
Retroperitoneal fibrosis – an unsolved mystery

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Introduction

Retroperitoneal fibrosis (RPF) is a rare disorder with unclear aetiology, which was first described by a French Urologist, Albarran in 1905 as a cause of ureteral obstruction (1) and by Perard and Orsini in 1937. In 1948 Ormand described 2 cases of ureteral obstruction due to RPF and the disease entity was described as idiopathic retroperitoneal fibrosis which was called after him.

RPF is an uncommon clinical entity with non-specific chronic inflammation causing entrapment of the retroperitoneal structures giving rise to its outcome and complications (2). Due to these presentations earlier it was called by many names such as, peri-aortitis, periureteritis and sclerosing retroperitoneal granuloma (3). Its true incidence is yet to be established, but estimates vary from 1:200,000 to 1:500,000 per year (4). The clinicians should have a high degree of suspicion in order to diagnose this. The imaging investigations has to be interpreted carefully in-order to exclude malignant retroperitoneal fibrosis which accounts to about 8-10% of them (5). Retroperitoneal biopsy has become almost mandatory to confirm before commencing treatment in-order to exclude malignant RPF.

Mainstay of treatment for idiopathic RPF is pharmacotherapy. In-order to achieve a good outcome, early treatment, before renal impairment sets in is mandatory. Non-responders to medical therapy and complicated patients need surgical intervention to minimize renal function deterioration.

Epidemiology

The estimated incidence is 1:200,000 to 1:500,000 per year (4,6). There is a male preponderance (3:1) (7) and it is typically found in the age group of 40-60 years (8). There had been a few cases presenting below the age of 18 as well (9). Almost 70% of RPF cases are Idiopathic with 8 to 10% being malignant and the rest due to inflammation or medication.

Pathology

The macroscopically RPF appears as a pale plaque of fibrotic tissue mass with ill-defined edges in the retroperitoneal space. This usually occurs in the region of lower abdominal aorta, but it also spreads to the regions of the iliac vessels. There had been cases where RPF has occurred in the posterior mediastinum as well. The fibrotic tissue mass encases the aorta, inferior vena cava, iliac vessels and the ureters, which are most susceptible (10), giving rise to its signs, symptoms and complications. RPF also involves the ovaries, ovarian vessels, fallopian tubes and the uterus (11).

The microscopic appearance is of a non-specific inflammation of varying degrees depending on the disease severity. In early stage there will be collagen bundles with capillary proliferation and inflammatory cells. In the late disease it will consists of acellular, avascular, dense fibrotic tissue (12). Immunohistochemistry becomes mandatory in some cases to establish the definitive diagnosis.

Aetiology

A wide variety of causes have been implicated as causes of RPF, but in a majority (~70%) of cases an identifiable cause is not found, categorized as idiopathic RPF (7). The rest of it with a cause can be considered under several categories (Table 1).

Table 1. Aetiology of retroperitoneal fibrosis

1. Idiopathic RPF
 2. Chronic inflammatory conditions
 3. Autoimmune disease related retroperitoneal fibrosis
 4. Trauma to retroperitoneal region
 5. Severe atherosclerosis
 6. Drug induced
 7. Malignant retroperitoneal fibrosis
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Inflammation to the retroperitoneal space can be caused by intra-abdominal conditions like appendicitis, ulcerative colitis, diverticulitis, previous surgical interventions of the retroperitoneum (aortic, uereteric surgery), urine or contrast extravasation and radiotherapy. Injury to this space can give rise to haemorrhage and urine extravasation leading to RPF (13). There had been many instances where a number of autoimmune diseases and connective tissue disorders (Table 2) were co-exciting with RPF, suggesting its aetiology (14).

Table 2. Autoimmune and connective tissue disorders associated with RPF

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- Systemic lupus erythematosus
 - Rheumatoid arthritis
 - Scleroderma
 - Systemic vasculitis:
 - Takayasu’s disease
 - Henoch-Schonleinpurpura
 - Polyarteritisnodosa
 - Recurrent polychondritis
 - Immune-complex glomerulonephritis
 - Immune thrombocytopenia
 - Autoimmune phenomena:
 - Positive direct Coombs; ANA positivity
 - ANCA positivity (c-ANCA, anti-Pr3; p-ANCA, anti-MPO)
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Table 3. Drugs which are suspected to cause RPF

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- Ergot-alkaloids: methysergide, bromocriptine, dihydro-ergotamine, pergolide, lysergic acid diethylamide
 - Beta-adrenergic blocking agents: timolol, propranolol, sotalol, metoprolol, pindolol, oxprenolol, acebutolol
 - Analgesics: aspirin, phenacetin, codeine, paracetamol
 - Antihypertensive agents: hydralazine, methyl dopa, hydrochlorothiazide, reserpine
 - Miscellaneous: amphetamines, haloperidol, sulpha-derivatives, anticonvulsants, anti-histamines, ampicillin, glibenclamide
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There are many drugs (Table 03) which have been implicated to cause RPF. Out of those, convincing evidence is only available for long term usage of methysergide (15) and bromocriptine.

Malignancy induced RPF or malignant retroperitoneal fibrosis accounts for 8-10% of the cases (5). Metastatic disease of the lung, breast, prostate and colo-rectal carcinoma are the commonest among them (16). Lymphoma, sarcoma, cervical and urinary tract malignancy also give rise to malignant RPF (17).

Clinical presentation

Symptoms in the early stage are generally non-specific, with abdominal discomfort, loin pain and lower back-ache being the commonest. Other frequent symptoms are loss of weight, anorexia and malaise. Duration of symptoms prior to diagnosis is usually 6 months or more (12). Urological symptoms are less frequent in the early stage.

When the disease progresses with advanced fibrosis, more specific and severe symptoms due to entrapment and compressive effects on the retroperitoneal structures become evident. Compression on the ureters can give rise to loin pain with varying degrees of severity depending on the degree of obstruction. In bilateral ureteric obstruction, patients can even present with oliguria or anuria. There had been cases of men with testicular swelling and women with endometriosis secondary to RPF. Other rare symptoms are lower limb claudication, oedema and abdominal angina.

Findings on examination are usually unremarkable. In advanced cases and malignant RPF there may be findings related to the complications or the primary disease.

Investigations

There should be a very high degree of suspicion to diagnose this entity early. Investigating tools should be used carefully to increase the accuracy and detect or exclude malignant RPF.

Imaging

Conventional radiography

This is of very limited value with regard to diagnosis of RPF. Usually x-ray kidney, ureter and bladder (KUB) or chest x-ray is done well before suspecting RPF to exclude more common pathology (eg: ureteric calculi).

Intravenous pyelography

Before the cross-sectional imaging era this was used to diagnose RPF with its classical triad; delayed renal excretion (20% – unilateral, 68% – bilateral), Hydronephrosis with proximal hydroureter and medial deviation of the middle third of the ureter (classical

sign of RPF) with tapering of the ureter (Figure 1) at L4-L5 vertebral level (18). The sensitivity and specificity of this triad is very low since the classical sign is present in 20% of unaffected normal individuals.

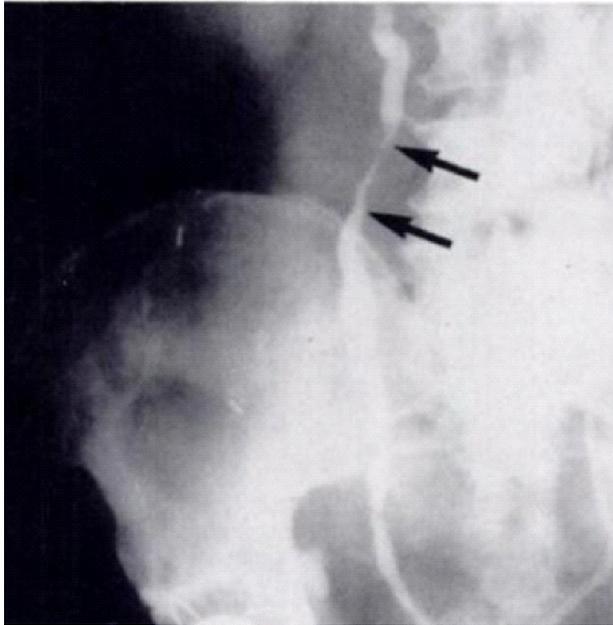


Figure 1. Classical tapering of the ureter on intravenous pyelogram found in idiopathic retroperitoneal fibrosis.

Ultrasonography

This is another tool with very little value in diagnosing RPF. But it is useful in detecting complications and for follow up to assess treatment response and suspect recurrence.

Computed tomography

CT is the imaging modality of choice for diagnosis of RPF. It has additional benefits of detecting the location, extent, effect on the adjacent or entrapped structures and underlying cause in some cases. It also helps to exclude malignancy to a certain extent and in localizing during biopsy procedures and follow up. CT will show a hypo-echogenic mass in the retroperitoneum in the lower aortic region with entrapment of the great vessels and ureters. CT will also show complications with its degree, such as hydronephrosis with cortical thinning or non-excreting kidneys.

There are several features that may help to differentiate malignant RPF from idiopathic RPF, which should be carefully looked for before embarking on diagnosis and commencing treatment.

In malignant RPF the fibrotic mass is bulkier and tends to displace the aorta anteriorly (Figure 2) from the spine

and the ureters laterally (19), whereas in idiopathic RPF it tethers the structures to the spine leaving hardly any space between the two structures. But the sensitivity and specificity is poor. In malignant ones there is more nodularity and lobulations in the periphery, but in idiopathic disease the fibrotic area appears as a plaque like density with peripheral infiltration. This again is not a very accurate feature to differentiate the two entities (20).



Figure 2. Contrast enhanced CT scan of abdomen showing retroperitoneal mass encasing and pushing aorta anteriorly (which is a feature of malignant RPF), left renal hydronephrosis with bilateral percutaneous nephrostomy tubes, in a female with malignant RPF due to lymphoma.

Courtesy: The Department of Urology, National Hospital of Sri Lanka.

Magnetic resonant imaging (MRI)

MRI has the advantage of avoiding irradiation and iodinated contrast medium. It can provide a large field of view covering many structures entrapped and their complications. But it is not superior to CT in differentiating malignant and idiopathic RPF since it is often difficult to do so (21).

Isotope studies or scintigraphy

These will only show the disease activity and will be helpful in the follow up of pharmacotherapy for idiopathic RPF (22). There is no value in differentiating the malignant entity.

Biopsy

All non-invasive investigating tools such as imaging had not been specific enough to confidently exclude malignancy induced RPF. Therefore some authorities consider retroperitoneal biopsy as a mandatory diagnosis confirming step before treating this disease (19,23).

The biopsy technique depends on the location, extent, suspected underlying malignancy or other secondary cause, availability of CT/MRI, operator experience and the patient preference. Out of many techniques such as fine needle aspiration (FNA), CT guided tru-cut biopsy, trans-caval retroperitoneal biopsy, laparoscopic or open deep incisional biopsy, the last one has the best yield, and preferred by many authors. CT guided FNA or core biopsies are considered less reliable than surgical biopsies (24).

Even on biopsy the malignant areas may be missed. Therefore a careful search for an occult malignancy with intelligent use of imaging combined with biopsy can reduce the chances of missing a malignant RPF before treating.

Treatment

Treatment should be focused on removal of the underlying cause or suppression of inflammation and correction of complications. Preservation of renal function is one of the important steps in management of RPF. Early intervention will have an advantage of preventing glomerular loss. RPF secondary to a drug may regress when the drug is withdrawn (34).



Figure 3. Bilateral nephrostograms in a patient with malignant RPF. The right lower ureter intussusceptions (found later during exploration) following ureteroscopy. Courtesy: The Department of Urology, National Hospital of Sri Lanka.

Depending on the degree of obstruction of the ureters, decompression of the kidneys should be a priority. This could be achieved by retrograde ureteric stents/

catheters or percutaneous nephrostomy tube insertion (25). Although retrograde ureteric stenting is easy there can be many complications that can even make the future procedures more complicated (Figure 3).

Percutaneous nephrostomy has many advantages over retrograde ureteric stenting. It can be done under local anaesthesia as an in-ward procedure when the patient is not fit to undergo general anaesthesia. It can be used to perform antigradenephrostograms to assess the degree of ureteric obstruction with the exact location as well (Figure 3). This will also help to evaluate treatment response to pharmacotherapy.

No controlled therapeutic trials had been conducted due to the rarity of the disease. Treatment for idiopathic RPF aims at suppression of inflammation. In order to achieve clinicians have tried many drugs including various combinations as well.

Table 4. Pharmacotherapeutic agents used for idiopathic RPF

Immunosuppressants:

- Corticosteroids
- Azathioprine (+/- corticosteroids)
- Cyclophosphamide (+/- corticosteroids)
- Mycophenolate-mofetil (+/- corticosteroids)
- Cyclosporin
- Penicillamine

Hormonal therapy

- Tamoxifen
- Medroxyprogesteroneacetate
- Progesterone

Pharmacotherapy

Corticosteroids as the primary modality of therapy had been tried in about 200 cases of in the literature (26,27,28). There had been a good response in about 80-85% of the cases and the rest had recurred, most within 1 year. For the recurrences various policies had been adapted, such as re-introduction of steroids, combining steroids and azathioprine and ureterolysis with steroids, which has resulted in complete response (27). Steroids are effective in prompt improvement of symptoms within a few days with a fall in ESR as well (27). It also causes a reduction of retroperitoneal mass and a resolution of obstructive uropathy (29). However, some authors are reluctant to use steroids as primary therapy before performing an open or laparoscopic

biopsy to exclude malignant RPF (23). This is usually combined with a surgical procedure at the same time, such as ureterolysis or omental wrap.

There are various regimens of corticosteroids given for RPF, ranging from prednisone 30 - 75 mg/day for 4 weeks to 19 months. Majority had been treated for over 6 months. Most widely accepted one is a high dose (40-60 mg/day) for six weeks followed by a gradually reduced maintenance dose (5-10 mg/day) for another 6-12 months depending on the response (27).

In steroid-resistant cases, once there is no doubt about a malignancy other immune-suppressants can be tried alone or in combination (30). Azathioprine (2 mg/kg) and prednisone combination had been used successfully when the response to steroids alone is inadequate (8).

Since 1991, after tamoxifen was used by Clerk et al, it had been successfully used as the primary therapy for RPF in many cases (31,35). A dose of 20-30 mg/day (range: 10-40 mg/day) over a period of 12 months (9-20 months) had been used. The response had not been remarkable with a complete response in less than 50% of cases after treating for 12 months. The disease response with regard to symptom improvement and regression of retroperitoneal mass is slower and less than that with steroids (32). This can be used as an

alternative for steroid-resistant idiopathic RPF, a steroid-sparing agent as well as in recurrence following steroid therapy (36).

The combination of steroids with azathioprine or cyclophosphamide, once again with different duration and dosages, has also been reported to be successful (8,33). Corticosteroids combined with mycophenolatemofetil had been used successfully and it had been used as a steroid sparing agent as well (37,38).

Surgical intervention

Surgical intervention becomes important from the presentation of the patient when the kidneys need to be decompressed urgently. Afterwards, in order to perfect the diagnosis, an open or a laparoscopic biopsy will be helpful.

Indwelling ureteral stents (double "J" stents) are of great value in decompressing kidneys at presentation. They can be kept until the response to pharmacotherapeutic agents take place. There are few disadvantages of inserting them early. It can obscure the classical diagnostic features on imaging. Stent induced peri-ureteritis may make the subsequent dissection difficult during ureterolysis and repeated interventions can give rise to many complications (Figure 3).



Figure 4. Right sided lower ureteric replacement with appendix on a pedicle and the left ureteric replacement with an ileal segment.

Courtesy: The Department of Urology, National Hospital of Sri Lanka.



Figure 5. Right lower ureteric replacement with appendix on a pedicle.

Courtesy: The Department of Urology, National Hospital of Sri Lanka.

Percutaneous nephrostomy (PCN) has many advantages over ureteral stenting, when used to decompress kidneys. It can be performed under local anaesthesia, it can help to provide a nephrostogram and it will not obscure the classical diagnostic features on imaging. According to some authors introduction of infection is less with PCN than ureteric stenting.

Other options like endoluminal balloon dilatation and ureteral self-expanding stents also had been tried with limited success.

The conventional definitive surgical approach had been open biopsy, ureteric exploration with ureterolysis and transposition of the ureters (laterally or preferable intraperitoneally) or omental wrapping of ureters (39,40). When there are unhealthy ureteric segments which cannot be salvaged, either due to inflammation or dissection, resection of the unhealthy ureteric segment and regaining continuity is essential. Uretero-ureterostomy, Boari flap with or without psoas hitch, appendicular interposition and ureteric replacement with an ileal segment on pedicle are options (Figures 4, 5). Uretero-neocystostomy or re-implantation and auto transplantation of kidney also has been described to salvage kidney (41).

In recent years, use of steroids following surgical management, to reduce recurrence has gained acceptance. There had been a significant reduction in recurrence rates when surgery was combined with steroids than surgery alone (30).

Follow up

Long term follow up is mandatory as recurrences had been reported within 1 to 10 years (10). Majority had been within 1 year from treatment. Response to treatment should be assessed with CT scanning. Some authorities advise CT scanning at 6 months and 1 year as routine follow-up (42). Regular assessment of renal functions, ESR and ultrasonographic evaluation of the kidneys to exclude hydronephrosis is sufficient as the basic follow up. If there is any deterioration or abnormality in them, a CT scan will be necessary (43). In idiopathic RPF, the prognosis is relatively good with a mortality below 9%, provided properly investigated and treated (5).

References

- Kottra JJ, Dunnick NR. Retroperitoneal fibrosis. *Radiol Clin North Am* 1996; 43: 1259-75.
- Srinivas V, Dow D. Retroperitoneal fibrosis. *Can J Surg* 1984; 27(2): 111-3.
- Dehner LP, Coffin CM. Idiopathic fibrosclerotic disorders and other inflammatory pseudotumors. *Semin Diagn Pathol* 1998; 15: 161-73.
- Kottra JJ, Dunnick NR. Retroperitoneal fibrosis. *Radiol Clin North Am* 1996; 34: 1259-75.
- Lepor H, Walsh PC. Idiopathic retroperitoneal fibrosis. *J Urol* 1979; 122: 1-6.
- Higgins PM, Bennett-Jones DN, Naish PF, et al. Non-operative management of retroperitoneal fibrosis. *Br J Surg* 1988; 75: 573-7.
- Bommel EFH van, Spengler J van, Hoven B van der, Kramer P. Retroperitoneal fibrosis: report of 12 cases and review of the literature. *Neth J Med* 1991; 39: 338-45.
- McDougal WS, MacDonell RC. Treatment of idiopathic retroperitoneal fibrosis by immunosuppression. *J Urol* 1991; 145: 112-4.
- Snow BW, Garrett RA. Retroperitoneal fibrosis in children. *Urology* 1984; 23(6): 569-72.
- Gilkeson GS. Retroperitoneal fibrosis: a true connective tissue disease. *Rheum Dis Clin North Am* 1996; 22: 23-38.
- Stovall TG, Ling FW. Retroperitoneal fibrosis presenting as an abdominopelvic mass. *Obstet Gynecol* 1988; 71: 482-3.
- Buff DD, Bogin MB, Faltz LL. Retroperitoneal fibrosis: report of selected cases and a review of the literature. *N Y State J Med* 1989; 89(9): 511-6.
- Amis ES Jr. Retroperitoneal fibrosis. *AJR* 1991; 157: 321-9.
- Kaipainen O, Jantunen E, Kuusisto J, Marin S. Retroperitoneal fibrosis with antineutrophil-cytoplasmic antibodies. *J Rheumatol* 1996; 23: 779-81.
- Silberstein SD. Methysergide. *Cephalalgia* 1998; 18: 421-35.
- Koep L, Zuidema GD. The clinical significance of retroperitoneal fibrosis. *Surgery* 1977; 81: 250-7.
- Fromowitz FB, Miller F. Retroperitoneal fibrosis as host-response to papillary renal cell carcinoma. *Urology* 1991; 38: 259-63.
- Vivas I, Nicolas AI, Velazquez P, et al. Retroperitoneal fibrosis: typical and atypical manifestations. *Br J Radiol* 2000; 73: 214-22.
- Amis ES Jr. Retroperitoneal fibrosis. *AJR* 1991; 157: 321-9.
- Fagan CJ, Larrieu AJ, Amparo EG. Retroperitoneal fibrosis: ultrasound and CT features. *AJR* 1979; 133: 239-43.

21. Arrive L, Hricak H, Tavares NJ, et al. Malignant versus nonmalignant retroperitoneal fibrosis: differentiation with MR imaging. *Radiology* 1989; 172: 139-43.
22. Vaglio A, Buzio C. Chronic periaortitis: a spectrum of diseases. *Curr Opin Rheumatol* 2005; 17: 34-40.
23. Baker LRI, Mallinson WJW, Gregory MC, et al. Idiopathic retroperitoneal fibrosis. A retrospective analysis of 60 cases. *Br J Urol* 1988; 60: 497-503.
24. Bullock N. Idiopathic retroperitoneal fibrosis. *BMJ* 1988; 297: 240-1.
25. Heidenreich A, Derakhshani P, Neubauer S, Krug B. Treatment outcomes in primary and secondary retroperitoneal fibrosis. *Urologe A* 2000; 39: 141-8.
26. Morandi LP, Grob PJ. Retroperitoneal fibrosis. Response to corticosteroid therapy. *Arch Intern Med* 1971; 128: 295-8.
27. Bommel EFH van, Boeve E, Weimar W. Retroperitoneal fibrosis: current concepts. *Eur Urol Update Series* 1993; 2: 18-23.
28. Alexopoulos E, Memmos D, Bakatselos S, et al. Idiopathic retroperitoneal fibrosis: a long-term follow up study. *Eur Urol* 1987; 13: 313-7.
29. Kardar AH, Kattan S, Lindstedt E, et al. Steroid therapy for idiopathic retroperitoneal fibrosis: dose and duration. *J Urol* 2002; 168: 550-5.
30. Wagenknecht LV, Hardy JC. Value of various treatments for retroperitoneal fibrosis. *Eur Urol* 1981; 7: 193-200.
31. van Bommel EFH, Hendriksz TR, Huiskes AWLC, Zeegers AGM. Brief communication: tamoxifen therapy for nonmalignant retroperitoneal fibrosis. *MD Ann Intern Med* 2006; 144: 101-6.
32. Higgins PM, Bennett-Jones DN, Naish PF, Aber GM. Non-operative management of retroperitoneal fibrosis. *Br J Surg* 1988; 75: 573-7.
33. Harreby M, Bilde T, Helin P, Meyhoff HH, Vinterberg H, Nielsen VA. Retroperitoneal fibrosis treated with methylprednisolone pulse and disease-modifying antirheumatic drugs. *Scand J Urol Nephrol* 1994; 28: 237-42.
34. Stewart TW Jr. Idiopathic retroperitoneal fibrosis-past and present. *N V State J Med* 1989; 89: 503-4.
35. Clark CP, Vanderpool D, Preskitt JT. The response of retroperitoneal fibrosis to tamoxifen. *Surgery* 1991; 109(4): 502-6.
36. Cogan E, Fastrez R. Azathioprine. An alternative treatment for recurrent idiopathic retroperitoneal fibrosis. *Arch Intern Med* 1985; 145(4): 753-5.
37. Swartz RD, Lake AM, Roberts WW, Faerber GJ, Wolf JS Jr. Idiopathic retroperitoneal fibrosis: a role for mycophenolatemofetil. *Clin Nephrol* 2008; 69(4): 260-8.
38. Adler S, Lodermeier S, Gaa J, Heemann U. Successful mycophenolatemofetil therapy in nine patients with idiopathic retroperitoneal fibrosis. *Rheumatology (Oxford)* 2008; 47(10): 1535-8.
39. Osborn DE, Rao PN, Barnard RJ, Ackrill P, Ralston AJ, Best JJ. Surgical management of idiopathic retroperitoneal fibrosis. *Br J Urol* 1981; 53: 292-6.
40. Lindell OI, Lehtonen T. Surgical treatment of ureteric obstruction in idiopathic retroperitoneal fibrosis. *Scand J Urol Nephrol* 1988; 110 (Suppl): S299-302.
41. Deane AM, Gingell JC, Pentlow BD. Idiopathic retroperitoneal fibrosis – the role of autotransplantation. *Br J Urol* 1983; 55: 254-6.
42. Brooks AP, Reznick RH, Webb JAW, Baker LRI. Computed tomography in the follow-up of retroperitoneal fibrosis. *Clin Radiol* 1987; 38: 597-601.
43. Rauws EAJ, Mallens WMC, Bieger R. CT scanning for the follow up of corticosteroid treatment of retroperitoneal fibrosis. *J Comput Assist Tomogr* 1983; 7(1): 113-6.

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