Unusual association of diseases/symptoms

Idiopathic retroperitoneal fibrosis presenting with recurrent bilateral uveitis

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Summary

Patients with recurrent uveitis are often evaluated for the presence of underlying systemic disease. The authors describe a 55-year-old black female who presented with isolated recurrent anterior uveitis. Laboratory evaluations were notable for elevated inflammatory markers. She subsequently developed left lower extremity painless swelling; ultrasound evaluation was negative for deep venous thrombosis. CT scan of her abdomen and pelvis demonstrated multiple amorphous soft tissue densities throughout the small bowel mesentery and retroperitoneum, associated with left-sided hydronephrosis. Histopathology of a retroperitoneal mass demonstrated retroperitoneal fibrosis (RPF). Treatment with systemic corticosteroids led to shrinkage of her mesenteric and retroperitoneal masses, resolution of uveitis and normalisation of inflammatory markers. Albeit rare, RPF should be considered in the diagnostic investigation of patients with recurrent uveitis, especially those with abdominopelvic or lower extremity complaints.

BACKGROUND

Retroperitoneal fibrosis (RPF) is a rare disorder characterised by progressive inflammation and fibrosis throughout the retroperitoneum, often leading to compression of abdominal viscera and entrapment of the ureters or arteriovenous system.^{1 2} RPF may present with fever, weight loss, fatigue, lower extremity oedema, abdominal and flank pain and renal insufficiency.¹ Occasionally, RPF manifests beyond the retroperitoneum at sites including the mediastinum, thyroid gland, maxillary sinuses and retrobulbar region.³ In some cases, RPF has been characterised as part of a systemic condition known as IgG4-related systemic disease (IgG4-RSD), based upon a histopathology of lymphoplasmacytic infiltration with abundant IgG4-positive plasma cells and fibrosis in various organs.⁴ RPF is idiopathic in over 75% of cases,³ but may also occur secondary to underlying malignancy (i.e., lymphoma, sarcoma or carcinoid), medication (i.e., methysergide, β -blockers and hydralazine), infection (i.e., tuberculosis, histoplasmosis and actinomycosis), or connective tissue disorder.^{1 2} Treatment of secondary RPF is geared towards management of the underlying disease. Corticosteroids are usually effective in suppressing the inflammatory process in idiopathic RPF, although various immunomodulatory agents have been used when response to steroids is suboptimal.^{2 3}

Uveitis encompasses a heterogeneous group of intraocular inflammatory disorders that may lead to vision-threatening complications. Uveitis is idiopathic in up to 50% of patients,⁵ or may be associated with various infections, autoimmune disorders, malignancies or medications.⁶ To our knowledge, idiopathic RPF has been reported only once in association with isolated uveitis in the absence of underlying systemic disease.⁷ Herein we describe a patient presenting with recurrent anterior uveitis, followed by systemic symptoms ultimately leading to a diagnosis of idiopathic RPF.

CASE PRESENTATION

A 55-year-old black female with type 2 diabetes mellitus and benign thyroid nodules presented with acute left eye redness, pain and photophobia. She was diagnosed with left anterior uveitis and treated successfully with prednisolone acetate and bromfenac eye drops. Four months later, she developed recurrent left eye symptoms and was treated topically for left anterior uveitis and episcleritis.

Table 1 Laboratory data at initial rheumatology presentation

Parameter (units)	Value	Normal range
WBC ($\times 10^3$ /mcl)	6.3	4.0–10.5
Haemoglobin (g/dl)	12.2	11.5–15
Platelets ($\times 10^3$ /mcl)	361	140–415
BUN (mg/dl)	20	5–26
Creatinine (mg/dl)	1.19	0.57–1
GFR (ml/min/1.73)	57	>59
Serum protein (g/dl)	7.2	6–8.5
Albumin (g/dl)	3.8	3.5–5.5
ESR (mm/h)	58	0–30
C-reactive protein (mg/l)	7.5	0–4.9
Rheumatoid factor (IU/ml)	7.7	0–13.9
ANA (AU/ml)	49	0–99
Anti-ds DNA (IU/ml)	1	0–9
C3 (mg/dl)	143	90–180
C4 (mg/dl)	42	9–36
CH50 (U/ml)	60	22–60
ACE (U/l)	16	12–68
ANCA titre	<1:20	<1:20
HLA-B27	Negative	
Lyme IgG/IgM antibody	<0.91	<0.91
RPR	Non reactive	Non reactive
<i>T. pallidum</i> antibody	Non reactive	Non reactive

ACE, angiotensin converting enzyme; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; HLA, human leukocyte antigen; RPR, rapid plasma reagin; WBC, white blood cell.

Figure 1 (A) Retroperitoneal mass associated with left hydroureter and hydronephrosis (white arrow). (B) Multiple foci of amorphous soft tissue densities noted along the left pelvic wall and left common/internal iliac region (black arrow). (C) Resolution of left hydroureter and hydronephrosis following laparotomy and 2 months of steroid treatment (white arrow). The left kidney is atrophic. (D) Decrease in size of soft tissue densities in left pelvic wall and iliac region following 2 months of steroid treatment (black arrow).

Two weeks later, she developed right eye pain with redness, and was diagnosed with right eye anterior uveitis. Celecoxib 200 mg twice daily was added, with slow improvement.

Six months following her initial uveitis presentation, she developed progressive left lower extremity painless swelling, and presented for rheumatologic evaluation. She denied fevers, chills, night sweats, weight loss, cough, chest pain, shortness of breath, rash, sicca symptoms, Raynaud's phenomenon, arthritis, muscle pain or stiffness, fatigue, numbness or tingling, or change in urinary or bowel habits. She did report sinus congestion, rare epistaxis and occasional nasal ulcerations in the past, but denied such symptoms at presentation.

INVESTIGATIONS

Laboratory evaluations were notable for elevated inflammatory markers and mild renal insufficiency. All serologic testing performed was negative (table 1). Urinalysis was negative for protein and cells. Total IgG level was 780 mg/dl (normal 700–1600 mg/dl), IgG4 level was 4 mg/dl (normal 1–291 mg/dl) and IgM, IgA and IgG1–IgG3 subtypes were within normal range. An intradermal skin test for tuberculosis was negative within the preceding year.

Ultrasound of her left lower extremity was negative for deep venous thrombosis. CT scan of her abdomen and pelvis demonstrated multiple foci of amorphous soft tissue densities in the right lower quadrant small bowel mesentery, left pelvic sidewall and left common and internal iliac region, associated with left-sided hydroureter and hydronephrosis (figure 1A,B). Chest radiograph was without evidence of hilar lymphadenopathy or infiltrates. A subsequent CT scan of her chest revealed a few subcentimeter pulmonary nodules; there was no significant mediastinal or axillary lymphadenopathy, and no evidence of parenchymal disease. Colonoscopy demonstrated sigmoid diverticulosis. The patient ultimately underwent exploratory laparotomy and partial small bowel resection. Biopsy of a right lower quadrant retroperitoneal mass revealed fibrovascular tissue admixed with lymphocytes and plasma cells (figure 2). Immunohistochemical stains for lymphoma were negative, and histopathology was consistent with RPF. Staining for IgG4 was not performed.

DIFFERENTIAL DIAGNOSIS

The diagnostic considerations for systemic disease associated with recurrent uveitis are protean, including infections (i.e., Lyme disease, tuberculosis, syphilis, herpesviruses

Figure 2 Biopsy of a retroperitoneal mass (hematoxylin and eosin). Thick bands of anastomosing hyalinised fibrous collagen are admixed with lymphoplasmacytic infiltrates and surround adipose tissue. Standard immunohistochemical stains for lymphoma were negative. Staining for IgG4 was not performed.

and toxoplasmosis), autoimmune diseases (i.e., ankylosing spondylitis, sarcoidosis, inflammatory bowel disease, systemic lupus erythematosus and vasculitis) and malignancies.^{5–6} Clinically, our patient described prior sinusitis, nasal ulcers and epistaxis, which could support a diagnosis of granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis). Although GPA has been associated with RPF,^{8–9} in our patient antineutrophil cytoplasmic antibodies were negative and there were no additional signs or symptoms suggestive of systemic vasculitis. There was also concern for sarcoidosis, but this was deemed less likely in the absence of classical pulmonary findings and a normal angiotensin converting enzyme level (table 1).

Prior to her laparotomy, there was significant concern for disseminated abdominopelvic malignancy or lymphoma. However, the absence of ascites and other significant constitutional symptoms did not support this. Following histopathologic analysis and in the absence of obvious comorbid systemic illness, she was diagnosed with idiopathic RPF. The temporal association with her recurrent uveitis was intriguing.

TREATMENT

Upon diagnosing idiopathic retroperitoneal fibrosis and sufficiently excluding associated infections or malignancy, the patient was treated with prednisone 40 mg daily. Her insulin regimen was adjusted to manage the resultant steroid dysglycemia complicating her diabetes.

OUTCOME AND FOLLOW-UP

Follow-up CT scan of her abdomen and pelvis 2 months after initiation of steroid treatment revealed decreased size of all retroperitoneal masses, with interval resolution

of the left hydroureter and hydronephrosis (figure 1C,D). Her erythrocyte sedimentation rate and C-reactive protein normalised to 1 mm/h and 4.4 mg/l, respectively. All retroperitoneal masses continued to decrease in size on a follow-up CT scan 4 months later (not shown). Her uveitis resolved completely with oral prednisone and has not since recurred.

The patient has undergone a gradual prednisone taper lasting over 1 year, and presently takes prednisone 5 mg daily. Retroperitoneal masses have stabilised and there has been no further radiographic concern for obstruction. Pulmonary nodules have remained stable on serial chest CT scans performed approximately every 6 months. Steroid-sparing therapy with oral colchicine was attempted,³ but was complicated by severe diarrhoea.

DISCUSSION

A systemic aetiology for our patient's recurrent uveitis remained elusive until she later presented with left lower extremity oedema. She was found to have mesenteric and retroperitoneal masses causing left iliac compression and left hydroureter, and ultimately diagnosed with RPF upon laparotomy and biopsy. As anterior uveitis is one of the most common inflammatory disorders of the eye, the observed association between her recurrent uveitis and subsequent diagnosis of retroperitoneal fibrosis may have been due to chance. However, various autoimmune diseases typically associated with uveitis have been reported in the setting of RPF, including ankylosing spondylitis, inflammatory bowel disease and sarcoidosis.^{10–12} Thus, we postulate that the association between uveitis and RPF is clinically significant, and further investigation into shared immunopathogenic mechanisms between RPF and uveitis is warranted.

Upon diagnosis of idiopathic RPF, it was felt that her pulmonary and thyroid nodules may have been associated manifestations of this disease. Such manifestations have been reported in association with RPF, as well as with the IgG4-RSD.^{3 4} Polyclonal elevations of serum IgG4 are found in many patients with the IgG4-RSD, but IgG4 level in this patient was within the lower range of normal. Since IgG4 staining of her retroperitoneal biopsy was not performed, a diagnosis of IgG4-RSD could not be confirmed.

RPF has been associated with other ocular disorders including episcleritis, orbital pseudotumour and xanthomatosis.^{13–15} To our knowledge, this constitutes the second report in the English literature of RPF associated with isolated uveitis, in the absence of an underlying systemic disorder.⁷ Our case supports the consideration of RPF in the diagnostic evaluation of recurrent uveitis in appropriate patients, such as those presenting with abdominopelvic, renal or lower extremity signs and symptoms.

Learning points

- ▶ The diagnostic investigation of systemic illness associated with recurrent uveitis merits consideration of various infections, autoimmune diseases and malignancies.
- ▶ Retroperitoneal fibrosis (RPF) is a rare disorder characterised by progressive inflammation and fibrosis throughout the retroperitoneum, and may manifest at sites beyond the retroperitoneum.
- ▶ Various ocular disorders, including uveitis, may be clinically associated with RPF.
- ▶ Albeit rare, RPF should be considered in the broad diagnostic investigation of recurrent uveitis in appropriate patients, such as those with abdominopelvic or lower extremity complaints.

Competing interests None.

Patient consent Obtained.

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