Granulomatous Vasculitis

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KEYWORDS

• Granulomatosis with polyangiitis • Eosinophilic granulomatosis with polyangiitis
• Microscopic polyangiitis • Polyarteritis nodosa • Cutaneous polyarteritis nodosa

KEY POINTS

- Systemic vasculitides are a group of disorders characterized by inflammation of the blood vessels.
- Granulomatosis with polyangiitis (GPA) is characterized by granulomatous inflammation of upper and lower airways, and by vasculitis of small and medium vessels, of which glomerulonephritis is common.
- Glomerulonephritis and lung hemorrhage are common manifestations of microscopic polyangiitis (MPA).
- The common presentations of polyarteritis nodosa (PAN) are in form of constitutional symptoms, with gastrointestinal (GI), nervous system, and cardiac involvement.
- Treatment is in form of immunosuppression and depends on the type of clinical presentation.

INTRODUCTION

Vasculitic disorders are characterized by inflammation of the blood vessels, which can either result in ischemia/infarction due to partial or total occlusion of the involved blood vessels, or cause hemorrhage due to the rupture of weakened vessel wall. The clinical manifestations depend on the size, type, and site of the blood vessels involved. These disorders may be primary, which in most cases are idiopathic, or secondary to other causes such as infections, connective tissue diseases, drugs, or hypersensitive disorders.

NOMENCLATURE AND CLASSIFICATION SYSTEM OF VASCULITIS

There have been various classification and nomenclature systems of vasculitis. Although it was Kussumaul and Maier who gave the first detailed clinical and pathologic report of systemic arteritis involving the medium and small vessels in 1866, it was Parla Zeek who made the first attempt to classify vasculitis, when she described 5 distinct vasculitides from the literature review.[1] In 1990, criteria for 7 types of systemic vasculitis were published by the American College of Rheumatology (ACR). These criteria were based on patient data from 48 centers, and the basis of diagnosis of each type was expert opinion.[2–8] These criteria had their limitations in the form of failure to include/identify MPA as a separate entity, lack of application of antinuclear cytoplasmic antibodies (ANCA), and the use of physician opinion as diagnostic gold standard.[9] The most widely cited nomenclature system is the Chapel Hill Consensus Conference (CHCC) system, which proposed the names and definitions of common systemic vasculitides in 1994.[10] This

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nomenclature system was revised in 2012.[11] Among the changes that have been incorporated in the revised nomenclature include division of small-vessel vasculitis into categories of ANCA-associated vasculitis (AAV) and immune complex vasculitis, replacing Wegener granulomatosis with GPA, and replacing Churg-Strauss syndrome with eosinophilic granulomatosis with polyangiitis (EGPA). There have been attempts to classify the vasculitides based on their histopathologic manifestations, especially the division into granulomatous and nongranulomatous vasculitis among small-, medium- and large-vessel vasculitis. Savage and colleagues[12] tried to simplify it by incorporating the histopathologic element of granuloma formation (**Table 1**).

This review discusses the etiopathogenesis, clinical manifestations, and treatment of AAVs, namely, GPA; EGPA; MPA, which is a nongranulomatous small-vessel AAV, which shares clinical manifestation with GPA and EGPA; classic PAN, a nongranulomatous medium-vessel vasculitis and Cutaneous PAN.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY–ASSOCIATED VASCULITIDES

AAVs comprise 3 conditions, namely, GPA, EGPA, and MPA. They share a common feature in the form of ANCA positivity and have been clubbed together in the revised CHCC 2012. ANCA comprise a heterogeneous group of antibodies. These antibodies are usually detected by indirect immunofluorescence (IIF) or enzyme-linked immunosorbent assay (ELISA). Three patterns are observed on IIF, namely, cytoplasmic ANCA or cANCA, perinuclear ANCA or pANCA, and atypical ANCA or aANCA. It is recommended to use both the techniques for detection of ANCA.

ETIOPATHOGENESIS

The environmental factors may have a role in the disease pathogenesis. This is supported by variation in geographical distribution, relationship with exposure to silica, hydrocarbons and various drugs.[13] Infections such as *Staphylococcus aureus* have often been noted to precede the onset or flares of AAV, with decreased relapse rates reported after use of cotrimoxazole. Discovery of anti–lysosomal associated membrane protein 2 (LAMP2) antibodies in sera of patients with focal necrotizing glomerulonephritis defined the link between infection and AAV more clearly. Similar disease could be induced in animal models after immunizing with LAMP2.[14] Genetic associations, both human leukocyte antigen (HLA) and non-HLA, have been studied in various populations; these include, but are not restricted to, association of HLA-DRB1*04, DPB1*0401, PRTN3 (A546G poly), AAT polymorphisms (SERPINA1) with GPA, HLA-DRB4 with EGPA, and HLA-DRB1*0901 with MPA. There is unconfirmed or conflicting association with IL2RA, IL-10, LILRA2, CD226, and FCRIIIb.[15–23]

Distinct genetic association of HLA-DP, SERPINA1, and PRTN3 with anti-proteinase 3 (PR3) and HLA-DQ with anti-myeloperoxidase (MPO) ANCA has been shown in the genome wide association study (GVAS) study.[24] These results suggest that the future classification of AAV may be

Table 1
Classification of vasculitis based on histopathologic feature of granuloma formation

	Large-Vessel Vasculitis	Medium-Vessel Vasculitis	Small-Vessel Vasculitis
Granulomatous inflammation	Temporal arteritis Takayasu arteritis		Granulomatosis with polyangiitis[a] Eosinophilic granulomatosis with polyangiitis[b]
Nongranulomatous inflammation		Classic polyarteritis nodosa Kawasaki disease	Microscopic polyangiitis IgA vasculitis[c] Essential cryoglobulinemic vasculitis Cutaneous leucocytoclastic vasculitis

[a] Previously known as Wegener granulomatosis.
[b] Previously known as Churg-Strauss syndrome.
[c] Previously known as Henoch-Schönlein purpura.
Adapted from Savage CO, Harper L, Adu D. Primary systemic vasculitis. Lancet 1997;349:553–8; with permission.