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Diagnosis and classification of granulomatosis with polyangiitis (aka Wegener's granulomatosis)

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ABSTRACT

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's Granulomatosis) is an autoimmune small vessel vasculitis which is highly associated with anti-neutrophil cytoplasmic antibodies (ANCA). The hallmarks of this condition are systemic necrotising vasculitis, necrotising granulomatous inflammation, and necrotising glomerulonephritis. The aetiology of granulomatosis with polyangiitis is linked to environmental and infectious triggers inciting onset of disease in genetically predisposed individuals. Anti-neutrophil cytoplasmic antibodies are pathogenic and play an important role in the pathogenesis of this disease, although ANCA positivity is not essential for a clinical diagnosis of granulomatosis with polyangiitis. Granulomatosis with polyangiitis is diagnosed based on clinical manifestations of systemic vasculitis and histological evidence of necrotising vasculitis or granulomatous inflammation. This small vessel vasculitis may present as limited disease of the ears, nose and upper airways or mild, moderate or severe systemic disease. Immunosuppression and adjuvant therapies have contributed to the improved prognosis of granulomatosis with polyangiitis over the past decades. Treatment strategies are tailored to the severity of the disease. They are based on published evidence of the efficacy and safety of the immunosuppressive drugs indicated to manage active vasculitis and maintain clinical remission. This review will summarise the history, aetiology, pathogenesis, classification, diagnosis and management of granulomatosis with polyangiitis.

1. Introduction

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's Granulomatosis) is an autoimmune small vessel vasculitis which is highly associated with anti-neutrophil cytoplasmic antibodies (ANCA) and has clinical manifestations which include systemic necrotising vasculitis, necrotising granulomatous inflammation, and necrotising glomerulonephritis. It was first described in the medical literature in a clinical case report in the late 19th century and was formerly known by the eponymous name, Wegener's Granulomatosis, after Friedrich Wegener who described the clinical triad associated with this disease in 1936. The use of disease-descriptive, aetiology based nomenclature is now recommended and preferable to the use of eponymous names, therefore since 2011 Wegener's Granulomatosis has been known as granulomatosis with polyangiitis (abbreviated to GPA). This was recommended by the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) and American Society of Nephrology (ASN) and is the name which should be used in clinical practice and medical literature for the ANCA-associated vasculitis, formerly known as Wegener's Granulomatosis [1].

2. Epidemiology

The annual incidence of GPA is 5–10 cases per million population with equal frequency in males and females [2]. GPA is very rare in childhood and young adults. The reported peak incidence of GPA is in the 7th decade of life between the ages of 65 and 70 years [3]. The published point prevalence of GPA ranges between 24 and 157 cases per million with a distinctly higher prevalence of GPA amongst Caucasians, especially those from Northern Europe, compared to Asian, African, Afro-Caribbean and African-American populations [2–4].

3. Aetiology

The aetiology of GPA may originate from infectious, environmental, chemical, toxic or pharmacological triggers in people who are genetically predisposed to this autoimmune disease [2].

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3.1. Infectious triggers

Infectious triggers include bacterial, mycobacterial, fungal or viral infections of the ears, nose and respiratory tract. *Staphylococcus aureus* nasal carriage is a common trigger of GPA flares.

3.2. Environmental triggers

Environmental triggers which may contribute to the onset of GPA are pollution, smoking, inhaled toxins, inhaled chemicals and exposure to metals, such as mercury or lead [4].

3.3. Drug-induced ANCA-associated vasculitis

Drug induced ANCA-associated vasculitis differs from primary ANCA-associated vasculitis and coincides with the initiation of a drug. It usually subsides with discontinuation of the offending drug, however in genetically predisposed people it may be the inciting event to the onset of GPA. Examples of drugs known to trigger drug-induced ANCA-vasculitis are antibiotics: cefotaxime, minocycline; anti-thyroid medication: benzylthiouracil, carbimazole, methimazole, prophythiouracil; anti-tumour necrosis factor alpha agents: adalimumab, etanercept, infliximab; psychoactive drugs: clozapine, thioridazine; other drugs: allopurinol, cocaine, D-penicillamine, hydralazine, levamisole, phenytoin and sulfasalazine [5].

3.4. Genetics

Genetic predisposition to ANCA associated vasculitis has been studied and familial association studies report a 1.56 increased relative risk of developing GPA in people who have a first degree relative with GPA [4].

There is an increased susceptibility to proteinase-3 ANCA associated vasculitis with certain genetic variants. MHC class II HLA-DP1*0401 has a strong association with PR3-AAV GPA; MHC class II HLA-DRB1*15 genotype in African-Americans is associated with a 36× increased risk of PR3-AAV and MHC class II HLADRB*1501 allele in Caucasians is associated with a 73× increased risk of PR3-AAV [4]. Single nucleotide polymorphisms (SNPs) in certain genes may predispose to GPA. A SNP in *SERPINA1*, a gene which encodes for α_1-antitrypsin, which is a neutral serine protease inhibitor of the proteinase 3 enzyme, is linked to GPA and a SNP in *PRTN3*, a gene which encodes proteinase 3 is also associated with GPA [4]. *CTLA-4* gene polymorphism is linked to the development of GPA because the action of T lymphocytes is inhibited due to defective binding of CTLA-4, expressed mainly on CD4+ T lymphocytes, to CD80 and CD86 on antigen presenting cells (APCs) [4,6].

4. Pathogenesis

The immunopathogenesis of GPA is complex and involves the generation of ANCA against proteinase 3 (PR3) in approximately 80% of GPA patients and against myeloperoxidase (MPO) in approximately 10% of GPA patients [4]. Antibodies against lysosome associated membrane protein-2 (LAMP-2) may also play a role in the pathogenesis of GPA via a process of molecular mimicry [4].

At present, the immunopathogenesis of GPA is thought to stem from environmental or infectious triggers in a genetically predisposed individual who lacks tolerance to ANCA self-antigens. The noxious triggers lead to an inflammatory response with secretion of pro-inflammatory cytokines and ANCA production in genetically predisposed individuals. *Staphylococcus aureus* is a common micro-organism implicated in the pathogenesis of GPA and the recurring, relapsing nature of the disease may be linked to persistent colonisation of nasal passages with this organism. *Staphylococcus aureus* produces super-antigens which activate B and T cells, and via a process of molecular mimicry *Staphylococcus aureus* can also induce AAV [4].

Patients with GPA generally have elevated B lymphocyte stimulator factors, such as B cell activation factor (BAFF) and a relative abundance of T follicular helper cells (TFH) compared to healthy individuals [7,8]. This could explain the increased frequency of self-reactive B lymphocytes in GPA patients. These self-reactive B lymphocytes may mature into long-lived plasma cells which secrete ANCA, the pathogenic antibody associated with GPA, which binds to proteinase 3 on neutrophil and monocyte surfaces. In the presence of ANCA, neutrophils and monocytes generate and release reactive oxygen species, proteases, cytokines and neutrophil extracellular trap products (NET-derived products) are generated [4]. Dendritic cells can be activated by NET-derived products through toll-like receptors (TLR) and the release of interferon-alpha (IFN-α) impairs T regulatory cell function [4]. Activation of the alternative complement pathway, results in the formation of the membrane attack complex (C5b6789 MAC) which promotes ANCA associated neutrophil activation, inflammation and tissue damage [4].

These pro-inflammatory pathways lead to the development of necrotising systemic vasculitis, necrotising glomerulonephritis and granulomatous inflammation predominantly of the airways, which are hallmarks of GPA.

5. Clinical manifestations of GPA

Patients with clinically active granulomatosis with polyangiitis may present with constitutional symptoms of disease such as general malaise, myalgia, arthralgia, anorexia, weight loss and pyrexia.

Cutaneous signs such as leucocytoclastic vasculitis, digital infarcts, purpura, cutaneous ulcers and gangrene occur in GPA, however they are non-specific manifestations of systemic vasculitis which contribute to a clinical diagnosis of GPA and are not pathognomonic [9].

Mucocutaneous and orbital manifestations of active GPA include oral ulcers, oral granulomatous lesions, episcleritis, scleritis, conjunctivitis, keratitis, uveitis, retinal vasculitis, retinal arterial or venous thrombosis, retinal exudates, retinal haemorrhages, blurred vision, blindness, proptosis and orbital granulomatous masses [10].

Ear, nose and upper airway clinical manifestations are common amongst GPA patients. Sensorineural hearing loss and conductive hearing loss result in auditory morbidity. Nasal signs of active GPA include persistent, recurrent nasal discharges, blood-stained nasal discharge, epistaxis, nasal crusting, nasal ulceration, nasal bridge collapse, nasal granulomatous lesions, parasinus and sinus inflammation, with associated regional tenderness [11]. Upper airway obstructive disease occurs in the form of subglottic or tracheal stenosis [11]. Lower respiratory tract manifestations of active GPA include cough, breathlessness, stridor, wheeze, small airway obstruction, pulmonary nodules, cavitating lung lesions, pleuritis, pleural effusions, pulmonary infiltrates, pulmonary haemorrhage, due to alveolar capillaritis and respiratory failure [12].

Cardiovascular GPA clinically presents as small vessel vasculitis, occlusive vascular disease, pericarditis, pericardial effusions, cardiomyopathy, valvular heart disease, ischaemic hear disease and heart failure [11].

Gastrointestinal GPA manifests as an acute abdomen secondary to peritonitis or bowel ischaemia which may be secondary to mesenteric vasculitis [13].

Renal GPA is a diffuse pauci-immune crescentic necrotising glomerulonephritis which can be clinically suspected if the patient has haematuria, proteinuria, cellular casts on urine cytology, and