

Retroperitoneal fibroses: aetiopathogenesis and taxonomic assessment

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Abstract. – Retroperitoneal fibrosis (RPF) is a chronic retroperitoneal inflammatory process that can entrap the retroperitoneal structures, mainly the ureters and the great vessels. Aetiology, clinical features and diagnostic appearance in several cases are protean. A true idiopathic form is present in any cases of RPF in which no potential aetiological condition may be identified. The pathogenesis of the idiopathic RPF appears today to be related to IgG4 autoimmune mechanisms (“hyper-IgG4 disease”). Otherwise, RPF in the presence of aortic atheromatous inflammation (atheromatous aortitis), has been included, more than twenty years ago, among the secondary forms, since this condition appears to be elicited by antigen-acting oxidized-LDL and/or ceroid, that are present within the atheromatous plaque. Aetiology of other secondary RPF_s refers to medications (drug-induced), infections, traumas, malignancies. Recent advances in imaging techniques (TC, RM, ¹⁸F-FDG/PET or hybrid TC/PET), together with laboratory findings (CRP, ESR, IgG, IgG4, autoantibodies, etc), allow to identify the active phases of the inflammatory process. The review focuses on the pathogenetic features of RPF_s and some issues concerning their taxonomic assessment.

Key Words:

Retroperitoneal fibrosis, Atheromatous aortitis, Systemic fibrosclerosis, Hyper-IgG4 disease, Autoimmune-mediated disease.

Introduction

Retroperitoneal fibrosis (RPF), first described, in 1905, by the French urologist Albaran and, then, fully recognized, in 1948, by Ormond¹, is characterized by a wooden fibrous chronic inflammatory plaque that covers and can entrap many retroperitoneal structures and organs. The

urinary tract may be affected via ureteral encasement, with subsequent chronic obstructive nephropathy. The epidemiological assessment of RPF is not well established, the idiopathic form (Ormond’s disease) accounting more than half (55÷60%) of cases, in comparison with the rest (secondary forms) that may be the outcome of a variety of known conditions such as traumas, infections, several drugs, neoplasms. Its prevalence of 1÷2/200,000 makes it a rare disease. Middle-aged men are affected twice to three times as often as women²⁻⁵.

Aetiopathogenesis of Secondary Retroperitoneal Fibroses

Although there are no standardized taxonomic criteria for RPF_s, a just aetiological classification of secondary forms is here outlined (Table I), with the explanatory short-cuts of an over-simplifying schematism. RPF in the presence of *aorto-iliac atheromatous inflammation* (atheromatous aortitis) has been included, more than twenty years ago, among the secondary RPF_s⁷⁻¹⁰, since this condition has been recognized to be elicited by both hapten-acting oxidized-low density lipoproteins (LDLox) and ceroids, oxidized lipoproteic polymers that are present within the aortic atheromatous plaques and result from LDL oxidation by ROS, *reactive oxygen species*^{7,8}. Otherwise, human *Cytomegalovirus* (hCMV) appears today to be involved in initiating the pathogenetic process of atherosclerosis as well as that one of systemic sclerosis, because the anti-hCMV (US28 and UL122 peptides) antibodies can induce an endothelial damage by modulating the expression of genes encoding for molecules proapoptotic into the endothelial cells¹¹, whereas oxidative stress-promoted infections (*Chlamydia*, *Mycoplasma*, *Archeonanobacteria*, *Helicobacter*) of atheromatous plaque can, in turn, increase aortic and periaortic inflammatory process¹².

Table 1. Aetiologic factors of secondary retroperitoneal fibroses.

Traumatic:	Accidental Iatrogenic	<ul style="list-style-type: none"> – Retroperitoneal haematomas and/or urinomas – 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 radiotherapy restricts the damage)
Infectious:		<ul style="list-style-type: none"> – Retroperitoneal specific granulomas (tuberculosis, actinomycosis, histoplasmosis) – Retroperitoneal spread from chronic mediastinitis or from contiguous urogenital/intestinal infections
Resulting from chronic immune inflammatory diseases:		<ul style="list-style-type: none"> – Atheromatous aortitis – Non-atheromatous systemic autoimmune vasculitides (Takayasu's disease, giant cell arteritis, Wegener's granulomatosis, polyarteritis nodosa, etc) – Connective tissue autoimmune inflammatory diseases (systemic lupus erythematosus, scleroderma, rheumatoid arthritis, etc.) – Inflammatory bowel disease (Crohn's disease)
Dismetabolic:		<ul style="list-style-type: none"> – Xantogranulomatous histiocytosis (Erdheim-Chester disease); amyloidosis
Occupational:		<ul style="list-style-type: none"> – Exposure to asbestos
Drug-induced:		<ul style="list-style-type: none"> – Lysergic acid derivatives (methysergide, ergotamine, cabergoline, pergolide, bromocriptine, LSD, etc); β-adrenergic blockers; dopamine agonists (methyldopa); hypotensives and diuretics (hydralazine, chlorothiazide, reserpine); analgesics (phenacetin, aspirin, paracetamol); some antitumoral chemotherapeutics
Neoplastic (malignant RPF):		<ul style="list-style-type: none"> – Desmoplastic response to primary or metastatic retroperitoneal tumors – Paraneoplastic fibrosis from extra-retroperitoneal tumors (e.g., carcinoid tumor)

The LDLox/ceroid-related antigenic phenotype is able to induce 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. This last also is able to involve, besides the aortic adventitia *vasa vasorum*, the surrounding periaortic tissue^{7,8,13}. 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^{7-9,13-15}. Early distribution of active RPF around atheromatous aorta, first emerged from autopsy findings, has also been confirmed in living patients by CT-imaging¹⁶. Moreover, an increased incidence of RPF in men rather than in women may be explained by the higher occurrence of atherosclerosis in male population.

Macrophage activation by oxidized lipoproteins results in release of tumor necrosis factor- α (TNF- α), that can induce the cytoplasm \rightarrow nucleus translocation of nuclear factor (NF) – κ 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 (iNOS), matrix-metallo-proteinases, intercellular (ICAM) – and vascular (VCAM) cell adhesion molecules¹⁷. Moreover, Janus Kinases (Jak_s) and signal transducers and activators of transcription (STAT_s) 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 an antibody-mediated immune response¹⁸. As far as allergic atheromatous aortitis is concerned, the progressive inflammatory involvement of aortic wall, from the media to the adventitia, is characterized by a change from Th1 cell-immune mediated pattern (Th1 lymphocyte infiltrates) to Th2 one with clonal expansion of plasma cells and IgG hypersecretion, together with fibro- and myofibroblast activation^{8,19}. Intriguingly, given the role of Jak_s-STAT_s in modulating cytokine network in any phase of the immune response, targeting some specific STAT_s by selective Jak inhibitors could receive considerable attention as therapeutic measure¹⁸.

Several growth factors (transforming growth factor- β , TGF- β ; 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 by fibrogenesis activation from the fibroblasts. Particularly, TGF- β is able to induce the change of fibroblasts in myofibroblasts with following hyperproduction of extracellular matrix components (mainly collagen, fibronectin, tenascin, glycosaminoglycans)^{20,21}; nevertheless, high concentrations of TGF- β in the cellular environment appear to counteract the phlogogenic response by inducing, through a negative feed-back, macrophage deactivation, hence T-lymphocyte suppression together with fibroblast inhibition, thus blocking the immune response and further fibrogenesis²²⁻²⁷. On this matter, tamoxifen, a nonsteroidal anti-oestrogenic drug chemically described as 1-[4-(2-dimethylaminoethoxy) phenyl] trans-1, 2-diphenyl-1-butene, is thought to be effective against the RPF, particularly of the idiopathic form, by increasing TGF- β release from fibroblasts, thus playing an anti-inflammatory role²²⁻²⁶. Other strategies to block either TGF- β or PDGF signaling (antibodies against TGF- β and PDGF; tyrosine kinase inhibitor Imatinib) are only at the early stage of clinical development²⁷.

Some RPF_s are today thought to be secondary to anatomoclinically well-described, even tough of unknown aetiology, *non-atheromatous syste-*

mic vasculitides (Takayasu's arteritis, giant cell arteritis, 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 anti-neutrophil cytoplasmatic antibodies (ANCA), that promote, in turn, through circulating immune complexes, an 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, in polyarteritis nodosa. Subsequent cytokine-cascade activation, immune response and pathogenetic features of vasculitis-related RPF reproduce stereotypically the atherosclerosis-induced multistep phlogogenic pathway²⁸⁻³⁴.

A subset of secondary RPF_s is due to the lengthy use of *some drugs* such as ergot-derivatives (e.g., ergotamine, methysergide, bromocriptine, LSD), β -adrenergic blockers, hydralazine, dopamine agonists (e.g., methyl dopa; cabergoline and pergolide, as ergot-derivatives), analgesics (e.g., phenacetin, paracetamol, aspirin), amphetamines, antitumoral chemotherapeutics³⁵⁻⁴⁰. The pathogenetic mechanism of lysergic acid derivatives, chiefly of methysergide (methyl-butanolamide of the lysergic acid), a strong antiserotonin drug, could consist partly in their haptenic role or, alternatively, in a rebound release of serotonin, by serotonin 5-HT_{2B} and 5-HT_{2A} receptor stimulation, together with phlogogenic mediators (histamine, prostaglandins, kinines), following from a prolonged intake of low-dose antiserotonin drug. Otherwise, even the migraine, by itself, induces raised serum concentrations of TGF- β and phlogogenic cytokines. Ergot derivative-induced RPF is often associated with fibrotic reactions of lung, pleura, heart-valves and pericardium. Interestingly, similar lesions are observed in the presence of the *carcinoid tumor*, which is known to release not only serotonin, thus acting by serotonin-mediated fibrogenetic mechanism, but also several phlogogenic mediators such as prostaglandins, histamine, kallikrein, together with profibrotic growth factors (TGF- β , bFGF, PDGF, etc)^{10,21,40,41}.

Other secondary retroperitoneal fibrosis may result from desmoplastic reaction to *retroperitoneal primary malignancies* (sarcomas, Hodgkin's or non-Hodgkin's lymphomas) or to *retroperitoneal metastases* of ubiquitous carcinomas, particularly

of the colon, prostate, breast, thus identifying the malignant subset of secondary RPF_S^{2-5,42-44}, among which the desmoid tumor-induced mesenteric fibrosis, in the field of Gardner syndrome, is also included⁴⁵.

Myofibroblastic tumours, which, in the past, have been improperly called «inflammatory pseudotumours», must be nosologically classified among the neoplastic pathology^{46,47}.

Inflammatory bowel disease (*Crohn's disease*), in 5÷10% of cases, by spreading to retroperitoneal tissue, mainly to its right side, can promote RPF⁴⁸.

Pathogenesis of Idiopathic Retroperitoneal Fibrosis

Before labelling a RPF condition as “idiopathic”, any identifiable cause should be excluded. Interpretation of the literature lead to think that a subset of RPF, in the past labelled as idiopathic, might actually be an epiphenomenon of advanced atheromatous aortitis. Therefore RPF in the presence of aorto-iliac atheromatosis is properly included among the secondary RPF. True idiopathic forms, instead, are present in any case of RPF, such as in children or in patients without significant atherosclerosis, in which no potential aetiological condition may be identified^{2,3,7-10,15,16,21,25}. In such occasions, the term “idiopathic” keeps still its rightful place⁴⁹ against any suggestion of its systematic abandonment in favour of “autoallergic periaortitis”⁵⁰.

Pathogenetic hypotheses and theories for idiopathic RPF refer to an immune-mediated mechanism, as well as it is inferred not only from raised

concentration of acute-phase reactants (CRP, C-reactive protein; ESR, erythrocyte sedimentation rate) and positive autoantibodies, but also from associated autoimmune diseases, involving other organs and structures, in the background of multisystem connective tissue disorder (Table II). Histological appearance is characterized by a lymphoplasmacytic inflammation with IgG4-positive cells and remarkable fibrosis, thus suggesting the label of «hyper-IgG4 disease». Infiltrating plasma cells are unreactive for anti-IgG4 antibodies and serum IgG4 concentrations are extremely elevated. Frequent systemic involvement of this process refers to new concept of IgG4-associated multifocal systemic fibrosis (IgG4-related sclerosing disease)⁵¹⁻⁵⁷. Another clue to an autoimmune origin of idiopathic retroperitoneal fibrosis is its significant association with HLA-DRB1*03, an allele linked to several autoimmune conditions⁶⁰. The pathogenetic pathway of idiopathic RPF mimics the pathogenetic stereotype of the immune-mediated secondary one⁵¹⁻⁶².

Pathological Findings

The *histological* appearance of RPF varies according to its activity and 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 and eosinophils. Sometimes, transmural infiltration

Table II. Pathogenetic background of idiopathic retroperitoneal fibrosis.

Genetic component:	– HLA-B27 or HLA-DRB1*03 haplotype
Systemic immuno-mediated component:	<ul style="list-style-type: none"> – Positive serum autoantibodies (ANCA); raised acute-phase reactant levels (ESR, CRP); high serum IgG4 concentrations – Histology for immune-mediated inflammatory process; marked infiltration of IgG4-positive plasma cells (“hyper-IgG4 disease”) – Association, sometimes, with autoimmune-mediated parenchymatous diseases (thyroiditis, pancreatitis, glomerulonephritis, etc), in the field of “IgG4-related sclerosing 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, Riedel's thyroiditis, induratio penis plastica, etc.). Besides the aetiology, the pathogenetic links among these diseases are unknown. – Sensitivity, in the early active cellular phase, to immunosuppressant therapy

together with fibrinoid necrosis of medium-sized and capillary retroperitoneal vessels is observed^{2,3,9,10,61-63}. Interestingly, hypercellularity-related metabolic activity and hypervascularity of both the early “active” phases and the focal relapse into activity during the late stages, may also be properly identified by image findings: high contrast enhancement CT, increased signal intensity on T2-weighted RM, positive ⁶⁷Ga-citrate- and ^{99m}Tc-hIgG scanning, ¹⁸F-deoxyglucose high uptake in positron emission tomography (FDG-PET) or in hybrid FDG-PET/CT as far as plaque morphology is also concerned^{3,5,21,42,64-68}.

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 fibrous tissue is often placed around the vessels and nerves^{1-4,10,15,16,30,42,62,63}.

The *macroscopic* appearance of the “mature” RPF is that of a wooden fibrotic plaque which is usually centralized at the level of the caudal lumbar vertebrae and that surrounds abdominal aorta and iliac vessels, often involving ureters, inferior vena cava, while rarely continuing, as fibrous mediastinitis, above the diaphragma, 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 are drawn toward the middle line (lateralized only in case of aortic aneurysm) and, although their lumen retains its virtually normal width, the own transport dynamics is often impaired with following urostitis 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.

The micro- and macroscopic appearances of both primary-idiopathic and secondary RPF are almost identical, except, on the one hand, the more localized extension of certain secondary RPFs (e.g., trauma- or infection-related fibrosis) and, on the other hand, the irregularly shaped malignant RPF within which fibrous tissue neoplastic cells may be shown^{3-5, 9,10,42,56,57,69-71}.

Conclusions

To try and draw some conclusions from this review, a thorough assessment, with critical mind, of the term retroperitoneal *fibrosis* leads to validate it just regarding the late stages, actually with fibrous and clinically more significant features, whereas it appears to be inappropriate to describe and identify the early cellular-vascular, certainly no fibrous, stages; therefore, more properly, the term «retroperitoneal connective tissue chronic inflammatory disease», inclusive of both cellular (“unstable”, “immature”) and fibrous (“stable”, “mature”) phases, could likely be preferred.

Moreover, a better understanding of the process underlying some forms of this disease is now reducing the incidence of “idiopathic” cases; thus, for instance, the atheromatous aortitis-related retroperitoneal inflammatory process (chronic periaortitis) has been included among the secondary forms, because this condition appears to be induced, through immune-mediated mechanisms, by antigen-acting ceroids⁷⁻¹⁶. Intriguingly, pathogenetic links between the retroperitoneal inflammatory process (periaortitis) and the atheromatous aortitis could lead to suggest statin treatment as prevention, at least, of its progression. The statins are hypothesized to have, in addition to lipid lowering, also inflammatory effects, such as reduction in the CRP levels, suppression of both the adhesion molecule expression and macrophage/lymphocyte release^{72,73}.

A true *idiopathic form*, instead, is present in any case in which no potential aetiological condition (or underlying known disease) may be identified; in such conditions, the term “idiopathic” keeps still its rightful place^{49,50}. However, some histological features of idiopathic RPF, as well as of other autoimmune sclerosing diseases, suggest a hyper-IgG4 involvement in its pathogenesis (“hyper-IgG4-positive plasma cell disease”)⁵²⁻⁵⁷.

As far as profibrotic growth factors (particularly TGF-β) in the pathogenesis of late fibrous stages are concerned, tamoxifen, because of its interference with fibrogenetic process, has been included, more than fifteen years ago, in the *pathogenetic* treatment of idiopathic RPF²²⁻²⁶. Other strategies to block either TGF-β or PDGF signaling (anti-TGF-β and anti-PDGF antibodies; Imatinib, tyrosine kinase inhibitor) are at the early phases of clinical trial²⁷.

Moreover, considering that other biomolecular factors (TNF-α, NF-κB, Jak_s-STAT_s system, etc)

play a significant role in the cell molecular pathway of the autoimmune chronic inflammatory diseases (ACID_s), a multi-targeted *cell-therapy*^{17,18,74-77}, such as TNF- α blocking antibodies and Jak_s-STAT_s inhibitors, either alone or in association with steroid/conventional immunosuppressant regimen, could be a realistic challenging perspective in the management of RPF.

References

- 1) ORMOND JK. Bilateral ureteral obstruction due to envelopment and compression by an inflammatory process. J Urol 1948; 59: 1072-1079.
- 2) BANI-HANI KE, BANI-HANI IH, AL-HEISS HA, OMARI HZ. Retroperitoneal fibrosis. Demographic, clinical and pathological findings. Saudi Med J 2002; 23: 711-715.
- 3) ESTRADE V, TRAXE O, SIBONI M, HAAB F. Retroperitoneal fibrosis. Ann Urol 2004; 38: 3-13
- 4) BURKHART SOARES S, FEHR A, BRANDT AS, ROTH S. Retroperitoneal fibrosis. Aktuelle Urol 2007; 38: 221-231.
- 5) VAN BOMMEL EFH, SIEMES CL, HAK LE, VAN DER VEER S, HENDRIKSZ TR. Long term renal and patient outcome in idiopathic retroperitoneal fibrosis treated with prednisone. Am J Kidney Dis 2007; 49: 615-625.
- 6) NELIUS T, REIHER F, LINDENMEIR T, KALINSKI, RAU O, FILLEUR S, ALLHOFF EP. Idiopathic retroperitoneal fibrosis: Ormond's disease. Aktuelle Urol 2006; 37: 284-288.
- 7) MITCHINSON MJ. Chronic periaortitis and periarteritis. Histopathology 1984; 8: 589-600
- 8) PARUMS DV. The spectrum of chronic periaortitis. Histopathology 1990; 16: 423-431.
- 9) VAN BOMMEL EFH. Retroperitoneal fibrosis. Neth J Med 2002; 60: 231-242.
- 10) ALBERTI C, SACCHINI P, CORTELLINI P, ROSSI A. Retroperitoneal fibrosis: some new acquisitions about pathogenesis and diagnostics. Arch It Urol 1991; 63: 25-35.
- 11) LUNARDI C, DOLCINO M, PETERLANA D, BASON C, NAVONE R, TAMASSIA N, TINAZZI E, BERI R, CORROCHER R, PUCCETTI A. Endothelial cell's activation and apoptosis induced by a subset of antibodies against hCMV: relevance to the pathogenesis of atherosclerosis. PLoS ONE 2007; 2: e473.
- 12) LIBBY P. Inflammation in atherosclerosis. Nature 2002; 420: 868-874.
- 13) MITCHINSON MJ. Insoluble lipids in human atherosclerotic plaques. Atherosclerosis 1982; 45: 11-15.
- 14) PARUMS D, MITCHINSON MJ. Demonstration of immunoglobulins in neighbourhood of advanced atherosclerotic plaques. Atherosclerosis 1981; 38: 211-216.
- 15) MITCHINSON MJ. Retroperitoneal fibrosis revisited. Arch Pathol Lab Med 1986; 110: 784-786.
- 16) DIXON AK, MITCHINSON MJ, SHERWOOD T. Computed tomographic observations in periaortitis. A hypothesis. Clin Radiol 1984; 35: 39-42.
- 17) VERMA IM. Nuclear factor (NF)-kB proteins. Ann Rheum Dis 2004; 63(Suppl 2): ii 57- ii 61.
- 18) O'SHEA JJ. Targeting the Jak/STAT pathway for immunosuppression. Ann Rheum Dis 2004; 63 (suppl 2): ii 67- ii 71.
- 19) RAMSHAW AL, PARUMS DV. Immunohistochemical characterization of inflammatory cells associated with advanced atherosclerosis. Histopathology 1990; 17: 543-552.
- 20) KOVACS EJ, DI PIETRO LA. Fibrogenic cytokines and connective tissue production. FASEB J 1994; 8: 854-857.
- 21) ALBERTI C. Retroperitoneal fibroses: an up-date. Urol Prat 2002; 2: 40-54.
- 22) CLARK CP, VANDERPOOL D, PRESKITT JT. The response of retroperitoneal to tamoxifen. Surgery 1991; 109: 502-506.
- 23) AL RABI N, GRAZIANI R, CERRUTO MA, BALDASSARRE R, FICARRA V, ARTIBANI W. Clinical and radiological evolution of a case of idiopathic retroperitoneal fibrosis treated with tamoxifen. Scand J Urol Nephrol 2002; 36: 391-392.
- 24) ALBERTI C. The rationale of tamoxifen in the management of retroperitoneal fibrosis and Peyronie's disease. Acta Urol Ital 1996; 10: 7-11.
- 25) VAN BOMMEL EFH, HENDRIKSZ TR, HUISKES AW, ZEEGERS AG. Brief communication: tamoxifen therapy for idiopathic retroperitoneal fibrosis. Ann Intern Med 2006; 114: 101-106.
- 26) PUCE R, PORCARO AB, CURTI P, GIRELLI D, PANTALENA M, MALOSSINI G, TALLARIGO C. Treatment of retroperitoneal fibrosis with tamoxifen: case report and review of literature. Arch Esp Urol 2000; 53: 184-190.
- 27) DENTON CHR, MERKEL PA, FURST DE, KHANNA D, EMERY P, HSU VM, et al. Recombinant human anti-TGF β 1 antibody therapy in systemic sclerosis. Arthritis Rheum 2007; 56: 323-333.
- 28) CID CM. New development in the pathogenesis of systemic vasculitis. Curr Op Rheum 1996; 8: 1-11.
- 29) MIOSEC P. Autoimmune pathologies. Revue Prat 2004; 54: 2187-2193.
- 30) COTCH MF, RAO JK. New insights into the epidemiology systemic vasculitis. Curr Op Rheum 1996; 8: 19-25.
- 31) BACOM PA. The spectrum of Wegener's granulomatosis and disease relapse. N Engl J Med 2005; 352: 330-332.

- 32) LAUNAY D, HACHULLA E. Inflammatory aortitis. *Presse Med* 2004; 33: 1334-1340.
- 33) LEVIN A, KASEM S, MADER R, NAPARSTEK Y, FRIEDAM G, BEN-YEHUDE A. Wegener granulomatosis with back pain, periaortitis and dural inflammation developing while receiving monthly cyclophosphamide. *J Clin Rheumatol* 2006; 12: 294-297.
- 34) BANGARD C, LOTZ J, ROSENTHAL H, GALANSKI M. Erdheim-Chester disease versus multifocal fibrosis and Ormond's disease: a diagnostic dilemma. *Clin Radiol* 2004; 59: 1136-1141.
- 35) GRAHAM JR, SUBY HI, LE COMPTE PR, SADOWSKY NL. Fibrotic disorders associated with methysergide therapy for headache. *N Engl J Med* 1966; 274: 359-368.
- 36) ALBERTI C, MACALUSO G, CULZONI V, FREDDI M, POTENZONI D. Histological findings on drug-induced periurethritis in animal model. *Rass Urol Nefrol* 1968; 6: 234-240.
- 37) WALLER EA, KAPLAN J. Pergolide-associated valvular heart disease. *Compr Ther* 2006; 32: 94-101.
- 38) CAI FZ, TESAR P, KLESTOV A. Methysergide-induced retroperitoneal fibrosis and pericardial effusion. *Int Med J* 2004; 34: 297-298.
- 39) AGARWAL P, FAHN S, FRUCHT SJ. Diagnosis and management of pergolide-induced fibrosis. *Mov Disord* 2004; 19: 699-704.
- 40) FASSINA A, BERTO RB, MAZLOUM R, GOTTARDO F, ARTIBANI W. Retroperitoneal fibrosis after chemotherapy. *Eur Urol* 2007; 51: 270-271.
- 41) MODLIN IM, SHAPIRO BS, KIDD M. Carcinoid tumors and fibrosis: an association with no explanation. *Am J Gastroenterol* 2004; 99: 2466-2478.
- 42) KOTTRA JJ, DUNNICK NR. Retroperitoneal fibrosis. *Radiol Clin North Am* 1996; 43: 1259-1275.
- 43) USHER SM, BRENDLER H, CIAVARRA VA. Retroperitoneal fibrosis secondary to metastatic neoplasm. *Urology* 1977; 9: 191-194.
- 44) SADHU A, SEN S, SEAL S, SHARMA SK. Metastasis, an unusual course of retroperitoneal fibrosis. *Indian Med Assoc* 2006; 104: 642-644.
- 45) LOCUFIER A, VANHULLE A, MORCELS R. Gardner syndrome and desmoid tumours. *Acta Chir Belg* 1993; 93: 230-232.
- 46) COFFIN CM, WATTERSON J, PRIEST JR, DEHNER LP. Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor); a clinical and immunohistochemical study of 84 cases. *Am J Surg Pathol* 1995; 19: 859-872.
- 47) GIGLIO M, MEDICA M, GERMINALE F, TIMOSSI L, ROMAGNOLI A, TONCINI C, CARMIGNANI G. Retroperitoneal inflammatory myofibroblastic tumours: analysis of biological pathological and clinical features. *Urologia* 2001; 68: 44-48.
- 48) SHIELD DE, LYTTON B, WEISS RM, SCHIFF M. Urologic complications of inflammatory bowel disease. *J Urol* 1976; 115: 701-705.
- 49) SHABBI M. Ormond disease: what's in a name? *BJU International* 2004; 94: 192.
- 50) BAKER LRI. Auto-allergic periaortitis (idiopathic retroperitoneal fibrosis). *BJU International* 2004; 92: 663-665.
- 51) NEILD GH, RODRIGUEZ-JUSTO M, WALL C, CONNOLLY JO. Hyper-IgG4 disease: report and characterisation of new disease. *BMC Med* 2006; 4: 2.3
- 52) NIYAJMA N, KOIKE H, KAWAGUCHI M, ZEN Y, TAKAHASHI K, HARA N. Idiopathic retroperitoneal fibrosis with IgG4-positive-plasmacyte infiltrations and idiopathic chronic pancreatitis. *Int J Urol* 2006; 13: 1442-1444.
- 53) TANABE T, TSUSHIMA K, YASUO M, URUSHIHATA K, HANAOKA M, KOIZUMI T, FUJIMOTO K, KUBO K, UEHARA T, SHIGEMATSU S, HAMANO H, KAWA S. IgG4-associated multifocal systemic fibrosis complicating sclerosing sialoadenitis, hypophysitis and retroperitoneal fibrosis, but lacking pancreatic involvement. *Intern Med* 2006; 45: 1243-1247.
- 54) WU J, CATALAMO E, COPPOLA D. Retroperitoneal fibrosis (Ormond's disease): clinical pathologic study in eight cases. *Cancer Control* 2002; 9: 432-437.
- 55) KAMISAWA T, OKAMOTO A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006; 41: 613: 625.
- 56) ILIE CP, PEMBERTON RJ, TOLLEY DA. Idiopathic retroperitoneal fibrosis: the case for non surgical treatment. *BJU International* 2006; 98: 137-140.
- 57) TANIGUCHI T, KOBAYASHI H, FUKUI S, OGURA K, SAIGA T, OKAMOTO M. A case of multifocal fibrosclerosis involving posterior mediastinal fibrosis, retroperitoneal fibrosis and a left seminal vesicle with elevated serum IgG4. *Hum Pathol* 2006; 37: 1237-1239.
- 58) PIZZINI AM, CORRADO S, RADIGHIERI E, FERRETTI G, CARANI C, PAPI G. Hashimoto's thyroiditis associated with idiopathic retroperitoneal fibrosis: case report and review of the literature. *Int J Clin Pract* 2007; 61: 162-164.
- 59) EMCH TM, MILLER MA. Retroperitoneal fibrosis involving the left kidney in patient with remote history of Riedel's thyroiditis. *AJR* 2005; 184: S97-S98.
- 60) MARTORANA D, VAGLIO A, GRECO P, ZANETTI A, MORONI G, SALVARANI C, SAVI M, BUZIO C, NERI TM. Chronic periaortitis and HLA-DBR1*03: another link to an autoimmune origin. *Arthritis Rheum* 2006; 55: 126-130.
- 61) MARCOLONGO R, TAVOLINI IM, LAVEDER F, BUSA M, NOVENTA F, BASSI P, SEMENZATO G. Immunosuppressive therapy for idiopathic retroperitoneal fibrosis: a retrospective analysis of 26 cases. *Am J Med* 2004; 116: 194-197.
- 62) VAGLIO A, SALVARANI C, BUZIO C. Retroperitoneal fibrosis. *Lancet* 2006; 367: 241-251.

- 63) JOIS RN, GAFFNEY K, MARSHALL T, SCOTT DG. Chronic periaortitis. *Rheumatology* 2004; 43: 1441-1446.
- 64) TALATI S, ABGHARI R, KOCHKODAN JJ, HELMER SR. Use of Ga-67 imaging in diagnosis and follow-up after steroid treatment of retroperitoneal fibrosis. *Clin Nucl Med* 1995; 20: 995-997.
- 65) MITNICK H, JACOBOWITZ G, KRINSKY G, EBERLE M, ROSENZWEIG B, WILLIS D, ROCKMAN C, RILES T. Periaortitis: gadolinium-enhanced magnetic resonance imaging and response to therapy in four patients. *Ann Vasc Surg* 2004; 18: 100-107.
- 66) SCHEEL AK, MELLER J, VOSSHENRICH R, KOHLHOFF E, SIEFKER U, MÜLLER GA, STRUTZ F. Diagnosis and follow-up of aortitis in the elderly. *Ann Rheum Dis* 2004; 63: 1507-1510.
- 67) MELLER J, STRUTZ F, SIEFKER V, SCHEEL AK, SAHLMANN CO, LEHMANN K, et al. Early diagnosis and follow-up of aortitis with 18 FDG-PET and MRI. *Eur J Nucl Med Mol Imaging* 2003; 30: 730-736.
- 68) SALVARANI C, PIPITONE N, VERSARI A, VAGLIO A, SERAFINI D, BAJOCCHI G, SALVO D, BUZIO C, GRECO P, BOIARDI L. Positron emission tomography (PET): evaluation of chronic periaortitis. *Arthritis Rheum* 2005; 53: 298-303.
- 69) MAÑERO C, NAVAS-PAREJO A, PRADOS MD, GARCÍA-VALDECASAS J, HORNOS C, ESPIGARES MJ, MANJÓN M, HERVÁS J, LÓPEZ R, PEÑA M, CEREZO S. Acute obstructive renal failure secondary retroperitoneal mass. *Nefrologia* 2004; 24(Suppl 3): 49-55.
- 70) GILKESTON GS, ALLEN NB. Retroperitoneal fibrosis: a true connective tissue disease. *Rheum Dis Clin North Am* 1996; 22: 23-38.
- 71) AZIZ F, CONJEEVARAM S, PHAN T. Retroperitoneal fibrosis: a rare cause of both ureteral and small bowel obstruction. *World J Gastroenterol* 2006; 12: 7061-7063.
- 72) PALINSKI W, NAPOLI C. Unraveling pleiotropic effects of statins on plaque rupture. *Arterioscler Tromb Vasc Biol* 2002; 22: 1745-1750.
- 73) NISSEN SE, TUZCU EM, SCHOENHAGEN P, CROWE T, SASIELA WJ, TSAI J, ORAZEM J, MAGORIEN RD, O'SHAUGHNESSY C, GANZ P; REVERSAL OF ATHEROSCLEROSIS WITH AGGRESSIVE LIPID LOWERING (REVERSAL) INVESTIGATORS. Statin therapy, LDL cholesterol, C-reactive protein and coronary artery disease. *N Engl J Med* 2005; 352: 29-38.
- 74) FERRACCIOLI GF, GREMESE E. Biological therapies in autoimmune chronic inflammatory disease (ACIDs). *Eur Rev Med Pharmacol Sci* 2006; 10: 37-40.
- 75) RADBRUCH A, THIEL A. Cell therapy for autoimmune diseases: does it have a future. *Ann Rheum Dis* 2004; 63: ii96- ii101.
- 76) KEYSTONE EC. The utility of tumor necrosis factor blockade in orphan diseases. *Ann Rheum Dis* 2004; 63 (Suppl 2): ii79- ii83.
- 77) WORMALD S, HILTON DJ. Inhibitors of cytokine signal transduction. *J Biol Chem* 2004; 279P: 821-824.