Retroperitoneal Fibrosis

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Objectives

1. Define retroperitoneal fibrosis and review its epidemiology
2. Describe the pathogenesis of retroperitoneal fibrosis
3. Discuss the clinical manifestations and evaluation of patients with retroperitoneal fibrosis
4. Review current medical and surgical strategies for treatment of retroperitoneal fibrosis
Case: Mrs. VN

- 58 F, previously healthy
  - Visiting Paris and became oligoanuric
  - SCr 700
  - US done in hospital: bilat hydro, ?RPF
  - Bilateral ureteral stents
  - Denied constitutional Sx
- PMHx: Hypothyroid PSHx: Thyroidectomy
- Meds: Thyroxine, esomeprazole
- All: NKDA
- Social: Retired analyst, distant smoking Hx

Mrs. VN

- Physical Exam:
  - No abnormalities detected
  - Abdomen benign, NT, no masses

- Plan:
  - Basic blood work
  - CT abdo/pevis
**CT KUB**

![CT KUB Image]

**Labs**

- Hg: 103
- SCr: 160 (Nov 3) → 181 (Nov 30) → 185 (Jan 3)
- ESR: 16 (N <30)

**Biopsy:**

- Technically challenging given without contrast
- Risk of contrast induced nephropathy felt to be significant in light of poor renal function
- Risk of malignancy (eg. Lymphoma) felt <10%
- Deferred
Mrs. VN

• Medical therapy initiated (Dec 2011)
  – Prednisone 50mg PO every other day x 2mos then taper
• Pt requested definitive therapy w ureterolysis
  – Plans made to r/a this in spring
  – Monitor w monthly blood work and stent change until this time.

Mrs VN (Jan 1, 2012)
History

- Initially described by Albarran (1905)
- Defined as disease entity by Ormond (1948)
- Known by a number of names:
  - Ormond’s disease
  - Periureteritis fibrosa
  - Periureteritis plastica
  - Chronic periureteritis
  - Sclerosing retroperitoneal granuloma
  - Fibrous retroperitonitis

Epidemiology

- Incidence estimated <1/100,000*
- Men are 2-3x more affected
- No ethnic predilection
- No familial clustering
- Idiopathic (2/3) vs. Secondary (1/3)
- Most common between 40-60yrs of age
  - Exceptions exist at either extremes of...

Epidemiology

Idiopathic retroperitoneal fibrosis in children.
Chan SL, Johnson HW, McLoughlin MG.
[Case Reports. Journal Article]
UI: 458972

Authors Full Name
Chan, S L. Johnson, H W. McLoughlin, M G.

View Abstract

AB A case of idiopathic retroperitoneal fibrosis in an 11-year-old boy is presented. A review of 7 previous case reports revealed that there was no characteristic presentation in this disease process and that the diagnosis usually is suspected on an excretory urogram. The treatment is primarily surgical but corticosteroids may be helpful in selective cases.

Anatomy

• Usually centered over L4/L5
  – Caudally to sacral promontory, occasionally extending along iliac vessels
  – Cephalad to renal hilum
  – Laterally to outer edge of psoas
**Extension and spread**

- Fibrosis may extend outside of retroperitoneum in 15%
- May extend as high as mediastinum or as low as the common iliac bifurcation

**Etiology: Idiopathic RPF**

Two leading theories for pathogenesis:

1. Local: exaggerated immune-mediated peri-aortitis
Etiology: Idiopathic RPF

1) Local peri-aortitis
   - Macrophages present oxidized LDL and ceroid from atherosclerotic plaque to B and T cells
   - Lymphocyte activation
   - Inflammatory reaction spreads to peri-aortic retroperitoneum

Localized peri-aortitis:

- Problematic because:
  - Constitutional symptoms
  - Positive autoantibodies
  - Elevated acute phase reactants
  - Associated autoimmune conditions
- May imply manifestation of a systemic autoimmune condition rather than an exaggerated local process
IRPF: Associated Conditions

- Fibrotic processes found elsewhere in 15%
- Other inflammatory/autoimmune
  - Metachronous vs. synchronous; underDx → ?frequency

| Reidel’s fibrosing thyroiditis | Amyloidosis |
| Orbital pseudotumor            | Erdheim-Chester disease |
| Sclerosing cholangitis         | Polyarteritis nodosa   |
| Sclerosing mediastinitis       | Systemic Lupus Erythematos |
| Mesenteric fibrosis            | Hashimoto Thyroiditis  |
| Autoimmune pancreatitis        | Glomerulonephritis     |
| Ankylosing spondylitis         | Small/medium vessel vasculitis |
| Rheumatoid arthritis           | Uveitis                |
| Primary biliary sclerosis      | Psoriasis              |

Etiology: Idiopathic RPF

- Other possible mechanisms:
  - Anti-fibroblast antibodies
    - Shown to activate fibroblast activity in vitro
    - Present in about 1/3 of those with IRPF
  - Primary B-Cell disorder
    - Biopsies from those with IRPF have show clonal and oligoclonal B-cells
  - Genetic
    - HLA-DR1*03 allele associated with IRPF and other autoimmune conditions (T1DM, myasthenia gravis, SLE)
Secondary Causes

### Table 40-2.

**Suspected Causes of Retroperitoneal Fibrosis**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Inflammatory processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methysergide</td>
<td>Ascending lymphangitis</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Chronic inflammatory bowel disease</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Asbestosis</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>LSD</td>
<td>Erdheim-Chester disease</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>β Blockers</td>
<td>Retroperitoneal fibrosis plaque</td>
</tr>
<tr>
<td>Ergotamine alkaloids</td>
<td>Abdominal and pelvic surgery</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Ruptured visera</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Henoch-Schönlein purpura with hemorrhage</td>
</tr>
<tr>
<td>Pergolide</td>
<td>Periarteritis</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Aortic or iliac artery aneurysm</td>
</tr>
<tr>
<td>Chemicals</td>
<td>Inflammatory response to advanced atherosclerosis</td>
</tr>
<tr>
<td>Avitene</td>
<td>Collagen vascular disease</td>
</tr>
<tr>
<td>Methyl methacrylate</td>
<td>Infection</td>
</tr>
<tr>
<td>Talcum powder</td>
<td>Gonorrhea</td>
</tr>
<tr>
<td>Retroperitoneal tumors</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Chronic urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td>Radiation injury</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Biliary tract disease</td>
</tr>
<tr>
<td></td>
<td>Endometriosis</td>
</tr>
</tbody>
</table>

**Medications (most common)**

- **Ergot Alkaloids** (methysergide):
  - Reported in up to 12%\(^1\)
  - also associated with fibrotic reactions in pericardium, pleura and lungs
  - pathogenesis: ?serotonin mediated
- **Dopamine agonists** (methylprednisolone, pergolide)
- Other: analgesics, β-Blockers, Hydralazine, ...

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Medications

**TABLE 2. Patients With Traditional Risk Factors for RPF**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior radiation</td>
<td>3/48 (6)</td>
</tr>
<tr>
<td>Prior use of methylsergide</td>
<td>0/48 (0)</td>
</tr>
<tr>
<td>Prior use of pergolide</td>
<td>0/48 (0)</td>
</tr>
<tr>
<td>Prior use of β-blockers</td>
<td>4/48 (8)</td>
</tr>
<tr>
<td>Prior use of hydralazine</td>
<td>0/48 (0)</td>
</tr>
<tr>
<td>History of tuberculosis</td>
<td>0/48 (0)</td>
</tr>
<tr>
<td>History of histoplasmosis</td>
<td>0/48 (0)</td>
</tr>
<tr>
<td>History of actinomyces</td>
<td>0/48 (0)</td>
</tr>
<tr>
<td>Prior abdominal or pelvic surgery</td>
<td>15/48 (31)</td>
</tr>
<tr>
<td>Occupation with risk of asbestos exposure</td>
<td>6/48 (12.5)</td>
</tr>
</tbody>
</table>

*Scheel and Feeley. Retroperitoneal Fibrosis: the clinical, laboratory, and radiographic presentation. Medicine 88(4) 2009*

Malignancy (8-10%)

- Desmoplastic response to retroperitoneal neoplasms
  - Primary: HL, NHL, sarcomas
  - Secondary: prostate, breast, colon
- Carcinoid tumors:
  - serotonin mediated mechanism
  - profibrogenic growth factors (PDGF, IGF, EGF, TGF a/b)
Clinical Manifestations

- Non-specific
- Reflect extent of disease and organs involved
- Typically grouped as:
  1. **Local**: due to the mechanical and compressive effects of the retroperitoneal mass
  2. **Systemic**: owing to the inflammatory nature of the disease

<table>
<thead>
<tr>
<th>Local</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (back, flank, abdo)</td>
<td>Fever</td>
</tr>
<tr>
<td>Varico-/hydrocele</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Testicular pain</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Constipation</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Frequency</td>
<td>N/V</td>
</tr>
<tr>
<td>Dysuria</td>
<td>Malaise</td>
</tr>
<tr>
<td>Leg edema</td>
<td></td>
</tr>
<tr>
<td>Claudication</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td></td>
</tr>
<tr>
<td>Poly vs Oligo-uria</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Manifestations

- Ureteral obstruction in 60-80%\(^1\)
  - Typically at level of common iliac vessels
- Often bilateral
- Subsequent acute or chronic renal failure is the most common and serious complication:
  - Uremia, oligoanuria


Lab Findings

- Lack diagnostic hematologic or biochemical values
  - ESR and CRP elevated in 80-100%\(^1\)
  - (+) Autoantibodies
  - Azotemia
  - Anemia
- Malignancy:
  - Hypercalcemia, Neoplastic markers, (+) FOB

Diagnostic Imaging

- Diagnosis of RPF primarily made with imaging
  - Ultrasound
  - CT
  - MRI
  - PET
  - IV Urography
  - Retrograde or antegrade pyelography
- Lack ability to discern 1° from 2°

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Diagnostic Imaging

**Ultrasound:**
- First line in Pt with renal impairment
- Hypoechoic, periaortic mass
- Associated hydronephrosis
- Limited by: obesity, bowel gas, bony structures

Sonography in the diagnosis of retroperitoneal fibrosis.
Sanders RC. Duffy T. McLoughlin MG. Walsh PC.
[Case Reports. Journal Article]
UI: 926270
Authors Full Name
Sanders, R C. Duffy, T. McLoughlin, M G. Walsh, P C.
View Abstract
AB The ultrasonic appearance of retroperitoneal fibrosis is characteristic: a smooth-bordered and relatively echo-free mass anterior to the sacral promontory. Sonography can be used to confirm the diagnosis, follow response to therapy and detect hydrenephrotic changes in the kidneys.

Diagnostic Imaging

Contrast-enhanced CT:
• Examination of choice if renal function permits:
  – Homogeneous plaque encasing RP structures
  – Similar attenuation to muscle
  – Contrast enhancement
• Extent of fibrosis, Lymphadenopathy, Malignancy
• Malignant RPF: ureters often displaced laterally, aorta anteriorly
Diagnostic Imaging

- Mass encasing aorta
- Left hydroureteronephrosis
- Mass encasing common iliac arteries


Diagnostic Imaging

MRI
- Advantages:
  - No iodinated contrast or radiation
  - Superior soft-tissue resolution

- Use of gadolinium may demonstrate increased enhancement in acute phase (monitor Dz activity)

- Heterogeneous signal on T2 may suggest malignant process
Diagnostic Imaging

**T1 weighted:**
- low signal (hypointense to mm)

**T2 weighted:**
- Acute phase: ↑T2
- Mature phase: ↓T2


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**Diagnostic Imaging**

**PET (18F-FDG):**
- Extent of Dz
- Relapse
- Tx response
- Cons: Low specificity, Expensive

**Diagnostic Imaging**

**IV Urography:**

1. Proximal hydro
2. Medial deviation
   - Normal in 20%
3. Extrinsic compression
   - Not specific (ureteral tumor, LAD, other inflammm process)

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**Diagnostic Imaging**

Retro/Antegrade Pyelography:

- Similar triad as IVP
- May use in renal impairment
- Performed with stent/NT placement
- Assess level and extent of ureteral involvement

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Campbell’s Urology. 10th Ed.
Differential Diagnosis

- **Retroperitoneal lymphoma***
- Sclerosing mesenteritis
- Desmoid type fibromatosis
- Inflammatory myofibroblastic tumor
- Erdheim-Chester disease
- Well-differentiated liposarcoma, sclerosing variant

Biopsy

- No accepted guidelines
- Confirm Dx and r/o malignancy
  - unable to do so with certainty any other way
- Strong indications:
  - Atypical location of mass
  - Work-up raises suspicion of underlying malignancy
  - Poor response to initial therapy
  - Undergoing surgery
    - At time of open/laparoscopic procedure
Biopsy

- CT guided percutaneous biopsy
  - Preferred
  - Core tissue Bx (e.g. Tru-Cut needle) preferred over FNA
  - Risk of sampling error (false negative)
- Surgical Biopsy
  - Inconclusive core Bx
  - Undergoing ureterolysis (send frozen)
  - Reduced sampling error vs perc Bx (more tissue)

Histopathology

- Grossly: white-tan, hard, ‘woody’ plaque
- Features of idiopathic and secondary RPF often indistinguishable
- Findings on biopsy reflect stage of disease and area of sample:
  - Early/margins: inflammatory component
  - Late/central: fibrosis is main feature
In some instances, idiopathic retroperitoneal fibrosis shows atypical localisations, which might be challenging and requires histological assessment.

Histopathology

- Sclerotic tissue
  - Fibroblasts
  - Type 1 collagen
- Inflammatory infiltrate
  - Lymphocytes
  - Plasma cells
  - Eosinophils
- Nodular (arrow) and diffuse pattern


Management

- Goals:
  1. Relieve obstruction
  2. Halt progression of fibrosis
  3. Prevent recurrence
  4. Interrupt acute-phase reaction and systemic manifestations
Initial Management

• Hydronephrosis, uremia:
  – Urgent decompression
    • Stents: improved QoL, retrograde studies
    • NT: critically ill
  – Close monitoring:
    • POD with appropriate fluid and electrolyte replacement
    • Renal function

Management

• Secondary RPF:
  – Tx underlying cause (if reversible)
  – Consider glucocorticoids if:
    • Severe manifestations of disease (eg. obstruction)
    • No improvement on follow-up imaging in 3-4mos.
  – Consider surgery if systemic therapy not indicated or ineffective
Management

• Idiopathic RPF: medical vs. surgical
  – Medical Tx has become 1st line:
    • Demonstrated good response
    • Morbidity of ureterolysis
    • Accuracy of image guided biopsy
    • Increasingly sensitive imaging modalities for Dx and f/u
  – No RCTs comparing the two

Medical Management

• Glucocorticoids:
  – Primary therapy for IRPF
  – Often used alone with no additional Tx needed
  – No consensus for optimal dose or duration
  – No established predictors for response
  – Mechanism:
    • Suppress cytokine release of acute-phase reaction
    • Inhibit collagen synthesis and maturation
    • Reduce inflammatory component

Medical Management

• Corticosteroids:
  – 3 largest studies with prednisone as monotherapy \(^1,2,3\):
    • >90% remission; relapse 11-25%
    • 30-60mg/day with tapering dose, sometimes up to 2yrs

– Response:
  • Pain and constitutional Sx
  • Size of RP mass
  • ESR, CRP, renal function/obstruction


Medical Management

• Vaglio and colleagues (2011):
  – 39 patients with new Dx of IRPF
    • Prednisone induction: 1mg/kg/day x 1month
    • 36 of 39 achieved remission
    • Those with remission randomized to further 8 months:
      – Tapering dose of prednisone, or;
      – Tamoxifen
    • Primary endpoint: relapse rate at 8 months
      – Prednisone: relapse in 1 of 18
      – Tamoxifen: relapse in 7 of 18 (5/7 remission with prednisone)

Medical Management

- Failure to respond:
  - Absence of clinical or radiographic improvement within 4-6 weeks of initiation:
    - Repeat evaluation with CT and Bx → verify Dx
  - Dx confirmed:
    - Continue high dose steroid (1mg/kg/day) x 4wks then taper down over 2-4months
    - Add additional medical therapy
    - Surgery
Medical Management

Immunosuppressive agents:
- Azathioprine
- Cyclophosphamide
- Cyclosporine
- Methotrexate
- Mycophenolate mofetil
- Combined with steroids to ↓ dose/duration

Medical Management:

Tamoxifen:
- estrogen receptor independent antifibrotic and antiangiogenic effects via TGF-B
  - Effective in regression of desmoid tumors
- Has been used as monotherapy: 74% response\(^1\)
- Maintenance with tamoxifen shown inferior to prednisone\(^2\) → indicated if:
  - Patients with C/I to steroids (DM, osteoporosis, PUD, infx)
  - Steroid sparing agent, poor response to steroids

Surgery

• Reserved use:
  1. Failed endoscopic relief of obstruction
  2. Obtain definitive Dx if malignancy suspected
  3. Failure of medical therapy

• Disadvantages:
  – No effect on systemic manifestations
  – May recur in up to half who have surgery alone

Open ureterolysis:
• Place ureteral stents pre-op to aid identification and dissection
• Midline, transperitoneal incision
  – consider bilateral ureterolysis even if unilateral Dz
• Mobilize colon medially
• Deep biopsies for frozen and permanent
• Dissect from distal, non-dilated segment proximally to normal tissue
Open Ureterolysis

- Ureteral excision usually unnecessary as not typically an invasive process
- If needed:
  - Ureteroureterostomy
  - Psoas hitch
  - Boari flap
  - Auto-transplantation
  - Ileal (or appendiceal) interposition
  - Nephrectomy

Ureteral Protection

Omental Wrap:
- Offers greatest protection,
- Provides blood supply to help prevent ischemia
Laparoscopic Ureterolysis

- First reported by Kavoussi (1992)
- Elashry et al. (J Urol 1996): Open v Lap
  - Concluded less morbid with advantages of MIS
  - 15% conversion
  - Equally effective (92% obstruction-free at 26mos)

- May be technically challenging


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Laparoscopic Ureterolysis

Srinivasan et al. (J Urol 2008):
- 70 patients with RPF, comparable pre-op variables
  - 34 lap vs 36 open (17.6% conversion)
  - Non-Sig differences in operative outcomes for:
    - OR time
    - Complication rate and obstruction free rate
    - EBL and transfusion requirements
    - LOS
  - Subgroup analysis of those with idiopathic RPF:
    - Reduced transfusion (3.4% v 13.7%) and
    - LOS (3.4d v 10.9d)
  - Conclusion:
    - comparable to open and must decide on case-by-case basis

Post-Op Considerations

- Ureteral Stricture:
- Disease recurrence
  - May benefit from post-operative steroids
- Long term f/u is warranted

Summary

1. Uncommon, incompletely understood, but treatable
2. Challenge to diagnose
3. Exclude important secondary causes
4. Steroids are primary treatment
5. Long-term surveillance