Primary systemic vasculitides as the bridge in immune-mediated disorders: small vessels for autoimmunity, medium vessels for autoinflammation

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ABSTRACT

Vasculitides have been classically considered to be mostly of autoimmune origin, but the role of the innate immune system is being increasingly recognized among primary systemic vasculitides. For example, Behçet's syndrome (BS) shares more common features with autoinflammatory disorders (AIDs) than autoimmune diseases (ADs) and has recently been considered to be a polygenic AID by several authors, while others have classified it as a "mixed-pattern" disorder. This review aims to make a balance between autoinflammatory and autoimmune features of primary systemic vasculitides, including sex prevalence, association and/or familial aggregation with others AIDs or ADs, with human leukocyte antigen (HLA) system and/or disease-specific autoantibodies, type of cellular infiltration (neutrophilic or lymphocytic), clinical pattern (episodic or progressive), size of involved joints when articular involvement occurs, presence of lymphadenopathy or hypergammaglobulinemia, and therapeutic benefit of colchicine, IL-1 inhibitors and rituximab.

Except for Henöch-Schonlein purpura, autoimmunity is usually predominant in small vessel vasculitides, where disease-specific autoantibodies are common. On the other hand, medium vessel and even variable vessel vasculitides such as BS often course with autoinflammatory features (e.g. increased levels of IL-1, neutrophilic infiltration) are often more obvious than those typical of autoimmunity. Therefore, it is possible that disorders like polyarteritis nodosa or Kawasaki disease may be considered as "mixed-pattern" diseases in the future. Finally, both the innate and adaptive immune systems can have significant roles in large vessel vasculitis.

Keywords: Adaptive immunity; Autoimmune diseases; Hereditary autoinflammatory diseases; Innate immunity; Vasculitis

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INTRODUCTION

Immune-mediated disorders (IMDs) are divided in four groups: autoimmune diseases (ADs), autoinflammatory disorders (AIDs), allergies and immunodeficiencies[1]. Vasculitis corresponds to the inflammation of blood vessels and is histologically defined by endothelial cell swelling, karyorrhexis and red cell extravasation[2,3]. Although vasculitis has been historically considered to be mostly of autoimmune origin, the role of the innate immune system is being increasingly recognized. For example, it is now clear that Behçet's syndrome (BS) shares more common features with AIDs than ADs and has been suggested by several authors to be a polygenic AID[3,4]. AIDs have been originally described as syndromes characterized by seemingly unprovoked episodes of inflammation due to dysregulation of the innate immune system but without a primary role for autoreactive T cells or autoantibodies[3]. Unlike ADs, immunopathogenesis occurs in the affected tissues and not in lymphoid organs, including the production of pro-inflammatory cytokines such as interleukin (IL)-1β (see Table I).[5]

Vasculitides are associated with several IMD, including AIDs, ADs and immunodeficiencies[2]. The 2012 Chapel Hill Consensus Conference (CHCC) established a nomenclature system that divides vasculitides in several groups: large vessel vasculitis (LVV), medium vessel vasculitis (MVV), small vessel vasculitis (SVV), varia-

TABLE I. DIFFERENCES BETWEEN AUTOINFLAMMATORY AND AUTOIMMUNE DISORDERS

	Autoinflammatory disorders	Autoimmune disorders
Sex	No prevalence	Female
Onset	Often during childhood	Commonly during adulthood
Triggers	Infections, stress, cold, urate crystals, sex hormones	Infections, stress, drugs, adjuvants, UV light
Primary immune system dysfunction	Innate	Adaptive (and innate)
Inheritance	Often inherited (monogenic)	Often acquired (polygenic)
HLA class II associations	Rare	Frequent
Elevated acute phase reactants	All AID	Some AD
Autoantibodies or autoreactive T cells	No	Yes
Organs where immunopathogenesis occurs	Affected organs	Lymphoid organs
Organ infiltration	Neutrophils	Lymphocytes
Pattern	Often episodic	Often progressive
Fever	Often prominent	Occasional
Constitutional symptoms	Resolve between flares	Persist between flares
Arthritis	Often acute, self-limiting and affecting large joints	Usually affects small joints with bone erosions
Periarticular involvement	No	Sometimes
Heart and renal involvement	Indirect (amyloidosis)	Direct
Treatment (1st line)	NSAID, colchicine, steroids	NSAID, steroids, immunosuppressive agents
Response to biologics	IL-1 inhibitors	Rituximab

AD – autoimmune diseases; AID – autoinflammatory disorders; HLA – human leukocyte antigen; IL-1 – interleukin-1; NSAID – nonsteroidal anti-inflammatory drugs; UV - ultraviolet

ble vessel vasculitis (VVV), single-organ vasculitis (SOV), vasculitis associated with systemic disorders (e.g. sarcoidosis) and vasculitis associated with probable etiologies (e.g. viral hepatitis)[6]. In this review, we aim to make a balance between autoinflammatory and autoimmune features of primary systemic vasculitides, in order to better ascertain the relative contributions of the innate and adaptive immune systems in each specific disorder. We have included primary systemic vasculitides in our review that are mentioned in the 2012 revised International CHCC nomenclature (LVV, MVV, SVV and VVV). For this purpose, a semi-systematic review has been conducted and the literature was searched by combinations of keywords such as "autoinflammatory disorders", "vasculitis", "autoantibodies" and "arthritis" in Medline database. Related relevant references of the selected articles were also considered. We have looked for specific features of vasculitides, including sex prevalence, association with others IMDs, human leukocyte antigen (HLA) system and/or disease-specific autoantibodies, type of cellular infiltration (neutrophilic or lymphocytic), clinical pattern (episodic or progressive), size of involved joints when arthritis is present, presence of lymphadenopathy and/or hypergammaglobulinemia, and therapeutic benefit of colchicine, IL-1 inhibitors (both commonly used in the treatment of AIDs) and rituximab (invariably restricted to the treatment of ADs instead of AIDs).

AUTOIMMUNITY AND AUTOINFLAMMATION IN SYSTEMIC VASCULITIDES

SMALL VESSEL VASCULITIS

SVV has been divided in immune complex-associated (ICAV) and antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV)[6]. AAV is a necrotizing vasculitis that shows few or no immune deposits, whilst ICAV is associated with significant vessel wall deposits of immunoglobulin and complement components[6]. AAV comprises granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA)[7]. ICAV includes Henoch-Schönlein purpura (HSP),

cryoglobulinemic vasculitis (CV), anti-glomerular basement membrane (GBM) disease and hypocomplementemic urticarial vasculitis syndrome (HUVS).

AAV is the most common primary SVV in adults[7]. Its gender distribution shows a slight male preponderance in most studies[8]. Overlap has been described with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)[9,10]. GPA is associated with HLA-DP, MPA with HLA-DQ and EGPA with HLA-DRB4[8,11]. However, the strongest genetic associations confirmed by genome-wide association studies (GWASs) are related to ANCA specificities: PR3-AAV is associated with HLA-DP and MPO-AAV is with HLA-DQ[11]. B cells play a major role in AAV because they produce pathogenic ANCA, which are then released on the surface of neutrophils by priming factors such as pro-inflammatory cytokines (e.g. TNF) and result in the death of neutrophils within vessel walls; infiltrating macrophages and T lymphocytes finally replace apoptotic neutrophils[7,12]. Cytokine profiling in AAV has demonstrated elevated serum levels of IL-10, IL-33 and CD40L[13]. MPA and GPA are typically multi-relapsing disorders, while EGPA classically follows a stepwise disease progression[14]. Arthralgia is often migratory, oligoarticular and occurs more frequently than arthritis, which typically involves the large joints.[15] Despite being negative in many cases (up to 60% of EGPA and 20% of GPA and MPA patients) and occurring in other disorders (e.g. ulcerative colitis, infections), ANCA are used in AAV for diagnosis, monitoring disease activity (mainly renal) and assessing risk of relapse, whilst ANCA specificities correlate with different clinical manifestations (e.g. PR3-AAV is often characterized by upper respiratory tract disease, MPO-AAV often courses with renal involvement)[7,16]. Glucocorticoids are the mainstay of treatment in AAV, either alone or in combination with other immunosuppressants, such as cyclophosphamide or rituximab[17]. In fact, rituximab has been approved by the US Food and Drug Administration for adults with severe forms of AAV as an alternative to cyclophosphamide for induction therapy, being superior to azathioprine in preventing relapses[18].

HSP, also known as IgA vasculitis (IgAV), constitutes the most common vasculitis of childhood and male preponderance approaches 2:1 among children[19]. A GWAS confirmed HLA class II region as the major susceptibility locus, even though DRB1 has no genome-wide significance[11]. About 10% of patients are homozygous for mutations of the MEFV gene[20,21]. In fact, HSP occurs in up to 7% of patients with familial Mediterranean fever (FMF) and occult cases of FMF are more frequent than expected among children with HSP[21,22]. Several cytokines are thought to be involved (e.g. IL-6, IL-8, TNF), but toll-like receptor (TLR)-2 and TLR-4 also appear to be upregulated[20,23]. Besides, IL1B and IL1RN genes have been suggested as predisposing factors[22,24]. In biopsies, leukocytoclastic vasculitis is characterized by infiltrating neutrophils in small vessel walls, but IgA deposits are often depicted[20,25]. Joint involvement occurs in up to 80% of patients and arthritis occurs as the initial manifestation in 15%, often migratory and involving large joints of the lower extremities[19,20]. HSP is typically a self-limiting disorder, but relapses occur in about 33% of cases during the first year and renal involvement can be chronic[19,25]. Serum levels of IgA are also elevated during the acute stage in about 50%[23,24]. IgA anti-endothelial cell antibodies (AECAs), IgA ANCA, IgA rheumatoid factor (RF) and IgA anticardiolipin antibodies have been detected in variable percentages[23,25]. Glucocorticoids and immunosuppressants are common first-line therapeutic options, despite being controversial[21,26]. Colchicine has demonstrated efficacy in 80% of patients with cutaneous leukocytoclastic vasculitis and has been used with efficacy in some cases of chronic IgAV[27]. Rituximab is probably the most promising biological drug in refractory and relapsing HPS, but anakinra has been reported to induce a partial response in a life-threatening case of HSP[20,28].

CV is a systemic inflammatory syndrome characterized by the presence of circulating cryoglobulins[29]. It is more prevalent in women (2-3:1)[30]. Mixed cryoglobulinemia (MC, types II and III) has been associated with ADs such as Sjögren's syndrome (SS) and SLE.[31] A genome-wide significant association has been detected at SNP rs9461776 between HLA-DRB1 and DQA1 in MC[32]. Chronic immune stimulation and lymphoproliferation are major pathogenic factors in CV and result in increased immune complex formation[33]. Biopsies usually demonstrate SVV with perivascular lymphomonocytic inflammation and leukocytoclastic vasculitis in skin samples is characterized by infiltrating T cells[34,35]. MC typically follows a chronic smoldering disease course[36]. Joint involvement is characterized by non-migratory symmetric arthralgia that typically involves the hands and knees (50-75%); arthritis is less prevalent and typically non-erosive, except in cases of RA overlap[37,38]. Mild to moderate hypergammaglobulinemia (IgM, IgA and/or IgG) characterize MC, while marked elevations in serum

immunoglobulins are commonly seen in type I CV[39]. Antinuclear antibodies (ANA), anti-dsDNA, anti-Sm, anti-Ro/SSa and anti-La/SSb antibodies point to associated ADs[35]. Treatment depends on associated disorders (e.g. myeloma drugs in type I cryoglobulinemia, direct-acting antiviral agents in HCV-related CV) and severity (e.g. glucocorticoids, cyclophosphamide, azathioprine)[29]. Rituximab is usually preferred in IgM MGUS and has demonstrated the greatest benefit in both noninfectious MC (with glucocorticoids) and HCV-related CV (with direct-acting antivirals), being considered the best biological option in MC[29,36].

Anti-GBM disease (Goodpasture syndrome) is a rare SVV that involves the glomerular and/or pulmonary capillaries and an archetypic AD caused by directly pathogenic autoantibodies[40]. It can coexist with AAV or IgA nephropathy[40,41]. A bimodal age distribution with peak incidences occurs in the third decade with a slight male preponderance and in the sixth and seventh decades with a slight female one. The original marked male predominance (9:1) has evolved to a lack of sex predominance in modern series of Caucasians[41-43]. Around 80% of patients inherit an HLA-DR2 haplotype, while DRB1 alleles either carry a susceptibility effect (especially DRB1*1501) or a protective one (DR7, DR1)[40,42]. Fibrinoid necrosis is common and crescentic formation constitutes the histopathological hallmark, while early and mild disease is characterized by segmental proliferative changes with infiltrating lymphocytes and/or neutrophils[40]. Anti-GBM disease often follows a rapidly progressive course and relapses are rare[40,41]. Arthralgia is rare and may not be related to anti-GBM disease[43]. Circulating anti-GBM antibodies are present in 90% and are usually directed at E_A or E_B epitopes of the NC1 domain of the 3 chain of type IV collagen[40-42]. Plasmapheresis, glucocorticoids and cyclophosphamide constitute the standard treatment[40]. Rituximab may be considered in patients with contraindications or intolerance to conventional treatment, but it seems to be more effective for pulmonary involvement[44].

HUVS (anti-C1q vasculitis) is an acquired deficiency of complement components and its pathogenesis relies on humoral autoimmunity[45,46]. HUVS can be secondary to SLE or SS and a female-male ratio of 8:1 has been observed[45]. In skin biopsies, leukocytoclastic vasculitis is present but infiltrates are typically mixed with neutrophils and lymphocytes[45]. Arthralgia is transient and migratory, often involving the hands, feet, elbows, ankles and knees, while arthritis is seen in up to 50%[45,47]. Anti-C1q antibodies are present in 95 to 100% of cases, along with other rarer autoantibodies (anti-DNA, anti-Sm, AECAs, antiphospholipids)[45,46]. Systemic glucocorticoids are the mainstay of treatment, but colchicine, immunosuppressants and rituximab have also been successfully used[45].

MEDIUM VESSEL VASCULITIS

Idiopathic systemic polyarteritis nodosa (PAN) is a primary necrotizing vasculitis that is not typically associated with glomerulonephritis or SVV.[14] Other forms of PAN have also been described such as hepatitis B (HBV)-associated PAN and cutaneous PAN, currently termed by the CHCC as cutaneous arteritis[14]. It is probably more prevalent in men, but a lack of sex predominance has also been reported[48,49]. Deficiency of adenosine deaminase 2 (DADA2) is considered by some authors to be a monogenic form of PAN[50,51]. PAN is the second most common vasculitis in FMF, affecting around 1% of patients[52]. Increased serum levels of IFNγ, IL-2 and IL-8 have been described, along with moderate elevations of TNF and IL-1β[48]. Vascular inflammatory infiltrates are typically mixed with macrophages, dendritic cells and abundant lymphocytes (neutrophils are common in fibrinoid necrosis)[14,48]. Arthralgia is seen in about 50% of patients and arthritis in 7.7% at disease onset, usually evanescent with oligoarthritis following an acute pattern and involving knees and ankles[14,53]. PAN has classically been described as a monophasic disorder, but relapses can occur in up to 20% of idiopathic cases[14,48]. ANCA are negative and, if positive, prompt differential diagnosis with AAV is mandatory. Glucocorticoids are the mainstay of treatment (exceptions include NSAIDs in cutaneous PAN, colchicine in FMF-associated and cutaneous PAN, and anti-TNF agents in DADA2), along with immunosuppressants in refractory or critical cases[14,48,51]. Anecdotal reports have suggested favorable results of IL-1 blockade and rituximab in selected patients[54,55].

Kawasaki disease (KD) is an acute MVV that constitutes the most common cause of acquired heart disease among children in developed countries[49,56-58]. It is more common in young boys (1.3-1.4:1) [57]. No single HLA or MHC class II haplotype is common to most patients and associations (e.g. HLA-DRB1, DQB2-DOB, B5, Bw51, Bw44) have not been widely replicated by GWASs[49,58]. It is histologically characterized by necrotizing arteritis in the early phases, with neutrophilic infiltration of the arterial wall, then followed by infiltra-

tion of T cells, primarily CD8+ cells[49,57,58]. Selection of Fc-specific Treg cells and their role in immune regulation possibly argue against autoimmunity[56]. Increased expression of autoinflammation-related genes (NLRP3, IL-1a and IL-1b, caspase 1, TLR mRNA levels) and pro-inflammatory cytokines (IL-1, IL-6, IL-18, TNF) has been documented, along with the role of IL-1 in myocarditis and aneurysm formation[56,59,60]. B cell activation occurs during the acute phase and AECAs may induce vasculitis and thrombosis[61,62]. KD has a self-limited monophasic course with low recurrence[49,56]. Besides the classical signs of fever (in virtually 100%, reflecting increased levels of TNF and IL-1), polymorphous rash (>90%), bilateral conjunctival injection (80-90%), mucositis (80-90%) and cervical lymphadenopathy (50%), arthritis has been described in about two thirds of patients and is usually self-limited[49,63]. It is sometimes characterized by a small joint polyarthritis of the lower extremities, followed by a large joint pauciarthritis during convalescence[49]. However, small joints may not be affected, while at least one large joint appears to be involved during the disease course in perhaps more than 90% of cases with arthritis[63]. Despite the common occurrence of AECAs, disease-specific autoantibodies have not been described[56]. Intravenous immunoglobulin and aspirin constitute the mainstay of treatment in KD[58]. Biologics are increasingly being used in refractory cases, not only TNF inhibitors, but also IL-1 blockade appears to be effective even in late phases and refractory disease[56,57,60].

LARGE VESSEL VASCULITIS

LVV affects the aorta and its major branches[6]. Takayasu's arteritis (TAK), also known as pulseless disease or aortic arch syndrome, usually involves the aorta and its large proximal branches[64-66]. A strong female predominance is consistent but variable (1.2-12:1) [64]. It can coexist with inflammatory bowel disease (IBD)[66,67]. Serum levels of pro-inflammatory cytokines are increased and IL-6, IL-12 and IL-18 serum levels have been associated with disease activity and relapse[65,66]. Inflammatory lesions are found in the vasa vasorum of the adventitia, comprising NK cells, $CD4^+$, $CD8^+$ and γ T cells, macrophages and neutrophils[65]. CD20+ cells are found around granulomas and circulating T cells are increased and exhibit a state of activation[66]. HLA-B52 has been described as the only HLA antigen to be associated with TAK beyond ethnicity, occurring in 0.7 to 11% of patients, but genome-wide significant associations have been described with HLA-B/MICA and HLA-DQB1/HLA-DRB1[11,64,65]. Although TAK has classically been considered a triphasic disease, it often follows a subacute to chronic relapsing course[64,66]. Non-specific arthralgia and myalgia are present in 13 to 41% of patients[66]. Joint involvement may constitute the most common extravascular manifestation and arthritis, including sacroiliitis, has been described in about 12% of patients, presenting with large joint (commonly shoulders) involvement in almost two thirds of cases of peripheral arthritis[66,68]. AECA, anti-aorta and antiphospholipid antibodies have been reported[65]. Glucocorticoids constitute the most effective treatment[67,69]. However, TNF inhibitors and tocilizumab have been successful in refractory cases with similar efficacy and animal models have also raised the possibility of therapeutic use of IL-1 antagonists since IL-1Ra deficient mice appear to develop an autoimmune phenotype with aortitis[65,67]. Rituximab has shown conflicting results in TAK[70].

Giant cell arteritis (GCA) is a granulomatous vascular syndrome that may course with cranial (temporal) arteritis, large vessel involvement (LV-GCA), systemic inflammation or polymyalgia rheumatica (PMR) [71,72]. GCA constitutes the most common primary vasculitis in the elderly and women are more susceptible (2-3:1)[71,73]. HLA class II gene loci have the strongest association (e.g. HLA-DRB1*04, DQA1*03, DQB1*03), as confirmed by GWASs[74]. Not only IFN-γ and IL-17 producing T cells are recruited in arterial walls, but also the adventitia hosts macrophages and dendritic cells expressing TLRs and become activated by pathogen-associated molecular patterns (PAMPs) or microorganism-associated molecular patterns (MAMPs), leading to production of IL-1 and IL-6; damage-associated molecular patterns (DAMPs) also act synergistically and stimulate inflammation[71,72]. B cells are not directly involved in pathogenesis and patients usually have no hypergammaglobulinemia or lymphadenopathy[75]. GCA has been considered both a T cell-dependent disease and an autoimmunoinflammatory syndrome[73,76]. Histological changes consist of arterial wall inflammation, internal elastic lamina fragmentation and intimal thickening, while multinucleated giant cells are seen in only about 50%, along with granulomatous inflammatory infiltrates of CD4+ T cells and macrophages at the intima-media junction and sometimes lymphomononuclear panarteritis with only occasional neutrophils[77]. GCA presents insidiously over weeks to months in the majority of cases but can be abrupt in 20%[77,78]. PMR has been regarded as a possible AID, due

to its (hyper)acute onset and recurring inflammatory flares with rapid remission, significant increase of acute-phase reactants, lack of autoantibodies, overlap with other IMDs, inconsistent HLA associations, increased expression of IL-1β in muscle tissue and conflicting data regarding immunosuppressive drugs[79]. Described autoantibodies in GCA are not specific, including antiphospholipid antibodies (30-80%) and those reacting with lamin C (32%), lamin A, vinculin, annexin A2 and A5, mitochondrial antigens and ferritin[76]. Glucocorticoids constitute the standard of treatment for both GCA and PMR[69,71]. Tocilizumab is the biological drug of choice in both syndromes and has been the first ever licensed treatment for GCA[71,74]. IL-1 antagonists may precociously inhibit adventitial macrophages and dendritic cells and anakinra has been successful in some patients with GCA, while trials are underway to assess the potential therapeutic benefit of anakinra and gevokizumab[71,74,80].

VARIABLE VESSEL VASCULITIS

BS is a multisystemic neutrophilic vasculitis where vasculopathy constitutes a cause of morbidity and mortality in up to 40% of patients[2,81]. Vasculitis frequently affects the venous system and almost always appears in the form of (inflammatory) thrombosis, while arterial inflammation is associated with aneurysms[2,3,52]. SVV is the most common type in BS, but LVV occurs in about 33%[52,82]. A male predominance was originally apparent in higher prevalence areas, but a lack of sex preponderance is more probable overall[83,84]. BS has been reported to be associated with or complicate the course of FMF[85]. Haploinsufficiency of A20 (HA20) courses with a phenotype similar to BS with VVV and recurrent oral, genital and/or gastrointestinal ulcers[2,52]. HLA-B51 constitutes the most significant genetic association as demonstrated by GWASs, explaining 20 to 30% of BS heritability[81,84,86]. In fact, HLA-B51 and increased IL-17 response appear to be responsible for neutrophil activation[82,86]. Both Th17 and Th1 cells seem to induce inflammation, while neutrophil activity is increased and the affected organs show infiltration by neutrophils (predominant in early stages) and lymphocytes[81,86]. Elevated levels of IL-1β and other pro-inflammatory cytokines (IL-33) have also been reported, as well as the activation of the innate immune system (NLRP3) via PAMPs and/or DAMPs, TLRs and P2X7r[4,81,87,88]. BS typically follows a relapsing-remitting pattern, whilst arthritis is often nonerosive, nondeforming, asymmetrical and oligoarticular, affecting large joints[81,84]. Treatment depends on organ involvement, but colchicine is widely used and particularly effective for erythema nodosum, arthritis and genital ulceration in females[84,89]. Treatments targeting innate cytokines have been successful, especially approved TNF inhibitors (for refractory and/or severe mucocutaneous, eye, arterial, gastrointestinal or neurological involvements, or refractory venous thrombosis) and apremilast (for aphthous ulcers), but also IL-1 antagonists[90]. A systematic review of IL-1 inhibitors has demonstrated that both anakinra and canakimumab induce a good control of mucocutaneous and ocular manifestations and anakinra was also effective in osteoarticular involvement[87]. However, the evidence for IL-1 inhibitors as a first-line therapeutic option in BS is lacking. IL-1 blockade may also be a therapeutic option for neuro-Behçet[89].

Cogan's syndrome (CS) is a rare vasculitis that courses with vestibulo-auditory dysfunction and intraocular inflammation, even though vasculitis may also affect large and medium vessels of the kidneys, skin, coronary arteries, aorta, muscles and central nervous system[91]. CS has been classically described as an AD of the inner ear and to coexist with disorders such as GPA, RA, sarcoidosis, juvenile idiopathic arthritis, SS, IBD and tubulointerstitial nephritis and uveitis (TINU) syndrome[91-94]. No gender predilection takes place in CS[91,93]. HLA associations may include haplotypes A9, Bw17, Bw35 and Cw4, but these have not been confirmed by GWASs[91]. Elevations of pro-inflammatory cytokines such as IL-1β has been documented in autoimmune inner ear disease[93]. Cell-mediated autoimmune reactivity has been suggested by the demonstration of lymphocyte activation, and histopathological examinations of the cochlea and cornea have demonstrated lymphocytic and plasma cell infiltration[91,92]. Autoantibodies against a "Cogan peptide" have been identified and their injection in rabbits has induced sensorineural hearing loss[93]. Relapses are very common[95]. Systemic manifestations occur in 33% (mainly in atypical forms and up to 80% in some series) and are similar to those seen in PAN[91,93,95]. CS may course with arthralgia and less often arthritis of large joints.[91] Like musculoskeletal involvement, lymphadenopathy is more frequent in atypical CS[94]. Anti-Hsp-70 antibodies have been described to occur in around 50% (more than 90% of patients in typical cases), along with antibodies directed against corneal antigens or constituents of the inner ear, pANCA, RF, ANA, anticardiolipin antibodies and low complement levels in a minority of cases[91,93,95]. Treatment depends on the presence of systemic symp-

toms, but glucocorticoids are the first therapeutic option[91-93]. Regarding biologics, TNF inhibitors have the best evidence in refractory cases, while the response to rituximab has been inconsistent[96]. Interestingly, a case of partial or near-complete remission has been described with IL-1 blockade[97].

DISCUSSION

Features that may be useful in differentiating ADs from AIDs are displayed in Table II but have some limitations. Others such as age at presentation were not considered as discriminating factors since polygenic AIDs and even late-onset monogenic AIDs have been increasingly recognized. Fever, precipitating factors and elevated acute-phase reactants have not been included because they constitute a common denominator for both AIDs and ADs. Periodic fever syndromes constitute only a minority of all AIDs. In relation to autoantibodies, only disease-specific antibodies have been considered: for example, AECAs are not specific and have been described not only in almost all primary vasculitides, but also in other diseases with vascular involvement[56]. Likewise, only HLA antigens with genome-wide significant associations were considered. Among primary systemic vasculitides, the preponderance of the innate immune system may be particularly appreciated in MVV, where serum elevation of IL-1β, episodic disease course, arthritis of large joints and neutrophilic infiltration are common (see Figure 1). This is reflected not only in KD and PAN, but also in VVV such as BS. Due to its strong association with major histocompatibility complex (MHC) class I antigen, BS has a link with adaptive immunity and has been designated as a "mixed-pattern" disorder[4,90]. Curiously, thromboangiits obliterans, or Buerger's disease, is an inflammatory segmental occlusive vascular disorder that has also been considered to be a MVV (not included in the 2012 revised CHCC nomenclature) and characterized by some features that argue in favor of autoinflammation, including elevated serum levels of IL-1β, large-joint arthritis and a relapsing-remitting pattern in most patients[98,99]. Response to IL-1 block-

TABLE II. FEATURES OF AUTOIMMUNITY AND AUTOINFLAMMATION AMONG PRIMARY SYSTEMIC VASCULITIDES

	AAV	ICAV*	PAN	KD	TAK	GCA	BS	CS
Autoimmunity features								
Female preponderance		+			+	+		
Association/familial aggregation with AD	+	+						+
Disease-specific autoantibodies	+	+						+
HLA associations (GWAS)	+	+		+	+	+	+	
Lymphocytic infiltration	+	+	+	+/-	+	+	+	+
Progressive pattern	+	+			+	+		
Arthritis of small joints		+						
Lymphadenopathy/hypergammaglobulinemia		+/-		+/-				+
Response to rituximab	++	+		++				
Autoinflammatory features								
Association/familial aggregation with AID			+				+	+
Monogenic form			+				+	
Increased IL-1			+/-	+	+/-	+	+	+
Neutrophilic infiltration	+	+	+	+	+	+/-	+	
Relapsing-remitting pattern	+		+	+	+	+/-	+	+
Arthritis of large joints	+		+	+	+	+	+	+
Response to colchicine			+/-				+	
Response to IL-1 inhibitors				+		+/-	+	

*except for IgA vasculitis.
AD – Autoimmune disorders; AID – Autoinflammatory disorders; AAV – ANCA-associated vasculitides; BS – Behçet syndrome; GCA – Giant cell arteritis; GWAS – genome-wide association study; ICAV – Immune complex-associated vasculitis; IL-1 – Interleukin-1; KD – Kawasaki disease; PAN – polyarteritis nodosa; TAK – Takayasu's arteritis.

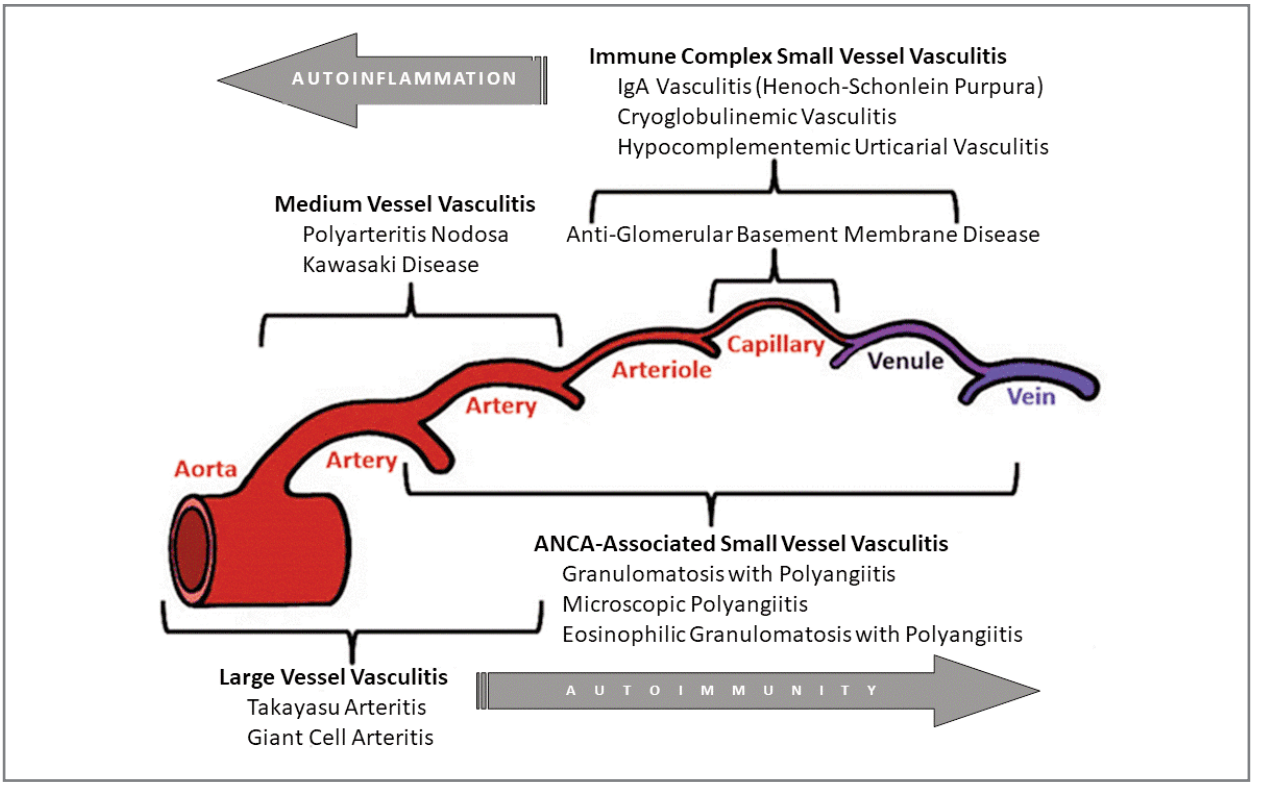

FIGURE 1. Distribution of vasculitides according to the size of involved vessels and the weight of autoimmunity and autoinflammation among them (adapted from Jennette et al., 2013)

ade has been observed not only in KD, but also BS, suggesting a probable role of IL-1β in their pathogenesis. Instead, the lack of disease-specific autoantibodies and response to rituximab argue against humoral autoimmunity. It is possible that when pathogenic mechanisms of MVV such as PAN and KD are further elucidated, these vasculitides may be recognized as "mixed-pattern" disorders.

On the other hand, autoimmune predominance is obvious in SVV, except for HSP. Association with ADs, disease-specific autoantibodies, HLA significant associations as assessed by GWASs, lymphocytic infiltration and response to anti-CD20 therapy are frequent in SVV. Therefore, many primary systemic SVV constitute archetypic ADs and autoantibodies might have a predilection for capillaries and small-sized vessels. Finally, LVV present several features of both autoimmunity and autoinflammation and specific mechanisms (e.g. IL-6 pathway) might be crucial in their pathogenesis. Since several ADs (e.g. SLE, RA) and AIDs (e.g. FMF, HA20, DADA2) course with vasculitic manifestations, it is not surprising to find autoimmune and autoinflammatory manifestations in primary systemic vasculitides[2,3].

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