Journal of Autoimmunity 48-49 (2014) 90–93

Contents lists available at ScienceDirect

Journal of Autoimmunity

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

The diagnosis and classification of microscopic polyangiitis

Cees G.M. Kallenberg*

Department of Rheumatology and Clinical Immunology, AA21, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 7 October 2013
Accepted 13 November 2013

Keywords:
Microscopic polyangiitis
ANCA-associated vasculitis
Anti-neutrophil cytoplasmic autoantibodies
Anti-myeloperoxidase antibodies
Myeloperoxidase (MPO)
Necrotizing and crescentic glomerulonephritis

ABSTRACT

Microscopic Polyangiitis (MPA) is a small vessel vasculitis. The disease is defined by the 2012 revised Chapel Hill Consensus Conference Nomenclature of Vasculitides [1] as necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e. capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent. MPA belongs to the ANCA-associated vasculitides (AAV). ANCA in MPA are predominantly directed against myeloperoxidase (MPO-ANCA) but may, in a minority of patients, be directed against proteinase 3 (PR3-ANCA). Not all patients, however, have ANCA. Microscopic polyangiitis (MPA) belongs to the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides. MPA is clinically characterized by small-vessel vasculitis primarily affecting the kidneys and the lungs but other organs may be involved as well. Renal involvement, which can be the only manifestation, is clinically apparent as rapidly progressive glomerulonephritis and histopathologically as pauci-immune necrotizing and crescentic glomerulonephritis. ANCA in MPA are mainly directed to myeloperoxidase (MPO-ANCA). Besides their diagnostic significance, MPO-ANCA appear pathogenic in MPA. Rituximab with steroids is at least as effective as cyclophosphamide with steroids for induction of remission.

1. Definition

Microscopic Polyangiitis (MPA) is a small vessel vasculitis. The disease is defined by the 2012 revised Chapel Hill Consensus Conference Nomenclature of Vasculitides [1] as necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e. capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.

MPA belongs to the ANCA-associated vasculitides (AAV). ANCA in MPA are predominantly directed against myeloperoxidase (MPO-ANCA) but may, in a minority of patients, be directed against proteinase 3 (PR3-ANCA). Not all patients, however, have ANCA.

2. History of the disease

Whereas Polyarteritis nodosa (PAN) was described already in 1866 by Kussmaul and Maier, microscopic polyarteritis, later on changed into microscopic polyangiitis, was suggested in 1985 as a disease entity by Savage et al. [2]. It was recognized as a disease in which rapidly progressive glomerulonephritis, not infrequently in conjunction with pulmonary capillaritis, were prominent findings. As this was not the case in classical PAN, MPA was considered a distinct entity. The discovery of ANCA supported the concept of MPA being a distinct disease entity since the vast majority of patients with MPA were positive for ANCA whereas patients with classical PAN were generally ANCA-negative.

3. Epidemiology

The incidence and prevalence of MPA are not exactly known. The AAV, mainly comprising granulomatosis with polyangiitis (GPA) and MPA, have been estimated to have an overall annual incidence of 17.2/million in the UK with MPA having an incidence of 5.9/million [3]. Whereas in the Northern European Caucasian population GPA predominates within the group of patients with AAV, MPA is more frequent than GPA in Southern Europe, Japan and China. Men are slightly more affected than women. The age at

Abbreviations: ANCA, antineutrophil cytoplasmic autoantibodies; CD11b, a β2-integrin cell-surface adhesion molecule involved in neutrophil adherence to and migration through vascular endothelial cells; ICAM-1, intercellular adhesion molecule 1; C5aR, C5a-receptor; PSV, primary systemic vasculitis; ACR, American College of Rheumatology; CHCC, Chapel Hill Consensus Conference; cPAN, classic polyarteritis nodosa; EGPA, eosinophilic granulomatosis with polyangiitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

* Tel.: + 31 50 3612945; fax: + 31 50 3619308.
E-mail address: c.g.m.kallenberg@umcg.nl.

0896-8411/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jaut.2014.01.023

presentation peaks around 60–65 years of age. There seems to be an increase in the incidence of MPA during the last two decades, which can be explained, in part, by the availability of ANCA testing.

4. Pathogenesis

The etiology of MPA is largely unknown. Environmental factors, such as silica exposure, have been suggested [4], but their precise role in etiopathogenesis is unclear. There is, however, increased evidence that MPA is an autoimmune disease in which ANCA, particularly those reacting with MPO, are pathogenic [5]. First, the vast majority of patients with MPA (95%) are positive for ANCA, directed to MPO in 70% of cases and in the remaining patients directed to proteinase 3 (PR3). Titers of ANCA frequently rise preceeding disease activity [6]. Secondly, both MPO-ANCA and PR3-ANCA are able, in vitro, to activate (primed) neutrophils to the production of reactive oxygen species and the release of lytic enzymes. In the presence of endothelial cells, this leads to endothelial detachment and lysis [5]. The most convincing argument for a pathogenic role of MPO-ANCA comes from studies in experimental animals. Immunizing MPO-deficient mice with mouse MPO resulted in their production of anti-mouse MPO antibodies. Splenocytes from these mice were injected into immunodeficient and normal mice which resulted in the development of severe necrotizing and crescentic glomerulonephritis and systemic necrotizing vasculitis including pulmonary capillaritis. Immune deposits were hardly present, consistent with a so-called pauci-immune vasculitis and glomerulonephritis which is seen also in patients with MPA (see later). Transfer of anti MPO-IgG alone into recipient mice resulted in focal pauci-immune glomerulonephritis which was strongly augmented by the simultaneous injection of lipopolysaccharide (LPS). In addition, the alternative pathway of complement was involved as well in lesion development [7]. Finally, different MHC class II genes are associated with MPO-ANCA and PR3-ANCA as well as with MPA and GPA, respectively. Interestingly, in support of a pathogenic role of ANCA, the associations are stronger with the autoantibodies than with the diseases [8]. Taken together, strong evidence now exists that MPO-ANCA are directly involved in the pathogenesis of MPA (Fig. 1) [9]. This is less clear for PR3-ANCA.

5. Clinical manifestations

MPA belongs to the systemic vasculitides indicating that multiple organs can be affected. Major organs involved in MPA are the kidneys and the lungs. Renal involvement is manifested by microscopic hematuria with cellular casts in combination with proteinuria which is, generally, not massive. In addition, deterioration of renal function frequently occurs clinically apparent as rapidly progressive glomerulonephritis. In 90% of patients the kidneys are

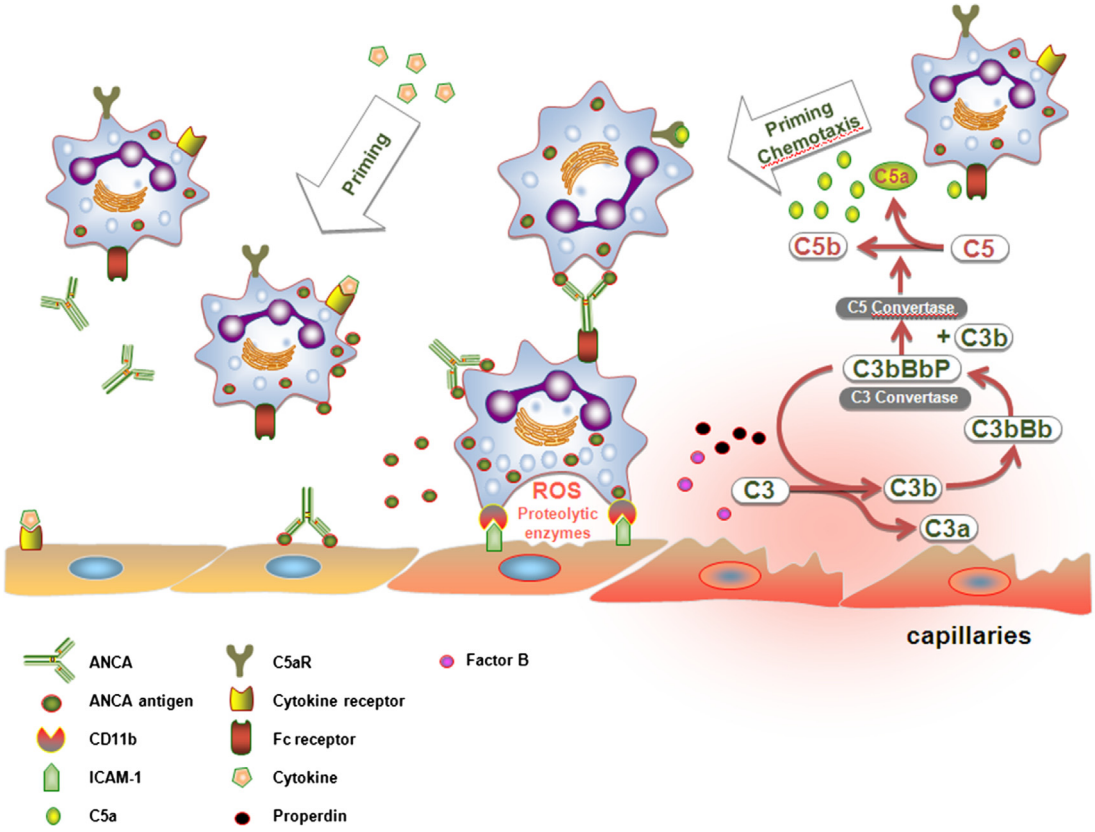

Fig. 1. Schematic representation of the neutrophil responses that are putatively involved in the pathogenesis of ANCA-associated small vessel vasculitis. Proinflammatory cytokines and chemokines (e.g. tumor necrosis factor) that are released as a result of local or systemic infection cause upregulation of the expression of endothelial adhesion molecules (e.g. selectins, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1), and prime neutrophils. Neutrophil priming causes upregulation of the expression of neutrophil adhesion molecules (CD11b) and translocation of the ANCA antigens from their lysosomal compartments to the cell surface. Engagement of dimers of the antigen-binding portion of ANCA with ANCA antigens on the cell surface, and interaction of the Fc part of the antibody with Fc receptors, activate neutrophils and cause increased adherence of neutrophils to vessel walls. ANCA-mediated neutrophil activation also triggers production of reactive oxygen radicals and causes neutrophil degranulation. The consequent release of proteolytic enzymes leads to vasculitis. The alternative pathway of complement activation plays a role as an amplification loop of the inflammatory response; factor B and properdin are released from activated neutrophils and together with C3 activate the complement system resulting in the production of the strong neutrophil chemoattractant C5a. Reprinted from ref. [9] with permission.