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Review

Microscopic polyangiitis: Advances in diagnostic and therapeutic approaches

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ABSTRACT

Microscopic polyangiitis (MPA) is an idiopathic autoimmune disease characterized by systemic vasculitis. The disease predominantly affects small-calibre blood vessels and is associated with the presence of antineutrophil cytoplasmic autoantibodies (ANCA). Microscopic polyangiitis was considered to be a disease entity by Savage et al. in 1985. Microscopic polyangiitis has a reported low incidence and a slight male predominance.
The aetiology of MPA remains unknown. There is, however, increased evidence that MPA is an autoimmune disease in which ANCAs, particularly those reacting with MPO, are pathogenic.
MPA belongs to the systemic vasculitides, indicating that multiple organs can be affected. The major organs involved in MPA are the kidneys and the lungs. As expected for an illness that affects multiple organ systems, patients with MPA can present with a myriad of different symptoms.
Ear, nose and throat (ENT) manifestations are not considered to be clinical symptoms of MPA, but in the majority of populations described, ENT involvement was found in surprisingly high percentages.
MPA is part of the ANCA-associated vasculitides, which are characterized by necrotizing vasculitis of small vessels. Diagnosis is mainly established by clinical manifestations, computed tomography (TC), ANCA antibody detection and renal and pulmonary biopsy.
The introduction of aggressive immunosuppressive treatment has substantially improved the prognosis.
The standardized therapeutic regimen is based on cyclophosphamide and corticosteroids. Using this regimen, remission can be achieved in most of the patients. Rituximab may represent an important alternative to cyclophosphamide for patients who may not respond adequately to antimetabolite therapies.

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1. Introduction

Microscopic polyangiitis (MPA) is an idiopathic autoimmune disease characterized by systemic vasculitis. The disease predominantly affects small-calibre blood vessels and is associated with the presence of antineutrophil cytoplasmic autoantibodies (ANCA). The association with ANCAs originally defined the group of ANCA-associated vasculitides, comprising granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg–Strauss syndrome) [1], which have different frequencies of ANCA-positivity [2,3].

Because it can lead to both pulmonary capillaritis and glomerulonephritis, MPA is a primary cause of pulmonary-renal syndrome, a group of disorders that includes Goodpasture's syndrome [4].

1.1. Historical overview

Polyarteritis nodosa was described in 1866 by Kussmaul and Maier. For years following this description, all patients with a non-infectious arteritis were classified as having polyarteritis nodosa. In 1923, Friedrich Wohlwill described two patients who appeared to have a novel form of polyarteritis nodosa that was characterized by the presence of glomerulonephritis and non-granulomatous inflammation of small-calibre blood vessels [5]. This "microscopic form of periarteritis nodosa" was gradually recognized as a new entity, distinct from classic polyarteritis nodosa.

In 1954, Godman and Churg noted that the "microscopic form of periarteritis" was closely related to WG and CSS [6]. During the ensuing years, it gradually became clear that these three forms of systemic vasculitis were also linked by the presence of anticytoplasmic antibodies directed against neutrophils. Antineutrophil cytoplasmic antibodies were first reported in association with focal segmental glomerulonephritis in the 1980s [2].

Microscopic polyarteritis, later changed to microscopic polyangiitis, was classified as a disease entity in 1985 by Savage et al. [7].

In 1988, Jennette and Falk reported that serum from patients with WG, renal-limited vasculitis, and MPA was associated with antibodies that created a perinuclear staining pattern [8].

In 1994, the Chapel Hill Consensus Conference (CHCC) proposed the term "microscopic polyangiitis" to describe patients with a small-vessel vasculitis that was characterized by the absence of immune complex deposition on immunofluorescence and the presence of pulmonary capillaritis and glomerulonephritis [9]. The new name emphasized the differences between this phenomenon and "classic" polyarteritis nodosa, which was defined as a medium-vessel vasculitis that spared the arterioles and venules.

Insights from vasculitis research over the past decade led to a 2012 revision of the 1994 CHCC nomenclature, focusing more on aetiology, pathogenesis, pathology and clinical characteristics as the basis for categorization. MPA was described as a pauci-immune disease with an absence of granuloma formation or prominent eosinophilia associated with myeloperoxidase (MPO) ANCA [3,10].

2. Epidemiology

There seems to have been an increase in the incidence of MPA over the last two decades, which can be explained, in part, by the availability of ANCA testing. Microscopic polyangiitis has a reported incidence of 2.7 to 94 per 1 million [11,12] and a slight male predominance (male:female ratio of 1.8:1) [13–15], with an average age of onset between 50 and 60 years [13,14,16].

Overall, however, the incidence of MPA is higher in southern Europe than in northern Europe; for example, the incidence of MPA in Norway is 2.7 per million, [17] but rises to 11.6 per million in Spain [18]. The incidence and prevalence of MPA in other parts of the world is less clear, but the prevalence seems to be higher in European populations [16]. Other studies indicate that the frequency does not appear to be affected by latitude [11,12,19].

3. Etiopathogenesis

The aetiology of MPA is largely unknown. Environmental factors, such as silica exposure, have been suggested [20], but their precise role in the etiopathogenesis is unclear. There is, however, increased evidence that MPA is an autoimmune disease in which ANCA, particularly those reacting with MPO, are pathogenic [21]. Microscopic polyangiitis is associated with myeloperoxidase ANCA in 58% of cases and with proteinase 3 (P3) ANCA in 26% of cases [22]. Some patients are ANCA-negative [23].

Titers of ANCA frequently increase preceding disease activity [24]. MPO-ANCA and PR3-ANCA are able, in vitro, to activate (primed) neutrophils to produce reactive oxygen species and release lytic enzymes. In the presence of endothelial cells, this leads to endothelial detachment and lysis [21]. The most convincing argument for a pathogenic role of MPO-ANCA comes from studies in experimental animals. Two animal models support a potential role for MPO-ANCA in the pathogenesis of MPA [25,26], demonstrating that MPO-ANCA are sufficient to induce pulmonary capillaritis and glomerulonephritis given the correct biologic milieu.

Additional support of this role comes from a case report describing pulmonary haemorrhage and renal insufficiency in a newborn infant, presumably mediated by the passage of MPO-ANCA from mother to foetus [27]. A subsequent case report, however, documents that placental transmission of MPO-ANCA is not sufficient to induce disease [28].

Finally, different MHC class II genes are associated with MPO-ANCA and PR3-ANCA as well as with MPA and GPA. Interestingly, in support of a pathogenic role of ANCA, the associations are stronger with the autoantibodies than with the diseases [29]. Taken together, there is strong evidence that MPO-ANCA are directly involved in the pathogenesis of MPA [30]. This is less clear for PR3-ANCA.

The development of vasculitis likely requires the presence of several co-factors, including genetic predisposition, in order for ANCA to be pathogenic. It is interesting to note that not all patients with active vasculitis are ANCA positive and that MPO-ANCA titers themselves poorly correlate with disease activity in MPA. These observations imply that