



Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

The kaleidoscopic manifestations of systemic vasculitis

1. Introduction

The IXth Menarini International Symposium on Autoimmunity took place in Seville (Spain) in December 2010, and focused on “The kaleidoscopic manifestations of systemic vasculitis”, addressing both pathogenic and clinical aspects of Anti-Neutrophil Cytoplasmic Autoantibody-Associated Systemic Vasculitis (AASV). Moreover, two specific topics related to primary angiitis of the central nervous system and cocaine-induced midline destructive lesions were covered.

The term vasculitides encompasses a group of inflammatory disorders that may affect any organ/system by damaging its blood supply. Virtually any size or type of vessel may be involved; for example, involvement of glomerular capillaries leads to necrotizing glomerulitis, while involvement of larger arteries can cause renal infarction and ischemia [1].

ANCA associated vasculitides are systemic autoimmune diseases of unknown cause that affect small (to medium) sized blood vessels. They include granulomatosis with polyangiitis (formerly Wegener's granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome) [2–4].

AASVs are rare diseases and must be diagnosed and treated early because they may rapidly develop organ failure and death. Indeed, the prognosis of untreated ANCA-associated systemic vasculitis (AASV) is poor with up to 90% of patients dying within 2 years. When appropriately treated, AASVs are no longer fatal but run a chronic relapsing course with accumulating drug-related morbidity in over 50% of the patients. Early diagnosis and treatment may prevent progression to end organ damage and lengthen healthier life [5].

The discovery of ANCA in the late eighties and the introduction of ANCA testing in the clinical practice in the following decades, have stimulated research in this area. In the last 10 years several advances have been achieved in different fields of AASV.

2. Animal models

Rodent models of both myeloperoxidase (MPO) ANCA and proteinase 3 (PR3) ANCA associated vasculitis have been developed, which have provided important clues into the pathogenesis of AASV [6,7].

The ability of ANCA IgG to cause pauci-immune necrotizing and crescentic GN and vasculitis has been demonstrated in a mouse model. Wild-type or immunodeficient mice that receive anti-MPO antibodies intravenously develop pauci-immune focal necrotizing GN with crescents. This GN is mediated by neutrophil activation and can be prevented by neutrophil depletion [6,7]. A similar model has also

been developed in the rat by immunizing animals with human MPO, resulting in the development of antibodies that cross-react with rat MPO and are able to induce pauci-immune glomerular necrosis and crescents resembling the human picture [6,7].

3. In vitro studies

Evidence for a pathogenic role for ANCAs comes from numerous in vitro observations.

Several in vitro observations suggest mechanisms by which ANCA can cause vascular injury. Priming of neutrophils by cytokines, as would occur with a viral or bacterial infection, causes neutrophils to increase expression of ANCA antigens on their surfaces, where they are accessible to interact with ANCA. Cytokine-primed neutrophils that are exposed to ANCA release toxic oxygen metabolites, and kill cultured endothelial cells. ANCA-antigen complexes adsorb onto endothelial cells, where they could participate in in situ immune complex formation. ANCA activation of neutrophils is mediated by both F(ab)₂ binding to neutrophils and Fc receptor engagement. Neutrophils that have been activated by ANCA adhere to endothelial cells and release mediators of inflammation and cell injury. Evidence that activation of the alternative complement pathway may play a role in amplifying ANCA-induced inflammation has been accumulated [6–9].

4. Pathogenesis

Clinical and experimental animal data support the hypothesis that ANCA can activate neutrophils and cause vasculitis, especially if there is a concurrent synergistic proinflammatory stimulus. The requirement for a synergistic inflammatory process may be reflected in the very frequent association of the onset of ANCA small-vessel vasculitis with viral or bacterial infections. Such infections may cause the production of high levels of circulating cytokines that could serve as priming factors for neutrophils [6–12]. Environmental factors have been considered important in the development of ANCA, including silica, infection especially with *Staphylococcus aureus*, and drugs [13,14].

How ANCAs are generated is not known. However, studies suggesting that molecular mimicry and responses to complementary peptides may be initiating events for ANCAs have been recently published (reviewed in [8]). Two mechanisms that have been proposed for the origin of the ANCA autoimmune response are molecular mimicry of the autoantigen by a bacterial peptide and induction of autoimmunity through an immune response to the complementary peptide of the autoantigen (PR3) that secondarily results in antibodies against the autoantigen. Kain et al. have proposed that molecular mimicry of

lysosomal-associated membrane protein 2 (LAMP-2) by the bacterial adhesin FimH can induce circulating anti-FimH antibodies that cross-react with LAMP-2, which can cause pauci-immune glomerulonephritis and small vessel vasculitis. Others have not confirmed this theory. Another novel theory for induction of the ANCA autoimmune response postulates that the initial immune response is against an epitope that is on antisense peptide (complementary autoantigen peptide) or a mimic of an antisense peptide rather than against a sense autoantigen peptide [8]. In Fig. 1 the events conducting to AASV are schematically summarized.

5. ANCA

In addition to their pathogenic role, ANCAs are considered a sensitive and specific serologic marker of AASV [12].

According to the international guidelines, combining indirect immunofluorescence and PR3-ANCA/MPO-specific immunoassays assures the optimal diagnostic specificity.

Despite their diagnostic value, the performance of the widespread immunometric assays for ANCA testing has been disappointing, particularly for the low sensitivity. In recent years, more "sensitive" assays have been developed, using the microplate as well as fully the automated technologies, with promising preliminary results. In addition to a careful revision of methodological aspects and clinical significance of ANCA in AASV, a description of the new methods and techniques of ANCA testing has been covered [15].

6. Ear nose and throat (ENT) manifestations

Most of the initial symptoms of Wegener's granulomatosis, now called granulomatosis with polyangiitis (GPA) begin in the head and neck region with a wide spectrum of involvement of any site ranging from the nasal septum, paranasal sinuses, oral mucosa, larynx and even the external, middle and internal ear [16]. Diagnosis may be delayed because the onset is heterogeneous and sometimes limited to one organ. The differentiation from other conditions that mimic GPA such as lymphoma and infections is of critical importance to initiate appropriate treatment. The otorhinolaryngologic manifestations and complications of GPA as well as their surgical management are reviewed in the article by Trimarchi et al. [17] and the role of the

otorhinolaryngologist as an integral member of the multidisciplinary care team for patients with GPA is specified [17].

7. Cocaine-induced midline destructive lesions (CIMDL)

Upper respiratory tract involvement of GPA needs to be differentiated from an increasingly recognized phenomenon which is represented by cocaine-induced midline destructive lesions (CIMDL). Occasionally, cocaine-induced lesions cause extensive destruction of the osteocartilaginous structures of the nose, sinuses and palate that can mimic other diseases such as tumors, infections, and immunological diseases, in particular GPA. In several instances these lesions are clinically indistinguishable from granulomatosis with polyangiitis (Wegener's) limited to the upper respiratory tract. Moreover, positive antineutrophil cytoplasmic antibody (ANCA) test results may be found in an unexpectedly large proportion of patients with CIMDL, increasing diagnostic difficulties. In CIMDL patients these ANCAs are primarily directed against human neutrophil elastase (HNE), generate a perinuclear (P-ANCA) staining pattern on ethanol-fixed neutrophils, and do not react with myeloperoxidase (MPO). About half of these CIMDL patients may also have coexisting ANCA that react with proteinase 3 (PR3). CIMDL seem to be the result of a necrotizing inflammatory tissue response triggered by cocaine abuse in a subset of patients predisposed to produce ANCA, particularly those reacting with HNE. The presence of these HNE-ANCAs seems to promote or define the disease phenotype [18].

8. Cutaneous vasculitis

Berti E. et al. have covered the topic of skin involvement in cutaneous and systemic vasculitis. Cutaneous vasculitides are a heterogeneous group of inflammatory disorders affecting skin blood vessels. They may be triggered by several factors, such as infection or drug, or may be related to underlying diseases, notably connective tissue or malignancies. However, vasculitis occurs without any demonstrable triggering agents in a relevant number of patients. On the other hand, vasculitic skin lesions may manifest as a component of vasculitis affecting also internal organs. In addition to the vast area of cutaneous vasculitides, the variety of cutaneous manifestations that may develop during the course of the main systemic vasculitides,

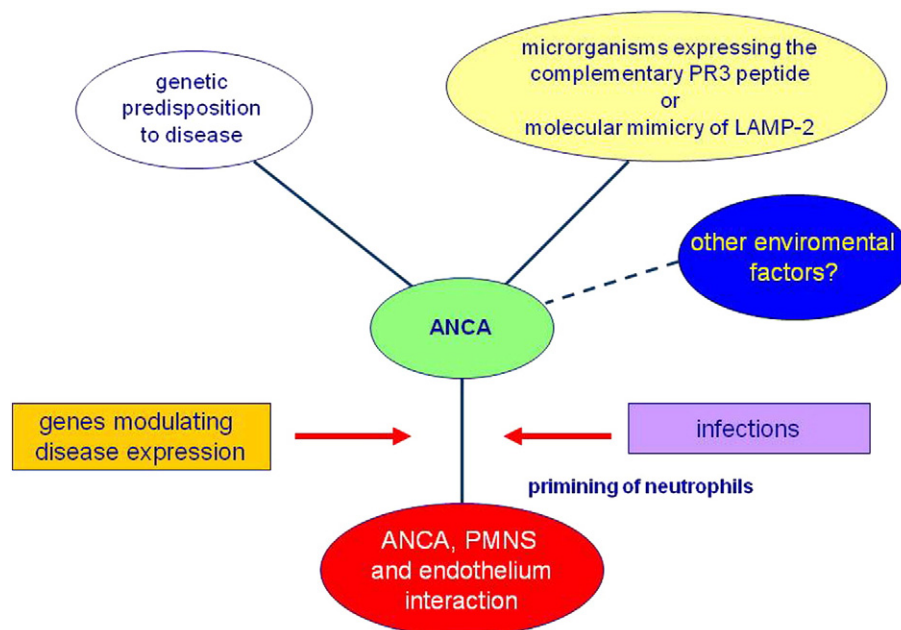


Fig. 1. Schematic events conducting to anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. Abbreviations: PR3, proteinase 3; LAMP-2, lysosomal-associated membrane protein 2; PMNS, polymorphonuclear neutrophils.

such as Wegener's granulomatosis, Churg–Strauss syndrome and polyarteritis nodosa has been analyzed in details [19].

9. Renal involvement

Renal involvement is a common and often severe complication of AASV. Kidney involvement is generally characterized by a pauci-immune necrotizing and crescentic glomerulonephritis with a very rapid decline of renal function (rapidly progressive glomerulonephritis). The presence and severity of kidney involvement are the major determinants of patient outcome [20,21]. On the basis of the extension of the lesions and their characteristics (active or sclerotic), the European Vasculitis Study Group (EUVAS) has proposed a histopathological classification for ANCA-associated glomerulonephritis [22]. The classification scheme has four general categories of lesions namely focal, crescentic, sclerotic, and mixed. Preliminary results have shown that the proposed classification system is of prognostic value for 1- and 5-year renal outcomes [22,23].

With the exception of Churg–Strauss syndrome (CSS), where kidney involvement is not a prominent feature, renal disease is present in about 70% of patients with GPA and in almost 100% of patients with microscopic polyangiitis (MPA). If untreated necrotizing and crescentic glomerulonephritis has an unfavorable course leading in a few weeks or months to end stage renal disease.

Several recent studies have shown that serum creatinine at diagnosis, sclerotic lesions and the number of normal glomeruli at kidney biopsy are the best predictors of renal outcome.

10. Primary angiitis of the CNS (PACNS)

Primary angiitis of the CNS (PACNS) is a rare disorder resulting in inflammation and destruction of CNS vessels without evidence of vasculitis outside the CNS. PACNS is poorly understood, and formidable challenges to our understanding and management of the disease remain: few clinicians are highly experienced with the disease, the clinical presentations are non-specific, we lack highly efficient non-invasive modalities for diagnosis, no useful animal models exist to aid our understanding of the disease, and no randomized trials of treatments have been done. Despite such limitations, substantial progress has been made including growing recognition of a specific constellation of epidemiological, clinical, neuroradiographic, and laboratory findings that could enhance diagnostic accuracy [24]. A clear view of multiple clinical and pathological disease subtypes with prognostic implications within the spectrum of PACNS is now accepted.

While primary angiitis of the central system (PACNS) remains a rare entity, the poor specificity of the available diagnostic tests and its multiple mimics create a major diagnostic challenge. Recently, there have been advances in understanding PACNS and differentiating it from its mimics. A recent breakthrough is the proposal of reversible cerebral vasoconstriction syndromes (RCVS) as a unifying concept for a group of disorders that highly mimics PACNS [24,25].

11. Treatment

The combination of prednisone and cyclophosphamide is now established as the treatment of choice and leads to control of the disease in 80% of the patients. Treatment of AASV can be divided into three phases: therapy for induction of remission, for maintenance of remission and therapy for refractory and relapsing disease. In addition, the treatment must be tailored to the stage and severity of the disease and a new classification of AASV has been introduced: localized vasculitis, early systemic vasculitis, generalized vasculitis, severe renal vasculitis and refractory vasculitis. So far the combination therapy of glucocorticoids and conventional immunosuppressive drugs has mainly been used to control disease. This approach has led

to a significant improvement in outcome in spite of persistently high mortality and morbidity rates [26–28].

In the last 10 years several randomized controlled trials have been performed with the aim of optimizing the existing therapeutic regimens and testing new drugs and schemes. Among them, important results which have been introduced in the clinical practice regards:

- the efficacy of methotrexate in inducing remission in early systemic ANCA associated vasculitis
- the value of cyclophosphamide pulses to reduce adverse effects and morbidity of oral cyclophosphamide
- the role of azathioprine and methotrexate to maintain remission
- the additive effect of plasma-exchange in the severe forms of ANCA-associated renal vasculitis.

Besides conventional treatment, biologics have emerged as a new treatment option [25–32]. In particular, Rituximab (RTX) has emerged as an alternative for cyclophosphamide in the remission induction of patients with generalized and severe disease on the basis of uncontrolled and randomized controlled trials [29–36].

In spite of significant advances in treatment, refractory vasculitis still occurs in 4–5% of patients and cases with fatal outcome can be seen [37]. New more effective and safer therapies are needed.

Little is known about pregnancy and fetal outcome in women with vasculitis, mainly because of the median age of these patients and the severe course of the disease; however, with the progressive achievement of a longer life expectancy and a better quality of life the number of pregnancies observed during the course of such diseases is increasing and such topic deserves further studies [38,39].

In this issue, reports of current data discussed at this meeting are presented as concise and structured review by experts in this field.

References

- [1] Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994;37(2):187-92.
- [2] Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997;337:1512-23.
- [3] Savage CO, Harper L, Adu D. Primary systemic vasculitis. *Lancet* 1997;349:553-8.
- [4] Falk RJ, Gross WL, Guillevin L, Hoffman GS, Jayne DR, Jennette JC, et al. Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis. *Arthritis Rheum* 2011;63(4):863-4.
- [5] Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011;70(3):488-94.
- [6] Lepsen N, Abdulahad WH, Kallenberg CG, Heeringa P. Immune regulatory mechanisms in ANCA-associated vasculitides. *Autoimmun Rev* 2011 Dec;11(2):77-83.
- [7] Hu N, Westra J, Kallenberg CG. Dysregulated neutrophil–endothelial interaction in antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides: implications for pathogenesis and disease intervention. *Autoimmun Rev* 2011 Jul;10(9):536-43.
- [8] Jennette JC, Falk RJ, Gasim AH. Pathogenesis of antineutrophil cytoplasmic autoantibody vasculitis. *Curr Opin Nephrol Hypertens* 2011;20(3):263-70.
- [9] Kallenberg CG. Pathogenesis of ANCA-associated vasculitides. *Ann Rheum Dis* 2011;70(Suppl. 1):i59-63.
- [10] Salama AD, Little MA. Animal models of antineutrophil cytoplasm antibody-associated vasculitis. *Curr Opin Rheumatol* 2012;24(1):1-7.
- [11] van Timmeren MM, Heeringa P. Pathogenesis of ANCA-associated vasculitis: recent insights from animal models. *Curr Opin Rheumatol* 2012;24(1):8–14.
- [12] Lochman I, Král V, Lochmanová A, Lupač J, Cebebauer L. ANCA in the diagnosis of neutrophil-mediated inflammation. *Autoimmun Rev* 2011;10(6):295-8.
- [13] Chen M, Kallenberg CG. The environment, geoepidemiology and ANCA-associated vasculitides. *Autoimmun Rev* 2010 Mar;9(5):A293-8.
- [14] Farhat SC, Silva CA, Oriane MA, Campos LM, Sallum AM, Braga AL. Air pollution in autoimmune rheumatic diseases: a review. *Autoimmun Rev* 2011 Nov;11(1):14-21.
- [15] Radice A, Bianchi L, Sinico RA. Anti-neutrophil cytoplasmic autoantibodies (ANCA): methodological aspects and clinical significance in systemic vasculitis. *Autoimmun Rev*. <http://dx.doi.org/10.1016/j.autrev.2012.08.008>.
- [16] Schilder AM. Wegener's granulomatosis vasculitis and granuloma. *Autoimmun Rev* 2010;9(7):483-7.
- [17] Trimarchi M, Sinico RA, Teggi R, Bussi M, Specks U, Meroni PL. Otorhinolaryngological manifestations in granulomatosis with polyangiitis (Wegener's). *Autoimmun Rev*. in press.

- [18] Trimarchi M, Bussi M, Sinico RA, Meroni PL, Specks U. Cocaine-induced midline destructive lesions—an autoimmune disease? *Autoimmun Rev*. in press.
- [19] Marzano AV, Vezzoli P, Berti E. Skin involvement in cutaneous and systemic vasculitis. *Autoimmun Rev*, <http://dx.doi.org/10.1016/j.autrev.2012.08.005>.
- [20] Rutgers A, Sanders JS, Stegeman CA, Kallenberg CG. Pauci-immune necrotizing glomerulonephritis. *Rheum Dis Clin North Am* 2010;36(3):559-72.
- [21] Lee RW, D'Cruz DP. Pulmonary renal vasculitis syndromes. *Autoimmun Rev* 2010;9(10):657-60.
- [22] Berden AE, Ferrario F, Hagen EC, Jayne DR, Jennette JC, Joh K, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol* 2010;21(10):1628-36.
- [23] Sinico RA, Di Toma L, Radice A. Renal involvement in anti-neutrophil cytoplasmic autoantibody associated vasculitis. *Autoimmun Rev*, <http://dx.doi.org/10.1016/j.autrev.2012.08.006>.
- [24] Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. *Lancet Neurol* 2011;10(6):561-72.
- [25] Hajj-Ali RA, Calabrese LH. Primary angiitis of the central nervous system. *Autoimmun Rev*, <http://dx.doi.org/10.1016/j.autrev.2012.08.004>.
- [26] Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* Mar 2009;68(3):310-7.
- [27] Carruthers D, Sherlock J. Evidence-based management of ANCA vasculitis. *Best Pract Res Clin Rheumatol* Jun 2009;23(3):367-78.
- [28] Pietrogrande M, De Vita S, Zignego AL, Pioletti P, Sansonno D, Sollima S, et al. Recommendations for the management of mixed cryoglobulinemia syndrome in hepatitis C virus-infected patients. *Autoimmun Rev* 2011;10(8):444-54.
- [29] Holle JU, Gross WL. Treatment of ANCA-associated vasculitides (AAV). *Autoimmun Rev*, <http://dx.doi.org/10.1016/j.autrev.2012.08.007>.
- [30] Isenberg DA. Rituximab—it was the best of times, it was the worst of times. *Autoimmun Rev* 2012;11(11):790-1.
- [31] Gómez-Puerta JA, Quintana LF, Stone JH, Ramos-Casals M, Bosch X. B-cell depleting agents for ANCA vasculitides: a new therapeutic approach. *Autoimmun Rev* Nov 21 2011;11(9):646-52.
- [32] Ferri C, Cacoub P, Mazzaro C, Roccatello D, Scaini P, Sebastiani M, et al. Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: results of multicenter cohort study and review of the literature. *Autoimmun Rev* Nov 2011;11(1):48-55.
- [33] Szekanez Z, Szántó S, Szabó Z, Váncsa A, Szamosi S, Bodnár N, et al. Biologics—beyond the joints. *Autoimmun Rev* 2010;9(12):820-4.
- [34] Borchers AT, Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. *Autoimmun Rev* May 2012;11(6-7):A544-54.
- [35] Ramos-Casals M, Perez-Alvarez R, Diaz-Lagares C, Cuadrado MJ, Khamashta MA, BIOGEAS Study Group. Autoimmune diseases induced by biological agents: a double-edged sword? *Autoimmun Rev* Jan 2010;9(3):188-93.
- [36] Comarmond C, Plaisier E, Dahan K, Mirault T, Emmerich J, Amoura Z, et al. Anti TNF- α in refractory Takayasu's arteritis: cases series and review of the literature. *Autoimmun Rev* 2012;11(9):678-84.
- [37] Rutgers A, Kallenberg CG. Refractory vasculitis. *Autoimmun Rev* 2011;10(11):702-6.
- [38] Gatto M, Iaccarino L, Canova M, Zen M, Nalotto L, Ramonda R, et al. Pregnancy and vasculitis: a systematic review of the literature. *Autoimmun Rev* May 2012;11(6-7):A447-59.
- [39] Carvalheiras G, Faria R, Braga J, Vasconcelos C. Fetal outcome in autoimmune diseases. *Autoimmun Rev* May 2012;11(6-7):A520-30.

Renato A. Sinico

Clinical Immunology Unit and Renal Unit, Department of Medicine, Azienda Ospedaliera Ospedale San Carlo Borromeo, via Pio Secondo, 3 – 20153 - Milano, Italy

Corresponding author. Tel.: +39 0240222489; fax: +39 0240222222.

E-mail address: renatoalberto.sinico@fastwebnet.it (R.A. Sinico).

Pierluigi Meroni

Department of Clinical Sciences and Community Health, University of Milan, Division of Rheumatology, Istituto G. Pini and IRCCS Istituto Auxologico Italiano, Milano, Italy

Available online xxxx