

# Revisiting the retroperitoneal fibroses: are there any significant news about their aetiopathogenesis and diagnostic approaches?

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**Abstract.** – **BACKGROUND**, Many articles on retroperitoneal fibroses (RPF<sub>s</sub>), published over the last ten years, seem to set out as innovative the carried-out both diagnostic procedures and therapeutic measures, while a careful examination of the literature identifies them as a sheer application of previous acquisitions. Surely, instead, several interesting advances have been pointed-out in the field of pathogenesis, particularly regarding significant immunological correlations between yet so-termed idiopathic form and some systemic immune-mediated disorders.

**AIM**, To resume such topic as far as the pathogenetic implications are concerned, moreover taking into due consideration both the diagnostic modalities and, secondarily, the therapeutic measures innovatingly set out since the Eighties/Nineties of past century.

**AETIOLOGY**, The protean aetiopathogenesis of secondary RPF<sub>s</sub> is outlined, moreover up-to-dating an old taxonomic assessment. Before labelling a RPF as idiopathic any identifiable cause should be excluded as well as a possible correlation, synchronously or diachronously, with well-labelled multi-system autoimmune diseases, among whose the autoimmune responses to apoptosis-derived immunogenic material as primary source of autoantigens, the newly recognized hyper-IgG4-related sclerosing disease, besides well-known systemic fibrosclerotic disorders.

**DIAGNOSTICS**, Laboratory findings may be sometimes consistent with a specific aetiology of secondary RPF<sub>s</sub> (e.g.: circulating anticardiolipin antibodies, high both serum 5-hydroxy-tryptamine and urinary 5-hydroxy-indolacetic acid, elevated serum tumor markers). Since the Eighties, CT and MRI are the most suitable imaging modalities for RPF, often resorting to contrast enhancement nevertheless taking into account the risk of either iodinated contrast-induced nephropathy or Gd-based material-dependent “nephrogenic systemic fibrosis”. Nuclear medicine, particularly with 18F-FDG-PET, besides to assess RPF “activity” and detect multi-focal fibroinflammatory diseases, can also tailor the therapeutic management according to dynamic course of the disease.

**CONCLUSIONS**, As against plenty of pathogenetic news, no innovative idea has been recently produced about diagnostics and therapy of RPF<sub>s</sub>, that might cause a knowledge structure break compared with the two last decades of the past century.

*Key Words:*

Atheromatous aortitis, Drug-induced fibrosis, Hyper IgG4 disease, Diagnostic imaging, Nephrogenic fibrosis.

## Introduction

Retroperitoneal fibrosis (RPF), whose first description dates back to 1905, when French urologist Albarran<sup>1</sup> reported the surgical treatment-related macroscopic findings of a wide fibrous retroperitoneal process entrapping the ureters, has been afterwards properly recognized, in 1948, by Ormond<sup>2</sup>, as a disease characterized by a wooden chronic fibro-inflammatory plaque that covers and often entraps various retroperitoneal structures and organs.

Since early second half of the past century, an important research developed to define the aetiopathogenesis of such disease, sometimes identifying some different causes – hence various secondary RPF<sub>s</sub> – while mostly the aetiology remaining obscure (idiopathic RPF). The historical approach to the identification of secondary forms allows to point out a first phase – peculiar of the Sixties-Eighties of the last century – with prevalent interest in the drug-induced ones, through either clinical studies or animal research<sup>3-16</sup>, and a subsequent phase particularly aimed at both identifying either atheromatous or nonatheromatous vascular disease-related RPF and recognizing a possible immune mechanism-mediated pathogenesis<sup>17-26</sup>. Just since that time, the availability of more suitable both immunohistochemistry and

molecular analysis tools together with the development of imaging technologies, such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine, supplied a reliable assessment of RPF different etiopathogenetic factors, as have been at that time pointed out in various original works and highlighted in some literature reviews<sup>7,9,16,27-31</sup> and merely drawn-on over the last ten years. The better knowledge of aetiopathogenetic pathway underlying either atheromatous aortitis- or nonatheromatous aortic aneurysm-related RPF has progressively reduced the amount of the formerly through idiopathic RPF.

Restrictly to the idiopathic form, indeed, the prevalence seems to be about of 0.1/100,000/year while its prevalence accounting about of 1.38/100,000 inhabitants according to epidemiologic study in a Finland area. Middle-aged men are affected twice or three time as often as women, though reports of this disease in children and in the elderly are not uncommon<sup>32-36</sup>.

Considering that surgical treatment of idiopathic RPF may only relieve – as debulking-decompressive measure – the ureteral obstruction while resulting unable to prevent both disease progression and its possible relapse, since the Sixties of the last century, medical therapy modalities have been proposed, resorting at first to corticosteroids and immunosuppressants and, even from the beginning of the Nineties, to the tamoxifen, alone or as a second-line treatment, according to that has been suitably reported in the literature<sup>7,9,25,31,37-58</sup>.

### Aetiopathogenetic Considerations

Whereas with regard to *idiopathic RPF*, no specific cause, by definition, may be proved but sometimes merely hypothesized and moreover considering quite questionable its inclusion, together with inflammatory aortic aneurysm and perianeurysmal RPF, under the muddling common cover-term “chronic periaortitis”, a taxonomic aetiopathogenetic *assessment*, on the basis of established causative factors, may be rightly out-lined about the secondary RPF<sub>s</sub> (Table I)<sup>7,15,16,29-31,34,40,59</sup>.

### Aetiopathogenesis of Secondary Forms

Secondary RPF<sub>s</sub> are the end results of a chronic retroperitoneal inflammatory process elicited by a variety of causes, including traumatic in-

juries, persistent infections, protracted drug administration, immune-allergic responses to different stimuli, and neoplastic and paraneoplastic conditions<sup>7,16,27,29,30,34,62</sup>. Though in absence of standardized taxonomic criteria, a long time ago an aetiological over-simplifying classification has been proposed, then rearranged and up-dated (Table I).

A wide range of either accidental or iatro-induced *traumatic conditions* can promote, through an inflammatory-fibrogenic reaction, a RPF, usually localized within the trauma area<sup>7,16,31,63-66</sup>. Also nonatheromatous aortic aneurysm-related RPF – *perianeurysmal retroperitoneal fibrosis* – could be likely explained as a fibrogenic reaction to both “pulsed load stress” of retroperitoneal soft tissue from the aneurysm abnormal wall pulsations (fibrous process similar to Dupuytren’s contracture as occurs in pneumatic drill workers) and perianeurysmal blood product deposit – particularly hemosiderin – due to repeated microhemorrhages resulting from the tiny leaks of aneurysmal wall (chronically leaking aneurysm)<sup>7,34,63,67</sup>. Moreover, CCchemokine receptor 5 (CCR5) Δ 32 polymorphism genotype may be associated with a higher risk of developing a non-atheromatous aneurysm-dependent chronic periaortitis<sup>68</sup>.

*Infection-related RPF* may result from local spread, by contiguity, of either chronic specific granulomas as that occurs from a paraspinal “abscess” following vertebral tuberculosis (Pott’s disease), or chronic intestinal and urogenital infections (colon diverticulitis, pyeloureteritis, etc) as well as of chronic mediastinitis<sup>7,16,31,34,69-71</sup>.

A subset of secondary RPF<sub>s</sub> is due to the lengthy use of some *drugs* such as ergot-alkaloids or their derivatives (e.g., ergotamine, methysergide, LSD, bromocriptine), kydralazine, β-adrenergic blockers, dopamine D-1 type receptor-agonists (e.g., methyl-dopa; cabergoline and pergolide, as ergot-derivatives), analgesics (e.g., aspirin, phenacetin, paracetamol), amphetamines, antitumoral chemotherapeutics<sup>3-14,72-78</sup>. Methysergide (methyl-butanolamide of the lysergic acid) is a serotonin (5-hydroxytryptamine, 5HT) receptor-antagonist to treat not only the headache but also diarrhoea due to carcinoid syndrome. The mechanism of lysergic acid derivative-related fibrogenesis remains still unknown, although it might consist in a drug aptenic role or, alternatively, in a rebound-release of 5HT and, in turn, of phlogogenic mediators (histamine, kinines, prostaglandins) following a prolonged intake of

**Table I.** Aetiologic conditions of secondary retroperitoneal fibroses.

• Traumatic:	
– Accidental	– Retroperitoneal haematomas and/or urinomas
– Iatro-induced	– Diagnostic procedures: percutaneous biopsy; urinary tract or vascular catheterization (contrast material extravasation); ureteroscopy; barium enema extravasation
	– Therapeutic procedures: retroperitoneal open or laparoscopic or even endourological surgery; haemorrhoid veins or varicocele sclerosing injection; abdominal-pelvic external beam deep radiotherapy (today, conformal 3D-intensity modulated radio-therapy, up to 6D-image-guided stereotactic-RT, considerably restricts the damage)
• Infectious:	– Retroperitoneal specific granulomas (tuberculosis, actinomycosis, histoplasmosis)
	– Retroperitoneal spread from chronic mediastinitis or from contiguous urogenital and intestinal infections (large bowel diverticulitis)
• Drug-induced:	– Lysergic acid derivatives (methysergide, ergotamine, cabergoline, pergolide, bromocriptine, LSD, etc); $\beta$ -adrenergic blockers; dopamine agonists (methyl dopa); antihypertensives and diuretics (hydralazine, chlorothiazide, reserpine); analgesics (phenacetin, aspirin, paracetamol); some antitumoral chemotherapeutics
• Resulting from chronic immunemediated inflammatory diseases:	– Atheromatous aortitis
	– Non-atheromatous systemic autoimmune vasculitides (as for large vessels: Takayasu's disease, giant cell arteritis; as for medium-small vessels: Wegener's granulomatosis, polyarteritis nodosa, etc)
	– Connective tissue systemic autoimmune inflammatory diseases (systemic lupus erythematosus, scleroderma, rheumatoid arthritis, etc.); systemic autoimmune parenchymatous diseases (thyroiditis, pancreatitis, glomerulonephritis, etc)
	– Hyper-IgG4-related systemic sclerosing disease
	– Inflammatory bowel disease (Crohn's disease, spreading through mesenteric roots)
• Granulomatous multisystem disorders:	– Xantogranulomatous histiocytosis (Erdheim-Chester disease)
	– Sarcoidosis
• Occupational:	– Exposure to asbestos
• Neoplastic (malignant RPF):	– Desmoplastic response to primary or metastatic retroperitoneal tumors
	– Paraneoplastic fibrosis from extra-retroperitoneal tumors (eg., carcinoid tumor)
• Other conditions:	– Endometriosis-related RPF (fibrous reaction to endometriotic nodules and their periodic bleeding)
	– Amyloidosis (twenty-eight different misfolded protein-related as much types of the disease)

(Mod. from Alberti C. Riv Radiol 1979; 19: 369-378).

antiserotonin drugs. Besides RPF, lysergic acid derivatives can induce a fibrotic process of heart-valves, pericardium, lung and pleura. While regarding idiopathic RPF, males predominate over women by a factor of two-three to one, in methysergide-induced RPF such ratio is reversed because of a larger prevalence of the headache – hence a bigger resort to such drug – in the women<sup>27,29,30,34,63</sup>. Interestingly, serum pro-inflammatory cytokines (IL-1 $\beta$ , IL-6) concentrations are higher in patients with migraine – while lower anti-inflammatory IL-10 serum levels – compared to healthy individuals, it suggesting, in migraine patients, a significant proinflammatory background<sup>79</sup>.

About the symptomatic treatment of Parkinson's disease, rather than resorting to above-mentioned ergot derivatives, it is today preferable the use of pramipexole, whose pharmacodynamic profile – very low affinity for D1-type re-

ceptors as well as for 5HT2A and 5HT2B receptors – allows to avoid the risk to induce both RPF and lung/heart-valve fibrotic processes<sup>80</sup>.

As far as *immune disease-related* RPF<sub>s</sub>, that one in the presence of aorto-iliac atheromatous inflammation (atheromatous aortitis) has been included, more than twenty-five years ago, among the secondary RPF<sub>s</sub> since such condition has been recognized to be elicited by both hapten-acting oxidized low-density lipoproteins (LDLox) and ceroids, which consist of oxidized lipoproteic polymers that are present within the aortic atheromatous plaques and result from LDL oxidation by ROS, *reactive oxygen species*<sup>17,18,34,40,61-63,82-84</sup>. The LDLox/ceroid-related antigenic phenotype is able to cause LDLox/ceroid receptor expression on macrophage and endothelial cell surface, hence anti-LDLox/ceroid antibody production and circulating immune-complexes deposition onto endothelium,

resulting in its impaired function (*endothelial dysfunction*). When the aortic media is breached, such hapten-acting oxidized lipids may be presented, by the plaque dendritic cells and macrophages, to both T- and B-immunocompetent lymphocytes, which, in turn, are recruited and activated in aortic media/adventitia, thus triggering a self-perpetuating inflammatory reaction, that involves, besides the aortic adventitia *vasa vasorum*, the surrounding periaortic tissue<sup>17,61,81</sup>. Several findings may support this pathogenetic mechanism: LDLox/ceroid leakage in the retroperitoneum because of the splitting of atheromatous aortic wall; IgG closely juxtaposed to extracellular LDLox/ceroid; ceroid-carrier macrophages (*foam cells* because their appearance) not only in aortic media and adventitia but also in regional lymph-nodes; serum antibodies to LDLox and ceroids more frequent in subjects with atheromatous aortitis than in sound controls<sup>17,18,31,59,61,81,85</sup>. Early distribution of active RPF around atheromatous aorta, first emerged from autopsy findings, has also been confirmed in living patients by CT-imaging<sup>26</sup>. Moreover, an increased prevalence of RPF in men rather than in women may be explained by the higher occurrence of atherosclerosis in male population.

To go into some details, macrophage activation by oxidized lipoproteins results in release of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), that can induce the translocation, from the cytoplasm into the nucleus, of nuclear factor (NF)- $\kappa$ B, one of the pivotal modulators of proinflammatory gene expression, since it is able to promote the transcription of several cytokines, cyclooxygenase-2, inducible nitric oxide synthetase (iNOS), matrix-metallo-proteinases, intercellular (ICAM)- and vascular (VCAM) cell adhesion molecules<sup>86</sup>. Moreover, Janus Kinases (Jak<sub>s</sub>) and *signal transducers and activators of transcription* (STAT<sub>s</sub>) have been proved to have a critical role in regulating immunity and inflammation by certain families of cytokines. In fact, raised expression of STAT1-mRNA is present in T-/B-lymphocytes and in fibroblasts of focal inflammatory infiltrates. IL-12, by activating STAT4, drives differentiation of naive T cells to T helper (Th) 1 cells, that, in turn, trigger a cell-mediated immune response, while IL-4, through activation of STAT6, promotes Th2 cell-differentiation, hence a B-cell-antibody-mediated immune response<sup>87</sup>. As far as allergic atheromatous aortitis is concerned, the progressive inflammatory involvement of aortic wall, from the media to the adventitia, is charac-

terized by a change from Th1 cell-immune mediated pattern (Th1 lymphocyte infiltrates) to Th2 one with clonal expansion of plasma cells and IgG hypersecretion, even together with persistent fibro- and myofibroblast activation<sup>24,61,88</sup>. Intriguingly, given the role of Jak<sub>s</sub>-STAT<sub>s</sub> in modulating cytokine network in any phase of the immune response, targeting some specific STAT<sub>s</sub> by selective Jak inhibitors could receive considerable attention as therapeutic measure<sup>82,87</sup>.

Several growth factors (transforming growth factor- $\beta$ 1, TGF- $\beta$ 1; basic fibroblast growth factor, bFGF; platelet-derived growth factor, PDGF, etc) play a profibrotic role, by driving the evolution of inflammatory periaortic-retroperitoneal process towards the fibrous phenotype through fibroblast activation. Particularly, TGF- $\beta$  is able to induce the change of fibroblasts in myofibroblasts with following hyperproduction of extracellular matrix components (mainly collagen, fibronectin, tenascin, glycosaminoglycans)<sup>89,90</sup>. Indeed myofibroblasts are key cellular mediators of fibrosis because they, when activated by paracrine signals from macrophages/lymphocytes or even by their own autocrine factors, play an important role as the primary collagen-producing cells. Moreover, besides from the fibroblasts, myofibroblasts are generated from endothelial cells through a process termed *endothelial-mesenchymal transdifferentiation* as well as from circulating fibroblast-like cells deriving from bone marrow stem cells<sup>63</sup>. Among above profibrotic growth factors, the pleiotropic cytokine TGF- $\beta$ 1 is the chief inducer of the fibrogenic process where the Smad (Sma, *Drosophila* + MAD, mothers against decapentaplegia, *Caenorhabditis*) pathway represents, about it, the direct target on fibroblastic cells<sup>90,91</sup>.

Some RPF<sub>s</sub> are today thought to be secondary to anatomoclinically well-labelled, even tough of unknown aetiology, *non-atheromatous systemic vasculitides* (as for large vessels: Takayasu's arteritis, giant cell arteritis; as for medium-small vessels: Wegener's granulomatosis, polyarteritis nodosa, etc), which are due to autoimmune-mediated mechanisms resulting from acquired antigenic phenotype of some neutrophil cytoplasm constituents, with following production of antineutrophil cytoplasmic antibodies (ANCA), that promote, in turn, through circulating immune complexes, the endothelial damage. Two major autoantigens within azurophil granules have been found: proteinase 3 (PR3) and

myeloperoxidase (MPO), PR3-ANCA showing a remarkable specificity for Wegener's granulomatosis, and the MPO-ANCA, instead, for polyarteritis nodosa. Subsequent cytokine-cascade activation, immune response and pathogenetic features of vasculitis-related RPF reproduce stereotypically the atherosclerosis-induced multi-step phlogogenic pathway<sup>21-23,25,93-98</sup>.

Several multi-organ fibrotic processes, also including RPF, may be today considered as fibroinflammatory disorders linked with newly recognized "hyper IgG4-related sclerosing disease" (IgG4-RSD), a multi-system sclerosing disorder, particularly involving, synchronously or metachronously – besides the retroperitoneum – pancreas (sclerosing pancreatitis, sometimes with pancreatic cancer), thyroid (Riedel' sclerosing thyroiditis), prostate gland (prostatitis), kidney (tubulo-interstitial nephritis), salivary glands (sclerosing sialoadenitis), lung (interstitial pneumonitis), mesenteria (mesenteric sclero-panniculitis), sometimes bile ducts (sclerosis cholangitis) and aorta (scleroaneurysmatic aortitis). The label of IgG4-RSD is due to the histopathological appearance that is characterized by a remarkable infiltration of lymphocytes and lympho-plasma cells immunoreactive for anti-IgG4 antibodies, together with tissue/organ fibrosclerosis, and meanwhile elevated serum IgG4 levels<sup>82,99-109</sup>.

Among the protean pathogenetic conditions of the autoimmune diseases, one mustn't disregard that the *apoptosis-derived materials* may be considered as a primary source of autoantigens which act as target of the autoimmune response, particularly when the activity of scavenger system (macrophages, dendritic cells, etc) is inadequate to remove immunogenic cell residuals (apoptotic cell bodies). Therefore, although systemic autoimmune diseases might reflect the confluence of genetic and environmental events, however the immunogenic apoptotic material is primarily involved in both activating and self-perpetuating autoimmune processes<sup>83,92</sup>. The immunoproteasomes are able to produce peptide-molecules that act as immunogenic epitopes towards the immune cells such as dendritic cells, thus leading to immune-mediated disorders (94).

Other secondary RPF<sub>s</sub> may result from desmoplastic reaction to *retroperitoneal primary malignancies* (Hodgkin's or non-Hodgkin's lymphomas, sarcomas) or to *retroperitoneal metastatic spread* of ubiquitous carcinomas, particularly of colon, prostate, breast, thus identifying a meta-tumoral sub-set of RPF where the desmoid

tumor-induced mesenteric fibrosis, in the field of Gardner syndrome, is also included<sup>9,27-29,33,34,110-112</sup>. Otherwise, some findings of the idiopathic RPF may sometimes mimic a T-cell malignant lymphoma, especially when fibro-collagenous tissue and fat mainly contain T-cell infiltrates<sup>113</sup>.

In patients with ubiquitous extraperitoneal tumors, a *paraneoplastic RPF* may develop as fibrous process mediated by various tumor-generated growth factors (TFG- $\alpha$  and - $\beta$ , PDGF, VEGF, etc), prostaglandins, cytokines (bradykinin, kallikrein, histamine, etc). Mainly related to 5HT-dependent fibrogenic mechanisms, the RPF in the field of carcinoid syndrome, moreover including fibrosis of heart valves, pericardium, lung and pleura, similarly to methysergide-induced lesions<sup>9,31,82,110,111,114-11</sup>.

Nosologically classified among the retroperitoneal neoplastic pathology, the *myofibroblastic tumors*, in the ancient times improperly named "inflammatory tumors" – mainly affecting the childhood – which appear as a huge infiltrating mass histologically showing myofibroblast proliferation together with inflammatory and mixoid areas. Such tumors often recur after surgical treatment while uncommonly metastasizing<sup>117,118</sup>.

Quite different from RPF, the *retroperitoneal fibromatosis* must be considered as fibrosing disorder due to uniform fibroblast proliferation, likely originating from the muscle epi-perimysia<sup>119</sup>.

Even though unusually (5, 10% of cases), the inflammatory bowel disease (*Crohn's disease*), by spreading to retroperitoneal tissue, mainly to its right side, can promote RPF. The proliferation of adipocytes (fat hyperplasia) adjacent to Crohn's enteritis comes before the panniculitis and mesenteric-retroperitoneal fibrosis<sup>120,121</sup>

### **Pathogenesis of Idiopathic Retroperitoneal Fibrosis**

Before labelling a RPF condition as "idiopathic", any identifiable cause should be excluded. Various interpretations of the literature lead to think that a subset of RPF, in the past labelled as idiopathic, might be considered as an epiphenomenon of advanced atheromatous aortitis. Therefore, RPF in the presence of aorto-iliac atheromatosis has been properly included among the secondary RPF.

The *true idiopathic form*, instead, – as anatomic-clinical entity in itself – is present in any case of RPF, such as in children or in patients without significant atherosclerosis, in which nei-

ther potential specific cause nor inclusion in a well-labelled multi-organ disease may be identified<sup>31,33,34,36,59,61,62,82,122,123</sup>. In such occasions, the term “idiopathic” keeps still its rightful place<sup>122</sup> against any suggestion of its systematic abandonment thoughtlessly in favour of “autoallergic peri-aortitis”<sup>125</sup>.

Pathogenetic hypotheses and theories for idiopathic RPF refer to so far unknown cause-related immune mechanisms, as it is inferred not only from the presence of serum autoantibodies but also from associated multi-organ autoimmune diseases, in the background of a systemic autoimmune protean disorder (Table II). Indeed, the demarcation between idiopathic and secondary RPF remains still unclear considering that the disease may occur synchronously or diachronously in the setting of different autoimmune conditions such as thyroiditis (Riedel’s, Hashimoto’s, Graves’ variants), lupus erythematosus, medium- and small-sized vessel angioitis (polyarteritis nodosa, Wegener’s granulomatosis) primary biliary cirrhosis, membranous nephropathy and ANCA-positive glomerulonephritis. In such circumstances, RPF should be properly defined *tout court* as component of a well-labelled multi-organ autoimmune – though aetiologically unclear – disorder rather than idiopathic disease in itself<sup>23,25,34,40,93-98,126-137</sup>. Moreover, as above highlighted, RPF histological appearance is sometimes that of *IgG4-related sclerosing disease*, with infiltrating plasma cells immunoreactive for anti-IgG4 antibodies, together with high serum IgG4 concentrations<sup>99-109</sup>.

As a possible genetic predisposition of idiopathic RPF, besides the old-timely indicated association with HLA-B27 antigen, a further

clue has been put forward because of its significant association with HLA-DRB1\*03, an allele just linked to several autoimmune conditions<sup>22,34,138-140</sup>.

### Pathological Findings

The *microscopic appearance* of RPF varies according to its dynamic evolution, thus changing from active, cellular and highly vascular stage – cellulitis and capillary vessel proliferation together with lipocyte disruption by interstitial oedema – to fibrotic-avascular stage.

In the early phases, the inflammatory infiltrate consists of both B (CD 20+) and T (CD 4+) lymphocytes, plasma cells, macrophages (CD68+) and histiocytes. Sometimes fibrinoid necrosis of medium-sized and capillary retroperitoneal vessels is also observed<sup>7,27,29,30,31,33,34,62,82</sup>. Interestingly, hypercellularity-related metabolic activity and hypervascularity of both the early “active” phases and the focal relapse into activity even during the late stages, may be properly identified also by image findings: high contrast enhancement CT, increased signal intensity on T2-weighted RM, positive <sup>67</sup>Ga-citrate and <sup>99m</sup>Tc-hIgG scanning, and <sup>18</sup>F-fluoro-deoxyglucose high uptake at a positron emission tomography (FDG-PET)<sup>27,29,34,144-146</sup>.

Sequentially, in the late stages, fibroblast and myofibroblast infiltrates, collagen deposition and bundling of argiophil fibrils, then true fibrosclerotic plaque with scattered calcifications are seen, the “mature” plaque resulting from a compaction of hyalinized collagen fibers containing few cells<sup>7,27,29,31,34,59,62,82,137,147</sup>.

**Table II.** Immune-mediated pathogenetic background of idiopathic retroperitoneal fibrosis.

• Genetic support:	– -HLA-B27, HLA-DRB1*03 haplotype (allele associated with several autoimmune disorders)
• Links with various immunomediated systemic diseases:	– Positive serum antineutrophil cytoplasmic antibodies (ANCA); antinuclear antibodies (ANA); anti-smooth muscle antibodies; anti-fibroblast antibodies; high serum IgG4 concentrations, especially in the “hyper-IgG4 disease” – Histology for immune-mediated inflammatory process; marked infiltration of IgG4-positive plasma cells (“hyper-IgG4 disease”) – Association with autoimmune-mediated parenchymatous diseases (thyroiditis with serum anti-thyroglobulin and/or anti-thyroid microsome antibodies, pancreatitis, glomerulonephritis, etc), sometimes in the field of “hyper-IgG4 disease” – Synchronous or metachronous inflammatory fibrous involvement of various organs and structures, in the range of multifocal or systemic fibrosclerosis (orbital pseudotumor, mediastinal fibrosis, sclerosing cholangitis, induratio penis plastica, etc.).
• Therapeutic criteria:	– Sensitivity, in the active cellular phases, to immunosuppressants

(Mod. from Alberti C. Eur Rev Med Pharmacol Sci 2007; 11: 375-382).

The *macroscopic appearance* of the “mature” RPF is that of a wooden fibrotic plaque usually starting at the aortic bifurcation and centralized at the level of the caudal lumbar vertebrae, often involving ureters, inferior vena cava, while rarely continuing above the diaphragm as fibrous mediastinitis or/and spreading down to the pelvis and to the scrotum with the testicular fibrous encasement, or/and extending into the mesenteric roots (sclerosing mesenteritis). *Fibrous ureteral envelopment* is often an early feature of RPF; the ureters, although not pathognomically, are drawn toward the middle line (lateralized, instead, in case of aortic aneurysm) and, although their lumen retains its virtually normal width, the own urinary transport dynamics is often impaired – aperistaltic-motionless ureter – with following uroastasis and hydronephrosis, hence renal failure. Retroperitoneal big vessels can tolerate fibrous encasement better than urinary tract, because their hemodynamics depends on pressure gradient rather than on peristaltic activity.

Unusually RPF can also involve, cephalad, duodenum, distal choledocus, under-diaphragmatic esophagus, portal vein, whereas, caudally, sigmoid colon, urinary bladder, prostate gland and seminal vesicles. Sometimes, in the field of IgG4-RSD, also the pancreas may be involved – sclerosing pancreatitis, at times with added pancreatic carcinoma – together with other organs<sup>7,31,34,99-109,123,137,148-154</sup>.

The micro- and macroscopic appearances of both primary-idiopathic RPF and secondary RPF<sub>s</sub> are often similar except, on the one hand,

the more localized extension of certain secondary RPF<sub>s</sub> (e.g., trauma- or infection-related fibrosis) and, on the other hand, the irregularly shaped malignancy-dependent RPF where neoplastic cells may be shown within the fibrous tissue.

### Clinical Appearance and Diagnostic Approaches

At the onset of the idiopathic RPF and sometimes even of the secondary RPF<sub>s</sub>, the clinical appearance is insidiously nonspecific, such as to suggest more frequently occurring diseases. So, an essential condition to promptly recognize the RPF is “a high degree of suspicion”<sup>155</sup>. The progression of retroperitoneal fibroinflammatory process gives rise to either *localized manifestations*, as mechanical-compressive effects of the fibrous mass, or *systemic expressions* as phlogistic background of the disease (Table III)<sup>7,27,29,31,34,123,155,156</sup>.

The *patient’s case history* must be thoroughly investigated to find the causes of a possible secondary RPF: back traumas, open or endoscopic retroperitoneal surgery, abdominal-pelvic radiation therapy, lengthy use of anti-migraine or anti-hypertensive drugs, carcinoid syndrome, etc. At the *physical examination*, the findings are often not very significant: at the most, a tender, hardly palpable, abdominal mass with a possible periumbilical bruit, at the auscultation, when an aortic aneurysm is present. Just considering the as-

**Table III.** Symptoms and clinical signs of RPF<sub>s</sub>.

<p><b>a) Localized (retroperitoneal mass-related compressive effects)</b></p> <ul style="list-style-type: none"> <li>• Pain (back, side, abdominal), in most cases dully constant, sometimes with ureteral colic-like features as result of ureteral entrapment</li> <li>• Oedema of the lower extremities, due to retroperitoneal venous/lymphatic involvement</li> <li>• Leg deep vein thrombosis, dependent on lately fibrous plaque-induced retroperitoneal vein compression</li> <li>• Hydrocele, varicocele, scrotal discomfort, due to gonadal vessel involvement</li> <li>• Claudication, Leriche’ syndrome from aorto-iliac entrapment</li> <li>• Renovascular hypertension, resulting from fibrous stenosis of the renal artery</li> <li>• Portal hypertension; jaundice (due to sclerosing cholangitis)</li> <li>• Superior vena cava syndrome, pulmonary hypertension, constrictive pericarditis, when also mediastinal fibrosis occurs</li> <li>• Haematuria, oligoanuria, urinary infection- and/or uraemia-related clinical manifestations</li> <li>• Dysuria, frequency</li> <li>• Constipation, mal-absorptive enteritis, chylous ascitis, when RPF affects also the mesenteric roots</li> </ul> <p><b>b) Systemic (inflammatory process-related constitutional effects)</b></p> <ul style="list-style-type: none"> <li>• Fatigue, myalgia, arthralgia</li> <li>• Mild fever, anaemia (due to cytokine-driven autoimmune pathogenesis)</li> <li>• Anorexia, nausea</li> <li>• Weight loss</li> <li>• Specific causative disease-related symptoms/signs as far as secondary RPF<sub>s</sub> are concerned</li> </ul>
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pecificity of the clinical appearance, the diagnosis of RPF is often delayed as to its onset, thus it relentlessly leading to advanced disease-related serious complications, such as particularly ureteral obstruction and hydronephrosis with following renal failure<sup>7,31,34,41,62,144,155-157</sup>. Therefore, an early *diagnosis* of RPF should be chiefly aimed to preserve the renal function, together with avoiding the possible development of a hypertensive condition<sup>155</sup>.

*Laboratory findings* may be mainly useful to assess the evolutive phase of RPF while no specific circulating markers have been identified. Active phase-reactants – ESR (erythrocyte sedimentation rate), CRP (C-reactive protein),  $\alpha_2$ -globulins –, that reflect the disease activity, can monitor its natural dynamic course and, in addition, the therapeutic response and a possible relapse<sup>7,31,34,35,41,154-157</sup>. The battery of laboratory tests includes, besides the complete blood count and renal function profile (blood cystatin-C and creatinine levels, serum electrolyte concentration), the assay of autoimmune disease-related markers such as a antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), anti-thyroglobulin antibodies, rheumatoid factor, and furthermore IgG and IgG4 serum levels<sup>31,62,82,99-109,123,145,148,155,158,159</sup>.

Sometimes, the laboratory tests are consistent with a specific aetiology of secondary RPF<sub>S</sub>: e.g., circulating anticardiolipin-antibodies point to atheromatous aortitis, high both serum 5HT and urinary 5-hydroxyindolacetic acid suggest a carcinoid syndrome, whereas elevated concentrations of serum tumor markers (CA 19-9, CEA, CA-125, CA 15-3, etc), hypercalcemia, positive fecal occult blood test allow to recognize a malignancy-related RPF<sup>7,30,31,114-116</sup>. Either needle- or open *biopsy* is sometimes required to both differentiate an idiopathic RPF from that secondary ones and identify either benign or malignant primitive retroperitoneal fibrotic disorders (fibromatosis, fibroblastic tumors, histiocytomas, fibrosarcomas, etc)<sup>155</sup>.

The development of *imaging technologies* (US, CT, MRI, nuclear medicine) in the Eighties-Nineties of the last century, has allowed to both largely avoid the resort to invasive diagnostic procedures – including the biopsy – by displaying essential findings on the involvement of retroperitoneal structure and to differentiate between idiopathic RPF and secondary forms whose identifying the causative conditions,

moreover monitoring the dynamic course of disease together with the therapeutic response. As a first-line imaging examination (Table IV), especially for uraemic patients, the *ultrasound scan* (echography, sometimes with Doppler-study) shows, particularly with regard to idiopathic RPF, a iso-hypoechoic plaque, sometimes entrapping the ureters – squeezing disease – with consequent unilateral or bilateral hydronephrosis. Aortic aneurysm is clearly shown when perianeurysmal RPF occurs. Unfortunately, on sonography, early phases of RPF may be missed because of US poor sensitivity, particularly when the fibrous plaque is masked by fluid and gas filling up the bowel loops. Otherwise, sonography, together with elastography, may be very useful to detect a Riedel's thyroiditis, associated with RPF<sup>27,34,160-163</sup>.

Currently, *CT and MR imaging techniques* are the most suitable modalities in the study of RPF (diagnosis, differentiation between idiopathic RPF and secondary forms, identification of dynamic stages), meanwhile allowing the assessment of involved retroperitoneal structures. The fibrotic process, on the unenhanced CT, is seen as homogeneous mass isodense (30 ÷ 50 U.H.) with psoas muscles, enveloping the aorto-iliac bifurcation and sometimes entrapping the ureters. The retroperitoneal lipomatosis, instead, is hypodense (-60 ÷ -110 U.H.) as the fat tissue. Malignancy-related RPF, dissimilarly to idiopathic form, mostly produces an anterior displacement of the aorta while laterally of the ureters. After administration of a contrast material, the enhancement of the plaque reflects the activity of fibroinflammatory plaque, the acute-early stage, characterized by greater vascularity/cellularity, enhancing to higher degrees. Multislice (multidetector)-CT allows a multiplanar 3D-postprocessing that is particularly useful to study the fibrous involvement of retroperitoneal vascular structures, and, by resort to 3D-volume rendering, to achieve a retroperitoneal vascular mapping<sup>153,155,161,164-168</sup>. The renal pelvis dilatation may be lacking when the fibrous process also involves the renal sinus. If the uro-CT is ineffective because of renal failure, the resort to retrograde uretero-pyelography may be necessary to properly identify the extent of ureteral dynamic involvement by the fibrous plaque, while the ureter remaining anatomically patent to retrograde probe (aperistaltic-nonstenotic ureter).

Better than CT, *MR imaging* can define the morphology and size of RPF, multiplanarly

**Table IV.** Imaging techniques and findings.

<ul style="list-style-type: none"> <li>• Ultrasound examinations (B-mode, contrast-enhanced, colour-Doppler)</li> <li>• Intravenous urography, uro-CT*</li> </ul>	<ul style="list-style-type: none"> <li>– Hypo-anechoic, hypovascularized fibrous plaque (late phase)</li> <li>– Renal pelvis dilatation</li> <li>– Aortic atheromatosis; aortic aneurysm</li> <li>– Unilateral or bilateral hydronephrosis (unless there is even fibrous involvement of renal sinus)</li> <li>– Ureteral medialization (no pathognomonic sign)</li> <li>– Diuretic furosemide test may show an early pyeloureteral dynamic imbalance</li> <li>– Sometimes, “stunned or hibernating kidney” (enhanced and persistent nephrographic phase without urographic phase)</li> <li>– Fibrous mass isodense (CT) with psoas muscles</li> <li>– Contrast-enhancement (CT) in “active phases” (early stage, relapse) of dynamic fibroinflammatory process</li> <li>– Multiplanar image post-processing, 3-D-volume rendering to achieve a proper retroperitoneal vascular mapping</li> </ul>
<ul style="list-style-type: none"> <li>• Magnetic resonance (unenanced or enhanced by paramagnetic Gd<sup>3+</sup>-based contrast materials)*</li> </ul>	<ul style="list-style-type: none"> <li>– In the late stage, the hypovascularized fibrous plaque has low intensity signal on T1-as well as on T2- weighted images whereas the early “active” hypervascularized oedematous fibroinflammatory plaque shows a high intensity signal on T2-weighted images. Lipomatosis (as well as fat tissue) has high intensity signal in T1- and T2-weighted images</li> </ul>
<ul style="list-style-type: none"> <li>• Nuclear medicine</li> </ul>	<ul style="list-style-type: none"> <li>– Radiopharmaceuticals for renal imaging and functional study (individual kidney function; split function): <sup>99m</sup>Tc-MAG, <sup>99m</sup>Tc-DMSA, <sup>99m</sup>Tc-DTPA</li> <li>– Imaging of “active” fibroinflammatory process, by use of <sup>67</sup>Ga-citrate, <sup>111</sup>In-labelled autologous leucocytes, <sup>99m</sup>Tc-human immunoglobulins, etc</li> <li>– <sup>18</sup>F-FDG-PET, showing not only the RPF “active” phases but also other active foci in multi-organ systemic diseases</li> </ul>
<ul style="list-style-type: none"> <li>• Fusion-imaging (PET/CT, PET/MR)</li> </ul>	<ul style="list-style-type: none"> <li>– CT-MR morphological/PET functional finding integration</li> </ul>

\*In patients with renal function impairment, x-ray-iodinated contrast media – especially ionic hyperosmolar agents – may induce the well-known CIN, contrast-induced nephropathy, as well as Gd-based MR-contrast materials – especially nonionic linear Gd-chelates, less stables than the ionic macrocyclic ones – may trigger the newly recognized NSF, nephrogenic systemic fibrosis. (Mod. from Alberti C. et al. *Urologia* 2006; 73: 205-216).

showing its relationships with surrounding structures and organs. The sole disadvantage of MRI is its inaptitude to show vascular calcifications. The MR study may be carried out either in unenhanced conditions or resorting to paramagnetic contrast media (nonionic linear Gd-contrast agents such as Gd-EDTA, or ionic macrocyclic Gd-contrast agents such as Dotarem), by routinely using T1- and T2-weighted spin-echo scans with fat signal saturation images. The “mature” hypovascularized fibrous plaque has a low intensity signal on T1- as well as on T2-weighted images with a poor contrast enhancement, while the early “immature” active, hypervascularized fibro-inflammatory plaque shows a high intensity signal on T2-weighted images, as it has been clearly pointed-out a long time ago<sup>27,29,30,31,34,62,168-176</sup>. Unfortunately a high signal on T2-weighted images cannot differentiate the active phase of benign RPF from malignant RPF because such

finding depends on hypervascularization that is present in both conditions, whereas an inhomogeneous signal on T2-weighted images more reliably reflects a malignancy-associated RPF. Interestingly Gd-enhanced RMI is currently used to monitor the response to therapy<sup>27,29,146,155,175-177</sup>.

It’s likely that *molecular MRI* with intravenously administered type I-collagen targeted EP-3533 probe might noninvasively identify the fibrotic tissue in relation to collagen-derived hydroxyproline concentrations.

Urographic findings may be also achieved by Gd-based paramagnetic contrast materials – particularly by Gd-MAG3 (mercaptoacetyl-triglycine), a new MR-contrast agent – and gadolinium bolus intravenous injection can allow high definition angiographic images, particularly helpful to study aortic inflammatory aneurysms and large vessel vasculitides, with diagnostic accuracy equivalent to invasive angiography; how-

ever, one mustn't disregard the potential Gd-based contrast agent-induced development of *nephrogenic systemic fibrosis* (NSF), as it is common knowledge, since 2006<sup>98,178-181</sup>. NSF, previously named "fibrosing dermatopathy", is a life-threatening generalized fibrotic disorder occurring in subjects with severe renal impairment as result of the use of gadolinium-based contrast agents because of release of cytotoxic free Gd-ions (nonionic linear Gd-chelates, as Gd-EDTA, are less stable than the ionic macrocyclic ones), particularly under microenvironmental tissue condition of metabolic acidosis. Free Gd-ions are able to trigger a TFG $\beta$ -mediated fibroblast/myofibroblast activation with following increase in collagen production<sup>179-181</sup>. For such reasons, the use of Gd-paramagnetic contrast materials to avoid nephrotoxic risks related to iodinated x-ray contrast media, in patients with renal insufficiency, is at least incorrect.

*Nuclear medicine studies* offer intriguing means to both provide a quantitative assessment of renal perfusion and glomerular function (individual kidney function, split function), degree of ureteral obstruction and evaluate the "activity" features of the fibroinflammatory plaque, whose identifying the dynamic phases of natural history and the response to the medical treatment.

Several radiopharmaceuticals are available for renal imaging and functional studies: <sup>99m</sup>Tc-MAG (mercaptoacetyl triglycine), <sup>99m</sup>Tc-DMSA (dimercaptosuccinic acid), <sup>99m</sup>Tc-DTPA (diethylenetriamine-pentacetic acid), that have the important advantage of the absence of systemic pharmacological side-effects and allergic reactions. Diuretic renogram is a provocative modality to identify early conditions of pyeloureteral dynamic imbalance in RPF patients<sup>182</sup>.

As far as radioisotope-based imaging of the fibroinflammatory process is concerned, <sup>67</sup>Gallium-citrate has been used, at first, to show early-active stages of RPF. Afterwards, to detect the fibro-inflammatory process, other tracers have been used such as autologous <sup>111</sup>In-labelled leucocytes or nanometer-sized <sup>99m</sup>Tc-labelled colloids or even <sup>99m</sup>Tc-human immunoglobulins, thus these nuclear medicine procedures proving to be also useful as follow-up after medical therapy<sup>29,30,34,40,141,155,183-188</sup>.

The resort to [<sup>18</sup>F]-FDG-PET (<sup>18</sup>Fluoro-deoxyglucose-positron emission tomography), as functional imaging technique widely used in tumor- and inflammatory process patients, has become more and more frequent, since the early Nineties, also in patients with RPF, allowing not

only the assessment of inflammatory activity of the retroperitoneal mass – although about that no providing a differential diagnosis between neoplastic and inflammatory processes – but also, as whole body-imaging modality, showing, besides the RPF, other sites of multi-focal disorders, such as systemic fibrosclerosis, and the unknown primary malignant process whose RPF may represent a paraneoplastic epiphenomenon. Moreover [<sup>18</sup>F]-FDG-PET is useful to tailor the therapeutic management of RPF to active phases of the disease, PET findings often tallying with laboratory activity data (ESR, CRP, fibrinogen)<sup>64,97,98,115,130,142-146,155,189-192</sup>. Fusion imaging (PET/CT, PET/MRI) allows to integrate functional PET findings with either CT- or MRI-morphologic aspects<sup>97,143,146,162,192,194</sup>.

Moreover PET, by means of <sup>11</sup>C-5-hydroxytryptophan (precursor of 5-HT, serotonin), allows to suitably identify the carcinoid tumor and its metastases in patients with carcinoid syndrome-related RPF<sup>195</sup>.

### Emerging Considerations and Future Perspectives

Considering the above review of the literature on the diagnostic strategy of RPF<sub>s</sub>, it wouldn't seem that, about it, emerge, over the last ten years, quite *specific* innovative knowledges in comparison to those has been formerly pointed out, particularly with reference to the idiopathic form. Just from this point of view, the proper treatment of any subject, both on the humanities and positive sciences, should include the pre-comprehension of its historical significant aspects without overlooking them because of either carelessness or purposely and superciliously.

Instead, a better understanding of *general* pathophysiological mechanisms underlying the multi-organ autoimmune processes (e.g., hyper-IgG4-related sclerosing disease, multisystem connective tissue protean disorders) has involved a proper RPF taxonomic rearrangement (Table I), with reducing the assessment range of the true idiopathic form, still unrelated to well-labelled diseases. So, in the field of "hyper-IgG4 syndrome" could be today included some sclerosing processes, among which quite the IgG4-related RPF<sup>34,99-109,124,125,188</sup>. Indeed, as stated above, the novel anatomico-clinical entity IgG4-RSD is a multiorgan protean connective tissue immunopathological disorder, characteristically responsive to corticosteroids, that implies a fi-

brosclerotic process with lympho-plasmacell infiltration mainly made up of polyclonal IgG4 plasma cells, together with significantly high serum IgG4 levels<sup>100,103,104,108,109,188</sup>.

The true idiopathic RPF would be recognized in any case in which neither potential causative condition nor underlying systemic diseases may well-labelled systemic diseases may be identified, in such circumstances the term “idiopathic” keeping still its rightful place<sup>34,124,125,188</sup>. Otherwise, already twenty-five years ago, the atheromatous aortitis-induced RPF has been included among the secondary forms, because this condition appears to be triggered, through immune-mediated mechanisms, by antigen-acting ceroids<sup>17-19,26,30,31,34,85,124,125,188</sup>. Intriguingly, pathogenetic links between the retroperitoneal fibro-inflammatory process (periaortitis) and the atheromatous aortitis could suggest statin treatment as preventive measure, at least, of its progression<sup>82</sup>. Indeed, the statins are hypothesized to have, besides the lipid lowering, also anti-inflammatory effects, as it is shown by decrease in CRP levels, suppression of both the macrophage/lymphocell release and adhesion molecule expression<sup>196</sup>.

About the aspecific pathogenetic factors underlying autoimmune disorders, the immunogenic apoptotic material must be considered, as it just recently has been underlined, a primary source of autoantigens that are responsible for an autoimmune response, particularly when the scavenger system (dendritic cells, macrophages, etc) is insufficient to remove immunogenic apoptotic products<sup>92</sup>.

With regard to profibrotic role played by some growth factors (especially TGF- $\beta$ ) in the pathogenesis of late fibrous stage of RPF, *tamoxifen*, because of its interference with the fibrogenic process, more than twenty years ago, has been innovatively included – alone or in association with either corticosteroids or immunosuppressants – in the *pathogenetic therapy* of the idiopathic RPF<sup>40,47-58,198</sup>, about it more recently either reporting its therapeutic reliability even in paraneoplastic RPF resistant to corticosteroids<sup>199</sup> and to treat also the hyper-IgG4-related RPF<sup>200</sup> or just merely rearranging posology, timing administration modalities together with assessment of the effectiveness *versus* other drugs.

Furthermore looking to novel biotherapies, given the significant role of different biomolecular factors (TNF- $\alpha$ , Jak<sub>S</sub>-STAT<sub>S</sub> complex, NF- $\kappa$ B) in the cell molecular pathway of chronic autoimmune inflammatory diseases, a multi-targeted bio-therapy (TNF- $\alpha$  blocking antibodies, Jak<sub>S</sub>-STAT<sub>S</sub> complex inhibitors, anti-human

CD20 antibodies (Rituximab), either alone or combined with steroids/immunosuppressants, could represent a challenging prospect for the management of idiopathic RPF<sup>86,87,201-204</sup>. Just the same could be suggested regarding the therapeutic potential of F8-IL10 (antibody F8 fused to anti-inflammatory IL10), directed against fibronectin/tenascin-C to inhibit collagen production<sup>205</sup>. There is today a growing interest in the potential use of phosphodiesterase-4 (PDE4) inhibitors, as anti-inflammatory cAMP elevating agents, in the treatment of autoimmune disorders, among which particularly the rheumatoid arthritis and sometimes associated pathologies – such as RPF – because these drugs can suppress TNF- $\alpha$  driven immune/inflammatory responses<sup>206</sup>.

To reasonably lower the “inflated” amount of diagnosed idiopathic RPF oddly ran up in a short time – given the well-known statistical rarity of such disease – it is advisable to meticulously exclude all possibilities of doubt about the occurrence of secondary RPF<sub>S</sub>, among which the paraneoplastic forms<sup>110,111,114-116,197</sup>.

Towards the diagnostics of RPF<sub>S</sub>, the current imaging chances (US, CT, MRI, nuclear medicine) are essentially like those achieved over the Eighties-Nineties of the last century<sup>30,34,40,141-146,160-178</sup>. Important risks have emerged, some years ago, as a result of the use of gadolinium-based paramagnetic materials in patients with severe renal impairment, given the potential development of *nephrogenic systemic fibrosis*. On such account it appears to be utterly mistaken to adopt Gd-enhanced MR diagnostic procedures, in patients with renal insufficiency, as an alternative to iodinated contrast-enhanced x-ray imaging, in order to avoid a contrast-induced nephropathy<sup>179-181</sup>.

Lastly, to go into sheer term details, a proper assessment, with critical mind, of the term “retroperitoneal fibrosis” may be validated only as regard to its late, clinically significant, fibrotic stages, while it seems to be inappropriate to identify the early, mainly inflammatory cell characterized phases, hence suggesting a suitable adoption of the generic term “retroperitoneal chronic connectivitis”, properly including both early cellular inflammatory - and late fibrous phases<sup>82</sup>.

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