

# Microscopic polyangiitis: from pathogenesis to treatment

## Abstract

Microscopic Polyangiitis (MPA) is a systemic pauci-immune necrotizing vasculitis of small-calibre vessels characterized by the absence of granulomas. MPA is an autoimmune disease but its aetiology remains obscure. MPA is associated with presence of antineutrophil cytoplasmic autoantibodies (ANCA) but not all patients with MPA have ANCA. There is strong evidence that not all ANCA are pathogenetic. It seems that specific epitopes determine ANCA pathogenicity. Given that MPA is a systemic vasculitis, multiple organs could be affected resulting in a wide spectrum of signs and symptoms. The kidneys and lungs are the most typical organs involved in MPA. Notably, MPA is the major cause of pulmo-renal syndrome. MPA has a poor prognosis if not treated but the use of aggressive immunosuppressive treatment has improved the prognosis and the patient's survival. Rituximab could be considered as an alternative treatment for severe disease, for patients who do not respond adequately to the immunosuppressive treatment and for patients with relapses. However, the long-term safety of Rituximab in MPA is unknown and it should be elucidated by further studies. Interestingly, kidney transplantation is safe and effective and it has a good prognosis in MPA patients with ESRD.

**Keywords:** ANCA, microscopic polyangiitis, treatment, vasculitis

Volume 5 Issue 2 - 2017

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**Received:** June 26, 2017 | **Published:** August 17, 2017

## Introduction

The term vasculitides refers to a group of inflammatory disorders involving any size or type of vessel. Microscopic Polyangiitis (MPA) is a systemic pauci-immune vasculitis of glomerular capillaries leading to necrotizing glomerulonephritis.<sup>1</sup> Renal involvement is particularly frequent in small vessel systemic necrotizing vasculitis called anti-neutrophil cytoplasmic autoantibody associated vasculitis (AAV), including MPA, granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis. Renal involvement in MPA is of particular importance because it is associated with poor prognosis and increased mortality.<sup>2</sup> In particular, the presence of renal impairment and dialysis dependence at diagnosis increases the risk of death in AAV patients.<sup>3,4</sup>

The main clinical presentation in MPA is rapidly progressive glomerulonephritis (RPGN) characterized by rapid decrease of glomerular filtration rate (GFR), microscopic haematuria, erythrocyte cast, presence of proteinuria (usually less than 3g) and hypertension. Lungs are usually also affected in MPA. Lung manifestations consist of diffuse alveolar haemorrhage due to pulmonary capillaritis.<sup>1,2</sup> The pathogenesis of MPA is unknown. There is increasing evidence that environment factors in association with a genetic predisposition are involved in the pathogenesis of MPA. In addition, a pathogenic role for ANCA has been proposed.<sup>5</sup> Histological confirmation of vasculitis remains still the gold standard of the diagnosis of MPA. The therapy of MPA consists of remission induction strategies in order to achieve remission of the disease and remission maintenance strategies. Kidney transplantation should be considered as first option in AAV patients which are in remission more than one year.<sup>6</sup>

## History

In 1866, Kaussmal and Maier were the first to describe completely a case report of a 27-year old man with systemic vasculitis. The term polyarteritis nodosa (PN) was introduced to describe all the patients with noninfectious arteritis.<sup>1</sup> In 1923, a new distinct

entity from PN was described the so-called "microscopic form of periarteritis nodosa" characterized both by the presence of glomerulonephritis and non-granulomatous inflammation.<sup>7</sup> Later, a stretch correlation of "microscopic form of periarteritis nodosa" with Wegener's granulomatosis and Churg-Strauss syndrome now called granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis was described respectively.<sup>8</sup> In 1985, the term microscopic polyarteritis was replaced by the term microscopic polyangiitis.<sup>9</sup> After three years Jennete and Falk reported an association of the disease with ANCA.<sup>10</sup> In 1994 the Chapel Hill Consensus Conference (CHCC) introduced the term microscopic polyangiitis describing a small vessel vasculitis characterized by rapid progressive glomerulonephritis and pulmonary capillaritis with the absence of immune complex deposition on immunofluorescence.<sup>2</sup> Finally, according to 2012 revision of CHCC classification, MPA was reported as a pauci-immune small-vessel vasculitis with absence of granulomas or eosinophilia associated with myeloperoxidase (MPO-ANCA).<sup>11,12</sup>

## Epidemiology

An increased incidence has been reported especially in southern Europe.<sup>13</sup> The incidence of MPA is 2,7 to 94 per 1 million with a slight male predominance.<sup>14</sup> However, other data do not correlate the incidence of MPA with the latitude.<sup>1,15,16</sup> The average age of onset is between 50 and 60 years.<sup>13,17,18</sup>

## Pathogenesis

The aetiology of MPA is unknown. Environmental factors including silica exposure may be implicated in the pathogenesis but their exact role is obscure.<sup>19</sup> There is ongoing evidence that MPA is an autoimmune disease in which ANCA play a crucial role. In the majority of the cases MPO-ANCA has been detected but autoantibodies against Proteinase 3 (PR3) have also been reported in MPO patients.<sup>20</sup> Data from animal studies, reported that ANCA may activate (primed) neutrophils to produce reactive oxygen species and several

lytic enzymes resulting in endothelial detachment and lysis.<sup>21–23</sup> In accordance, passage of MPO-ANCA from mother to fetus may cause pulmonary hemorrhage and renal failure to newborn.<sup>24</sup> Interestingly, not all ANCA are pathogenic.<sup>25</sup> Paradoxically a subpopulation of patients which fulfill the criteria for ANCA associated vasculitis are negative for both MPO and PR3-ANCA.<sup>26,27</sup> In this regard, there are no differences in kidney lesions between patients with ANCA negative pauci immune vasculitis and ANCA positive patients.<sup>25</sup> Whereas, more severe renal lesions including glomerulosclerosis and interstitial fibrosis observed in ANCA negative and MPO-ANCA positive patients in comparison with PR3-ANCA patients.<sup>25</sup> Interestingly, overall mortality was the same between ANCA-positive and ANCA negative patients with vasculitis.<sup>27</sup> Additionally, it should be emphasized that some MPA patients are ANCA negative suggesting another pathogenetic mechanism different from the above. In support, rituximab is also effective in ANCA negative patients with vasculitis suggesting that there is an alternative pathogenetic mechanism different from this mediated by the production of ANCA by the B cells.<sup>28</sup>

There is evidence that for the development of MP a specific type of ANCA against specific epitopes is required.<sup>25</sup> Roth et al.<sup>29</sup> reported a total of 25 different epitopes of MPO-ANCA in patients with active disease, with remissions, ANCA-negative vasculitis and controls. Interestingly, 12 of these epitopes were correlated to active disease, while 8 epitopes were also identified in healthy subjects and for this reason were termed nature epitopes. Interestingly, there is an association of ANCA with different MHC class II genes suggesting a genetic predisposition.<sup>30</sup>

### Clinical manifestations

MPA is a systemic vasculitis indicating that several organs can be affected. Renal involvement occurs in the majority of the cases and it is manifested by microscopic haematuria, mild proteinuria, casts and deterioration of renal function due to rapidly progressive glomerulonephritis.<sup>31</sup> Notably, MPA may be restricted only to the kidney without other organ involvement. This rare condition is characterized as idiopathic necrotizing, crescentic glomerulonephritis. Pulmonary involvement occurs less frequently. MPA patients with lung involvement present dyspnea, cough and hemoptysis due to alveolar haemorrhage. Capillaritis with fibrinoid necrosis is the typical pathologic feature in MPO patients with lung involvement.<sup>31</sup> Of note, MPA is the most frequent cause of pulmonary-renal syndrome. Besides the general malaise and myalgias with arthralgias, skin involvement including purpura, livedo reticularis, nodules, urticaria and skin ulcers may be the initial presenting signs.<sup>31</sup> Gastrointestinal manifestations consist of abdominal pain and bleeding. Neurological involvement is common.<sup>30</sup> Peripheral neuropathy (mononeuritis-symmetrical polyneuropathy) is the predominant manifestation while involvement of the central nervous system has also been reported.<sup>31</sup> Ear nose and throat manifestations are less frequent in MPA patients.<sup>31</sup>

### Diagnosis

At present, there is no specific diagnostic tool for MPA. Diagnosis should be based on clinical symptoms and signs from various systems affected and on pathological feature. Nonspecific markers of inflammation including leucocytosis, increased sedimentation velocity, increased PCR and normocytic anaemia are indicative but not diagnostic for MPA disease. The absence of ANCA does not exclude the diagnosis. Pathological feature of pauci-immune necrotizing small-vessel vasculitis in biopsy, confirms the diagnosis of MPA. The absence of granulomatous inflammation differentiates MPA from GPA.<sup>32</sup>

### Prognosis

The prognosis of MPA is poor without treatment (annual mortality rate above 90%). Interestingly, the introduction of aggressive immunosuppressive drugs has substantially improved the prognosis.<sup>2</sup> More specifically, the cumulative survival of MPA patients with renal involvement at 1 and 5 years was 82% and 76% respectively.<sup>5</sup> ESRD observed in 28% of MPA patients. Risk factors for ESRD were serum creatinine at the time of the diagnosis, African American race and severity of histological lesions at biopsy.<sup>5</sup> The mortality in ESRD patients due to MPA was around 50% the prognosis was worse in patients with pulmo-renal syndrome.<sup>33,34</sup> Death occurring during the first year of MPA immunosuppressive treatment was related primary to insufficient treatment response, several infections, cardiovascular disease and malignancy.<sup>4</sup> Disease relapse occurred in 35% of MPA patients.<sup>5</sup>

### Treatment

Induction treatment consists of immunosuppressant's including cyclophosphamide (2mg/kg/day for 3-6 months) plus corticosteroids (1mg/kg/day) with tapering reviewed in.<sup>31</sup> In more severe cases can precede the use of methylprednisolone iv (500mg or 1 gr 3 times). Intravenous pulse cyclophosphamide (15mg/kg) is also effective compared to oral treatment with lesser side effects. In more severe cases, with renal failure and lung involvement plasma exchange is indicated (seven exchanges over 2 weeks) reviewed in.<sup>31</sup> Use of plasma infusion is limited to patients with relapse or to those resistant to immunosuppression treatment.<sup>7</sup> The long term effect of plasmapheresis on patients' outcome is unknown. Whether duration of plasma exchange therapy should be tailored to ANCA titers has not been yet studied.

Once remission (absence of clinical manifestations of GN) has been obtained, maintenance therapy with Azathioprine (AZA) (2mg/kg/day) for 12 months should be added. Mycophenolate mofetil (MMF) is an alternative but it is less effective than AZA reviewed in.<sup>31</sup> Rituximab (anti-CD20) (375mg/m<sup>2</sup> once weekly for 4 weeks) plus corticosteroids per os even without maintenance treatment has been proposed as an alternative to immunosuppressants (cyclophosphamide switched to AZA as maintenance therapy) for induction of remission in severe cases with renal involvement and in patients which do not respond to immunosuppression reviewed in.<sup>31</sup> Moreover, Rituximab could be considered as another effective option for the relapses. However, the long-term toxicity of Rituximab should be elucidated by further studies.

### Renal transplantation

Despite the major advances in the treatment of MPA, a large number of patients with MPA develop end stage renal disease (ESRD).<sup>35</sup> AAV patients with ESRD on dialysis have a worse prognosis compared to those without dialysis independent renal function.<sup>36</sup> However, the overall mortality of AAV patients on dialysis is similar to those non-diabetic patients on dialysis.<sup>37–39</sup> Renal transplantation (RTx) is the first choice of treatment in these patients. According to Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines for Glomerulonephritis.<sup>6</sup> RTx is another therapeutic option in AAV patients with more than one year of disease remission.<sup>6</sup> Of note, the definition of the remission is not widely acceptable by all but usually it requires the absence of systemic clinical symptoms. In addition, ANCA positivity at the time of RTx should not be considered as a contraindication.<sup>35</sup> The risk of relapse is present but usually it decreases after RTx due to the more efficient anti-rejection therapy

and the use of the immunosuppressant's.<sup>40,41</sup> The treatment for disease relapses after transplantation in AAV patients does not differ from that of non kidney transplanted AAV patients raising the increase dose of corticosteroids to plasma exchange therapy based on the severity of the disease.<sup>41,42</sup> Notably the use of cyclophosphamide remains also the gold standard and it has been successfully used in disease relapses after RTx. Rituximab could be considered as an alternative option to treat relapses after kidney transplantation.<sup>43,44</sup>

## Conclusion

- i. Microscopic polyangiitis is a systemic idiopathic autoimmune disease involving small-calibre blood vessels.
- ii. ANCA's under certain circumstances are pathogenic.
- iii. Multiple organs are affected but predominantly kidneys and lungs are involved. Kidney involvement is characterized by rapidly progressive glomerulonephritis whereas diffuse alveolar haemorrhage due to capillaritis is the main pulmonary manifestation.
- iv. The diagnosis is based on clinical symptoms and ANCA's detection but tissue biopsy is the gold standard.
- v. Older age, females, serum creatinine at diagnosis, chronic lesions and crescents at renal biopsy and response to therapy and flares are predictive factors for kidney function.
- vi. The choice of therapy should be based on disease severity. Treatment strategies include cyclophosphamide with corticosteroids as therapy induction and Azathioprine as a remission maintenance therapy. However, Rituximab should be considered as an alternative therapy for patients who do not respond to immunosuppressant's and for disease relapses.
- vii. Kidney transplantation is safe and effective and has a good prognosis in AAV patients with ESRD.

## Acknowledgements

None.

## Conflicts of interest

All authors declared there are no conflicts of interest.

## Funding

None.

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