-fast smear and culture, including tuberculin skin test, was negative.

The beta-blocker was discontinued, and prior to laparotomy with ureterolysis and omental wrapping of the ureters in the following month, the serum creatinine concentration declined to 1.9 mg/dl. Postoperatively, the blood pressure was normal without antihypertensive therapy, and the serum creatinine concentration gradually declined to 1.1 mg/dl. Intraoperative findings revealed normal-appearing ureters to the level of the sacral promontory, at which point they were found to be encased in a dense fibrotic retroperitoneal mass. There was no evidence of tumor, lymphoma, or ovarian cancer. Pathology was significant for adipose tissue containing dense connective tissue infiltrated with lymphoid cells, lymphocytes, eosinophils, and rare histiocytes.

Discussion

This case illustrates a typical presentation of retroperitoneal fibrosis, with some atypical features suggesting an association of collagen vascular disease. Idiopathic retroperitoneal fibrosis most commonly occurs in people 40 to 60 yr of age, with a 2:1 male-to-female predominance (4,5). Clinical presentation of retroperitoneal fibrosis is variable, depending upon the stage of presentation. Early symptoms manifest as malaise, anorexia, weight loss, fever, backache, and hypertension (6). There is often an associated pain that is described as a dull ache in the girdle distribution, originating in the lumbosacral region, without relief with change in position but often relieved with the use of aspirin and without the use of narcotics (1,6,7). The later stage of this disease often presents with symptoms secondary to an obstructive uropathy and azotemia (6). Urinary findings have most frequently been reported as anuria and microscopic hematuria (8,9). Other less common clinical presentations of retroperitoneal fibrosis include lower-extremity edema and even thrombophlebitis from fibrotic impingement of the inferior vena cava (3,4), claudication from arterial compromise (10), and intestinal ischemia secondary to mesenteric fibrosis (8,11). Our patient had some typical features of retroperitoneal fibrosis, including malaise, hypertension, and hematuria. She also presented with atypical symptoms of an inflammatory arthritis, Raynaud's phenomenon, skin lesions, and migraines. These atypical symptoms suggest a systemic inflammatory or vasculitic component to her syndrome.

The diagnosis of retroperitoneal fibrosis is primarily made with the use of imaging studies, as the history and laboratory findings are somewhat nonspecific in this uncommon disease. The classic triad evident upon excretory urography is proximal

Figure 1. Retrograde pyelogram demonstrating a small left kidney with normal left ureteral caliber and blunted left calyces, and marked right hydronephrosis to the level of L5, at which point the ureter becomes normal in caliber. Note the medial deviation of the ureters at the L5 level, as well as the lateral displacement of the kidneys.
hydroureteronephrosis, medial deviation of the ureters, and extrinsic compression of the ureters (1,4,6). A small percentage (2.5%) of patients may show no evidence of hydronephrosis on renal ultrasound (5). Retrograde pyelography is also useful because it avoids dye nephrotoxicity and allows access for placement of ureteral stents (1,4,6). More recently, radioisotope renography has been utilized for anuric patients because it has the ability to confirm obstructive uropathy and show relative amounts of renal function (6). Computer-assisted tomography is considered the examination of choice to visualize the extent of fibrosis as well as to assess for lymphadenopathy and tumor (1,6,8,12). The differentiation of fibrosis from tumor by CAT or magnetic resonance imaging is not considered completely reliable, and open biopsy is still the preferred method to confirm the diagnosis of retroperitoneal fibrosis (1,6).

Pathologic findings in this disease most frequently include a woody, fibrous pink tissue enveloping the abdominal aorta, inferior vena cava, and the ureters (1,6,7,9,12). The tissue has rarely been found to invade the psoas muscles and ureters (6). Limited forms of retroperitoneal fibrosis involve fibrosis extending from the level of the renal hilum to the common iliac blood vessels; the more rare extensive form has been found to extend into the mesenteric root and into the mediastinum, with involvement of neighboring organs (4). Microscopically, the disease appears as a subacute, nonspecific inflammatory reaction in fibrous tissues. Early in the disease, there are collagen bundles interspersed with lymphocytes, pleomorphic cells, polymorphonucleocytes, eosinophils, and macrophages (1,4). Giant cells, granulomas, and histiocytes can also be seen in the earlier inflammatory stage of the disease (1). Later stages of the disease manifest as acellular fibrosis (6,8).

The etiology of retroperitoneal fibrosis has been considered to be idiopathic, with the exception of a few associations (1,6,7,10). The list of associations (Table 1) appears to be growing since the introduction of this disease entity in 1948 by Ormond (13). Ormond initially described two distinct groups of retroperitoneal fibrosis cases: the first group had symmetrical fibrosis of both ureters in which no inciting inflammation could be found, and the second group had more localized fibrosis with a causal tumor or inflammation that could be elucidated (10,13). Earlier reports of "periureteral fibrosis" have considered retroperitoneal fibrosis to be an aggressive inflammatory response to varied stimuli (10). Que and Mandema (10) postulated that in addition to a localized response to irritation, there may also be a "predisposition to collagen disease."

The pathogenesis of retroperitoneal fibrosis is unclear. This process is a chronic inflammatory response to a number of possible inciting factors, including infection, tumor, and atherosclerosis, and systemic processes such as vasculitis, lupus, and other autoimmune reactions. The reaction to advanced inflammatory atherosclerosis with retroperitoneal fibrosis has been studied by a number of investigators (15–17). Figure 2 portrays this process: a specific inflammatory response to oxidized lipids, in areas of pre-existing atherosclerosis, has been postulated as one possible inciting event in the resultant periaortitis (15). Cerebroside is an oxidized low-density lipoprotein (LDL), and it has been proposed that there is an autoallergy to this substance; to note, autoantibodies to ceroid have been found in patients with periaortitis (16,17). This inciting event promotes an influx of chronic inflammatory cells to the area of atherosclerosis (14–17). Hughes and Buckley (14) described a predominance of macrophages in areas of periaortitis. Macrophages become lipid-laden foam cells in atherosclerotic plaque and have also been found to secrete substances that cause cell proliferation (16). Other researchers have found an abundance of T and B lymphocytes, plasma cells, and (less frequently) eosinophils in areas of periaortitis (16,17). The infiltrating

**Spectra of periaortitis**

**Localized immune response to ceroids**

- Chronic inflammatory cells
  - B & T Lymphocytes
  - Macrophages
  - Plasma cells
  - Eosinophils

**Cytokines & Growth factors**

- IL-1, IL-2, IL-4, IL-6, Interferon gamma, PDGF, GM-CSF, TNF

**Fibroblast proliferation**

- Fibrosis

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**Table 1. Retroperitoneal fibrosis: associated findings in 491 patients**

<table>
<thead>
<tr>
<th>Findings</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>67.8</td>
</tr>
<tr>
<td>Methysergide</td>
<td>12.4</td>
</tr>
<tr>
<td>All malignancies</td>
<td>7.9</td>
</tr>
<tr>
<td>Mediastinal fibrosis</td>
<td>3.3</td>
</tr>
<tr>
<td>Periaortic inflammation-arteritis</td>
<td>2.4</td>
</tr>
<tr>
<td>Mesenteric fibrosis</td>
<td>2</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
<td>1.6</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>1.8</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>1.2</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>1</td>
</tr>
<tr>
<td>Reidel's thyroiditis</td>
<td>0.8</td>
</tr>
<tr>
<td>Other</td>
<td>5.3</td>
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</tbody>
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* From Reference 5.
inflammatory cells are then the source of numerous cytokines, growth factors, and profibrogenic substances (14,15). Specifically, macrophages secrete fibroblast growth factor, and T lymphocytes secrete fibroblast growth factor and collagen synthesis stimulating factor (17), thus resulting in fibroblast proliferation and fibrosis.

The patient we describe had no signs of a local inflammatory process inciting her fibrotic process; however, she did have signs and symptoms of a systemic inflammatory process; including a history of arthralgias, panniculitis, Raynaud’s disease, and a strongly positive anti-nuclear antibody titer. Numerous reports suggest an association of retroperitoneal fibrosis and collagen vascular disease (7,9,10,18–21). Bonnet et al. (19) reported a patient that presented with retroperitoneal fibrosis, including mesenteric, pulmonary, and periarticular fibrosis, and an associated panniculitis. Raynaud’s phenomenon has been described (10) in association with retroperitoneal fibrosis. A highly elevated anti-nuclear antibody titer has specifically been seen in cases of retroperitoneal fibrosis accompanied by signs and symptoms of an autoimmune process (9,10). Bashour reported a patient with retroperitoneal fibrosis preceding the presentation of her diagnosis of systemic lupus erythematosus; she was subsequently found to have membranous nephropathy and positive serology for systemic lupus erythematosus. The case presented here provides further clinical suspicion that supports an autoimmune process as the etiology of retroperitoneal fibrosis.

Besides local and systemic inflammatory processes inciting this fibrotic process, there are also numerous reports regarding the association of retroperitoneal fibrosis with medications. Likely medications associated with retroperitoneal fibrosis include methysergide, ergotamine, hydralazine, methyldopa, and phencacitin (7,21–23). The mechanism by which these medications cause retroperitoneal fibrosis is unclear. An immunologic mechanism has been postulated for cases associated with methyldopa and hydralazine (21). Germane to our case are reports of an association of retroperitoneal fibrosis with the use of β-adrenergic beta-blockers (7,21,22). Specific β-adrenergic beta-blockers, including acebutolol, metoprolol, atenolol, oxprenol, propranolol, and sotalol, have been implicated (22). One way β-adrenergic beta-blockers may produce retroperitoneal fibrosis is by decreasing the ratio of adenosine 3':5-cyclic monophosphate to cyclic glucose monophosphate, resulting in an increase in cellular proliferation (22). Nadolol has recently been associated with retroperitoneal fibrosis (11).

Interestingly, β-adrenergic beta-blockers have also been considered a possible etiology of a drug-related lupus syndrome (DRL) (24). Acebutolol has been the most frequent offender of a DRL syndrome, although labetolol, oxprenolol, metoprolol, propranolol, and pindolol have all been associated with DRL (24). Nadolol has not been specifically reported in the literature in association with DRL. DRL is a syndrome resembling systemic lupus erythematosus, except in a milder form; patients frequently present with malaise, fever, and arthralgias (25). More extensive involvement, with serositis, pleuritis, and pulmonary infiltrates, have been reported less frequently with DRL (24,25). The definitive factor that one must see to confirm the diagnosis of DRL secondary to a medication is the disappearance of symptoms when the patient is withdrawn from the medication. There are no reported cases of DRL associated with retroperitoneal fibrosis, nor are there reports of retroperitoneal fibrosis with concomitant β-adrenergic blocker use and a positive anti-nuclear antibody titer.

Treatment of retroperitoneal fibrosis has traditionally been approached in a surgical manner. There are two reasons for a surgical approach: relief of obstruction mechanically, and the performance of an open biopsy to rule out lymphoma or metastatic cancer (2,7,25,26). The use of long-term steroids treatment has also been utilized as an adjunct to surgery by some researchers (1,2,20,24). Harreby et al. (20) advocate the use of steroids and disease-modifying antirheumatic drugs without surgery, arguing that the potential risks of surgery—including ureteric leakage, thromboembolism, and recurrent fibrosis—as well as long-term use of high-dose steroids can be avoided with the use of methylprednisolone pulse and azathioprine therapy (20). Arguments against the treatment of retroperitoneal fibrosis with medical therapy alone include the potential of missing a diagnosis of lymphoma or cancer, as the patient would be without the benefit of open biopsy and exploration. Computer-assisted tomographic-guided needle biopsy has been suggested as a possible alternative to open exploration and biopsy; however, there are no randomized studies for comparison of these two approaches (2,20). Our patient is doing well after ureterolysis with omental wrapping of the ureters and initial urinary stenting. Nadolol was also discontinued.

In summary, retroperitoneal fibrosis is an uncommon disease that often presents in a subtle manner. The case described is possibly an unusual presentation of a β-adrenergic blocker inciting both a lupus syndrome and an associated retroperitoneal fibrosis. The etiology of retroperitoneal fibrosis is unclear; however, the list of associations is growing. A common underlying factor, an inciting local or systemic inflammatory process, is suspect. Further investigation regarding the autoimmune nature of this chronic inflammatory process may help clarify the underlying pathogenesis.

References

**Nephrology Training Program at The Pennsylvania State University College of Medicine and Milton S. Hershey Medical Center**

The Division of Nephrology at the Pennsylvania State University offers a 2- or 3-year program in clinical nephrology and/or research training in nephrology. These programs prepare physicians for careers in both academic and clinical nephrology. The five members of the division are very active in patient care, research, and teaching activities. The program accepts one fellow per year. The clinical training program covers a full array of experiences in consultation service, dialysis, hypertension, inpatient service, renal transplantation, and outpatient consultation. All modalities of dialysis are available, including hemodialysis, hemofiltration, continuous venovenous hemofiltration dialysis, hemoabsorption, and all forms of peritoneal dialysis. Approximately 80 dialysis patients are followed-up at the University Hospital, including hemodialysis and peritoneal dialysis patients.

There is an active transplant service that performs 60 to 80 kidney transplants per year. This program also performs kidney/pancreas transplants and liver transplants. The inpatient and consultation service are combined into one active service that follows an inpatient census of 20 to 30 patients on a daily basis. The fellows gain experience in invasive procedures, including vascular access for acute hemodialysis and diagnostic renal biopsies.

The faculty’s research interests include cellular calcium homeostasis and the role of calcium in signal transduction, cellular and molecular mechanisms of experimental glomerular and interstitial fibrosis, impact of different induction immunosuppressive agents on allograft survival, roles of cytokines in dialysis-associated hypotension, and hepatobiliary diseases in renal transplant patients.

Jonathan R. Diamond, M.D., and his laboratory staff are working to elucidate the mechanisms that propagate initial renal injury to fibrosis. The central hypothesis is that infiltrating monocytes enter injured renal tissue and elaborate cytokines, which augment the initial damage and propagate the lesion, resulting in an end-stage condition. Specific attention is focused on the regulatory mechanisms of chemokine and adhesion molecule expression as well as expression patterns of transforming growth factor beta a pluripotential peptide growth factor that upregulates matrix proteins and tissue inhibitors of metalloproteinases. Three different rat models are used, including a ureteral obstruction model that may be clinically relevant to our case of retropertitoneal fibrosis.