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Chronic Periaortitis as a Systemic Autoimmune Disease

Chang-Hee Suh
Rheumatology, Ajou University School of Medicine
Korea

1. Introduction

Chronic periaortitis is an idiopathic disease whose hallmark is the presence of a fibro-inflammatory tissue arising from the adventitia of the abdominal aorta and the common iliac arteries and extending into the surrounding retroperitoneum and frequently encasing neighboring structures such as the ureters and the inferior vena cava (Mitchinson, 1984; Parums, 1990). It should be regarded as a generalized disease with three different pathophysiological entities, specifically idiopathic retroperitoneal fibrosis, inflammatory abdominal aortic aneurysms, and perianeurysmal retroperitoneal fibrosis (Vaglio et al., 2003; Jois et al., 2004).

Idiopathic retroperitoneal fibrosis is characterized by periaortic fibroinflammatory tissue, which often causes obstruction of the ureters and other adjacent abdominal structures by extending into the retroperitoneum (Mitchinson, 1970; Gilkeson & Allen, 1996). A dilated aorta is usually not present in idiopathic retroperitoneal fibrosis. Its initial signs and symptoms are often nonspecific, such as malaise, anorexia, weight loss, fever, and flank, back, or abdominal pain. Inflammatory abdominal aortic aneurysms characteristically develop the mass around a dilated aorta, but usually do not cause obstructions (Crawford et al., 1985; Pennell et al., 1985). It usually presents with typical symptoms and signs characterized by the triad of abdominal or back pain, a pulsatile and sometimes tender abdominal mass, and an elevated erythrocyte sedimentation rate. Perianeurysmal retroperitoneal fibrosis, which represents a link between these two diagnoses, involves an abdominal aortic aneurysms surrounded by fibroinflammatory tissue that encases other abdominal organs (Serra et al, 1980).

These definitions may be a little confusing, and it would probably be more appropriate to distinguish aneurysmal from nonaneurysmal forms of chronic periaortitis; idiopathic retroperitoneal fibrosis may be referred as non-aneurysmal chronic periaortitis, where as inflammatory abdominal aortic aneurysms and perianeurysmal retroperitoneal fibrosis as aneurysmal chronic periaortitis (Vaglio et al., 2006).

It is important to diagnose chronic periaortitis early in its course in order to attempt to prevent the severe secondary complication of renal failure due to ureteric obstruction and the potentially fatal consequence of aortic rupture (Jois et al., 2004). Although most studies have considered these entities separately, these conditions have common clinical and histopathologic findings, and thus probably represent different manifestations of the same disease.

2. Epidemiology

The prevalence of chronic periaortitis is not well known; the only available epidemiological data concern idiopathic retroperitoneal fibrosis and inflammatory abdominal aortic aneurysms. Reports from Duke University and the Mayo Clinic estimate that the incidence of idiopathic retroperitoneal fibrosis is less than 1 per 10,000 patients (Gilkeson & Allen 1996). A recent study conducted in Finland on idiopathic retroperitoneal fibrosis has demonstrated that its incidence and prevalence are 1/1,000,000 person-year and 1.38 cases/100,000 inhabitants (Uibu et al., 2004). On the other hand, data regarding the incidence of the aneurysmal forms of chronic periaortitis in the whole population are lacking, however they represent about 4% to 10% of all abdominal aortic aneurysms (Rasmussen et al, 1997; von Fritschen et al., 1999; Yusuf et al., 2007).

Chronic periaortitis frequently develops in middle-aged adults with a mean age of approximately 60 years, but it may also occur in children (Miller et al. 2003; Uibu et al., 2004; Vaglio et al., 2006). Men are affected two to three times as often as women and that is even more pronounced in the inflammatory abdominal aortic aneurysms (Gilkeson & Allen 1996; Uibu et al., 2004; Vaglio et al., 2006).

There is no evidence of a clear ethnic predisposition or familial clustering, and the disease has been reported in twins and siblings only in anecdotal cases (Duffy et al., 1984; Doolin et al. 1987). A few studies have addressed the question whether genetic factors may contribute to the development of chronic periaortitis. Recent studies have suggested that immunogenetic factors may be involved in the pathogenesis of the disease (Rasmussen et al., 1997; Martorana et al., 2006).

A case-control study evaluated the prevalence of HLA alleles in patients with inflammatory abdominal aortic aneurysms compared with healthy subjects found that in the inflammatory abdominal aortic aneurysms a genetic risk determinant mapping at the HLA-DRB1 locus (Rasmussen et al., 1997). Additionally, they identified HLA-DRB1*15 and B1*0404 as predisposing alleles.

Another recent case-control study on patients with chronic periaortitis and healthy controls in order to investigate the role of HLA in the susceptibility to chronic periaortitis revealed that the frequency of the HLA-DRB1*03 allele was markedly higher in patients with chronic periaortitis than in the controls (Martorana et al., 2006). The HLA-DRB1*03 allele is a well-known marker of autoimmunity, since it is associated with a number of autoimmune diseases, which include systemic lupus erythematosus and autoimmune thyroid disease (Davidson and Diamond, 2001). Also, the HLA-B*08 allele was significantly associated with chronic periaortitis and it is itself linked to a wide range of immune-mediated diseases. Furthermore, the comparison of the clinical and laboratory characteristics of HLA-DRB1*03-positive and HLA-DRB1*03-negative patients showed that the HLA-DRB1*03-positive patients with chronic periaortitis have higher acute-phase reactant levels at the time of diagnosis (Martorana et al., 2006). These results could imply that the HLA system not only confers susceptibility to the development of the disease but also plays a role in the modulation of the inflammatory response.

More recently, CC chemokine receptor 5 (CCR5) gene delta 32 polymorphism has been mapped in 100 patients with chronic periaortitis (Boiardi L et al., 2011). The distribution of the CCR5 gene delta 32 genotype differed between patients with chronic periaortitis and controls (P = 0.01). The CCR5 gene delta 32 allele was more frequent in patients with chronic periaortitis [P = 0.02, odds ratio (OR) 2.8 (95% CI 1.2, 6.4)]. Furthermore, CCR5 gene delta 32

allele occurred more frequently in patients with inflammatory abdominal aortic aneurysms than in patients with idiopathic retroperitoneal fibrosis [P = 0.001, OR 6.4 (95% CI 2.1, 19.1)]. The CCR5 gene delta 32 allele frequency was higher in inflammatory abdominal aortic aneurysms patients without established atherosclerotic disease compared with controls [66.7 vs 5.6%, P = 0.00001, OR 34.0 (95% CI 7.4, 156.3)].

The CC chemokine receptor 5 is expressed on many immune cells, particularly Th1 cells, and acts by binding to different chemokines, including RANTES, MIP-1α and MIP-1β. The CCR5 gene delta 32 polymorphism creates a truncated, nonfunctional receptor and probably shifts the immune response toward a Th2 pattern. Interestingly, the association between the CCR5 gene delta 32 polymorphism and aneurysmal chronic periaortitis is even stronger in patients without overt atherosclerotic disease, which suggests that immune mechanisms independent of atherosclerosis play a role in the pathogenesis of chronic periaortitis (Vaglio et al., 2011).

Additionally, environmental and occupational agents have been shown to contribute to susceptibility to chronic periaortitis. In a recent study, it has been demonstrated that asbestos exposure is associated with a markedly increased risk of developing the chronic periaortitis, and smoking is also a significant risk factor (Uibu et al., 2004; Hellmann et al., 2007). Although smoking is an established risk factor for classical atherosclerotic abdominal aortic aneurysms, its frequency is even higher in patients with inflammatory abdominal aortic aneurysms (Nitecki et al., 1996; Hellmann et al., 2007).

3. Pathology

Chronic periaortitis affects the aortic wall and the surrounding retroperitoneum. The classical macroscopic appearance of chronic periaortitis is grossly a whitish and hard periaortic mass which extends between the origin of the renal arteries and the bifurcation of the common iliac vessels and often distorting medially the ureters but histologically there is a continuum of lesions ranging from acute changes to chronic damage (Mitchinson, 1970).

In the early stages of chronic periaortitis, or in patients with a prominent acute-phase reaction, the tissue is highly inflammatory, with numerous lymphocytes, plasma cells, macrophages and scattered eosinophils and loose deposits of collagen matrix in thick, irregular bands (Mitchinson, 1970; Corradi et al., 2007). In late disease, these aspects evolve, either spontaneously or after glucocorticoid therapy, into a relatively acellular fibrous tissue. Perivascular involvement of the thoracic aorta is not uncommon, while rarely atypical localizations such as peri-duodenal, peri-pancreatic and pelvic sites have also been found (Hughes & Buckley, 1993; Corradi et al., 2007).

Microscopic examination shows signs of active mononuclear cell inflammation in a framework of fibrous tissue and fibroblasts (Serra et al, 1980; Gilkeson & Allen, 1996). The background of chronic periaortitis consists of varying degrees of fibrosis, characterized by a mild-to-moderate and mitotically inactive fibroblasts and myofibroblasts, which are immuno-histochemically positive for vimentin and, in the more cellular areas, for α-smooth muscle actin (Vaglio et al., 2006). The fibrous component is particularly abundant in the late stages when the tissue becomes relatively avascular and acellular; its distribution is usually diffuse, but sometimes perivascular and perineural.

The inflammatory infiltrate includes mononuclear cells such as T and B lymphocytes, macrophages and plasma cells, although scattered eosinophils can also be found

(Mitchinson, 1970). The majority of lymphocytes, macrophages and most vascular endothelial cells are HLA-DR-positive. The Ki67 and BerH2 staining is found in B cells and T-helper cells, indicating that these cells were proliferating and activated (Meier et al., 2007). Two main inflammatory patterns are usually seen, perivascular and diffuse. The perivascular aggregates consist mainly of B lymphocytes and a smaller component of plasma cells, macrophages, and T lymphocytes, most of which are CD4+ (Corradi et al., 2007). Sometimes, these follicular aggregates show a germinal center architecture. The sclerotic component consists of thick fascicles of type-I collagen, irregularly distributed along the lesion; a pathological hallmark is the presence of a regular circumferential fibrous bundle surrounding blood vessels and nerves. On the other hand, the diffuse infiltrate has an equal percentage of T cells and B cells. Scattered eosinophils are common, whereas neutrophils are rare (Mitchinson, 1970; Vaglio et al., 2003). In cases of severe inflammation, there may be focal infiltration of the small and medium-sized retroperitoneal vessels, with frank vasculitis and fibrinoid necrosis.

The aortic wall also shows particular changes, such as atherosclerotic degeneration of the intima, medial thinning, and marked adventitial inflammation and fibrosis. The composition of the inflammatory infiltrate in the aortic wall is similar to the retroperitoneal one, with diffuse and perivascular patterns. The adventitial inflammatory infiltrate is often organized in lymphoid follicles (Sakata et al., 2008), which are examples of ectopic lymphoneogenesis and expression of a highly structured inflammatory or immune-mediated response. Adventitial vasa vasorum in aortas of chronic periaortitis show inflammatory infiltration up to frank necrotizing vasculitis, endarteritis obliterans, or obliterative phlebitis (Vaglio et al., 2003; Sakata et al., 2008). These aortic wall changes are found in all chronic periaortitis disease entities, regardless of the presence of aneurysmal dilatation.

It is interesting to note that autopsy studies have documented the presence of adventitial inflammation in aortic sections lacking periaortic fibrosis, which may suggest that aortitis could precede the development of adventitial and periadventitial fibrosis (Mitchinson, 1970). Another autopsy studies have shown that moderate adventitial inflammation and fibrosis may not be limited to the abdominal aorta, but may also involve its thoracic aorta (Mitchinson, 1972).

Molecular analysis of aortic biopsies in patients with chronic periaortitis shows gene transcripts consistent with lymphocyte activation, such as IFN-γ, IL-1α, IL-2 and IL-4, in keeping with the concept that chronic periaortitis is an active inflammatory aortic disease (Ramshaw et al., 1994).

4. Pathogenesis

Chronic periaortitis is idiopathic in nature, and its pathogenesis remains a matter of debate. Initially, it was postulated to represent a local inflammatory reaction to antigens such as ceroid and oxidised low-density lipoproteins (LDL), which can be found in the atherosclerotic plaques of the abdominal aorta (Parums et al., 1986; Parums et al., 1990; Ramshaw & Parums, 1994). Since an intact media constitutes an immunoprivileged site, the capacity of lipids deposited in the intima and media to elicit an inflammatory reaction in the adventitia may depend on the thinning or breach of the media itself, with consequent transit of the lipids. These can be processed by adventitial macrophages and presented to B and T cells, thus eliciting a local inflammatory reaction which eventually leads to adventitial and peri-aortic inflammation and fibrosis.

Morphologic and experimental findings showed that adventitial inflammation also seems to be more marked where the media is thinner (Mitchinson, 1972; Mitchinson 1984; Parums et al., 1990). IgG has been detected in close apposition to extracellular ceroid, and serum antibodies to oxidized LDL and ceroid were more common in patients with chronic periaortitis than in healthy individuals (Parums et al., 1986; Parums et al., 1990). Furthermore, a wide spectrum of adhesion molecules and gene products for cytokines, such as interleukin-1α, interleukin-2, interleukin-4, and interferon-γ, have been detected in the aortic adventitia, thus strengthening the hypothesis that chronic periaortitis is associated with active adventitial chronic inflammation (Ramshaw & Parums, 1994; Ramshaw et al., 1994).

According to this hypothesis, advanced atherosclerosis is a *sine qua non* for the development of chronic periaortitis, which may be an exaggerated local immune response to plaque antigens. The notion that chronic periaortitis is secondary to atherosclerosis is challenged by several findings. There was no substantial difference in the incidence of advanced atherosclerosis between patients with chronic periaortitis and healthy controls (Uibu et al., 2004; Breems et al., 2000). Also, chronic periaortitis may affect patients without atherosclerosis, and it has been reported in pediatric patients (Miller et al., 2003). A recent study showed no significant differences in anti-ox-LDL antibody levels between patients with chronic periaortitis and controls (van Bommel et al., 2011).

Furthermore, a number of findings support the hypothesis that chronic periaortitis may be a manifestation of systemic disease rather than the result of a local reaction. These include its constitutional symptoms, the high acute-phase reactant levels, autoantibody positivity, and the frequent association with other autoimmune diseases (Gilkeson & Allen, 1996; Demko et al., 1997; Vaglio et al., 2003; Marcolongo et al., 2004). Additionally, the association with HLA-DRB1, a marker of autoimmune diseases, is an additional clue to its autoimmune origin (Martorana et al., 2006).

Chronic periaortitis also has histologic similarities to large vessel vasculitis such as giant cell arteritis and Takayasu's arteritis; prominent adventitial inflammation and the involvement of the vasa vasorum (Ramshaw et al., 1994; Vanoli et al., 2005; Vaglio et al., 2006; Salvarani et al., 2008), and sometimes extends beyond the abdominal aorta (Mitchinson 1972; Cid et al., 1998; Jois et al., 2004). In addition, in some patients with chronic periaortitis the disease involves not only the abdominal aorta and the iliac vessels, but also other vascular territories such as the thoracic aorta. This finding was already observed long time ago by autopsy studies (Mitchinson, 1972). Recently, in a study using 18F-fluorodeoxyglucose positron emission tomography, it have also shown that in some patients with chronic periaortitis the high 18F-fluorodeoxyglucose uptake in the abdominal aorta and in the common iliac arteries coexists with a pathologic uptake in the thoracic aorta and its main branches, which confirms the idea that chronic periaortitis is a systemic disease in some cases (Salvarani et al., 2005).

These findings strengthen the idea that chronic periaortitis may originate as a primary arteritis involving the aorta. The perivascular- and sometimes transmural-involvement of vasa vasorum may represent the initial event of the disease. Its centrifugal extension could induce a fibro-inflammatory periaortic reaction, whereas its centripetal spreading could promote atherosclerosis, medial thinning and aneurysm formation (Vaglio & Buzio, 2005; Vaglio et al., 2006).

Structural alterations of the aortic wall seen in chronic periaortitis result in part from degradation of the macromolecules, such as collagen and elastin. These changes are associated with excessive production of matrix metalloproteinases (MMPs), which are

assumed to orchestrate the widespread matrix destruction (Freestone et al., 1995). The inflammatory infiltrate is thought to play an etiologic role in aneurysm formation by direct local production of matrix-degrading enzymes and production of cytokines that induce resident mesenchymal cell production of MMPs (Newman et al., 1994). Recent findings suggest that both the local mesenchymal cell expression and the macrophage expression of MMPs are required for aneurysm formation (Longo et al., 2002).

Both fibrillar collagen and elastin are highly organized in the lamellar structure of the aortic media. One potential mechanism for the complementary role of MMP-2 and MMP-9 is that MMP-2 primarily acts as a collagenase-initiating cleavage of the triple helix into one- and three-quarter lengths. The single α chains could then be degraded by MMP-9, releasing the coiled elastin and causing it to become fattened and attenuated. Rupture and expansion rates of abdominal aortic aneurysms have been linked to MMP-2 and MMP-9 levels in tissue and plasma (Petersen et al., 2000). Such observations appear consistent with the increased medial atrophy observed within inflammatory abdominal aortic aneurysms, because activated MMPs may weaken the media by causing destruction of elastic and collagen fibers and smooth muscle cells.

As in many other immune-mediated diseases, environmental and infectious agents probably contribute to the pathogenesis of chronic periaortitis. As mentioned above, asbestos exposure and smoking are established risk factors (Uibu et al., 2004). It has been hypothesized that inflammation within the aortic wall may be a response to infection. Both herpes and cytomegalovirus have been described as potential agents (Tanaka et al., 1994). Recent interest has been focused on Chlamydia pneumoniae, which was found to be more prevalent in aneurysmal than in normal aortic tissue (Tang et al., 2005).

5. Clinical features

The clinical presentation of chronic periaortitis is insidious and vague. Lumbar, abdominal or flank pain is present in about 80% of the patients. It has been described as insidious, persistent and dull, poorly localized, unmodified by movement or rest. If the ureters are involved, the pain may be acute and colic-like (Baker et al., 1987; Vaglio et al., 2003; van Bommel et al., 2009). During the initial phases, patients may find relief using non-steroidal anti-inflammatory drugs, but the beneficial effect of these agents is transient (Gilkeson & Allen, 1996; Vaglio et al., 2006).

In addition to pain, the commonest clinical manifestations are systemic symptoms, most likely related to the inflammatory nature of the disease: about 40 to 80% of patients complain of fatigue, anorexia, weight loss and low-grade fever (Baker et al., 1987; Kardar et al., 2002; Vaglio et al., 2003; Scheel et al., 2009). Ureteral obstruction is the most frequent complication of idiopathic retroperitoneal fibrosis. It involves both ureters in a high percentage of cases (50–80%) and may occur simultaneously (Kardar et al., 2002; van Bommel et al., 2007). Ureteric obstruction is commonly due to edema or inflammation rather than fibrosis. This observation is supported by the fact that the obstruction can improve rapidly with corticosteroid therapy (Baker et al., 1987; Nitecki et al., 1996).

In cases of advanced bilateral ureteral obstruction, oliguria and symptoms secondary to uremic syndrome occur (Baker et al., 1987; Sterpetti et al., 1989; Jois et al., 2004). Varicocele and hydrocele, sometimes associated with testicular pain, are not uncommon, and also probably develop because of compression of the gonadal vessels (Baker et al., 1988; Vaglio et al., 2003). Constipation and claudication are less common. Lower limb edema and deep

venous thrombosis may occur, probably as a result of inferior vena cava and iliac vein involvement.

Physical examination usually reveals abdominal tenderness and sometimes a palpable, pulsatile and tender abdominal mass. A periumbilical bruit may be heard in patients with inflammatory abdominal aortic aneurysms (Crawford et al., 1985; Nitecki et al., 1996). The combination of abdominal pain, a pulsatile mass with overlying bruit, constitutional symptoms, and high levels of acute-phase reactants usually distinguish inflammatory abdominal aortic aneurysms from noninflammatory abdominal aortic aneurysms.

Laboratory examinations are useful, but not diagnostic for chronic periaortitis. Acute phase reactants such as the erythrocyte sedimentation rate and C-reactive protein are elevated in more than 80% of patients with active disease, in keeping with the presence of a systemic inflammation and are often used to monitor the clinical course of the disease (Kardar et al., 2002; Marcolongo et al., 2004; Vaglio et al., 2006). The erythrocyte sedimentation rate and C-reactive protein dramatically decrease or even normalize after a few weeks of therapy (van Bommel et al., 2007), whereas their sensitivity in heralding relapses is uncertain (Vaglio et al., 2005). A recent retrospective study investigated whether the erythrocyte sedimentation rate and C-reactive protein levels might predict response to glucocorticoid therapy, but found that baseline erythrocyte sedimentation rate and C-reactive protein did not discriminate between chronic periaortitis patients who experienced disease regression and those who showed mass stabilization or progression (Magrey et al., 2009).

Renal dysfunction is related to the severity of ureteral involvement, but only 18-21% of patients actually experiences end-stage renal failure (Baker et al., 1987; Nitecki et al., 1996). Normochromic, normocytic anemia is often present as a result of systemic chronic inflammation. Leukocytosis, eosinophilia, and polyclonal hypergammaglobulinemia may be disclosed in some patients (Gilkeson & Allen, 1996). If polyclonal hypergammaglobulinemia is present, it is worthwhile assessing serum immunoglobulin levels and, if available, IgG subclasses; IgG4 is high in chronic periaortitis patients with features of IgG4-related systemic disease (Vaglio et al, 2011; J.R. Stone, 2011).

Immunologic and autoimmune tests should always be assessed in patients with chronic periaortitis. Antinuclear antibodies have been reported in up to 60% of patients, whereas anti-dsDNA and antiextractable nuclear antigen antibodies are rare (Vaglio et al., 2003). Rheumatoid factor is not uncommon. The presence of these autoantibodies, although non-organ-specific and often positive at low titers, may be a clue to an autoimmune origin of chronic periaortitis. Alternatively, they may be the earliest manifestation of a smoldering disorder that will clinically emerge late in the course of chronic periaortitis.

On the other hand, certain autoantibodies actually indicate the presence of an associated autoimmune disease. When autoimmune thyroiditis coexists, antithyroglobulin and antithyroid microsome antibodies are positive (Vaglio et al., 2003). P-antineutrophil and C-antineutrophil cytoplasmic antibodies have been detected in a few cases of chronic periaortitis associated with small vessel vasculitis, such as Wegener granulomatosis and microscopic polyangiitis (Kaipiainen-Seppanen et al., 1996; Aslangul et al., 2003).

6. Evidence of systemic autoimmunity in chronic periaortitis

Although it has been considered a localized inflammatory disease secondary to atherosclerosis, several genetic, clinical, laboratory and pathologic findings suggest that chronic periaortitis is a systemic autoimmune disease, perhaps involving a vasculitic process of small and medium vessels (Table 1).

Autoimmune Component	Example
Genetics	Association with HLA-DRB1*03, DRB1*0404, DRB1*15 and HLA-B*08 Association with CC chemokine receptor 5 (CCR5) gene delta 32 polymorphism
Autoantibodies	Antinuclear antibody Anti-thyroid microsome and anti-thyroglobulin antibody Anti-neutrophil cytoplasmic antibody Rheumatoid factor Anti-smooth muscle antibody
Association with Autoimmune diseases	Autoimmune thyroiditis Rapidly progressive glomerulonephritis Systemic vasculitis Rheumatoid arthritis Juvenile rheumatoid arthritis Ankylosing spondylitis Systemic lupus erythematosus Antiphospholipid syndrome IgG4-related systemic disease
Histologic finding	Small vessel vasculitis of retroperitoneal vessels and aortic vasa vasorum Ectopic lymphoid follicles with germinal centers in periaortic retroperitoneum and aortic adventitia
Clinical manifestations	Constitutional symptoms, such as fever, fatigue, weight loss, anorexia and sleep disturbances Systemic involvement of large arteries
Laboratory findings	High erythrocyte sedimentation rate High C-reactive protein Anemia
Treatment response	Rapid response to corticosteroids
Prognosis	Chronic-relapsing course

Table 1. Summary of systemic autoimmune components implicated in chronic periaortitis

6.1 Genetics

Genetic association study revealed that patients with chronic periaortitis were associated with certain genetic markers, which is involved in the immune response and commonly associated with autoimmune or inflammatory disease. The HLA system plays a role in conferring susceptibility to chronic periaortitis (Rasmussen et al., 1997; Martorana et al., 2006). The bias in expression of specific HLA alleles are defining features of autoimmune disease.

The HLA-DRB1*03, DRB1*0404, DRB1*15 and HLA-B*08 alleles was significantly higher in patients with chronic periaortitis. These alleles are a well-known marker of autoimmunity, since it is associated with a number of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, giant cell arteritis, autoimmune thyroiditis, type 1 diabetes mellitus and myasthenia gravis.

The CC chemokine receptor 5 (CCR5) gene delta 32 polymorphism is associated with aneurysmal chronic periaortitis, which creates a truncated, nonfunctional receptor and probably shifts the immune response toward a Th2 pattern (Boiardi L et al., 2011).

6.2 Autoantibodies

Several autoantibodies are positive in varying proportions of patients, which may be a clue to an autoimmune origin of chronic periaortitis. Antinuclear antibodies are positive in up to 50–60% of the cases, although their titer is often low (Vaglio et al., 2003). Anti-thyroid microsome and anti-thyroglobulin antibodies may be positive in 25–30% (Martorana et al., 2006). Other autoantibodies, such as antineutrophil cytoplasmic antibodies, rheumatoid factor, and anti-smooth muscle may also be positive.

6.3 Association with autoimmune disease

Chronic periaortitis are frequently associated with autoimmune diseases involving other organs or structures. Two recent studies have showed a higher incidence of systemic autoimmune diseases. A case-control study comparing inflammatory abdominal aortic aneurysms and noninflammatory abdominal aortic aneurysms showed a higher incidence of systemic autoimmune diseases in the former group (Haug et al., 2003). In another study of 16 consecutive patients with chronic periaortitis, three had antineutrophil cytoplasmic antibody-positive rapid progressive renal disease, three had autoimmune thyroiditis, and one had rheumatoid arthritis (Vaglio et al., 2003).

Another frequently reported association is systemic vasculitides, which in most cases involve small and medium-sized vessel vasculitis, such as Wegener granulomatosis and polyarteritis nodosa (Akman et al., 1983; Hautekeete et al., 1990; De Roux-Serratrice et al., 2002) or unclassifiable systemic vasculitis (Hellstrom & Perez-Stable, 1966; Littlejohn & Keystone, 1981). Antineutrophil cytoplasmic antibody-associated vasculitic syndromes are more and more often reported.

Chronic periaortitis may frequently be associated with fibroinflammatory disorders affecting other organs, IgG4-related systemic disease, which have an autoimmune origin (Matsumoto et al., 2008; Ito et al., 2008; Kasashima et al., 2008; Sakata et al., 2008). Other rheumatic diseases reported in patients with chronic periaortitis include ankylosing spondylitis, juvenile rheumatoid arthritis, systemic lupus erythematosus and antiphospholipid syndrome (Leblanc et al., 2002; Tsai et al., 1996; Okada et al., 1999; Kim et al., 2010).

6.4 Histologic findings

Two peculiar histopathological findings may be interpreted as manifestations of autoimmunity. Firstly, about half of patients with chronic periaortitis had adventitial inflammation with vasa vasoritis in the small retroperitoneal vessels and the aortic vasa vasorum with mononuclear cell infiltration and sometimes fibrinoid necrosis (Mitchinson, 1970; Vaglio et al., 2003; Lindell et al., 1987). Secondly, the inflammatory infiltrate may be organized in lymphoid structures such as lymphoid follicles with germinal centers in both periaortic retroperitoneum and aortic adventitia (Ramshaw & Parums, 1994). Ectopic lymphoid microstructures with germinal centers have been found in autoimmune disorders, such as the synovium in rheumatoid arthritis (Weyand et al., 2001).

6.5 Clinical manifestations

Most patients with chronic periaortitis often complain of constitutional symptoms, such as fever, fatigue, weight loss, anorexia and sleep disturbances, which probably reflect the systemic inflammatory status (Baker et al., 1987; Vaglio et al., 2003). At least in a subgroup of patients, chronic periaortitis is a vasculitis affecting large vessels (Vaglio et al., 2011).

6.6 Laboratory findings

Chronic periaortitis usually present with high concentrations of acute-phase reactants such as erythrocyte sedimentation rate and C-reactive protein, varying degrees of anemia and, in a high percentage of cases, azotemia , which reflect the systemic inflammation (Kardar et al., 2002; Vaglio et al., 2006). The erythrocyte sedimentation rate and C-reactive protein can also be used to monitor the disease course (van Bommel et al., 2007).

6.7 Treatment response

The clinical manifestations of chronic periaortitis promptly subside after the initiation of glucocorticoids therapy, which again is well in agreement with their inflammatory nature. In most patients, they induce remission of the clinical symptoms, normalization of the acute-phase reactant levels, reduction in size of the retroperitoneal mass and also resolution of the obstructive complications (Kardar et al., 2002; Marcolongo et al., 2004; van Bommel et al., 2007; Magrey et al., 2009).

However, glucocorticoids have various significant side effects, which sometimes limit their prolonged use. The combination of glucocorticoids and immunosuppressants such as azathioprine, cyclophosphamide and methotrexate has recently been reported to yield favorable results in patients with chronic periaortitis (Marcolongo et al., 2004; Warnatz et al., 2005).

6.8 Prognosis

As is the case in many inflammatory and autoimmune diseases, chronic periaortitis also has a chronic-relapsing course. The frequency of relapses may depend on the treatment approach, as they occur in 10% to 50% of patients treated with surgery alone and in about 10% when combined immunosuppressive and surgical therapies are used (Baker et al., 1988).

7. IgG4-related systemic disease

In recent years, numerous studies have reported chronic periaortitis in association with IgG4-related systemic disease, a group of autoimmune and fibrosing conditions characterized by high serum levels of IgG4 and tissue infiltration by IgG4-bearing plasma cells (Vaglio et al, 2011; J.R. Stone, 2011). These conditions share common histopathologic characteristics, such as diffuse lymphoplasmacytic infiltration, irregular fibrosis, eosinophilic infiltration, and obliterative phlebitis (Neild et al., 2006; Deshpande et al., 2006; Masaki et al., 2009).

7.1 Idiopathic peritoneal fibrosis with IgG4-related systemic disease

It has become clear that in a subset of patients with idiopathic retroperitoneal fibrosis, the disorder is in fact occurring in the setting of IgG4-related systemic disease. For 10 years,

there were several reports that autoimmune pancreatitis could be associated with inflammatory masses within the retroperitoneum, and it was later recognized that both conditions were a manifestation of IgG4-related systemic disease (J.R. Stone, 2011).

In those reports revealed that the retroperitoneal involvement is typically not entirely diffuse, but present primarily as inflammatory masses that often primarily involve the abdominal aorta, the kidneys or the ureters (Hamano et al., 2002; Miyajima et al., 2006; Tanabe et al., 2006). The inflammatory masses are composed of lymphoplasmacytic inflammation and fibrosis with a substantial number of the plasma cells expressing IgG4. The nearly all patients revealed an aortic adventitial involvement, even in the absence of aortic aneurysm formation.

In a recent study of retroperitoneal biopsies of patients with idiopathic retroperitoneal fibrosis, 10 of 17 cases were felt to be due to IgG-related systemic disease (Zen et al., 2009). In these 10 patients, the fraction of plasma cells staining for IgG4 ranged from 35 to 76% compared with 0 to 10% for the other seven patients. Furthermore, for the patients with IgG4-related disease, the mean serum IgG4 concentration was 695 mg/dl (range 154–2330 mg/dl) compared with 30 mg/dl (range 10–53 mg/dl) for the other seven patients.

7.2 Inflammatory abdominal aortic aneurysms with IgG4-related systemic disease

There are several reports which have indicated that a subset of inflammatory abdominal aortic aneurysms cases is in fact a result of IgG4-related systemic disease (Sakata et al., 2008; Kasashima et al., 2008; Qian et al., 2009). A recent study comparing 11 cases of inflammatory abdominal aortic aneurysms to 12 cases of atherosclerotic abdominal aortic aneurysms and demonstrated that the aneurysms defined as inflammatory contained more IgG4+ plasma cells than those defined as atherosclerotic. However, in that study there was no clear delineation as to which inflammatory aneurysms actually represented involvement by IgG4-related systemic disease. In addition, the fraction of plasma cells expressing IgG4 was not reported for either aneurysms group, making it unclear if the enhanced number of IgG4+ plasma cells was simply a manifestation of more plasma cells in general being present in the aneurysms labeled as inflammatory.

There have been several cases reported of inflammatory abdominal aortic aneurysms, which were attributed to IgG4-related systemic disease, and which included pathologic evaluation of the aorta (Kasashima et al., 2008; Ito et al., 2008; Qian et al., 2009). Pathologically, most cases of IgG-4 related inflammatory abdominal aortic aneurysms showed the predominant involvement in adventitia with high fraction of IgG4+ infiltrating plasma cells and high serum IgG levels (J.R. Stone, 2011).

Kasashima et al. reported that four of 10 cases (40%) of inflammatory abdominal aortic aneurysm were due to IgG4-related systemic disease with prominent IgG4+ plasma cell infiltration and high-IgG4 serum levels, whereas the remaining six had a mild (IgG4+ and total) plasma cell infiltration. Inflammation was more evident and tissue eosinophilia predominated in the IgG4-related inflammatory abdominal aortic aneurysms, whereas some degree of neutrophilic infiltration and only rare eosinophils were found in the non-IgG4-related inflammatory abdominal aortic aneurysms. Because inflammatory aneurysms may represent 2–15% of all abdominal aortic aneurysms, this would suggest 1–6% of all abdominal aortic aneurysms could be due to IgG4-related inflammatory abdominal aortic aneurysms (J.R. Stone, 2011).

7.3 Thoracic aortitis with IgG4-related systemic disease

Until now, the six cases of thoracic aortitis due to IgG4-related systemic disease reported, which derived from surgical resections (Khosroshahi et al., 2009; J.H. Stone et al., 2009; Ishida et al., 2009; J.H. Stone et al., 2010; Kasashima et al., 2010). All six patients were men in an old age (65–74 years). The arch was the most commonly involved in five cases, with two cases having involvement of the ascending aorta, and only one case having involvement of the descending aorta. Five of the six patients presented with an aneurysm.

According to histologic assessment, all displayed a prominent lymphoplasmacytic infiltrate, with a high percentage of the plasma cells staining for IgG4 (74–89%). In addition, at least five patients showed an obstructive phlebitis within the adventitia. In three cases, there was a marked predominance for the adventitia compared with the media and intima (J.R. Stone, 2011). Serum IgG4 level was found to be markedly elevated in 2 patients who tested it and both of these patients had documented extra-aortic involvement.

Assessment of all thoracic aortitis cases surgically resected in a 5-year at one institute revealed that IgG4-related systemic disease was responsible for three of four cases of lymphoplasmacytic aortitis and 9% of all cases of thoracic aortitis (J.H. Stone et al., 2010). According to that study, IgG4-related aortitis was present in 0.5% of all thoracic aorta resections. In a subsequent study from Japan, assessment of 125 thoracic aorta resections revealed two cases of IgG4-related aortitis, indicating 1.6% of all resected thoracic aortas contained IgG4-related aortitis (Khosroshahi et al., 2010).

Although much remains to be clarified with regard to the pathogenesis of chronic periaortitis, it is conceivable that IgG4 may represent a link between chronic periaortitis and systemic fibro-inflammatory conditions. The analysis of IgG4-related cases may provide additional clues supporting the possible systemic large-vessel involvement in chronic periaortitis (Vaglio et al., 2011).

8. Conclusion

Chronic periaortitis is a chronic disease characterized by a retroperitoneal fibroinflammatory reaction surrounding the abdominal aorta, which may or may not be dilated. Although it has been considered a localized inflammatory response to advanced atherosclerosis, there is increasing evidence supporting the hypothesis of an underlying systemic autoimmune disease with vasculitic process involving small and medium vessels. Further studies are warranted in order to elucidate the potential triggers of the disease, the pathways leading to the aortic-periaortic inflammation and to the disproportionate fibrogenic reaction.

9. References

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