The Medical & Surgical Management of Retroperitoneal Fibrosis in the Minimally Invasive Era

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Disclosures

- None
Objectives

- Describe the typical presentation and pathophysiology of retroperitoneal fibrosis (RPF)

- Explain the differential diagnosis and typical imaging findings of RPF

- Discuss options for medical and surgical management for RPF and understand the pros and cons of each approach

- Demonstrate tips and tricks for minimally-invasive surgical management of RPF
Background

• Development of extensive fibrosis throughout retroperitoneum, typically centered over anterior surface of the 4th-5th lumbar vertebrae —> Entrapment and obstruction of retroperitoneal structures

• Incidence 1:200,000-1:500,000 / year, with peak incidence in patients 50-70 years old and M:F ratio of ~ 3:1

• Causes
  • ~70% idiopathic (Ormond’s disease)
  • 8% malignancy: Hodgkin or Non-Hodgkin lymphomas, myeloma, retroperitoneal metastases from prostate, breast, stomach, carcinoid, or colon cancer
  • Secondary to other factors such as infections (TB, Actinomycosis), trauma, radiotherapy, surgery, environmental exposures (tobacco, asbestos), and certain drugs (methysergid, bromocriptin, ergotamine, methyldopa, hydralazine, analgesics, β-blockers)

http://www.baus.org.uk/
Diagnostic Evaluation

- Because of nonspecific nature of clinical manifestations (CKD, HTN) and paucity of physical manifestations (dull lower back and flank pain), there is often considerable delay between onset of disease and diagnosis, which leads to late complications of advanced RPF.

- Laboratory studies have low sensitivity and specificity, but ESR and CRP may be useful to monitor treatment response (elevated in up to 80% cases).

- Imaging is essential for diagnosis and to monitor treatment response in RPF.

- Ureteral involvement reported in 80-100% of cases and may cause secondary acute or chronic renal failure.

- Tissue biopsy needed to confirm diagnosis and exclude mimics.
• CT most commonly used because it provides information on adjacent organs and vascular structures.
• Homogenous, infiltrating periaortic mass isodense to psoas muscle with mild enhancement and compressing or displacing ureter medial highly suggestive of RPF.
  • Anterior displacement of aorta-iliac vessels or lateral displacement of ureters by mass should heighten suspicion of secondary form
  • Presence of inhomogeneous signal in T2-weighted images —> likely secondary to malignant process
• **Hypointense** periaortic tissue on T1-weighted sequence and **hyperintense** tissue (for active disease) on T2-weighted sequences.

• **Active disease enhances** on MRI, but long-standing plaques show poor enhancement. Degree of enhancement on T2 MRI can be used to monitor disease activity and treatment response.

• **ADC** values may provide useful information in differentiating benign vs. malignant RPF.

• Major advantages of MRI over CT are superior contrast resolution and lack of exposure to iodizing radiation in patients who need frequent followup imaging.
Retrograde Pyelography

- Lack of distensibility without discrete ureteral stricture, and medial deviation of middle-third of ureter
Differential Diagnosis

<table>
<thead>
<tr>
<th>Benign retroperitoneal fibrosis</th>
<th>Malignant retroperitoneal fibrosis</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>Secondary to</td>
<td>Non Hodgkin lymphoma, carcinoid, multiple myeloma, pancreas-carcinoma, sarcoma</td>
</tr>
<tr>
<td>Secondary to</td>
<td>Drugs</td>
<td>retroperitoneal fibromatosis</td>
</tr>
<tr>
<td></td>
<td>Aortic aneurysm</td>
<td>inflammatory myofibroblastic tumour (inflammatory pseudotumour)</td>
</tr>
<tr>
<td></td>
<td>Retroperitoneal Infection</td>
<td>inflammatory malignant fibrous histiocytoma</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td>amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Retroperitoneal radiation therapy</td>
<td>infectious spondylodiscitis</td>
</tr>
<tr>
<td></td>
<td>Surgery / trauma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
<td></td>
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</tbody>
</table>

Imaging features that suggest malignant pathology include lateral displacement of the ureter, anterior displacement of the aorta, local bone destruction, and a large bulky lesion.
RPF Algorithm - 2006

Vaglio et al. 2006
RPF Algorithm - 2018

Biyani et al. 2017
Medical Management

Established Protocols:
• Corticosteroids (prednisolone)
• Tamoxifen
• Azathioprine

** Corticosteroids and azathioprine are most useful in patients with signs of inflammation (↑ESR, ↑CRP, elevated WBC count, and + ANA)

Experimental Protocols:
• Cyclophosphamide
• Mycophenolate mofetil
• Cyclosporine
• Medroxyprogesterone acetate
• Progesterone
Corticosteroids

- Ross and Tinckler first reported the use of corticosteroids in treatment of RPF in 1958
- Beneficial effect due to anti-inflammatory action and ability to inhibit fibrotic tissue maturation
- Standard protocol is prednisolone at 40-60 mg/d tapered to 10 mg/d within 2-3 months and discontinued after 12-24 months
- Timely dose reductions and cessation are important because of adverse effects associated with long-term steroid use
- Despite their proven success, using steroids as first-line therapy in RPF remains controversial because many clinicians believe that multiple deep biopsies are still essential to exclude malignancy
Corticosteroids

Long-term corticosteroid treatment can cause an array of adverse effects, including:

- Obesity
- Cushing syndrome
- Increased susceptibility to infections
- Hypertension
- Osteoporosis
- Cataracts
- Peptic ulcer disease
- Diabetes mellitus
Tamoxifen

- Clarke et al first described tamoxifen, a nonsteroidal antiestrogen, for treatment of RPF in 1991
- Various studies have used tamoxifen with a variable protocol (10-40 mg for 6 mo to 3 y)
- Tamoxifen increases synthesis and secretion of TGF-β, an inhibitory growth factor
- Van der Bilt et al - Retrospective study of 118 patients with RPF
  - Symptoms improved in 2 weeks with steroids vs. 4 weeks with tamoxifen
  - Mass regression at 1st follow-up CT observed in 84% of steroid cohort vs. 68% of tamoxifen cohort
  - Recurrence rate after successful initial treatment 63% with steroids vs. 21% with tamoxifen
- Adverse effect profile of tamoxifen is relatively low, but they are associated with increased risk of thromboembolism and ovarian cancer
Other Medical Therapy

**Azathioprine**

- Immunomodulator used for rheumatoid arthritis, Crohn's disease, ulcerative colitis, and kidney transplants to prevent rejection
- Reported use when steroid therapy has failed and as steroid-sparing drug
- Case reports and small series have used 6-week course of azathioprine (150 mg/d)
- Side effects include bone marrow suppression, GI upset, and increased risk of lymphoma

**Mycophenolate Mofetil**

- Immunosuppressive agent that blocks proliferation of T cells and B cells
- Case series have used MMF (1000 mg BID) in combination with prednisolone as steroid-sparing therapy with MMF (1000 mg bid) for 6-24 months
- Peri-aortic mass decreased by >25% in 89% of patients
- Complications included increased risk of recurrent UTIs and GI disturbances
## Contemporary Series of Medical Therapy for RPF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>References</th>
<th>No. of patients</th>
<th>Follow up (CT, MSL, other)</th>
<th>Side effects</th>
<th>Recurrence</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodiabone</td>
<td>Kasdi et al. (2001)</td>
<td>12</td>
<td>95/12 cases regression</td>
<td>Steroid related side effects</td>
<td>1 patient</td>
<td>3 cases</td>
</tr>
<tr>
<td></td>
<td>Van Brummel et al. (2007)</td>
<td>24</td>
<td>5 cases complete regression, 7 cases significant regression, 7 cases moderate regression</td>
<td>Steroid related side effects, 5 cases of anaemia side effects</td>
<td>31 patients</td>
<td>6 cases</td>
</tr>
<tr>
<td></td>
<td>Roy et al. (2003)</td>
<td>34</td>
<td>18/26 resolution (clinical, renal function tests and inflammation markers)</td>
<td>Steroid related side effects</td>
<td>7 patients</td>
<td>1 death (IHF related)</td>
</tr>
<tr>
<td>Prodiabone + terbutaline</td>
<td>Van Rooy et al. (2003)</td>
<td>40</td>
<td>15 cases in prodiabone arm/30 cases in terbutaline arm significant regression</td>
<td>Secondary Cushing and hypokalaemia, 6 patients in prodiabone arm</td>
<td>5 cases</td>
<td>4 cases</td>
</tr>
<tr>
<td></td>
<td>Brandt et al. (2011)</td>
<td>24</td>
<td>7 cases in prodiabone arm/8 cases in terbutaline arm significant regression</td>
<td>Steroid related side effects</td>
<td>2 cases treatment type not specified</td>
<td>8 cases</td>
</tr>
<tr>
<td>Prodiabone and colchicine</td>
<td>Menotti et al. (2001)</td>
<td>26</td>
<td>25/26 partial regression</td>
<td>3 cases of steroid effects, retinopathy</td>
<td>7 cases</td>
<td>1 case</td>
</tr>
<tr>
<td>Prodiabone and AZT or cyclophosphamide</td>
<td>Vissu et al. (2009)</td>
<td>15</td>
<td>15/15 partial regression</td>
<td>Steroid related side effects, leucopenia</td>
<td>not specified</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Vissu et al. (2009)</td>
<td>7</td>
<td>4/7 cases significant regression (mean, 79.8 ± 19.7%</td>
<td>Steroid related side effects</td>
<td>7 patients</td>
<td>1 case death by sepsis shock</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>Van Brummel et al. (2003)</td>
<td>16</td>
<td>14/10 partial regression</td>
<td>1 case reversible haematuria</td>
<td>1 patient</td>
<td>5 cases</td>
</tr>
<tr>
<td></td>
<td>Van Brummel et al. (2003)</td>
<td>55</td>
<td>36/55 resistance free survival</td>
<td>2 cases of pulmonary embolism</td>
<td>10 patients</td>
<td>11 cases</td>
</tr>
<tr>
<td>MMF + prodiabone</td>
<td>Soriano et al. (2001)</td>
<td>16</td>
<td>8/10 partial regression</td>
<td>1 case gastrointestinal symptoms, 1 case leucopenia</td>
<td>8 patients</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Soro et al. (2012)</td>
<td>26</td>
<td>20/24 partial regression</td>
<td>3 cases of Herpes zoster</td>
<td>3 patients</td>
<td>3 cases</td>
</tr>
</tbody>
</table>
Follow-up

- Biochemical markers (CRP, ESR, Cr) should be monitored every 4-8 weeks to assess treatment response.

- Radiologic assessment (CT/MRI) is performed every 3 months. Once disease is stabilized, scanning can be repeated at 6-month intervals.

- Recurrence of stenosis has been reported as late as 16 years — long-term follow-up is necessary.

- Patients with renal failure should be referred to nephrologist early in course of their disease and have continued nephrologic follow-up.

- Renal recovery usually observed within first 2 weeks of therapy, but some patients may not regain renal function until much later.
Medical Management:

Take-Home Points

• No currently available medical treatment seems to ‘cure’ idiopathic RPF

• Several medical treatments have been reported, but all carry significant burden related to side effects that have lifelong impact, not quantified by most studies published

• No controlled studies regarding any therapies, making choice of optimal drug subject to trial and error

• Most cohorts assessed very small numbers of patients and level of evidence is weak

• Lack of consensus regarding definition of treatment response and lots of variability in therapeutic objectives

• No universally accepted criteria for defining clinical or imaging ‘remission’ and thus no objective criteria for when to stop steroids or consider failure of medical treatment
Surgical Therapy for RPF
RPF Algorithm - 2018

Biyani et al. 2017
Surgical Therapy

- TEMPORIZING maneuvers recommended in presence of obstructive uropathy
  - PCN
  - Ureteral stent
  
  ***Long-term ureteral stenting is reasonable approach in high-risk and elderly patients, but do not underestimate cumulative risk of repeat general anesthesia every 6-12 months!!

- Definitive surgical management of retroperitoneal fibrosis consists of
  - Unilateral vs. bilateral ureterolysis
  - Biopsy of mass
  - Lateral vs. intraperitoneal transposition vs. omental wrapping

- Purpose of operation is to resolve the obstruction and to exclude underlying malignancy, NOT to treat the retroperitoneal fibrosis

- Surgical technique is not standardized and treatment outcomes largely only evaluate recovery of renal function and hydronephrosis
ARE YOU SERIOUS?
MIS Approach

- Open ureterolysis effective in 90% of patients, but associated with significant morbidity.

- MIS approach offers an equal success rate but with reduced mean hospital stay, use of analgesia, convalescence period, and morbidity.

- No prospective head-to-head comparison between open and lap/robotic ureterolysis in order to show superiority of one approach to the other and also no agreement regarding the need for, and what type of, adjuvant treatment.

- Other surgical techniques have been described, such as ureterolysis and wrapping with Gore-Tex, excision of the ureter and reanastomosis (U-U), posterior preperitoneal flap, and renal autotransplantation.

- Complication rates reported vary between 8 - 16% and include ureteral devascularization, tears and ureteral strictures, ureteral leakage, and urinary fistula, most of them amenable to a conservative approach.

Mufarrij and Stifelman first described robot-assisted laparoscopic ureterolysis with laparoscopic omental wrap in the treatment of idiopathic RPF in 2006.
Robotic Setup

- Camera Port
- 8mm Robotic Port
- 5mm Assistant Port
Alternative Setup

*** Identical to Robotic RPLND set-up for Xi ***
Take-Home Points

- Treatment paradigm still involves initial attempt at medical therapy with steroids or tamoxifen for patients with mild hydronephrosis, + PCN/stenting if abnormal renal function.

- Patients with moderate-severe hydroureteronephrosis should be offered immediate surgical intervention given the low likelihood of success with medical therapy alone.

- May consider adjuvant medical therapy for certain patients following surgery.

- Minimally invasive ureterolysis/U-U-U is now treatment of choice for surgical management of RPF.