Immunological Aspects of Systemic Vasculitis

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Contents

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Abstract

Primary vasculitis are commonly multifactorial disorders involving environmental, genetic and immunological factors. Several immune-based effector mechanisms are implicated in the vascular wall damage. These effector mechanisms commonly imply auto-antibodies or immune complexes - mediated cytotoxicity but the contribution of a T-cell mediated immune response has also been described, particularly in large vascular vasculitis. Despite advances in understanding the pathophysiological mechanisms of vasculitis, the triggering events initiating the disease remain largely undefined in most cases. This review highlights the recent advances in the etiopathogenesis of primary vasculitis. A better understanding of the immunological aspects of these disorders may provide insight into the development of novel therapeutical strategies.

1 Key Points

Primary vasculitides are commonly multifactorial disorders involving environmental, genetic, and immunological factors. Several immune-based effector mechanisms are implicated in the vascular wall damage. These effector mechanisms generally imply cytotoxicity mediated by autoantibodies or immune complexes but the contribution of a T-cell-mediated immune response has also been described, particularly in large-vessel vasculitis. Despite advances in understanding the physiopathological mechanisms of vasculitis, the triggering events initiating the disease remain largely undefined in most cases. This review highlights the recent advances in the etiopathogenesis

L. Hendaoui et al. (eds.), *Systemic Vasculitis,* Medical Radiology. Diagnostic Imaging,
DOI: 10.1007/174_2011_144, © Springer-Verlag Berlin Heidelberg 2012

of primary vasculitis. A better understanding of the immunological aspects of these disorders may provide insight into the development of novel therapeutic strategies.

2 Introduction

The pathogenesis of primary vasculitis is poorly understood and the triggering events initiating the inflammatory response remain largely undefined. Primary vasculitides are commonly multifactorial disorders involving environmental, genetic, and immunological factors. The contribution of the immune dysregulation in the pathogenesis of primary vasculitis may vary from one disease to another and several, yet not exclusive immune-mediated mechanisms are implicated in triggering the vascular wall damage. A better understanding of the immunological aspects of primary vasculitis may provide insight into the development of new therapeutic strategies.

3 Immune-Based Effector Mechanisms in Vasculitis

3.1 Autoantibody-Dependent Cell-Mediated Cytotoxicity

3.1.1 Anti-Neutrophil Cytoplasmic Antibodies

Anti-neutrophil cytoplasmic antibodies (ANCA) are closely associated with Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg–Strauss syndrome (CSS), and renal limited vasculitis, also called idiopathic necrotizing crescentic glomerulonephritis (NCGN). Accordingly, these small-vessel vasculitides are commonly referred to as the ANCA-associated vasculitis (Seo and Stone 2004).

ANCA are a group of autoantibodies directed against enzymes contained in the azurophil granules of neutrophils. Two major types of ANCA are described on the basis of indirect immunofluorescence patterns: cytoplasmic (c-ANCA) and perinuclear (p-ANCA) patterns. The c-ANCA pattern corresponds commonly to proteinase 3 (PR3), whereas p-ANCA antibodies are related to a large range of antigens, the most common one being myeloperoxidase (MPO). PR3-c-ANCA are strongly associated with WG with high specificity and predictive values, whereas MPO-p-ANCA are seen more commonly in MPA and CSS. p-ANCA not corresponding to MPO antigen but recognizing specificities for other proteins, including lactoferrin, elastase, and bactericidal permeability-inhibiting protein, are less specific and have been reported in a wide variety of inflammatory and infectious conditions. In general, there is no strict correlation between ANCA titers and disease activity, but some studies showed that relapses of disease are often preceded by a rise in ANCA levels [reviewed in Seo and Stone (2004)].

Although the role of ANCA in the pathophysiology of small-vessel vasculitis is still debated, several experimental and in vitro data support that ANCA are directly pathogenic. In vitro data helped to decipher the effects of ANCA on neutrophil functions and gave indirect evidence of the role of these autoantibodies in vascular damage. ANCA can activate neutrophils primed with TNF-α, leading to degranulation and release of lysosomal enzymes as well as production of inflammatory cytokines and reactive oxygen intermediates (Falk et al. 1990; Brooks et al. 1996). Activated neutrophils are thus able to exhibit cytotoxic effects towards endothelial cells (Ewert et al. 1992; Savage et al. 1992). Moreover, ANCA are capable of enhancing neutrophil adherence to endothelium through upregulation of adhesion molecules on both neutrophils and endothelial cells (Ewert et al. 1995; Johnson et al. 1997a, b; Muller Kobold et al. 1999). The direct effect of ANCA on endothelial cells may suggest that endothelial cells themselves express ANCA antigens. However this hypothesis remains controversial (Kallenberg et al. 2002).

Strong evidence for the pathogenic role of ANCA has been derived from in vivo studies. Experimental data from studies in mice showed that anti-MPO antibodies triggered a severe necrotizing and crescentic glomerulonephritis, a granulomatous inflammation, and a systemic necrotizing vasculitis, consistent with clinical features of ANCA-associated vasculitis (Xiao et al. 2002). Interestingly, as recipient mice were deficient in both T and B lymphocytes, a role of cellular effector functions in triggering tissue damage was thus unlikely (Xiao et al. 2002). Further experiments supported the role of neutrophils in triggering tissue damage in the anti-MPO-induced disease. The development of crescentic glomerulonephritis was indeed accompanied by glomerular accumulation of neutrophils and macrophages, and depletion of neutrophils

completely protected the mice from the ANCA-induced glomerulonephritis (Xiao et al. 2005). Contrasting with data obtained with MPO-ANCA, the effects of anti-PR3 antibodies in animal models have been less forthcoming (Tomer et al. 1995; Pfister et al. 2004; van der Geld et al. 2007) suggesting a possible pathophysiological difference between MPO-ANCA- and PR3-ANCA-associated disease (Franssen et al. 2000). Some sparse clinical data also support the pathogenic role of MPO-ANCA. For instance Schlieben et al. (2005) reported the case of a newborn who developed a pulmonary-renal syndrome following a passive placental transfer of maternal MPO-p-ANCA.

Additional data were used to try to decipher the initial pathophysiological events preceding the neutrophil attraction to the vascular wall. Interestingly, when products of activated neutrophils were infused into renal rat artery of MPO-immunized rats, pauci-immune vasculitis developed (Kallenberg et al. 2002). As suggested by Kallenberg et al. (2002) the adherence of cationic proteins such as MPO and PR3 released from activated neutrophils to glomerular capillaries is probably an initial mandatory event. Consequently, ANCA will interact with their cognate antigen and the in situ deposition of immune complexes will activate the complement system resulting in neutrophil attraction. Neutrophils will subsequently be activated by ANCA, thus initiating the different steps of the inflammatory process.

Altogether, in vitro and in vivo data suggest that ANCA induces endothelial damage through neutrophil activation, leading to degranulation, enhanced binding to the vascular endothelium, and release of neutrophil chemoattractants, thus sustaining an amplifying inflammatory loop. A previous priming of neutrophils by cytokines such as TNF-α or other stimuli may be necessary to enhance the expression of PR3 or MPO on the cell surface of neutrophils and make them accessible to ANCA interaction (Charles et al. 1991; Csernok et al. 1994; Hellmich et al. 2000). Alternately, MPO may passively bind to the cell surface of unstimulated neutrophils, leading to ANCA interaction without the need for priming (Hess et al. 2000). Interestingly, several studies pointed out that the binding of ANCA to antigen expressed on the surface of neutrophils is insufficient to fully activate these cells. Interaction of ANCA with Fc gamma receptors on neutrophils seems to be necessary (Reumaux et al. 1995; Ben-Smith et al. 2001).

3.1.2 Anti-endothelial Cell Antibodies

Anti-endothelial cell antibodies (AECA) are heterogeneous antibodies that react with various endothelial cell antigens. AECA have been detected in a broad range of autoimmune and inflammatory conditions including systemic vasculitis (Guilpain and Mouthon 2008). The prevalence of AECA in such disorders may vary from one study to another and discrepant results may be explained by the use of different techniques and sources of endothelial cells (Belizna et al. 2006; Guilpain and Mouthon 2008). The key role of AECA in the pathogenesis of systemic vasculitis remains unclear, and some authors consider the presence of AECA as an epiphenomenon. Some data, however, may support the involvement of AECA in tissue damage. In Takayasu arteritis (TA) and ANCA-related vasculitis, AECA have been reported to correlate with disease activity (Chan et al. 1993; Nityanand et al. 1997). Various potential pathogenic mechanisms of AECA have been described. Few studies reported that AECA could exert cytotoxic effects through complement-dependent cytotoxicity such as in Kawasaki disease (KD) or in TA (Fujieda et al. 1997; Tripathy et al. 2001) or via antibody-dependent cell cytotoxicity in ANCA-related vasculitis (Savage et al. 1991). Other data suggest that these antibodies could be pathogenic through the activation of endothelial cells, leading to upregulation of adhesion molecules and inflammatory cytokine production. In ANCA-mediated vasculitis, AECA may thus play an important role by facilitating the neutrophil adherence to endothelium via the upregulation of adhesion molecules on endothelial cells (Del Papa et al. 1996). In Henoch–Schönlein purpura (HSP), IgA AECA may enhance the induction of interleukin (IL)-8 production, a neutrophil chemoattractant cytokine (Yang et al. 2006), and could thus be involved in the neutrophil recruitment. Finally, the circulating AECA against aortic endothelial cells described in TA may be involved in the disease pathogenesis, not only through the activation of endothelial cells, but also via the induction of apoptosis (Chauhan et al. 2006).

3.2 Immune Complexes

Leukocytoclastic vasculitides (LV) are heterogeneous disorders characterized by lesions often limited to the skin and which may affect other organs

(Claudy 1998). They are mediated to a large extent by circulating antibodies and antibody-dependent effector mechanisms. The pathogenic role of the deposition of immune complexes in LV is well demonstrated in animal and human experimental models. Accordingly, LV is a hypersensitivity reaction similar to that obtained in the experimental Arthus reaction (Claudy 1998). However the antigen involved in the various LV differs and is often unidentified. Soluble immune complexes formed in antigen excess circulate until they deposit in blood vessels when flow is reduced at bifurcations. The activation of the complement pathway by immune complexes results in the generation of C3a and C5a anaphylatoxins leading to neutrophil attraction and basophil degranulation. The subsequent release of histamine increases vascular permeability and enhances the neutrophil migration through the vessel wall. Neutrophils are activated through Fc gamma receptors (Moser et al. 1995) leading to the release of lysosomal enzymes and reactive oxygen intermediates, causing vascular injury. Adhesion molecules and cytokines produced by endothelial cells increase transendothelial migration and adhesion of neutrophils (Claudy 1998). Along with the key role of activated neutrophils and endothelial cells, the direct cytotoxic effect of the complement's membrane attack complex is a further pathophysiological mechanism that may damage the endothelium (Kawana 1996). In later phases of LV characterized by lymphocytic infiltration, a different pathophysiological mechanism involving dendritic cells (DCs) and T cells may initiate a secondary cell-mediated immune response or contribute to self-perpetuation of the disease (Lotti et al. 1998).

Apart from the broad range of small-vessel vasculitis related to deposition of circulating immune complexes, Goodpasture syndrome is mediated by autoantibodies against basement membranes of kidneys and alveoli. Anti-GBM (glomerular basement membrane) antibodies binding to antigen in the capillary wall trigger antibody-dependent cytotoxic mechanisms leading to tissue damage. However compelling data suggest that unlike in LV, cell-mediated events involving different T cell subsets are also implicated in Goodpasture syndrome (Ooi et al. 2008).

3.3 T-cell-Mediated Immune Response

T lymphocyte response and granuloma formation are characteristic features of large vascular vasculitis. The activation of a cellular immune response orchestrated by $CD4^+$ T lymphocytes leads to the emergence of an inflammatory process throughout the artery's wall layers (panarteritis). DCs located at the adventitia–media border and activated by an unknown antigen have a crucial role in initiating the wall inflammation. The activated DCs thus provide the necessary co-stimulatory signals to trigger $CD4^+$ T cell activation; they also produce several chemokines, therefore recruiting $CD4^+$ T lymphocytes and macrophages to the vascular walls. The activated $CD4^+$ T lymphocytes undergo clonal expansion and secrete IFN-γ, which play a key role in activating the effector functions of macrophages. In the vicinity of $CD4^+$ T cells, macrophages release inflammatory cytokines in the adventitia, whereas in the media–intima border they secrete metalloproteinases and reactive oxygen intermediates, leading to the fragmentation of the internal elastic lamina and triggering the intimal hyperplasia and neoangiogenesis (Salvarani et al. 2008).

4 Etiopathogenesis of Vasculitis

4.1 Large-Vessel Vasculitis

Takayasu arteritis (TA) and giant cell arteritis (GCA) are granulomatous large-vessel vasculitis affecting vital arteries and causing vascular complications by either luminal occlusion or vessel wall destruction. TA and GCA typically differ in the age of onset and the vascular structure targeted by inflammation (Weyand and Goronzy 2003). Indeed, TA typically manifests in the aorta, its main branches, and the pulmonary arteries in young woman, whereas GCA affects the aorta and its more distal and extracranial branches in individuals over 50. Although TA and GCA are classically considered distinct on the basis of these different epidemiological and clinical features, a more detailed clinical examination revealed that similar signs and symptoms are often present in both diseases albeit at different frequencies, supporting that these disorders are the same disease with a broad spectrum of

phenotypes (Maksimowicz-McKinnon et al. 2009). Similarities in the histological abnormalities of these vasculitides further support this hypothesis. Actually, TA and GCA share the same pathogenic processes that distinguish them from other vasculitides. Compelling data—focusing mostly on GCA because of the accessibility of inflamed vascular lesions—pointed out that large-vessel vasculitides are T-cell-mediated diseases (Weyand and Goronzy 2003).

Vascular lesions are characterized by inflammatory infiltrates, often with granulomatous arrangements which are distributed as a panarteritis throughout the artery's wall layers, but preferentially located at the intima–media junction (Salvarani et al. 2008). The patchy granulomatous infiltrates are composed of lymphocytes, macrophages, and multinucleated giant cells (Weyand and Goronzy 2003). In TA, the lymphocyte population is composed of variable percentages of $CD4^+$ and $CD8^+$ T lymphocytes, NK cells, and $\gamma\delta$ T cells (Seko et al. 1994). As demonstrated in a mouse chimera model, $CD4^+$ T cells are key cellular players that orchestrate the inflammatory response in the vascular wall (Brack et al. 1997). In GCA, $CD4^+$ T lymphocytes produce IFN-γ, thus inducing and maintaining inflammatory infiltrates (Wagner et al. 1996). However IFN-γ-producing lymphocytes represented a minor subset of tissue-infiltrating T cells and they preferentially aggregate in the adventitial layer of the vascular wall, where they are intimately associated with the antigen-presenting cells (Wagner et al. 1996). While activated by the latter, lymphocytes secreting IFN-γ interact with macrophages, leading to the formation of the granulomas predominantly in the medial layer of the vascular wall. IFN-γ is indeed a major activating factor of the macrophage functions. Interestingly, IL-12—a monocyte/macrophage cytokine which is classically associated with granuloma formation—is absent from GCA lesions (Krupa et al. 2002). The role of IL-18—an alternative monokine cytokine—is suggested. In Takayasu arteritis, similar pathophysiological mechanisms of tissue lesions seem to be involved. However, cytotoxic effector functions of lymphocytes have been suggested. Indeed, diverse perforin-secreting killer cells ($\gamma\delta$ T lymphocytes, natural killer cells, and cytotoxic T lymphocytes) are involved in the pathogenesis of vascular damage in TA (Seko et al. 1994). Cytotoxicity of these cells seems to be triggered in part through the activation of the NKG2D pathway, as the expression of NKG2D as well as that of its ligand MICA are significantly enhanced in infiltrating T cells and aortic tissue, respectively (Seko et al. 2004). The role of $\gamma\delta$ T cells has been further supported by additional data obtained by Seko et al. Indeed, $\gamma\delta$ T cells—which represent nearly 30% of the infiltrating cells—exhibit a restricted repertoire, indicating that they recognize a specific locally expressed antigen (Seko et al. 2000). Interestingly, a recent study suggested that anti-aortic endothelial cell antibodies may play a role in the vascular dysfunction in TA, but the implication of autoantibodies in a T-cell-mediated disease remains to be clarified (Chauhan et al. 2006).

Nonetheless, strong evidence suggests that $\alpha\beta$ T lymphocytes are key players in the pathogenesis of large-vessel vasculitis. Although T cells infiltrating the tissue in GCA are highly diverse, clonotypes with identical T cell receptor can be isolated from distinct vascular lesions of the same patient but not in the peripheral blood, suggesting that a specific antigen is present in the arterial wall and is recognized by a small fraction of $CD4^+$ T cells at different locations (Weyand et al. 1994a; Martinez-Taboada et al. 1996). The mouse chimera model performed by Brack et al. further supports the hypothesis that vascular inflammation is orchestrated by a small number of T cell clonotypes specific for a locally expressed antigen. Indeed, when temporal artery biopsy specimens from patients with GCA were engrafted into mice with severe combined immunodeficiency (SCID), T cell clonotypes with identical T cell receptors were expanded in different mice that had been engrafted with tissue specimens from the same patient. Furthermore, the adoptive transfer of syngeneic tissue-derived T cells into engrafted SCID maintained the vascular lesions of GCA in human artery-mouse chimeras (Brack et al. 1997). Comparable data were obtained in TA. The restricted usage of TCR V α and V β genes by infiltrating T cells in Takayasu arteritis suggests the presence of a specific recognized antigen in the aortic tissue (Seko et al. 1996). However the target antigen recognized by the $CD4^+$ T cells remains undetermined (Weyand and Goronzy 2003). Implication of infectious agents has been supported by some epidemiological studies. The presence of

genomic material of Parvovirus B19 or *Chlamydia pneumoniae* has been demonstrated in temporal biopsies of GCA patients (Gabriel et al. 1999; Wagner et al. 2000; Haugeberg et al. 2001), but these data have not been corroborated by other studies (Helweg-Larsen et al. 2002; Regan et al. 2002). Nevertheless, an experimental model suggested that the media of large elastic arteries was an immunoprivileged site as it favors the persistence of pathogens or self-antigens leading to chronic vascular disease restricted to the great elastic arteries (Dal Canto et al. 2001).

Strong evidence suggests that vascular DCs, by activating both adaptive and innate immunity, play a central role in triggering and perpetuating in situ inflammation and determining the site specificity and the architecture of the emerging vasculitis. Human medium and large arteries are in fact populated by DCs located at the media–adventitia border that act as sentinels sampling the antigenic vascular environment. In temporal arteries affected by GCA, DCs, which are highly enriched, are activated as indicated by $CD83^+$ and $CD86^+$ expression, thus providing the necessary co-stimulatory signal to T cells triggering their activation (Krupa et al. 2002). DC/T cell interaction involves IL-18 but not IL-12 production (Krupa et al. 2002; Weyand et al. 2005). The activated DCs produce several chemokines such as CCL19 and CCL21, thus playing a critical role in recruiting T cells into the vascular wall. Activated vascular DCs also express CCR7, the ligand of these chemokines, explaining why these cells are trapped within the vascular infiltrates (Weyand and Goronzy 2003). Notably, vascular DCs display a broad spectrum of pattern-recognition receptors that recognize a series of pathogen-derived products, thus playing an important role at the interface between innate and adaptive immunity. Compelling recent data demonstrate that the engagement of the DCs innate immune receptors is involved in determining either the localization or the pattern of the vascular inflammation. Indeed several reports showed that while sensing bacterial pathogens, vascular DCs may initiate and perpetuate an adaptive immune response in the vessel (Weyand et al. 2005; Pryshchep et al. 2008). Additionally, Pryshchep et al. pointed out that the restricted feature of inflammation to certain anatomic sites within the vascular tree seems to be governed by the selective pattern of toll-like receptor (TLR) expression (Pryshchep et al. 2008). More recent work performed by Deng et al. (2009) demonstrated that the architecture of the emerging arteritis is also regulated by the vascular DC and depends on the type of TLR engaged. Indeed TLR4 ligation leads to transmural panarteritis, whereas TLR5 activation promotes an adventitial perivasculitis. The authors showed furthermore that TLR4-stimulated DCs preferentially produce CCL20, resulting in the recruitment and activation of $CCR6^+$ T cells, a subset which seems to be implicated in mediating vasculitis in GCA. Thus, different bacterial pathogens may induce distinct vasculitis, depending on the original danger signal, and vascular DCs shape the emerging immune response by differentially recruiting specialized T effector cells, thus triggering distinct types of vasculitis. Yet, the etiological agents initiating large-vessel vasculitis are not defined. As suggested by Deng et al., categorizing patients with large-vessel vasculitis according to the pattern of inflammation may help with the investigation of the etiological agents.

As mentioned above, macrophages are also a crucial component of the inflammatory vascular infiltrate in GCA, and different subsets of macrophages can be distinguished in situ. Thus, macrophages producing pro-inflammatory cytokines such as IL-1 and IL-6 were localized in the vicinity of IFN-γ-secreting $CD4^+$ T cells at the site of inflammation in the adventitia while collagenase-producing macrophages accumulate in the intima–media border of the inflamed vessel, suggesting their implication in the tissue injury (Weyand et al. 1996). Activated macrophages in the intima–media junctions also produced metalloproteases and reactive oxygen intermediates, thus playing a central role in the medial-wall damage leading to a non-stenosis arteritis [reviewed in Weyand and Goronzy (2003)]. The chronic activation of macrophages may induce the appearance of multinucleated giant cells. The latter cells were associated with the fragmentation of the internal elastic lamina (Weyand and Goronzy 2003). Production of large amounts of growth factors such as platelet-derived growth factor (PDGF) and angiogenic cytokines by giant cells and macrophages may lead to a prominent hyperplasia of the intima associated with an increased neovascularization causing lumen-occlusive complications (Kaiser et al. 1998; Kaiser et al. 1999). Interestingly, the activation of monocytes/macrophages was not restricted to the vessel wall in GCA but was also noted in the peripheral blood, suggesting

the implication of these cells in the systemic inflammatory syndrome (Wagner et al. 1994).

Several studies have demonstrated an association between the disease and specific human leukocyte antigen (HLA) alleles or other immune-related genes, supporting immunopathological mechanisms. In patients with GCA and polymyalgia rheumatica (PMR)—a closely related and frequently associated disease—the most commonly identified genetic association is with HLA-DRB1*04 allele (Weyand et al. 1994b). Polymorphism of HLA-B and MICA genes was recently associated with susceptibility to GCA, suggesting that several genes within the MHC might have independent effects in the susceptibility to this vasculitis (Gonzalez-Gay et al. 2007). Some allelic variants of HLA-DRB1 and HLA-B have also been associated with TA, but the identified alleles varied from one ethnic group to another, resulting in conflicting data (Dong et al. 1992; Yoshida et al. 1993; Charoenwongse et al. 1998; Kitamura et al. 1998; Mehra and Jaini 2000; Salazar et al. 2000; Lee et al. 2007; Soto et al. 2007). Interestingly, polymorphism of genes encoding INOS and I kappa-β-like protein was recently suggested to be associated with susceptibilities to GCA and TA respectively (Gonzalez-Gay et al. 2005; Shibata et al. 2006). As the allele variant of INOS associated with GCA has been related to increased promoter activity, a higher production of nitric oxide may possibly play a role in the pathogenesis of the vasculitis (Gonzalez-Gay et al. 2005).

Finally, a better identification of the pathogenic pathways in GCA and TA may help to identify novel potential therapeutic targets, hence raising the possibility of innovative and useful therapeutic applications (Weyand and Goronzy 2003). Several studies suggest that IL-6 plays a key role in sustaining disease activity in GCA, thus supporting the concept that IL-6 is a potential therapeutic target (Weyand et al. 2000). The important role of TNF-α in GCA is supported by the expression of TNF-α at the site of inflammation as well as the increased serums levels of this cytokine in patients refractory to corticosteroid treatment. Evidence is accumulating that anti-TNF-α monoclonal therapy may be an alternative treatment for patients with either GCA or TA who do not respond to classical treatments (Della Rossa et al. 2005; Tanaka et al. 2006; Uthman et al. 2006). However caution remains necessary until such data are confirmed by further randomized trials. Other attractive therapeutics may target IFN-γ, growth factors such as VEGF (vascular endothelial growth factor) or PDGF, metalloproteinases, or reactive oxygen intermediates. Neutralization of T cell stimulation by targeting CD28 co-stimulation seems another attractive therapeutic approach (Salvarani et al. 2008).

4.2 Medium-Vessel Vasculitis

4.2.1 Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is currently defined as a systemic transmural necrotizing vasculitis that affects predominantly medium-sized arteries. Vasculitis commonly occurs in kidneys involving renal arteries as well as in the gastrointestinal tract, nerves, skin, joints, and heart (Khasnis and Langford 2009). The necrotizing inflammation is characterized by fibrinoid necrosis and infiltration by polymorphonuclear leukocytes. The pathogenesis of PAN is still poorly defined, but in approximately 35% of patients, disease is related to hepatitis B virus (HBV). Additionally, HBV infection occurred in most patients during the year preceding PAN (Guillevin et al. 2005) and PAN is currently considered as a systemic manifestation of HBV infection. Notably, other viruses have been implicated in PAN such as hepatitis C virus, parvovirus B19, and human immunodeficiency virus (HIV) (Pagnoux and Guillevin 2008). Strikingly, the overall incidence of PAN decreased in the last decade, supporting the implication of infectious agents as etiological factors. Old reports suggested that the deposition of circulating immune complexes within the vessel wall is a key player in triggering the inflammatory vasculitis (Trepo et al. 1974; Zuckerman 1976; Pernice et al. 1979). The HBV infection associated with PAN is commonly characterized by high viral replication with HBe antigenemia further supporting the pathogenic role of viral Ag/Ab complex deposition in antigen excess. Few studies in kidneys and renal arteries are available and the HBV antigen involved in the deposition of immune complexes remains poorly defined (Trepo and Guillevin 2001). In HBV–PAN patients, the efficiency of plasma exchange further supports that PAN is an immune complex-mediated disease (Guillevin et al. 2005).

Testing for HBV in PAN is essential as clinical manifestations, treatment, and outcome of PAN depend on the presence or absence of HBV infection.

Indeed, in patients with HBV infection, glomerulonephritis and ANCA are almost absent and the disease is rarely relapsing (Guillevin et al. 2005). An accurate diagnosis of PAN subtypes may lead to a more effective treatment. When PAN is not associated with HBV infection, patients are usually treated with corticosteroids and immunosuppressants. In HBV–PAN patients, on the basis of the etiological role of HBV, treatment consists of a combination of an antiviral treatment and plasma exchanges preceded by a short-term administration of corticosteroids that aims to control severe manifestations (Guillevin et al. 2005).

4.2.2 Kawasaki Disease

Kawasaki disease (KD) is an inflammatory vasculitis that occurs in early childhood and frequently involves the coronary arteries. It thus represents a primary cause of acquired heart disease in children. Aneurysms appear 1–4 weeks after the onset of fever in approximately 20% of untreated children. Intravenous immunoglobulins (IVIG) have been shown to prevent coronary aneurysm formation and reduce fever and myocarditis.

The paucity of clinical material available for study has precluded a complete understanding of the pathological features of the vascular inflammation in KD (Burns and Glode 2004). Nevertheless, the earliest pathological change in the vessel appears to be an accumulation of T cells, macrophages, and monocytes in the subendothelium, preceding a transmural inflammation. IgA plasma cells are also found in the inflammatory infiltrates. Aneurysm formation results from the destruction of the media (Burns and Glode 2004).

The cause of KD is unknown as yet. However, it has been suggested that KD results from an abnormal immune response to various infectious agents in genetically susceptible children (Burns and Glode 2004). Several viruses (New Haven coronavirus, parvovirus B19, bocavirus, cytomegalovirus, etc.) have been implicated (Pinna et al. 2008). Some reports suggest the contribution of bacterial superantigens to the etiology of KD (Matsubara and Fukaya 2007), but this theory remains largely debated. Other investigators demonstrated the oligoclonality of the IgA response within the vascular wall of KD patients, supporting the involvement of a conventional antigen rather than superantigens (Rowley et al. 2001). Collectively, the data obtained by Rowley and colleagues support the theory of an inhaled pathogen (Burns and Glode 2004).

Various epidemiological data support the implication of a genetic predisposition to KD (Burns and Glode 2004). Several polymorphisms relating to KD susceptibility have been described (Pinna et al. 2008; Eleftheriou et al. 2009). Interestingly, a large genetic study pointed out the importance of the genetic variation of the receptor–ligand couple CCR5 and CCL3L1 in the susceptibility to KD (Burns et al. 2005). Burgner et al. (2009) recently reported the first genome-wide association study that identified novel variants associated with disease predisposition. A major recent study by Onouchi et al. (2008) reported an association of a functional polymorphism of inositol triphosphate 3-kinase (ITPKC) with KD susceptibility. As TPKC acts as a negative regulator of T cell activation, the authors suggested the implication of the described polymorphism in the immune hyper-reactivity in KD, therefore supporting the role of T cells in the pathogenesis of this vasculitis. Accordingly, a quantitative defect of CD25+ CD4+ regulatory T cells in the peripheral blood of KD patients has been demonstrated in the acute phase of the disease, further corroborating such a hypothesis (Furuno et al. 2004). The activation of monocytes/macrophages may also play a key role in KD (Burns and Glode 2004). Serum levels of pro-inflammatory monokines are indeed significantly enhanced in acute phases of the disease, and activated monocytes/macrophages have been demonstrated either in peripheral blood or in vascular lesions (Burns and Glode 2004).

4.3 Small-Vessel Vasculitis

4.3.1 Vasculitis Mediated by Immune Complexes

4.3.1.1 Leukocytoclastic Vasculitis

Leukocytoclastic Vasculitis (LV) Leukocytoclastic vasculitides are heterogeneous disorders characterized by lesions commonly limited to the skin but which may involve other organs such as joints or kidneys (Lotti et al. 1998). LV are small-vessel inflammatory diseases mediated mostly through the deposition of immune complexes. Many factors such as infections, drugs, chemical substances, and diseases associated

with immune complexes have been accused of the pathogenesis of LV (Claudy 1998). Histologically, skin lesions are characterized by dermal small-vessel necrotizing inflammation often with leukocytoclasis (Claudy 1998). Deposition of IgG, IgM, and/or complement in and around the vessel wall is usually detectable in the early phases, but some reports indicated that this may be noticed at various time-points (Grunwald et al. 1997). When IgAs are found, diagnosis of HSP is suspected. Hypocomplementemia is present when polymorphonuclear neutrophils (PNN) infiltration is dense, covering the whole of the dermis (hypocomplementemic vasculitis) (Claudy 1998). Interestingly, whereas the implication of the deposition of immune complexes in the initial phases of LV is well demonstrated, other pathogenic mechanisms seem to be involved in later stages characterized by a lymphocytic infiltrate (Lotti et al. 1998). Therapeutic approaches require the removal of the causative agent when identified. Otherwise, various local and systemic anti-inflammatory or immunosuppressive therapies are recommended (Lotti et al. 1998).

4.3.1.2 Henoch–Schönlein purpura

Henoch–Schönlein purpura (HSP) is the most common childhood primary systemic vasculitis. Although its cause is unknown, it is likely that IgA has a central role in the pathogenesis of the disease. Accordingly, IgA deposition in the vascular lesion in HSP is a characteristic feature of the disease (Shin et al. 2008) and emerged recently as an important diagnostic criterion (Ozen et al. 2006). Furthermore, evidence of increased serum IgA concentrations and circulating IgA-containing immune complexes further support this hypothesis. Interestingly, HSP and IgA nephropathy—a related disease—are associated with an abnormal glycosylation of O-linked oligosaccharides unique to the hinge region of IgA1 molecules (Lau et al. 2007). Such aberrantly glycosylated IgA1s are prone to induce IgA aggregation and form macromolecule complexes, a possible mechanism underlying the deposition of IgA immune complexes in the vessel wall and renal mesangium (Saulsbury 2001). The specificity of IgA antibodies in HSP has been addressed. Although the presence of IgA ANCA is still being debated (Ozaltin et al. 2004), other autoantibodies such as IgA anti-cardiolipin antibodies or IgA rheumatoid factors have been described (Saulsbury 1992; Yang et al. 2000). Recent studies by Yang et al. reported that circulating IgAs in HSP are directed against endothelial cells and that these antibodies are able to activate endothelial cells triggering their IL-8 production (Yang et al. 2002; Yang et al. 2006). Hence, the implication of the AECA in the PNN infiltration—another characteristic feature of the vascular lesion in HSP—has been raised.

The levels of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α are commonly increased in the acute phase of HSP, further supporting an immune-mediated pathophysiological mechanism (Yang et al. 2008). Moreover, deregulation of TGF-β production was reported in HSP. Serum levels of TGF-β are higher in acute HSP, and TGF-β-secreting T cells are activated in acute stages of HSP (Yang et al. 2000; Yang et al. 2004). TGF-β is a major immunosuppressive cytokine but also acts as a switch factor of IgA secretion. Hence, activation of TGFβ-secreting CD4+ T cells may explain the preferential differentiation of IgA-producing cells in HSP. Accordingly, the increased number of circulating IgA-producing cells is a specific feature of HSP which may differentiate this entity from other forms of leukocytoclastic vasculitis (Casanueva et al. 1988).

The familial clustering of HSP may indicate the contribution of a genetic background or environmental triggers (Shin and Lee 2008; Zhang et al. 2008). Polymorphisms of several genes such as IL-1, IL-1 antagonist, IL-8, and VEGF have been associated with disease susceptibility and/or with prognosis or renal involvement (Yang et al. 2008). An interesting report described an increased frequency of a TGF-β polymorphism at the promoter region in HSP, a polymorphism which was related to a higher transcriptional activity of the gene and increased plasma levels of TGF-β1 (Yang et al. 2004). Strikingly, this polymorphism seems to be associated with more severe clinical presentations.

Environmental factors, particularly infections, appear as triggering factors (Yang et al. 2008). Accordingly, HSP is preceded by an upper respiratory tract infection in 30–50% of patients. A wide range of infectious agents have been reported as potential triggers of HSP. The role of an antecedent streptococcal infection is commonly raised but is still debated (al-Sheyyab et al. 1996). The recent data reporting the presence of group A streptococcal antigen in the glomeruli of children with HSP may suggest the role of streptococcal infection in the pathogenesis of

the nephritis (Masuda et al. 2003). As reported by Yang et al., several pathogenic mechanisms may underlie the contribution of infection in disease triggering (Yang et al. 2008). Altogether, strong evidence suggests that HSP is a post-infectious inflammatory disease leading to the differentiation of IgA-producing plasma cells. IgA immune complexes are deposited in the vascular wall and the renal mesangium, leading to the activation of the complement and subsequently to tissue injury. Whether IgA immune complexes are formed in situ or deposited from circulating complexes is still being debated. Yang et al. suggested that circulating IgA may cross-react with endothelial cells and directly lead to endothelial damage through complement activation. IgA anti-endothelial autoantibodies may also act on the endothelial cells, enhancing the production of IL-8. Subsequently, IL-8 would recruit and activate PNN, causing vascular damage through the release of toxic granule contents and reactive oxygen intermediates.

4.3.1.3 Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis is a small-sized vessel leukocytoclastic vasculitis caused by the deposition of circulating immune complexes that consist of cryoglobulins. Cryoglobulins are monoclonal or polyclonal immunoglobulins that precipitate at temperatures below 37°C and redissolve on warming. They occur in patients with various diseases including Waldenström's macroglobulinemia, connective tissue diseases, and chronic infections, but they are in many cases "idiopathic" and are so-called essential mixed cryoglobulinemia (EMC) or cryoglobulinemic vasculitis. The role of hepatitis C virus (HCV) in the pathogenesis of EMC has rapidly been suspected following its identification in 1989. It subsequently has been confirmed by several epidemiological and laboratory findings [reviewed in Cacoub et al. (2002)]. The key role of HCV in the pathogenesis of EMC was further demonstrated by the presence of HCV antigens within the blood vessel of skin biopsies (Agnello and Abel 1997). The efficiency of IFN-α was an additional striking argument for the direct link between HCV and EMC [reviewed in Cacoub et al. (2002)]. HCV is a lymphotropic virus and the chronic infection of lymphocytes may give rise to various autoimmune and lymphoproliferative disorders (Ferri and Mascia 2006). More than 80% of patients with cryoglobulinemic vasculitis have HCV infection (Trejo et al. 2001; Ferri et al. 2004). Nevertheless, less than 10% of HCV-infected individuals develop cryoglobulinemic vasculitis (Ferri and Mascia 2006). These findings may indicate that additional factors such as environmental or genetic factors (De Re et al. 2007) are involved in triggering cryoglobulinemic vasculitis in HCV-infected individuals. Strong evidence suggested that persistent HCV infection induces a prolonged stimulation of B lymphocytes leading to B cell clonal expansion, a feature of EMC which has been demonstrated either in the peripheral blood, the bone marrow, or the liver (Lamprecht et al. 1999). Various mechanisms may support the B cell expansion of HCV-infected lymphocytes. Accordingly, HCV may directly activate cells as it bears an envelope protein E2 which is able to interact with CD81 molecule, a cell-surface protein that is part of the co-stimulatory receptor of the B lymphocytes (Pileri et al. 1998). Moreover, a chromosome (14; 18) translocation is commonly described in HCV-related cryoglobulinemic vasculitis and may lead to an enhanced survival of B lymphocytes (Ferri and Mascia 2006). Collectively, these mechanisms may underlie the production of anti-HCV antibodies that can form persistent immune complexes. Additionally, in HCV-infected patients, the molecular mimicry between HCV antigens and self autoantigens may further support the production of various organ-specific and non-organ-specific autoantibodies, therefore underlying the immunological disorders commonly complicating HCV infection (Ferri and Mascia 2006). The production of cryoprecipitating rheumatoid factors is a striking feature of HCV related-cryoglobulinemic vasculitis. Cutaneous vasculitis results from the deposition of multifaceted cryoprecipitating immune complexes consisting of IgM rheumatoid factors linked to IgG with anti-HCV reactivity (Lamprecht et al. 1999; Sansonno and Dammacco 2005). Noticeably, in HCV-infected patients, the prolonged B cell survival and the consequent activation of proto-oncogenes may lead to the emergence of lymphoproliferative disorders and malignancies (Ferri and Mascia 2006). The detection of HCV infection in patients with EMC is crucial as it has an important therapeutic implication. Accordingly, in patients with negative HCV serological markers and long-standing abnormal liver function tests, an occult HCV infection may be investigated by analyzing the presence of HCV RNA in liver biopsy specimens (Castillo et al. 2004).

In non-HCV-related cryoglobulinemic vasculitis, some studies reported an association with various other infectious agents such as HIV or Bacillus Calmette–Guérin (BCG) [reviewed in Lamprecht et al. (1999)]. HBV seems to play a minor role in EMC as it represents the possible causative agent in less than 10% of patients (Trejo et al. 2001; Ferri et al. 2004). Some data, however, may suggest that HBV-containing immune complexes play a pathogenic role in the glomerulonephritis associated with cryoglobulinemic vasculitis (Maya et al. 2008).

4.3.1.4 Urticarial Vasculitis

Urticarial vasculitis (UV) is a chronic recurrent disorder characterized by a cutaneous presentation resembling urticaria. Gastrointestinal, musculoskeletal, renal, or pulmonary systems may also be involved (Khasnis and Langford 2009). Skin lesions in UV commonly persist for more than 24 h, contrasting with those in ordinary urticaria, which are labile. Biopsy specimens show leukocytoclastic vasculitis often with endothelial damage. UV is usually divided into normocomplementemic urticarial vasculitis (NUV) or hypocomplementemic urticarial vasculitis (HUV), and the relation between these entities is not clearly defined (Davis and Brewer 2004). Patients with HUV are more likely to have systemic involvement such as angioedema or glomerulonephritis than those with NUV (Davis and Brewer 2004). HUVs are in most cases idiopathic but can also occur in patients with infections, neoplasia, hematological diseases, or connective tissue diseases such as systemic lupus erythematosus (SLE) or Sjögren syndrome (Davis and Brewer 2004). In active phases of the disease, patients have an elevated erythrocyte sedimentation rate and a hypocomplementemia with depressed CH50, C1q, C3, and C4. Anti-C1q antibodies are detectable in all patients with HUV syndrome (HUVS)—also called McDuffie syndrome—allowing the classification of this entity as an autoimmune disease (Wisnieski 2000). Anti-C1q antibodies may also be seen in other autoimmune conditions such as SLE. Whether these antibodies are implicated in the pathogenesis of HUVS or SLE remains unclear. However several data suggest that anti-C1q antibodies are pathogenic (Kallenberg 2008) and may contribute to glomerulonephritis in SLE by reacting with C1q bound to DNA/anti-DNA complexes. The latter complexes become less soluble and deposit within the vascular walls, thus triggering inflammation and destruction (Wisnieski 2000; Davis and Brewer 2004). As HUVS shares many features of SLE, some authors suggested that HUVS is a subtype of SLE (Davis and Brewer 2004). Genetic and environmental factors may possibly contribute to the pathogenesis of HUV, yet its etiology remains unknown (Davis and Brewer 2004).

4.3.1.5 Goodpasture Syndrome

Goodpasture (GP) syndrome is a rare autoimmune disease characterized by a rapidly progressive crescentic glomerulonephritis and pulmonary hemorrhage (Bergs 2005). The presence of antibodies directed to the glomerular basement membrane (GBM) in the serum is a characteristic feature of GP syndrome, and the immunofluorescence analysis of biopsies shows linear deposits of antibodies along the glomerular and alveolar basement membrane. Autoantibodies are mainly directed against the NC1 domain of the $\alpha 3$ chain of type IV collagen (Saus et al. 1988). Although various organs contain type IV collagen, these autoantibodies particularly target the basement membranes of the kidneys and alveoli because of an increased expression and accessibility of target epitopes (Bergs 2005). The pathogenic role of anti-basement membrane antibodies has been fully demonstrated by antibody transfer experiments in rodents (Ooi et al. 2008). Anti-GBM antibodies trigger cellular cytotoxic mechanisms through complement cascade activation, leading to an interruption of membrane integrity along with a rapid inflammatory response and tissue damage. The target epitopes are not normally exposed and are so-called cryptic antigens (Wieslander et al. 1985). It has been suggested that initiating inflammatory conditions such as infections or renal ischemia may alter the structure of GBM, leading to the exposure of cryptic epitopes and the loss of immune tolerance (Kalluri 1999; Ooi et al. 2008). Interestingly, evidence of genetic susceptibility to GP syndrome was illustrated by studies demonstrating the association of the disease with HLA-DR15, therefore suggesting a role of T cells in the pathogenesis of the disease (Phelps and Rees 1999). Hence, several experimental models of anti-GBM glomerulonephritis supported this hypothesis (Ooi et al. 2008). However, most of these studies were unable to differentiate between the role of T cells in generating autoantibody production or in triggering tissue damage (Ooi et al. 2008). Interestingly, a report

by Kalluri et al. (1997) demonstrated that passive transfer of alpha3 (IV) NC1 antibodies into T cell-deficient mice failed to produce nephritis, suggesting the implication of T cells as effector players of glomerular injury. Accordingly, T cell epitopes within the α3 NC1 domain have been described either in humans or in rodents, and strong evidence points to the involvement of a CD4+ and CD8+ T-cell-mediated immunity in Goodpasture glomerulonephritis [reviewed in Ooi et al. (2008)].

4.3.2 ANCA-Associated Vasculitis

Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg–Strauss syndrome (CSS), and idiopathic necrotizing crescentic glomerulonephritis (NCGN) are a group of diseases strongly associated with ANCA and commonly referred to as ANCA-associated vasculitis. They are characterized by systemic necrotizing vasculitis. In most cases, no immune deposits are found in the lesions, thereby differentiating them from vasculitis mediated by the deposition of immune complexes. The ANCA-associated vasculitides are so-called pauci-immune. Diagnosis of these small-vessel vasculitides is based on the presence of characteristic clinical and histological findings.

WG is a granulomatous, necrotizing, small- and medium-vessel vasculitis that predominantly involves the upper and lower airways as well as kidneys with frequently varied multisystemic manifestations (Khasnis and Langford 2009). WG affects either males or females and occurs in adults at all ages. The upper and lower respiratory tract lesions are characterized by granulomatous inflammation containing abundant macrophages and lymphocytes. The latter frequently cluster in a lymphoid tissue-like structure (Voswinkel et al. 2005). The renal lesion in WG is a focal, segmental, necrotizing, and crescentic glomerulonephritis with no immune complex deposits (Khasnis and Langford 2009). More than 80% of patients have positive PR3-ANCA results.

MPA is a necrotizing small-vessel vasculitis which shares many features with WG but lacks granulomatous inflammation. MPA occurs frequently in males with an average age of onset at 50 years (Khasnis and Langford 2009). It involves most commonly the kidneys and to a lesser extent the lungs. Multisystem manifestations involving joints, skin, and gastrointestinal tract are frequently found. In the lungs, inflammation involves capillaries, and the absence of linear immunofluorescence differentiates this disease from Goodpasture syndrome. The renal histology in MPA is similar to that seen in WG. ANCA are positive in approximately 80% of cases. Either PR3 or MPO may be recognized.

CSS is characterized by the association of systemic vasculitis with asthma and hypereosinophilia. The histological features of CSS include eosinophilic tissue infiltrates, extravascular granuloma formation, and small-vessel necrotizing vasculitis (Khasnis and Langford 2009). ANCA are less frequent. They are positive in approximately 30–50% of cases, recognizing predominantly MPO. Some authors suggested that CSS patients with anti-neutrophil antibodies may be phenotypically different from those who are ANCA negative (Pagnoux et al. 2007). Necrotizing glomerulonephritis predominated in ANCA-positive patients, whereas cardiomyopathy was more often observed in ANCA-negative patients.

As seen above, there is substantial evidence that ANCA are directly involved in the endothelial damage characterizing the ANCA-associated vasculitis. ANCA play a prominent role mainly through the activation of neutrophils. However, other cell targets of ANCA such as monocytes or glomerular epithelial cells have also been proposed, but their implication in the vascular damage remains to be confirmed (Savage et al. 2002). The implication of T lymphocytes as effector players is also less evident. Few studies demonstrate the presence of such cells at the vascular tissue sites, particularly in interstitial and periglomerular regions in kidney lesions (Cunningham et al. 1999; Aasarod et al. 2001; Weidner et al. 2004). However most of the accumulating reports demonstrating an activated cell-mediated immunity focused on the abnormalities of peripheral lymphocytes (Berden et al. 2009). Nevertheless, various experimental studies provided evidence for the role of Th1 lymphocyte response in mediating glomerular damage and crescent formation in ANCA-associated vasculitis (Holdsworth et al. 1999). A recent experimental model provided in vivo evidence of the interaction between humoral and cellular immunity in triggering renal injury (Ruth et al. 2006). The implication of cellular immunity has also been suggested in the development of granulomatous lesions in WG (Csernok et al. 1999). Voswinkel et al. (2005) recently suggested that such granulomatous formations are lymphoid tissue-like structures, giving rise to

autoantibody production and where activation of self-reactive T lymphocytes are essential to drive B cell maturation and PR3-ANCA formation. Finally, a role of eosinophils in the CSS is suspected but not fully elucidated. It is widely established that the pathophysiology of CSS involves three potential mechanisms underlying the three main successive phases of the disease: asthma, tissue eosinophil infiltration, and necrotizing vasculitis. Although ANCA contribute to the development of vasculitis lesions, eosinophil tissue infiltration together with the related cytotoxicity through the release of cytotoxic enzymes may be responsible for tissue lesions such as cardiomyopathy and pulmonary infiltrates (Kallenberg 2005; Pagnoux et al. 2007).

Although the effector mechanisms triggering tissue damage in ANCA-associated vasculitis are mainly identified, the initial event triggering the breakdown of self-tolerance to ANCA antigens is still being debated. ANCA are probably produced secondary to the exposure of cryptic epitopes, a pathogenic mechanism that may underlie the loss of immune tolerance.

The prominent role of T lymphocytes in the loss of immune tolerance is very likely. Several reports have documented the capacity of peripheral T cells from either active or inactive patients to proliferate to PR3 or MPO, suggesting a loss of T lymphocyte tolerance to neutrophil antigen [reviewed in Savage et al. (2002)]. The fact that most ANCA are of the IgG isotype further supports the implication of T lymphocytes in driving a secondary immune response against neutrophil antigens. Moreover, treatments targeting T cells induce remission in WG (Lockwood et al. 1996; Schmitt et al. 2004). Additionally, a functional defect of the circulating T regulatory lymphocytes (T regs) was recently demonstrated in patients with WG, suggesting the implication of T regs abnormalities in the loss of immune homeostasis (Abdulahad et al. 2007). However, the functional defect has been demonstrated in patients in remission and the effects of immunosuppressive therapies could not be excluded (Berden et al. 2009). Yet, the implication of environmental and genetic factors in the loss of immune homeostasis and the outcome of the disease has been frequently suggested. Experimental data showing that the presence of ANCA may not be sufficient to induce disease manifestations further support this hypothesis. Risk factors include genetic factors such as polymorphism of PR3, α1 antitrypsin, and Fc gamma receptor genes, drugs (propylthiouracil, hydralazine), chemical substances—in particular, silica and microbial agents (Kallenberg et al. 2002; Tervaert and Heeringa 2003). Among the genetic factors, a polymorphism of PR3 which may lead to an enhanced expression of this antigen on neutrophil surfaces suggests that an altered regulation of PR3 expression may play a role in pathogenesis (Gencik et al. 2000). Nevertheless, the infectious factors seem to be the most likely factor of susceptibility. The implication of *Staphylococcus aureus* has been proposed (Popa et al. 2002). In WG, chronic carriage of *S. aureus* constitutes a risk factor for the development of exacerbations (Popa et al. 2003). Several hypothetical mechanisms by which the infectious factors may underlie autoimmunity (Tervaert and Heeringa 2003) or trigger exacerbations (Kallenberg et al. 2002) have been proposed. Interesting work by Brons et al. (2000) suggested that staphylococcal acid phosphatase—a cationic protein of *S. aureus*—may bind to endothelial cells and localize in glomeruli. Antibodies specific for this phosphatase which are present in patients with WG may interact with the planted antigens, thereby initiating vasculitis. Another attractive theory called autoantigen complementarity proposed that the initiator of an autoimmune response is the protein that is complementary in structure to the autoantigen. Some patients with PR3-ANCA also have antibodies that react with peptides from complementary PR3 which show strong homologies with proteins from many microbes and viruses, particularly *S. aureus* (Preston et al. 2005). Alternately, the role of superantigens and peptidoglycans from *S. aureus*-induced skewing of T cell responses to pathogenic IL-17-producing T-helper cells (Th17) cannot be excluded (Abdulahad et al. 2009).

Finally, as the role of antibodies is well established in the pathogenesis of ANCA-associated vasculitis, a broad range of therapies targeting the humoral immunity such as plasmapheresis or IVIG have been tested in some patients, but their efficacy still has to be confirmed in randomized trials. Additionally, preliminary studies suggested the efficacy of anti-CD20 antibody (rituximab) (Keogh et al. 2005, 2006) in patients with refractory WG. The involvement of *S. aureus* in WG may have therapeutic consequences as treatment with co-trimoxazole led to the reduction in

the incidence of relapses (Stegeman et al. 1996). Recent findings supporting the contribution of cellular immunity in ANCA-associated diseases may provide new therapeutic strategies in refractory patients.

5 Conclusion

Despite recent advances in immunology and genetics, the etiology of primary vasculitis remains largely undetermined. Yet, there has been considerable progress in understanding the pathophysiological mechanisms of systemic vasculitis, thus providing significant insights. Ongoing work in understanding the pathogenesis of vasculitis may further contribute to the development of novel therapeutic approaches.

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