

Microscopic polyangiitis¹

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Abstract

Microscopic polyangiitis (MPA) refers to a necrotizing systemic vasculitis with few or no immune deposits that affects small vessels (ie, capillaries, venules and arterioles). Arteries, especially small arteries, are often but not always involved. Vessels of any type in any organ can be affected, resulting in a wide variety of signs and symptoms, and nonspecific clinical manifestations. Common signs and symptoms include nephritis, pulmonary hemorrhage, purpura, peripheral neuropathy, abdominal pain, myalgias and arthralgias. MPA is the most common antineutrophil cytoplasmic autoantibodies (ANCA)-associated small-vessel vasculitis. Most patients have positive myeloperoxidase MPOANCA (PANCA), although proteinase 3 PR3 ANCA (CANCA) may be also present. MPA has an incidence of approximately 1:100,000 with a slight predominance in men, and a mean age of onset of about 50 years. Treatment of patients with MPA consists of three phases: induction of remission, maintenance of remission, and treatment of relapse. Current induction therapy often consists of cyclophosphamide and corticosteroids.

Keywords

Microscopic polyangiitis, small-vessel vasculitis, antineutrophil cytoplasmic autoantibodies (ANCA), corticosteroid, cyclophosphamide.

Disease name

Microscopic polyangiitis (MPA)

Microscopic polyarteritis

Microscopic polyangiitis is a more appropriate name than microscopic polyarteritis because some patients show no evidence for arterial involvement.

Definition

Classification of systemic vasculitis

Vasculitis is an inflammation of vessel walls. It has many causes, although they result in only a

few histological patterns of vascular inflammation. Small-vessel vasculitis is defined as a vasculitis affecting vessels smaller than arteries, such as arterioles, venules and capillaries.

There is no widely accepted classification of primary vasculitis, although a working framework has been provided by a consensus reached by the leading investigators at a meeting in Chapel Hill, North Carolina in 1995. Systemic vasculitides form a heterogeneous group of

vascular inflammatory diseases that can be subdivided on the basis of the underlying histopathology, the type of vessels involved, the target organs involved, and the resulting clinical picture (table 1).

Table 1: The Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis

Large Vessel Vasculitis
Giant-cell arteritis – granulomatous arteritis of the aorta and its major branches, especially the extracranial branches of the carotid artery; usually in patients over 50 years old and associated with polymyalgia rheumatica.
Takayasu arteritis – granulomatous inflammation of the aorta and its major branches usually in patients <50 years old.
Medium Vessel Vasculitis
Polyarteritis Nodosa – necrotizing inflammation of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.
Kawasaki's Disease – arteritis of large, medium, and small arteries associated with the mucocutaneous lymph node syndrome, often involves the coronaries, usually occurs in children
Small Vessel Vasculitis
Wegener's granulomatosis
Churg-Strauss syndrome
Microscopic polyangiitis
Henoch-Schonlein purpura
Cryoglobulinemic vasculitis
Cutaneous Leukocytoclastic Vasculitis

Microscopic Polyangiitis

MPA is a necrotizing systemic vasculitis with few or no immune deposits that affects small vessels (*ie*, capillaries, venules and arterioles), although it occasionally involves medium-sized arteries.

MPA belongs to a category of vasculitis that also includes [Wegener's granulomatosis](#) (WG), Churg-Strauss syndrome (CSS), Henoch-Schönlein purpura, cryoglobulinemic vasculitis and others necrotizing polyangiitides.

MPA is the most common antineutrophil cytoplasmic autoantibodies (ANCA)-associated small-vessel vasculitis, and is characterized by

the presence of ANCA and few or no immune deposits in the involved vessels. The kidneys are the most commonly affected organs and are involved in 90% of patients who have this type of vasculitis. Patients often present with variable combinations of renal manifestations, palpable purpura, abdominal pain, cough, and hemoptysis. Most patients have positive myeloperoxidase MPOANCA (PANCA), although proteinase 3 PR3 ANCA (CANCA) may be also present.

Differential diagnosis

In recent years there has been substantial progress in identifying attributes of specific types of vasculitis, thus enabling accurate diagnosis.

MPA must be differentiated not only from other forms of small-vessel vasculitis, but also from medium-sized vessel vasculitis, such as polyarteritis nodosa and [Kawasaki disease](#).

MPA may cause a necrotizing arteritis that is histologically identical to that caused by polyarteritis nodosa (PAN). Clinical, epidemiological and pathological differences enable differentiation between MPA and PAN, as capillaries and venules are affected in MPA but not in PAN.

The absence or paucity of immunoglobulin localization in vessel walls helps distinguish MPA from immune complex-mediated small vessel vasculitis, such as Henoch-Schönlein purpura and cryoglobulinemic vasculitis.

The vasculitis in patients with MPA is pathologically indistinguishable from the vasculitis of WG and CSS. Granulomatous inflammation distinguishes WG from MPA. Asthma and eosinophilia distinguish CSS from MP.

MP, WG and CSS are all associated with circulating ANCA (table 2).

Table 2: Features that allow differentiation of microscopic polyangiitis from several other forms of small-vessel vasculitis

	Henoch-Schonlein Purpura	Cryoglobulinemic Vasculitis	Microscopic Polyangiitis	Wegener's Granulomatosis	Churg-Strauss Syndrome
Small-vessel vasculitis signs and symptoms	Yes	Yes	Yes	Yes	Yes
IgA-dominant immune deposits	Yes	No	No	No	No
Cryoglobulins in blood and vessels	No	Yes	No	No	No
ANCA in blood	No	No	Yes	Yes	Yes
Necrotizing granulomas	No	No	No	Yes	Yes
Asthma and eosinophilia	No	No	No	No	Yes

If a patient has systemic pauci-immune small-vessel vasculitis with no evidence for granulomatous inflammation, or asthma, the appropriate diagnosis is MPA

The diagnosis of MPA is essentially made by exclusion of other diseases, which is always a difficult task.

Frequency

MPA has an incidence of approximately 1:100,000, with a slight predominance in men, and a mean age at onset of about 50 years, although any age can be affected

Clinical manifestation

Vessels of any type in any organ can be affected, resulting in a wide variety of signs and symptoms, and nonspecific clinical manifestations. Common signs and symptoms include nephritis, pulmonary hemorrhage, purpura, peripheral neuropathy, abdominal pain, myalgias and arthralgias.

Constitutional signs and symptoms such as fever, arthralgias, myalgias, and "flu-like" symptoms are often present early in the disease. Arthralgias tend to be migratory, affect large and small joints with evidence of synovitis in 10-20%.

Blood vessels in the skin, lungs, kidneys, gut, nerves, and skeletal muscles are often involved but vary between the different patients. MPA may cause pulmonary-renal syndrome.

Skin: the most common cutaneous lesion is leukocytoclastic angiitis, which typically causes purpura and ulcerations; other lesions include erythematous tender nodules, focal necrosis, and livedo reticularis.

Peripheral neuropathy: mononeuritis multiplex is the most common neurological manifestation of MPA; this is caused by inflammation of epineural arterioles leading to ischemia of both sensory and motor nerves.

Gastrointestinal tract: inflammation of visceral blood vessels causes pain and elevated levels of tissue enzymes; gut ischemia causes abdominal

pain as well as bloody stools, and possible intussusception, perforation, and pancreatitis.

Respiratory tract: pulmonary manifestations range from fleeting focal infiltrates to massive pulmonary hemorrhage and hemoptysis secondary to alveolar capillaritis.

Histologic Findings

The basic acute vascular lesion of MPA is segmental vascular necrosis with infiltration of neutrophils and monocytes, often accompanied by leukocytoclasia and accumulation of fibrin.

MPA may cause necrotizing arteritis that is histologically identical to that caused by PAN. According to the Chapel Hill consensus conference on the classification of vasculitis, PAN and MPA can be distinguished pathologically by the absence of vasculitis in vessels other than arteries in patients with PAN, and the presence of vasculitis in vessels smaller than arteries, such as arterioles, venules, and capillaries, in patients with MPA.

The glomerulonephritis in MPA is characterized by focal necrosis, crescent formation, and the absence or paucity of immunoglobulin deposits.

Pulmonary manifestations consist of pulmonary alveolar capillaritis. Biopsy of the muscle and peripheral nerves may reveal necrotizing vasculitis epineural arteries.

The most common cutaneous lesion is leukocytoclastic angiitis affecting dermal venules. Necrotizing dermal arteritis also occurs.

Diagnostic methods

In patients with pauci-immune small vessel vasculitis, (MPA, WG, CSS), the 2 major antigen specificities are for myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA. These autoantibodies usually are detected by enzyme

immunoassays (EIA), using purified MPO and PR3 as substrate. ANCA also can be detected by indirect immunofluorescence microscopy (IFA). However, IFA without confirmatory EIA is not recommended because of the increased numbers of false-positive results with IFA. When alcohol-fixed neutrophils are used as substrate for IFA, PR3-ANCA usually causes cytoplasmic staining (C-ANCA), whereas perinuclear staining (P-ANCA) is usually associated with MPO-ANCA.

Laboratory Studies

Hematology lab studies

Leukocytosis

Anemia (normocytic anemia)

Elevated erythrocyte sedimentation rate (ESR)

Renal tests

Elevated serum BUN (blood urea nitrogen) and creatinine (70%)

Abnormal urine sediment

Proteinuria (80%)

Hematuria (67%)

Leukocyturia (44%)

Erythrocyte casts

Antineutrophil cytoplasmic antibodies

ANCA positive (80%)

Perinuclear ANCA related to myeloperoxidase

ANCA (60%)

Cytoplasmic ANCA related to proteinase-3

ANCA (40%)

Blood cultures to rule out bacterial endocarditis

Imaging Studies

Chest radiographs show diffuse parenchymal infiltrates secondary to pulmonary alveolar capillaritis and hemorrhage; other imaging studies are indicated for the complications of the disease and specific organ system involvement, such as abdominal CT scan for pancreatitis or mesenteric angiography to differentiate from MPA from PAN.

Other Tests

Ordered according to the specific organ system involved.

Electrocardiography is indicated for myocardial infarction, pericarditis, and congestive heart failure.

Gastrointestinal endoscopy in case of gastrointestinal bleeding.

Electromyography (EMG) in case of clinical evidence of neuropathy.

Biopsies

Skin biopsy if skin is involved

Open lung biopsy

Renal biopsy to help diagnose crescentic glomerulonephritis

Sural nerve biopsy if EMG results are consistent with sural nerve involvement

Treatment

Tremendous therapeutic advances have been made in recent years in the treatment of systemic necrotizing vasculitides, which are usually fatal if untreated. The primary aim of the treatment is to induce rapid remission with high drug doses at the expense of short-term toxicity. The next step is to taper the drug doses or switch to safer drugs, and maintain a low-dose therapy for a prolonged period to prevent disease relapse. Current outcome studies show a relatively high mortality despite treatment, especially in the elderly and in those with renal involvement.

Survivors may suffer relapsing disease and chronic morbidity due to vasculitic damage and the long-term consequences of immunosuppression.

The treatment should not be delayed until the diagnosis of MPA versus WG or CSS is made because all of these diseases warrant aggressive immunosuppressive therapy when there is active damage of major organ such as glomerulonephritis or pulmonary hemorrhage.

Treatment of patients with MPA includes three phases: (1) induction of remission, (2) maintenance of remission, and (3) treatment of relapse. Current induction therapy often consists of cyclophosphamide and corticosteroids. For aggressive disease, use of high-dose intravenous methylprednisolone for three days is recommended, combined with intravenous or oral cyclophosphamide. Tapering doses of prednisone should follow, along with cyclophosphamide maintenance for 12 to 18 months. The lowest dosage of steroids sufficient to control the disease should be used, and infection should be considered if the symptoms appear to exacerbate. For patients in sustained remission at 12 months, the use of all medications may be gradually discontinued. Patients whose symptoms are under good control must, nevertheless, be closely followed at six-month intervals for signs and symptoms of relapse. During treatment with these agents, complete blood counts and liver function tests should be performed periodically.

Other treatment regimens that may be of benefit include methotrexate, azathioprine, trimethoprim-sulfamethoxazole, plasma exchange, cyclosporine, intravenous immunoglobulin, and monoclonal antibodies.

During the use of potentially ulcerogenic immunosuppressive therapy, patients may be given H₂-blockers or proton-pump inhibitors. Prophylactic treatment with fluconazole orally for fungal infection may be considered, as well as trimethoprim-sulfamethoxazole (480 mg), three times weekly, for prophylactic treatment of patients with *Pneumocystis carinii* prophylaxis.

Unresolved questions

There are no agreement upon diagnostic criteria for small vessel vasculitis. The American College of Rheumatology published a classification approach in 1990 for use in clinical trials, but not for diagnosis; in 1994 the Chapel Hill International Consensus Conference proposed names and definitions for various vasculitides but no diagnostic criteria were suggested.

There are no clear therapeutic guidelines in the treatment of systemic necrotizing vasculitides.

There is incomplete knowledge of immunoregulatory defects and poor understanding of genetic / epidemiologic / environmental risk factors.

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