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Article

Surviving Complications of Retroperitoneal Fibrosis with Intermittent Relapses over a Period of 20 years: Case report and literature Review

Is it chronic progressive disease or intermittent relapses every time encasing a new structure?

Sobrevivir a las complicaciones de la fibrosis retroperitoneal con recaídas intermitentes durante un período de 20 años: reporte de un caso y revisión de la literatura

¿Es una enfermedad crónica progresiva o recaídas intermitentes cada vez que involucra una nueva estructura?

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SUMMARY

Idiopathic retroperitoneal fibrosis is a rare fibro-inflammatory disease of varied etiology which usually originates around aorta and spreads caudally along Iliac vessels into adjacent retroperitoneum causing ureteral obstruction as the most frequent complication.

A 53-year-old male patient presented with complaint of mild pain in both the legs off and on. On investigating further, we found that he had been struggling with intermittent relapses every 3-4 years for last 20 years since he was first diagnosed with Idiopathic Retroperitoneal Fibrosis. He was 33-year-old when he first developed the symptoms of anuria for 48 hours and was diagnosed with Idiopathic retroperitoneal fibrosis. This was followed by atrophy of left kidney and hypertension 6 years later, then hypothyroidism after another 3years and finally involvement of Inferior Vena Cava and acute Deep Vein Thrombosis of lower limbs after another 3-4 years. His deep vein thrombosis was well managed in time. He was put on glucocorticoids everytime he had a relapse and a complication.

We did a review of literature to understand recent advances about its pathogenesis, diagnosis, investigations and management. We searched in PubMed using terms like retroperitoneal fibrosis alone and in combination with related terms such as Inferior Vena Cava thrombosis, Deep Vein Thrombosis, Tamoxifen, Methotrexate. This case is unique as it is very rare to find acute Deep Vein Thrombosis in Idiopathic retroperitoneal fibrosis without development of any collaterals when Inferior Vena Cava lumen is compromised to almost complete obstruction.

After a follow up of 20 years patient is doing well in terms of physical activity and psychological wellbeing with anti-hypertensives, thyroxine and anti-coagulants. Is the disease-free interval actually free of the disease or it just subsided with immunosuppressants to become active after some time?

Keywords: Idiopathic Retroperitoneal Fibrosis; Inferior Vena Cava thrombosis; Hypothyroidism; Immunosuppressants; Obstructive uropathy.

1. Introduction

Retroperitoneal fibrosis (RPF) is a rare collagen vascular disorder of unclear cause, an uncommon fibrotic reaction. It was first described by french urologist Albarran 1905 as ureteral obstruction secondary to fibrotic changes in retroperitoneal space and established as a clinical entity in 1948 by Ormond (Vaglio & Moriatati, 2016; Carmel *et al.*, 2008). Usually described as chronic peri-aortitis, sclerosing retroperitoneal granuloma and obstructive uropathy, commonest sequalae of RPF is ureteral obstruction. Other types of renal involvement may occur, including stenosis of the renal arteries and veins, renal atrophy, and different types of associated glomerulonephritis (Vaglio & Moriatati, 2016). A disease of variable etiology, it is seen as a Systemic disease and inflammatory disease, also associated with various autoimmune disorders (Vaglio & Moriatati, 2016; Carmel et al., 2008, Hedgire *et al.*, 2013, van Bommel et al., 2009). With many possible hypotheses it has been seen to involve other structures either distant or adjacent (Carmel *et al.*, 2008, Scheel *et al.*, 2012). Some of the diverse manifestations may include mediastinitis, thyroiditis and sclerosing cholangitis and even ophthalmic tumors (Carmel *et al.*, 2008, Kaddouri *et al.*, 2017). Some investigators consider it to be part of IgG4-Related Disease (IgG4-RD) because of its association with many auto-immune disorders (Zhang *et al.*, 2017, Hedgire *et al.,* 2013, Khosroshahi *et al.,* 2013, Subramani *et al.*, 2019). As retroperitoneal fibrosis can be secondary to chemoradiation for another malignancy, it is essential to differentiate between primary or secondary RPF (Murakami et al., 2018). The diagnosis is made on the basis of Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), while Fluorodeoxyglucose Positron emission tomography ([18F] FDG PET) is a useful tool in disease staging and follow-up (Vaglio & Moriatati,

2016; Carmel *et al.,* 2008, Caiafa *et al.,* 2013). Management depends upon severity of the case ranging from immunosuppressants as sole treatment modality to surgical restoration of ureter patency, release of the ureters from the encasing fibrosis alongwith immunosuppressants (Zhou *et al.,* 2015). Although long term morbidity and mortality is not bad, relapses are known to occur. Studies with long-term follow-up (median, 48–61 months) provide mortality rates of 3.3%–7.3% (Vaglio & Moriatati, 2016). Relapse rates in various studies have been reported from 12- 72% (Vaglio & Moriatati, 2016, Kermani *et al.,* 2011). Our patient had relapses at the interval of 3-4 years presenting with bilateral ureteral obstruction as the first episode. This case is also unique in having rare development of acute Deep Vein Thrombosis (DVT) though involvement of Inferior Vena Cava (IVC) may have been progressing for some time but there were no signs of collateral development at the time of episode to suggest that.

Case History:

A 33-year-old young male presented with complaint of anuria for 48 hours in year 2001. He gave history of dull pain in lower back, mild fever, malaise, anorexia, nausea for 3-4 days. His kidney functions were altered with Blood Urea (Bl. Urea)- 80mg/dL & Serum Creatinine (S. Creatinine)- 6.5mg/dL, Erythrocyte Sedimentation Rate (ESR)-1 10 /1h and normal C-reactive protein (CRP). He developed mild hypertension immediately which came down to normal once obstruction was relieved indicating it was secondary to bilateral ureter obstruction.

Cystoscopy revealed bilateral ureteric obstruction at the level of L4, 15cm above ureteric orifices. Through Ureteroscope, bilateral ureteric catheterization dye study was done under Image Intensifier Television (IITV), which confirmed the narrowing of middle and lower one-third of both ureters below which both ureters were normal till bladder. Both ureters were seen medially at L5-S2. Findings were suggestive of bilateral ureteric stricture at L4 level. Bilateral Double 'J' (DJ) ureteric stent was put.

Ultrasonography revealed mild-moderate bilateral hydronephrosis with dilated calyces, dilated renal pelvis and dilated upper and mid ureters, more on right side with normal sized left kidney. There was no evidence of any calculus, PUJ (Pelviureteric junction) obstruction or polycystic disease. Cortico-medullary differentiation (CMD) was well preserved. CT scan (done after putting DJ stent) was suggestive of RPF with bilateral moderate hydronephrosis, moderate dilatation of ureters and presence of soft tissue opacity sized 7.4cm (TD)x2.3cm(AP)x11cm(CC) in midline around lower aorta, IVC & both ureters e/o retroperitoneal fibrosis. X-ray LS Spine didn't reveal any lytic lesions or enhancement of psoas shadow. SI (Sacro-Iliac) joints, vertebral bodies and Inter-vertebral Disc (IVD) space were normal. Color doppler showed Low impedance forward diastolic flow, increased Peak Systolic Velocity (PSV) at origin in Main Renal Artery (MRA) on right side and reduced PSV at origin in Left MRA, with no evidence of renal artery stenosis on either side (Table I).

Table I:

Renal Doppler showed low velocity flow (Reduced PSV and EDV) in left kidney with preserved waveforms as compared to right kidney. No definite evidence of hemodynamically significant renal artery stenosis in either kidney.

INDICES	PSV (Peak Systolic Velocity) cm/sec		EDV (End diastolic Velocity) cm/sec		RI (Resistive Index)	
	Right	Left	Right	Left	Right	Left
Main Renal Artery at origin	61	21	25	7.5	0.58	0.7
Main Renal Artery at hilum	63	19	33	6.5	0.52	0.8

INDICES	PSV (Peak Systolic Velocity) cm/sec		EDV (End diastolic Velocity) cm/sec		RI (Resistive Index)	
Segmental Artery	36	14	14	6.1	0.53	0.56
Lobar Artery	34	15	17	6.5	0.59	0.61
Renal Artery to Aorta ratio (RAR)=less than 3.5(normal)					Mean RI=0.53	Mean RI=0.66

Biopsy done after 15 days of acute incidence showed fibrocollagen bands with scattered adipose tissue, chronic non-specific inflammation with entire tissue infiltrated with chronic inflammatory cells, mainly lymphocytes and rare neutrophils. Bl. Urea & S. Creatinine returned to normal two days after putting DJ stent. He was put on prednisolone. ESR came down to 80/1h within one month and normal within 3months.

He was undergoing regular blood investigations and regular follow-up every year to monitor growth of RPF. ESR was found to be high in 2004, 2007, 2010 for which glucocorticoids were given.

First relapse occurred after 6years, in year 2007 when ESR was also raised he was diagnosed for hypertension and put on β-blockers and angiotensin receptor blockers (ARBs) (Tab Metoprolol 50mg and Tab Telmisartan 40mg). IVP (intravenous Pyelography) was done because of suspicion of atrophic left kidney on sonography, which revealed non-visualization of contrast on left side even after 5 hours, an atrophic and non-functional left kidney. Excretion of dye was normal on right side with medial course of right ureter and minimal irregularity of walls of middle and lower right ureter. Magnetic Resonance urography (MRU) revealed left Pelvi-ureteric junction as the obstructing site with dilated calyces and hydronephrotic changes of left kidney. Renal functions were within normal range.

Second episode of relapse occurred after another 3 years of onset of hypertension in year 2010 when he again had raised ESR for which glucocorticoids were repeated. This time he was diagnosed with hypothyroid and put-on Tab Thyronorm 100mcg.

Third relapse occurred after a gap of another three and a half years in Year 2013, he suddenly developed severe pain and stiffness in both the calf muscles. Doppler study revealed Thrombosis from IVC (Infrarenal level) to Bilateral Common Iliac Veins, External Iliac Veins, Common Femoral Veins, Deep Femoral Veins, Great Saphenous veins and smaller veins distally. Mid portion of IVC was not found to be distended. Caliber of IVC lumen was 1mm at the level of narrowing. There were mild renal parenchymal changes with scarring in both kidneys, more on left sides. Rt. Kidney measured 10cmx4.5cm and Lt. kidney was 8cmx3.8cm. Anti-Nuclear Antibody (ANA) profile immunoblot was non-conclusive for auto-immune diseases. He was thrombolysed with streptokinase 2.5 lacs bolus IV and 1 lakh/h for 24 hours. Creatine phosphokinase (CPK) was high 709 micrograms per liter (mcg/L) which came down to 307mcg/L after three days of thrombolysis. ESR was 20/1h, CRP was raised to 61.78mg/L, Fibrinogen level was 246 mg/dL while FDP was >=20 (Ref <5ug/ml). Kidney functions were deranged with Bl. Urea-70 mg/dL and S. Creatinine-1.9mg/dL which came down to 49 mg/dL and 1.5 mg/dL respectively after three days of thrombolysis. He was discharged with Tab Warfarin according to INR.

CT scan repeated after 2 months of acute DVT showed diffuse soft tissue lesion of 7.5cm (TD) x2.4cm (AP)x11.2cms (CC) size involving retroperitoneum encasing aorta and IVC, caudally extending to bilateral Iliac vessels, reaching up to presacral region. Post-contrast mild enhancement of above lesion was noted. Lesion was causing marked narrowing of IVC with thrombosis at infra-renal course

and thrombosis of both iliac veins. Multiple collateral veins could be seen in pelvic and anterior abdominal wall. Lesion was also seen encasing left renal pelvis. Left kidney had reduced markedly in size to 63mmx48mm while Right Kidney was normal, 108mmx62mm. There was no encasement of rt. ureter. A small hernia of 41x34 mm size was noted in anterior abdominal wall at supra-umbilical level with small bowel loops herniating through it. After a follow up of two months ESR was slightly raised to 35/1h and S. Creatinine had returned to normal 1.01mg/dL.

Diuretic Tc-99m DTPA (Technetium-99m Diethylenetriamine pentaacetate) renogram showed small sized Left kidney with significantly reduced perfusion and cortical tracer uptake and sluggish drainage pattern. Right kidney was normal in size, shape and position with prompt & normal perfusion, good cortical uptake of tracer and complete clearance of tracer from pelvicalyceal system by the end of study with no retention. Rt. kidney uptake was 80% and Left kidney uptake was 20 % (Table II). Repeat course of Prednisolone was given a fifth time. Repeat Diuretic Tc-99m DTPA renogram after the course of steroids did not show any changes.

Table II:

Tc-99m DTPA Renogram done after 3rd relapse of the disease showing small left kidney with decreased parenchymal function.

	Left Kidney		Right Kidney	
	Before the course of steroids	After Course of Steroids	Before the course of steroids	After Course of Steroids
% uptake	19.71	19.94	80.29	80.06
GFR- ml/min	10.7	10.62	43.6	42.64
	Small sized left kidney with significantly compromised parenchymal function.		Normal functioning and draining right kidney	

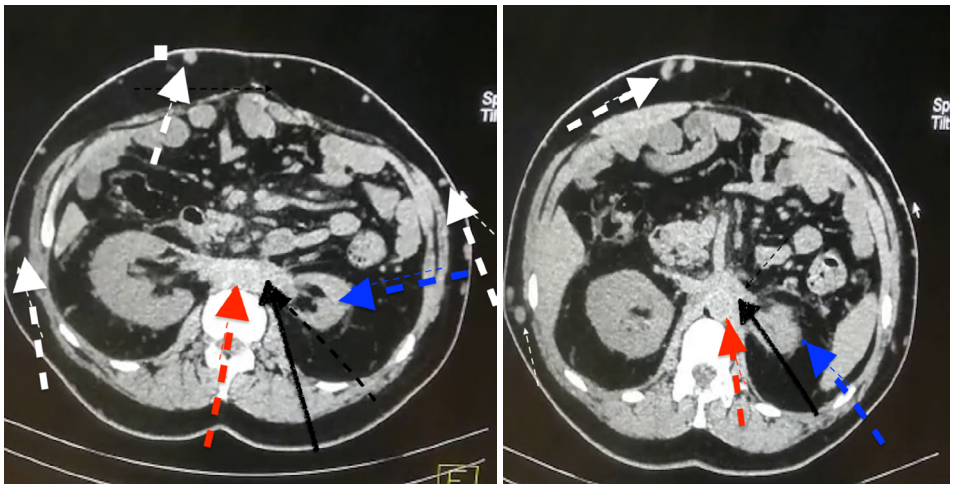
Within a year his lower limb venous system had recanalized below the entrapment portion of IVC except for bilateral Common Iliac Veins & Right External Iliac Vein.

After 5½ years of IVC obstruction and DVT, he developed small brain hemorrhage not resulting in any neurological deficit which was found to be due to high INR (International Normalized Ratio). Warfarin was therefore stopped and Apixaban was started.

When he came for follow up after 20 years of first episode, findings remain same for the lower limb venous system. His latest CT Scan shows an ill-defined soft tissue hypo-echoic lesion 8.8cm (TD) x2.9cm (AP)x12.2cm (CC) surrounding the vessels, which is slightly larger than the previous finding (Figure 1). While IVC caliber remains same 1-2mm. IVC, Iliac veins have completely been recanalized with multiple superficial collaterals seen around pelvis and in anterior abdominal Wall (Figure 1). Aorta has normal flow and caliber. Both kidneys show Cortical echogenicity, poorly differentiated cortico-medullary differentiation and changes of renal parenchymal disease on both sides. Renal artery Doppler showed Normal intra-renal perfusion on both sides, normal acceleration time on both sides, normal Resistive Index (R.I.) values & normal renal/aortic ratio at hilum and interlobar branches on both sides, normal forward flow in diastole with decrease in peak systolic velocity in left renal artery and its branches. His S. Creatinine fluctuates between 1.3 to 1.5 mg/dL. ESR has been normal till now.

Figure 1.

Recent (2019) Plain axial CT images (left) reveal hyperdense soft tissue mass representing retroperitoneal fibrosis (Black Arrow) seen surrounding and encasing the aorta (Red Arrow). Compression of IVC is seen which cannot be seen separately from the mass. In the second image (right), the fibrosis is seen encasing the origin of bilateral renal arteries and superior mesenteric artery. Venous Collateral channels are seen in anterior abdominal wall (White Arrows). Small left kidney present (Blue Arrow).



2. Literature Review

Epidemiology

IRPF is seen chiefly in adults between 40-60year age group, more frequently seen in males (M: F=2-3:1) with no ethnic predilection, an incidence of 1per 2,00,000 and prevalence of 1.3 per 1,00,000. More than 70% of RPF have been found to be idiopathic and 30% secondary to malignancies or medications (Vaglio & Moriatati, 2016, Carmel *et al.*, 2008, Kermani *et al.*, 2011). Occurrence in pediatric age group and familial occurrence is rarely seen (Carmel et al., 2008, Subramani *et al.*, 2019). Among inducing factors, smoking and exposure to asbestos have been suggested possibly as pathogenetic mechanisms based on findings of pleural fibrosis in patients with RPF (Scheel & Feeley, 2009, van Bommel *et al.*, 2009, Uibu *et al.*, 2008).

Symptoms

Early symptoms are non-specific and later symptoms are determined by encasement of surrounding structures. Most common symptoms are vague in nature like lower back pain, abdominal pain and lower extremity swelling which may be unilateral or bilateral (Vaglio & Moriatati, 2016, Zhang et al., 2017, Choi *et al.,* 1997). Flank/abdominal pain are usually dull and transiently respond to Nonsteroidal anti-inflammatory drugs (NSAIDs). Sometimes flank pain can be misdiagnosed to be due to ureteral colic. Decreased urine output may herald renal or ureteral involvement. Ureteral involvement may be unilateral or bilateral usually causing medial ureteral deviation. Incidence of Renal hypoplasia/atrophy has been reported around 8%–30%, cause of which is still unclear (Vaglio & Moriatati, 2016). Testicular pain, hydrocele, varicocele (due to encasement of spermatic vein), retrograde ejaculation and erectile dysfunction have also been reported alongwith IRPF (Vaglio & Moriatati, 2016). Less

common manifestations like frequency, hematuria, and dysuria may also be seen in some patients (Vaglio & Moriatati, 2016, Kermani *et al.*, 2011, Scheel & Feeley, 2009, van Bommel *et al.*, 2009). One-third of patients present with new-onset hypertension or worsening of preexisting hypertension at diagnosis, due to involvement of renal vascular peduncle causing compression of renal veins and renal arteries (Vaglio & Moriatati, 2016, Scheel & Feeley, 2009).

Venous compression, mainly of IVC is seen more commonly as compared to stenosis of aorta and Iliac arteries though IRPF originates around aorta and extends along iliac arteries. Patient may present with oedema in such cases, but collaterals usually develop due to slow progression of the venous encasement. Because of this reason, IVC syndrome, DVT, and pulmonary embolism are very rarely seen. Only 2% of IRPF have been reported to have Iliocaval thrombosis/occlusion (Kirby et al., 2020, Tanuma & Yokoo, 2002, Kermani *et al.,* 2011, Scheel & Feeley, 2009). Renal artery thrombosis though rare has been reported as a complication of IRPF (Francklyn *et al.*, 2013). Extension of the fibro-inflammatory process into retrohepatic area has also been reported in one case causing intrahepatic and extrahepatic biliary obstruction (Kirby et al., 2020). Involvement of thoracic aorta and epiaortic artery has been seen more frequently in females (Palmisano *et al.*, 2015). Extension of IRPF into mesenteric and celiac arteries can cause their stenosis and ischemic may resemble mesenteric vasculitis (Salvarani *et al.,* 2011). Rarely intestinal obstruction may occur and instances like duodenal stenosis and Rectosigmoid obstruction due to RPF have also been reported (Choi *et al.,* 1997, Jun *et al.*, 2001). In a rare case psedocyst formation in an established case of RPF has also been reported during relapse (Jansen *et al.*, 2010).

Diagnosis

IRPF is usually diagnosed by CT or MRI as they allow comprehensive evaluation of the extent of IRPF and are easy for doing follow-up (Vaglio & Moriatati, 2016, Carmel *et al.*, 2008, Choi *et al.*, 1997). An open, laparoscopic, or CT-guided retroperitoneal biopsy is usually done to obtain tissue diagnosis if feasible. Excretory urography or retrograde pyelography is done if renal functions are within normal limits to define the site and severity of the obstruction. Cystoscopy and ureteroscopy alongwith ureteric catheterization dye study under IITV allows placement of stent to relieve the obstruction temporarily and identifying the site of narrowing of the ureters at the same time. Recently Nuclear scintigraphy, [18F] FDG PET are seen as a means to assess and monitor the progress of IRPF (Treglia *et al.*, 2012, Zhang *et al.*, 2014).

Differential Diagnosis

Major pathologies that need to be differentiated from RPF include malignancies and infections. Malignant RPF is seen in 8% of cases with poor prognosis. So, knowledge of typical and atypical radiological features in a case of retroperitoneal fibrosis is essential to delineate between benign and malignant lesions (Vaglio & Moriatati, 2016; Carmel *et al.*, 2008). Among malignant lesions retroperitoneal lymphomas, sarcomas and retroperitoneal metastases (from colonic, breast, lung, genitourinary, or thyroid primary cancer) need to be clearly distinguished from IRPF (Vaglio & Moriatati, 2016, Carmel *et al.*, 2008, Mullineux *et al.*, 2018). Carcinoids too are known to cause lesion in retroperitoneal region even without metastasizing to the retroperitoneum.

Among infections, tuberculosis is considered the most notorious specially in developing countries as it can affect any organ in human body. It may reach retroperitoneum either through hematogenous route or directly from adjacent structures (Vaglio & Moriatati, 2016, Carmel *et al.*, 2008, Greco *et al.*, 2005). Histoplasmosis and Urinary Tract Infection (UTI) may also be associated with RPF. Another infection that can mimic IRPF, esp. in women with a history of intrauterine device use is pelvic

actinomycosis (Vaglio & Moriatati, 2016, Carmel *et al.*, 2008, Caiafa *et al.*, 2013, Yilmaz *et al.*, 2012). Inflammatory conditions like Crohns disease, Erdheim–Chester disease, Diverticulitis, Pancreatitis may also be associated with RPF (Carmel *et al.*, 2008, Diamond *et al.*, 2014). Common drugs linked to RPF include ergot alkaloids like methysergide, ergotamine and dopamine agonists like pergolide. Other drugs linked to RPF are Hydralazine, β-blockers (Scheel *et al.,* 2012, Scheel & Feeley, 2009), Methyldopa, Amphetamines, Analgesic (phenacetin), Cocaine and anti-TNFα (Tumor necrosis factor alpha) therapy (Vaglio & Moriatati, 2016, Carmel *et al.*, 2008, Couderc *et al.,* 2013). RPF is also known to occur rarely following radiotherapy and chemotherapy. Very rarely RPF can also occur following major abdominal surgery and trauma causing periaortic hematoma or renal injury (Vaglio & Moriatati, 2016, Carmel *et al.*, 2008).

Association with autoimmune or fibroinflammatory diseases

IRPF have long been associated with many auto-immune diseases, most common being Autoimmune Thyroiditis (Kaddouri *et al.*, 2017). In a study, anti-thyroperoxidase antibodies were found in 24.7% of cases with evidence of thyroiditis on ultrasonography, 25% of them developed hypothyroidism requiring L-thyroxine. Hashimoto thyroiditis and Riedel thyroiditis have been shown to be associated with IRPF. Other Autoimmune disorders linked with RPF include Rheumatoid arthritis, Primary biliary cirrhosis, Ankylosing spondylitis, Fibrosing mediastinitis, Membranous Glomerulonephritis, Systemic Lupus Erythematosus(SLE), Polyarteritis nodosa, Pan Hypopituitarism and Sclerosing mesenteritis (Vaglio & Moriatati, 2016, Carmel *et al.,* 2008).

Pathogenesis

Earlier IRPF thought be a localized reaction to antigen "ceroid" found in atherosclerotic plaques of the abdominal aorta (Vaglio & Moriatati, 2016, Meier *et al.*, 2007, Ramshaw *et al.*, 1994). Now, it is considered a systemic disease with multifactorial pathogenesis to explain its association with other autoimmune diseases and distant sites. HLA-DRB1*03, a risk factor for autoimmune diseases like SLE & Type 1 DM (Diabetes Mellitus) is also thought to make these patients prone to develop IRPF. Δ32 polymorphism of gene encoding CCR5 (C-C Chemokine receptor) and TTCCAT haplotype of gene encoding CCL11/eotaxin-1 have also been associated with IRPF (Mangieri *et al.*, 2012, Boiardi *et al.*, 2011). Proliferation of fibroblasts and collagen production was shown to be stimulated by CCR3 which is a receptor for CCL11/eotaxin1. CCR3 was found to be expressed by Eosinophils and mast cells (induced by Eotaxin1) (Carmel et al., 2008, Zhou *et al.,* 2015). A high proportion of B lymphocytes is seen in infiltrating cells in IRPF, which may act as precursors of plasma cells. B cells and fibroblasts were also shown to be activated by IL-6 (**Interleukin-6)**, which are produced by T-cells locally in IRPF (Ramshaw *et al.*, 1994).

3. Investigations

Laboratory Investigations

Acute-phase reactants such as ESR, IL6 and CRP levels are increased in the majority of patients at presentation. CRP and ESR are also routinely used to monitor disease activity but they are poor in predicting response to therapy and do not correlate with mass regression (Magrey *et al.*, 2009, Pelkmans *et al.*, 2012). Relapses occur when acute-phase reactants are still normal (Jansen *et al.*, 2010, Vaglio *et al.*, 2005). ANA profile is done as part of the screening for auto-immune diseases (found positive in range of 22.6-38%) (van Bommel *et al.*, 2009). Other antibody tests include Anti-smooth muscle antibodies

(ASMA), F-actin antibodies, and liver and kidney microsomes antibodies (anti-LKM1) for antibodies for auto-immune hepatitis. Antithyroglobulin antibody (TgAb) and Anti-thyroid peroxidase antibody (anti-TPO) are done to test for Hashimoto's thyroiditis in case of Hypothyroidism alongwith RPF.

Imaging

Abdomen X-ray may show a central soft tissue shadow or silhouetting of psoas shadow during late stages of RPF but is usually unremarkable if done before doubt of RPF. Under rare complications, features of intestinal dilatation, obstruction or pneumatosis related to infarction may be seen. Osseous associations may be seen in case of association with Ankylosing spondylosis, Pott's disease or metastatic disease (Carmel *et al.*, 2008). Chest radiographs may reveal a non-cardiogenic pulmonary oedema (↑ airspace density, pleural effusion, upper lobe venous diversion in absence of cardiomegaly) secondary to nephrogenic fluid overload, Pulmonary fibrosis secondary to SLE, Ankylosing spondylosis or Mediastinal widening secondary to mediastinal fibrosis.

Excretory urography

Diagnosis on excretory urography is done by presence of (a) Delayed renal contrast excretion, (b) Medial deviation of the middle third of ureters and (Scheel *et al.*, 2012) Tapering of the ureteral lumen at the L4- L5 (Carmel *et al.,* 2008). There is difference of opinion regarding pathogenesis of hydronephrosis and hydroureter associated with IRPF with some investigators believing altered ureteral peristaltic activity to be the cause rather than mechanical obstruction as ureteral catheters are able to pass through the area of narrowing (Carmel *et al.*, 2008). Unilateral Hydronephrosis is seen in 20% and bilateral hydronephrosis is seen in 68% of cases of IRPF. Sensitivity and specificity of this test are limited as medial deviation of ureter may occur in 20% of non-affected individuals (Carmel *et al.*, 2008). However, Excretory urography is important while for planning of surgical intervention.

Sonography

IRPF is seen as a hypoechoic/ anechoic mass on sonography, which is irregularly contoured but well demarcated. Doppler flow evaluation assessment has limited success in distinguishing it from malignant RPF but it can reveal the status of abdominal aorta or IVC. Ultrasonography has limitations markedly in early cases and in obese patients too. Overall sonography has poor sensitivity & specificity in detection of RPF. Only 25% yield corresponding abnormality on sonography once IRPF has been diagnosed on CT. Ultrasonography has importance in diagnosing coexisting diseases like Primary biliary cirrhosis, Bile duct dilation due to Common Bile Duct (CBD) stricture, Portal Hypertension (PHT) secondary to compression of portal vein or sclerosing pancreatitis (Carmel *et al.*, 2008).

CT Scan

IRPFs on CT scan are seen as paraspinal homogeneous plaques with irregular margins, surrounding the anterolateral sides of the abdominal aorta and encircling the common iliac arteries. The lesion is well demarcated & isodense to surrounding muscle (Vaglio & Moriatati, 2016, Carmel *et al.*, 2008, Caiafa *et al.*, 2013, Mirault *et al.*, 2012). Extension into adjacent organs like pancreas, mesentery and vascular structures can also be evaluated easily on CT. Sometimes extension into duodenum, pancreas, spleen that may occur may also be identified. IRPF has been described based on CT Scan according to involved structure like Aorta, IVC, Ureters and renal hilum compressing renal arteries/ veins (Scheel & Feeley, 2009). Efforts have been made to differentiate benign from malignant lesions but definite characteristics of malignant lesions have not yet been defined clearly. When a large & bulky lesion is seen displacing aorta and IVC anteriorly from spine and ureters laterally, diagnosis

of lymphadenopathy posterior to aorta and IVC is more likely. While in IRPF, abdominal aorta and IVC are not displaced anteriorly and ureters are displaced medially. Lymphoma has more cephalad distribution while IRPF is predominantly caudal to renal hilum (Carmel *et al.*, 2008). Local bone destruction is more likely to be due to underlying malignancy rather than IRPF. Degree of soft tissue enhancement on CT may correlate with activity of fibrotic process. In acute stages of IRPF, enhancement with increase of 20-60 Hafter contrast administration may be seen while little or no enhancement is seen in advanced or chronic disease. Renal impairment in many cases may not allow administration of IV contrast and sometimes fibrous reaction may not be seen on CT in one-third of patients with proven RPF.

MRI

Imaging features on MRI, differentiating malignant lesions specially lymphomas from IRPF based on extension are similar to CT scan. Lymphomas are seen as large mass chiefly in suprarenal region with perirenal extension and retroperitoneal lymph nodes. They show heterogeneity on T2-weighted imaging and contrast- enhancement but hyperintensity on T2-weighted imaging and hypervascularity on contrast-enhanced imaging were non-conclusive for the differentiating the two lesions. Apparent Diffusion Coefficient (ADC) value of lymphoma has been noted to be significantly lower as compared to IRPF (Rosenkrantz *et al.*, 2012). A bulkier lesion in retroperitoneal region, extending above origin of renal arteries, or displacing the aorta anteriorly and inhomogeneous intensity on MRI, is more likely to be malignant. Also, a malignant lesion in retroperitoneum causing medial displacement of ureters is less frequent than IRPF (Vaglio & Moriatati, 2016; Carmel *et al.*, 2008, Caiafa *et al.*, 2013, Mirault *et al.*, 2012). [18F] FDG PET allows whole-body imaging and helps in identifying extra-retroperitoneal lesions but has low diagnostic value, is very costly and not accessible to all. It is being used as follow-up to detect metabolic activity of residual disease after the treatment by some investigators (Vaglio *et al.,* 2005, Treglia *et al.*, 2012, Zhang *et al.*, 2014).

Histopathology

The percentage of IRPF diagnosed by biopsy ranges from 24%–77% (Vaglio & Moriatati, 2016, Kermani *et al.,* 2011). On gross examination, IRPF tissue looks pale, plaque like mass with ill defined margins and enveloping adjacent viscera, ureters and sometimes IVC. IRPF is seen as an aggregation of B and T lymphocytes in the initial phase followed by eosinophilic infiltration and capillary proliferation as the disease progresses forming a dense fibrous mass finally (Scheel *et al.,* 2012). Microscopic Examination shows fibroblastic proliferation and predominant presence of lymphocytes, macrophages, and vascular endothelial cells (Vaglio & Moriatati, 2016, Carmel et al., 2008, Corradi *et al.,* 2007). The fibrous tissue consists of extracellular matrix containing type I collagen fibers organized in thick irregular bundles around small retroperitoneal vessels. Fibroblasts can be seen in stages of activation and transition into myofibroblasts (a smooth muscle actin expression), which form the major source of collagen. Though clonal proliferation was shown, mitoses occurred rarely (Vaglio & Moriatati, 2016, Kaddouri *et al.*, 2017). Human Leukocyte antigen, HLA-DR (Human Leukocyte Antigen – DR isotype) may also be seen in many (Carmel et al., 2008). As plasma cells are the chief inflammatory cells, a ratio of IgG4+/total IgG+ plasma cell equal to 40% is considered to classify IRPF as "IgG4-RD" if infiltration of eosinophils, storiform fibrosis, and obliterative phlebitis are also present (Zhang *et al.*, 2017, Khosroshahi *et al.*, 2013, Zen *et al.*, 2009). Tryptase immunostaining is used to identify mast cells (Mangieri *et al.*, 2012). Comprehensive evaluation is necessary to rule out any neoplastic process.

Management

Main aim of management of IRPF is to relieve the ureteral obstruction as well as induce disease regression, using glucocorticoids either alone or in combination with other traditional immunosuppressants (Vaglio & Moriatati, 2016, Scheel *et al.,* 2012, Sili *et al.*, 2012). In case of acute renal impairment, immediate relief of ureteral obstruction is required by placing double-J stent or nephrostomy tube (Vaglio & Moriatati, 2016, Scheel *et al.,* 2012, Scheel *et al.*, 2013, Mertens et al., 2014). Both the procedures are considered safe and both have similar complication rates (Mertens *et al.,* 2014). This may be followed by open or laparoscopic ureterolysis and intraperitonealization and omental wrapping of the ureters to achieve more definitive resolution of ureteric obstruction, depending on the institute policy (Jadhav *et al.*, 2017). If ureteral obstruction is mild and not likely to affect renal functions, medical therapy may be started without surgical intervention and observed for regression of RPF. Surgical intervention may be needed if chronic residual hydronephrosis persists or renal functions are at risk of worsening. Glucocorticoids are used world-widely for regression of IRPF, but can have toxic effects (Sili *et al.*, 2012). Prednisolone is used in the dose of 0.75–1 mg/kg/day and is then tapered within 6–9 months to 5–7.5 mg/day (Brandt *et al.*, 2014, Laroche *et al.*, 2016). Tamoxifen, an anti-estrogen agent with potential antifibrotic activity was tried with variable results in patients with contra-indications/toxicity to glucocorticoids and its efficacy has not been proven in clinical trials (van Bommel *et al.*, 2009, Brandt *et al.,* 2014). Methotrexate has been suggested in relapsing IRPF either as a steroid-sparing agent or in combination with prednisolone (Vaglio & Moriatati, 2016, Sili *et al.,* 2012, Tanaka & Masumori, 2020). Relapse rate up to 72% have been observed in patients with IRPF making it as a chronic-relapsing disorder and some patients even experience multiple relapses (Vaglio & Moriatati, 2016). Combination of mycophenolate mofetil and prednisone has also been cited as an efficacious and safe treatment for IRPF, especially in patients with renal insufficiency because of its antifibrotic properties (Scheel *et al.,* 2012, Jois *et al.*, 2007). It has also been shown to inhibit T and B lymphocyte proliferation through its active metabolite, Mycophenolic acid (Scheel et al., 2013). Cyclophosphamide is another immunosuppressant used effectively as initial therapy but not as first-line therapy esp. in Antineutrophil Cytoplasmic Antibody (ANCA)-positive periaortic vasculitis with RPF, which is then followed by other immunosuppressants for maintenance (Vaglio *et al.,* 2002). All the patients need to be followed regularly using laboratory examinations, CT/MRI or ultrasonography to look for early detection of relapses.

4. Results

It has been 3 years since last episode of admission for complications related to RPF and 20 years since he was first diagnosed with this condition. He is leading a very active life at work place as well as at home. Till now our patient has managed to survive with mild renal impairment fluctuating between 1.4 – 1.6mg/dL.

5. Discussion

Diagnosis of IRPF and treatment is usually delayed because of vague clinical symptoms in the initial phase or delayed manifestation or occurrence in associated concomitant disease (Carmel *et al.,* 2008). This makes patients present late as they keep on tolerating mild discomfort which usually subside by analgesics available over the counter. IRPF is a rare collagen vascular disorder of unclear etiology (Vaglio & Moriatati, 2016). Smoking and Environmental exposure to asbestos have been postulated as the inducing agent, same cannot be cited in our patient as there is no evidence of pleural

thickening or pulmonary fibrosis and there is no history of smoking or any other substance abuse, though he has lived in regions having abundant asbestos but has no direct occupational exposure to it. He has worked in close proximity of animals specially cows and buffalos. Is it possible that he contacted some bovine infection inducing the fibrosis?

Our patient had early onset of illness at the age of thirty-three, when he presented with anuria twenty years ago. He is well built and never had loss of weight at any point of time. He didn't give history of pulmonary tuberculosis either. We obtained excellent correlation between findings of cystoscopy, RPG, MRU and biopsy. His symptoms at presentation were obstructive uropathy and he developed Hypertension 6 years after the diagnosis of RPF and was put on β-blockers later on. There is a possibility that some patients develop hypertension as a result of RPF requiring administration of β-blockers rather than being an inducing agent, as in our case.

We could not find any evidence of renal artery stenosis in our patient. In our patient cause of left renal atrophy seems to be encroachment of fibrotic process on the left pelvic ureter. In studies involving large number of patients cause of renal atrophy has not been established, which could be attributed to Renal artery stenosis, direct IRPF or the systemic disease-causing IRPF. It might also be possible that microscopic changes cannot be seen in earlier stages till the fibrotic process has done the damage.

We could not establish any kind of association with auto-immune disorder based on sonography and ANA profile in this patient though he developed hypothyroidism after 10 years of first episode of RPF which can be suggestive of auto-immune disorder as no other causative etiology could be found in this patient.

Our patient is a rare case of acute DVT which he developed 12 years of first episode of RPF, alongwith encasement of IVC almost completely obstructing it which is rarely seen in IRPF though IVC occlusion may be seen to varying degrees. Iliocaval thrombosis/occlusion occurs in only 2% of cases of RPF (Scheel *et al.*, 2012).

Although prognosis of IRPF is relatively good, chronic intermittent relapses of the disease can be psychologically and physically devastating for the patient. Varying degrees of chronic renal insufficiency occur in up to 32% of the patients, but end-stage renal disease is exceedingly rare (Sili *et al.*, 2012, Kermani *et al.*, 2011). Our patient had atypical symptoms at long and almost regular or cyclic intervals of 3-4 years with complications manifesting all of a sudden and mostly during the period between march and July, which could be just a co-incidence or seasonal variation. Elevation of ESR coincided every time he had a complication. The degree of acuity of the clinical manifestations every time of relapse is unusual and unique as the patient had been getting investigations done regularly every year. Venous compression secondary to RPF is typically a chronic process with development of extensive collateral circulation. But in our patient, it occurred without prior warning signs.

The cyclical nature of relapse in this case led us to think whether disease free interval of 3-4 years between acute episodes was actually a disease-free interval or was the disease in a continuous slow progressive state but due to intervention in form of immunosuppressants had become inactive for some time or gone into silent phase to be activated upon by some kind of trigger.

6. Conclusion

Subtle manifestations and vague symptoms make early diagnosis of Idiopathic retroperitoneal fibrosis difficult. It is a systemic fibro-inflammatory disease having association with auto-immune disorders and a chronic relapsing nature. Though CT and MRI, the two tests of choice in RPF

diagnosis are easily available, investigations like [18F] FDG PET are still not within reach of many patients. High index of suspicion, early investigations and follow-up can make early diagnosis and treatment possible and yield to more information about the disease. More research is required in the field of pathogenesis and treatment of IRPF.

7. Ethical Aspects:

Informed consent or approval from ethics committee

8. Conflict of Interest:

None

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11. Abbreviations:

[18F] FDG PET - Fluorodeoxyglucose Positron emission tomography
ADC - Apparent Diffusion Coefficient
ANA - Anti-Nuclear Antibody
ANCA - Antineutrophil Cytoplasmic Antibody
AP - Anteroposterior
Bl. Urea - Blood Urea
CBD - Common Bile Duct
CC – Cranio-Caudal
CCR - C-C chemokine receptor
CMD - Cortico-Medullary Differentiation
CPK - Creatine phosphokinase
C-reactive protein CRP
CT - Computed Tomography
DJ – Double 'J' (ureteric stent)
DVT – Deep Vein Thrombosis
Erythrocyte Sedimentation Rate - ESR
HLA-DR - Human Leukocyte Antigen -DR isotype
Idiopathic retroperitoneal fibrosis: IRPF
IgG4-Related Disease - IgG4-RD
IITV – Image Intensifier Television
IL-6 – Interleukin - 6
INR - International Normalized Ratio
IRPF – Idiopathic Retroperitoneal fibrosis
IVC – Inferior Vena cava
IVD - Inter-vertebral Disc
MRA - Main Renal Artery
MRI - Magnetic resonance imaging
MRU - Magnetic Resonance urography
NSAIDs - Nonsteroidal anti-inflammatory drugs
PHT - Portal Hypertension
PSV - Peak Systolic Velocity
R.I. - Resistive Index
RPF - Retroperitoneal fibrosis
S. Creatinine - Serum Creatinine
SLE - Systemic Lupus Erythematosus
Tc-99m DTPA - Technetium-99m Diethylenetriamine pentaacetate
TD - Transverse Diameter
TNFα - Tumour necrosis factor alpha
UTI – Urinary Tract Infection

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RESUMEN

La fibrosis retroperitoneal idiopática es una enfermedad fibroinflamatoria rara, de etiología variada que generalmente se origina alrededor de la aorta y se propaga caudalmente a lo largo de los vasos ilíacos en retroperitoneo adyacente causando obstrucción ureteral como la complicación más frecuente.

Reportamos el caso de un paciente varón de 53 años que se presentó con un dolor leve en ambas piernas. Al investigar más a fondo, descubrimos que había estado luchando con recaídas intermitentes cada 3-4 años durante los últimos 20 años desde que se le diagnosticó por primera vez fibrosis retroperitoneal idiopática. Tenía 33 años cuando desarrolló por primera vez los síntomas de anuria durante 48 horas y se le diagnosticó fibrosis retroperitoneal idiopática. Esto fue seguido por atrofia del riñón izquierdo e hipertensión 6 años después, luego hipotiroidismo después de otros 3 años y finalmente afectación de la vena cava inferior y trombosis venosa profunda aguda de las extremidades inferiores después de otros 3-4 años. Su trombosis venosa profunda se controló bien a tiempo. Le recetaron glucocorticoides cada vez que tenía una recaída y una complicación.

Hicimos una revisión de la literatura para comprender los avances recientes sobre su patogenia, diagnóstico, investigaciones y manejo. Se realizaron búsquedas en PubMed utilizando términos como fibrosis retroperitoneal sola y en combinación con términos relacionados como trombosis de la vena cava inferior, trombosis venosa profunda, tamoxifeno, metotrexato. Este caso es único, ya que es muy raro encontrar trombosis venosa profunda aguda en fibrosis retroperitoneal idiopática sin desarrollo de colaterales cuando la luz de la vena cava inferior está comprometida hasta una obstrucción casi completa.

Después de un seguimiento de 20 años, el paciente se encuentra bien en términos de actividad física y bienestar psicológico con antihipertensivos, tiroxina y anticoagulantes. ¿El intervalo libre de enfermedad está realmente libre de la enfermedad o simplemente disminuyó con inmunosupresores para activarse después de algún tiempo?

Palabras clave: Fibrosis retroperitoneal idiopática; Trombosis de la vena cava inferior; Hipotiroidismo; Inmunosupresores; Uropatía obstructiva.