Retroperitoneal fibroses: aetipathogenesis 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 aetiologic 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 RPFs 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, 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 Ormond, 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 women.

Aetiopathogenesis of Secondary Retroperitoneal Fibroses

Although there are no standardized taxonomic criteria for RPFs, 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 RPFs, 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. 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 cells, whereas oxidative stress-promoted infections (Chlamydia, Mycoplasma, Archeanobacteria, Helicobacter) of atheromatous plaque can, in turn, increase aortic and periaortic inflammatory process.
The LDLox/ceroid-related antigenic phenotype is able to induce LDLox/ceroid receptor expression on macrofage 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 controls7-9,13-15. Early distribution of active RPF around atheromatous aorta, first emerged from autopsy findings, has also been confirmed in living patients by CT-imaging.16 Moreover, an increased incidence of RPF in men rather than in women may be explained by the higher occurrence of atherosclerosis in male population.

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| Traumatic: | Accidental | – Retroperitoneal haematomas and/or urinomas |
|          | Iatrogenic | – 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 bean deep radiotherapy (today, conformal 3D-intensity modulated radiotherapy restricts the damage) |
| Infectious: | – Retroperitoneal specific granulomas (tuberculosis, actinomycosis, histoplasmosis) |
|          | – Retroperitoneal spread from chronic mediastinitis or from contiguous urogenital/ intestinal infections |
| Resulting from chronic immune inflammatory diseases: | – 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 erythematous, scleroderma, rheumatoid arthritis, etc.) |
|          | – Inflammatory bowel disease (Crohn’s disease) |
| Dismetabolic: | – Xantogranulomatous histiocytosis (Erdheim-Chester disease); amyloidosis |
| Occupational: | – Exposure to asbestos |
| Drug-induced: | – 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): | – Desmoplastic response to primary or metastatic retroperitoneal tumors |
|          | – Paraneoplastic fibrosis from extra-retroperitoneal tumors (e.g., carcinoma tumor) |

| Table I. Aetiologic factors of secondary retroperitoneal fibroses. |

The LDLox/ceroid-related antigenic phenotype is able to induce LDLox/ceroid receptor expression on macrofage 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 controls7-9,13-15. Early distribution of active RPF around atheromatous aorta, first emerged from autopsy findings, has also been confirmed in living patients by CT-imaging.16 Moreover, an increased incidence of RPF in men rather than in women may be explained by the higher occurrence of atherosclerosis in male population.

Macrofage activation by oxidized lipoproteins results in release of tumor necrosis factor-α (TNF-α), that can induce the cytoplasm → nucleus translocation of nuclear factor (NF) – kB, 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-metalloproteinases, intercellular (ICAM) – and vascular (VCAM) cell adhesion molecules.17 Moreover, Janus Kinases (Jak₃) and signal transducers and activators of transcription (STAT₃) 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 response. 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. Intriguingly, given the role of JakS-STATs in modulating cytokine network in any phase of the immune response, targeting some specific STATs by selective Jak inhibitors could receive considerable attention as therapeutic measure.

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, tenasin, glycosaminoglycans); 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 activation, thus blocking the immune response and further fibrogenesis. On this matter, tamoxifen, a nonsteroidal anti-oestrogenic drug chemically described as 1-[4-(2-dimethylaminoethoxy) phenil] 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 role. 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 development.

Some RPFs are today thought to be secondary to anatomoclinically well-described, even tough of unknown aetiology, non-atheromatous systemic 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 pathway.

A subset of secondary RPF 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 chemotherapeutics. 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-HT2B and 5-HT2A 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, kallicrein, togheter with profibrotic growth factors (TGF-β, bFGF, PDGF, etc). 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, among which the desmoid tumor-induced mesenteric fibrosis, in the field of Gardner syndrome, is also included.

Myofibroblastic tumours, which, in the past, have been improperly called «inflammatory pseudotumours», must be nosologically classified among the neoplastic pathology. Inflammatory bowel disease (Crohn’s disease), in 5–10% of cases, by spreading to retroperitoneal tissue, mainly to its right side, can promote RPF.

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 in 2,3,7-10,15,16,21,25. In such occasions, the term “idiopathic” keeps still its rightful place against any suggestion of its systematic abandonment in favour of “autoallergic periaortitis”.

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 immunoreactive 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 conditions.\(^{60}\) The phlogogenetic pathway of idiopathic retroperitoneal fibrosis mimics the pathogenetic stereotype of the immune-mediated secondary one\(^{51-62}\).

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 aedema) to fibrotic-vascular 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...
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 \(^{67}\)Ga-citrate- and \(^{99m}\)Tc-hIgG scanning, \(^{18}\)F-deoxyglucose high uptake in positron emission tomography (FDG-PET) or in hybrid FDG-PET/CT as far as plaque morphology is also concerned\(^1\).\(^3\).\(^21\).\(^42\).\(^64\).\(^66\).

Sequentially, in the late stages, fibroblast and myofibroblast infiltrates, collagen deposition and bundling of argirophil fibrils, then true fibroscrotic 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 encasement 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 urostasis 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 RPF\(^s\) (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\(^1\).\(^3\).\(^5\).\(^9\).\(^10\).\(^42\).\(^56\).\(^57\).\(^69\).\(^71\).

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 ceroids\(^7\).\(^16\). 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\(^22\).\(^71\).

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-\(\beta\)) 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 RPF\(^22\).\(^26\).

Other strategies to block either TGF-\(\beta\) or PDGF signaling (anti-TGF-\(\beta\) and anti-PDGF antibodies; Imafintib, tyrosine kinase inhibitor) are at the early phases of clinical trial\(^7\).

Moreover, considering that other biomolecular factors (TNF-\(\alpha\), NF-kB, Jak\(_s\)-STAT\(_s\) system, etc)
play a significant role in the cell molecular pathway of the autoimmune chronic inflammatory diseases (ACID), a multi-targeted cell-therapy\textsuperscript{7,18,74-77}, such as TNF-\(\alpha\) blocking antibodies and Jak\(_{6}\)-STAT\(_{3}\) inhibitors, either alone or in association with steroid/conventional immunosuppressant regimen, could be a realistic challenging perspective in the management of RPF.

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Retroperitoneal fibrosis: aetiopathogenesis and taxonomic assessment


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