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Loin pain hematuria syndrome

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CASE PRESENTATION

A 42-year-old Caucasian woman was referred for evaluation of recurrent episodes of right loin pain associated with intermittent microscopic and gross hematuria. She had been healthy until 2 years prior, when she developed right renal colic associated with a ureteral stone. She was treated with extracorporeal shock wave lithotripsy with complete resolution of symptoms. Two further episodes of renal colic resolved with conservative medical management.

The patient subsequently developed relapsing and remitting episodes of right loin pain. The episodes increased in frequency and the pain increased in severity over the next 18 months. Gross hematuria was noted during these episodes but not during the asymptomatic periods. There was no evidence of proteinuria, renal insufficiency, or recurrent nephrolithiasis. She was referred to our hospital for further evaluation and management.

Review of systems was unrevealing. On examination, the patient was afebrile, the blood pressure was 110/80 mmHg and the heart rate was 80 beats per minute. The body mass index was 24.7 kg/m^2. The remainder of the physical examination was unremarkable. The serum creatinine was 0.9 mg/dl, the hemoglobin was 13.9 g/dl, the platelet count was 181 000, and the white blood cell count was 7400. Serum electrolytes, liver function tests, and the prothrombin and activated partial thromboplastin times were normal. Urine dipstick was persistently negative for albumin. Urine protein excretion was not quantified. Urine microscopy at this unit revealed 0–2 red blood cells per high-powered field without dysmorphic erythrocytes or red blood cell casts. Previous urinalyses had demonstrated higher numbers of red blood cells. Computed tomography of the genitourinary tract revealed normal renal vasculature, no structural renal abnormalities, and no nephrolithiasis. Renal angiography was not performed. The patient was diagnosed with loin pain hematuria syndrome (LPHS).

The patient was managed with escalating doses of opiates for symptom control. At the time of evaluation, she took fentanyl 200 μg patch every 3 days and hydrocodone 7.5 mg daily; 2000 μg of transmucosal fentanyl was also used each day to manage breakthrough pain. Repeated urinalyses in between episodes of gross hematuria showed no evidence of proteinuria, or microscopic hematuria, and renal function remained normal.

In view of debilitating symptoms, the possibility of autotransplantation was discussed with the patient. The patient agreed to the procedure, and underwent laparoscopic right nephrectomy with renal nerve stripping, followed by autotransplantation into the right iliac fossa. An interposed polytetrafluoroethylene arterial graft was used. Renal biopsy performed at the time of operation revealed normal glomeruli, mild arteriosclerosis with hyalinosis, and minimal tubular atrophy and interstitial fibrosis. Immunofluorescence was negative. Electron microscopy performed on paraffin-digested sections revealed glomerular basement membranes of normal thickness.

FOLLOW-UP

After the autotransplantation was performed, the patient experienced prolonged postoperative pain, which gradually improved over several weeks. Five months after the operation, she was able to reduce the dose of methadone to 10 mg three times a day and was been able to return to work. However, there was recurrence of pain over the autograft 8 months post-surgery, requiring escalating doses of narcotics and she has applied for disability.

DISCUSSION

Epidemiology and clinical features of LPHS

The loin pain hematuria syndrome (LPHS) was first reported in 1967 in three female patients with recurrent attacks of severe flank pain and intermittent macroscopic hematuria in

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whom the diagnostic work-up provided no explanation for the symptoms.[1] It was not until 14 years after the initial description of LPHS that the disorder was first described in male patients. Whether this lag was due to levels of awareness of LPHS among physicians, gender differences in seeking medical care, or other factors is not certain. Recent reports of LPHS have included a higher percentage of male patients, ranging from 0 to 90% in different case series.[2] However, the majority of reported cases have been in women and 70% of the patients in the three largest series published to-date were female.[3–5] Although the age at onset has varied from the first to sixth decade of life, most patients who develop LPHS will begin to manifest symptoms in the third decade.[2] Most reports have not included information on ethnic background. However, most series are from Australia, Canada, or Great Britain, suggesting a white predominance in LPHS.

The predominant clinical features of LPHS are recurrent flank pain and hematuria. As with other causes of renal colic, the pain may radiate to the abdomen, inguinal area, or medial thigh. Although the pain most often is unilateral at the time of presentation, in the majority of patients bilateral pain will eventually develop. Pain episodes may be associated with low-grade fevers and dysuria, although there is no evidence of concurrent urinary tract infection. Hematuria may be gross or microscopic and may be absent during pain-free periods. Most patients will have both flank pain and hematuria at the time of first presentation. However, the disorder may present initially with only one manifestation. In some cases, the disorder has been diagnosed on the basis of recurrent flank pain alone in the absence of hematuria. Physical examination in the setting of an episode of flank pain may reveal fevers and tenderness in the costovertebral angle but is otherwise unremarkable; hypertension is not associated with LPHS. Initial reports described LPHS in women taking estrogen-containing oral contraceptive pills.[6] However, this association has not borne out in subsequent series. Pain episodes have not been associated with medication usage, physical exertion, menstruation, or local or systemic infection.[2] Many patients may report a history of nephrolithiasis (up to 47% in one study),[7] although renal stones must be absent during the pain episodes in order to diagnose LPHS.

An association between LPHS and psychiatric symptoms was reported in the initial reports of the syndrome. Subsequent reports have described an increased incidence of depression, somatization, and drug-seeking behavior in LPHS patients compared to the general population and some authors have suggested that LPHS may represent a type of somatoform pain disorder.[8,9] One group found an association between the onset of flank pain and the occurrence of psychologically important life events.[8] In the two largest series of LPHS reported in the literature to-date, all patients underwent formal psychiatric assessment.[3,4] However, the extent and results of these evaluations were not included in the published data.

A thorough evaluation for alternative etiologies of flank pain and hematuria should be conducted before making a diagnosis of LPHS. Laboratory and radiographic investigation in LPHS is generally unrevealing and abnormal findings described in individual patients have not been associated with LPHS on a consistent basis.[2] Renal function and levels of serum electrolytes are normal, as are standard hematologic and rheumatologic evaluations.[6] Urinary concentration and acidification remain intact, and urinary excretion of calcium, phosphate, uric acid, oxalate, and cysteine are normal.[2] Low-grade proteinuria has been reported in some patients, primarily in the setting of an attack of flank pain. Urine and blood cultures are sterile in the setting of flank pain.

Routine radiologic studies of the urinary tract in LPHS are unremarkable. When renal angiography has been performed, the most commonly reported findings include changes in the small vessels, such as widened bifurcations of the interlobar and interlobular arteries, a tortuous appearance to peripheral arteries, and focal avascular areas.[2] The angiographic findings may be bilateral, even in the presence of predominantly unilateral symptoms. Other reports have described patients with normal angiography, leading the authors to suggest that the angiographic findings were related to spasm induced by the radiocontrast rather than to an intrinsic structural abnormality.[10]

When renal biopsy has been performed in LPHS, the microscopic changes have included mild tubular atrophy, patchy interstitial fibrosis, glomerulosclerosis, arteriolar hyalinosis, and subcapsular cortical ischemia.[2] Immunofluorescence is negative. Electron microscopy in some patients reveals abnormally thin or thick glomerular basement membranes.[7,11]

Many biopsy specimens will demonstrate no structural or ultrastructural abnormality. However, recent data from Spetie *et al.*[7] suggest that renal biopsy should be performed on all patients in whom the diagnosis of LPHS is considered: of 43 patients who underwent renal biopsy as part of an evaluation for unexplained flank pain and hematuria, nine (21%) were diagnosed with immunoglobulin A nephropathy. Light microscopy in the remaining 34 patients showed evidence of glomerular hematuria. Electron microscopy revealed a thin glomerular basement membrane in nine patients (26.5%) and an unusually thick glomerular basement membrane in 11 patients (32.4%).

It has been proposed that the pathogenesis of flank pain in LPHS is due to glomerular capillary hemorrhage leading to intratubular obstruction by red blood cells.[7] Renal tubular obstruction then leads to interstitial edema and intraglomerular hypertension, which predisposes to further glomerular hemorrhage and tubular obstruction. In some patients, concurrent hypercalciuria or hyperuricosuria may contribute to the intratubular obstruction.[12] Renal parenchymal edema leads to stretching of the renal capsule and flank pain. Extrarenal factors such as renal capsule compliance and pain perception may also modulate the clinical expression of idiopathic LPHS.[7]

Treatment options

The long-term prognosis for patients with LPHS is excellent (Table 1). Renal function is typically normal at the time of initial presentation, and there have been no reports of subsequent deterioration in renal function owing to LPHS. In addition to analgesics, early treatment strategies included prolonged courses of antibiotics, antiplatelet therapy with aspirin or sulfinpyrazone, and anticoagulation with warfarin.[2] None of these additional agents proved effective. Given the excellent long-term prognosis in LPHS, the main therapeutic goal is symptom management with non-steroidal anti-inflammatory drugs and opiates as needed. Large opiate doses may be required to provide adequate pain relief. Patients may benefit from a multidisciplinary approach, which includes psychiatric evaluation and referral to a chronic pain specialist. Hebert *et al.*[11] reported seven patients with LPHS and thin basement membrane disease in whom the use of enalapril was associated with decreased frequency and intensity of pain episodes in four patients.

Approximately 30% of patients will experience a spontaneous resolution of their symptoms after a mean of 3.5 years with conservative medical management.[2] Unfortunately, in some patients symptoms persist or progress despite escalating doses of opiates. Topical analgesia with intraureteric capsaicin has been reported in several series.[13,14] However, enthusiasm for this treatment has been tempered by low rates of symptom control and anatomic complications including bladder mucosal ulceration, fibrotic stricture requiring a pyelocystoplasty, and the development of a non-functioning kidney requiring nephrectomy in three patients. Other interventions have been attempted in an effort to diminish renal nerve activity, including splanchnic nerve blockade, intercostal nerve blockade, celiac nerve blockade, transcutaneous electrical nerve stimulation, surgical sympathectomy, and dorsal rhizotomy.[3] These interventions have met with sporadic success, with none providing sustained analgesia on a consistent basis.

More invasive interventions have been performed in patients with intractable pain, including nephrectomy, renal denervation, and renal autotransplantation. Unilateral nephrectomy has been performed in the past, although it is no longer recommended as a treatment for LPHS given the tendency for symptoms to develop in the contralateral kidney following the operation. There are reports of patients who have undergone bilateral nephrectomy for debilitating symptoms, with subsequent complete relief of pain.[15]

Table 1 | Treatment strategies for loin pain hematuria syndrome

Non-surgical
Analgesics
ACE inhibitors
Nerve blockade
Intraureteric capsaicin
Surgical
Renal denervation
Sympathectomy and rhizotomy
Nephrectomy
Autotransplantation

ACE, angiotensin-converting enzyme.

The temporary relief seen in some patients following nerve blockade led to development of renal denervation with surgical stripping of the renal pedicle in combination with renal capsulotomy as a treatment for LPHS. Greenwell *et al.*[5] reported the results of 24 patients undergoing 33 renal denervation procedures using this technique. Twenty-eight percent of patients had complete relief of pain, although 14% of these patients developed pain in the contralateral kidney. Analgesic requirements decreased in 33% of patients without complete relief of pain. Thirty-eight percent of patients with recurrent pain subsequently underwent nephrectomy for pain control, and 33% of these patients developed contralateral symptoms following nephrectomy. It is assumed that the failure of surgical denervation to provide durable symptom control in most patients is due to renervation of the kidney.

Renal autotransplantation of the denervated kidney was first reported in 1982.[16] Autotransplantation may be associated with a lower risk of renervation, as the operation may allow for more complete stripping of the renal nerves and renervation may be more likely to occur when the kidney remains in its normal anatomic position. Sheil *et al.*[3] compared the outcomes in 40 renal autotransplantations and 24 renal denervation procedures performed in Australia over a 13-year period. Renal autotransplantation was more effective, with 76% of patients being pain free (mean follow-up 8.4 years) vs 33% (mean follow-up 8.0 years) in the renal denervation group. One patient required transplant nephrectomy owing to mechanical trauma to the autograft in the immediate postoperative period. Chin *et al.*[4] reported the results of 26 autotransplantations performed over a 12-year period. Eighteen patients (69%) were pain free at a mean follow-up of 84.7 months, and three additional patients had recurrent pain but reported reduced analgesic requirements and improved quality of life. However, two patients required nephrectomy resulting from mechanical complications of the operation, one for renal vein thrombosis and one for persistent graft ischemia. Parnham *et al.*[17] reported a lower success rate with 12 autotransplantations performed in 11 female patients. Only three patients (27%) were pain free; an additional five patients considered the operation a partial success. One patient had acute renal artery thrombosis requiring nephrectomy and one patient developed an urinoma requiring further surgical intervention. In patients for whom autotransplantation is successful, relief of pain is often immediate. However, pain can recur in the autotransplant, usually within 1 year of the operation (as in our case). Hematuria will often persist in the autotransplant.

Gill *et al.*[18] reported the first two cases of laparoscopic nephrectomy used for renal autotransplantation in LPHS, with good surgical results in both patients. Interposed polytetrafluoroethylene arterial grafts have been utilized in

an attempt to reduce the risk of heterotopic renervation, although there are not currently enough reports in the literature to establish the efficacy of this procedure.[19] Despite surgical innovations which allow for a less morbid and potentially more successful operation, renal autotransplantation remains a treatment of last resort for LPHS. The postoperative complications reported by Chin *et al.* and Parnham *et al.* serve as a cautionary note that the surgical complications seen in renal allograft recipients may also occur in renal autograft recipients.

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