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Wegener's Granulomatosis

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1. Introduction

Wegener's granulomatosis (WG) is a rare multisystemic autoimmune disease of unknown aetiology, characterized by necrotizing granulomatous inflammatory and pauci-immune vasculitis in small- and medium-sized blood vessels (capillaries, venules, arterioles and arteries) associated with antineutrophil cytoplasmic antibodies ($ANCA_S$) directed against proteinase 3 (PR3), a neutrophil serine protease, presented in primary azurophil granules of polymorphonuclear neutrophils (PMN) and lysosomes of monocytes. It typically produces granulomatous inflammation of the upper and lower respiratory tracts, and a segmental necrotizing glomerulonephritis (classic triad of disease), although any organ can be involved.

2. History and epidemiology

In 1897, Peter McBride described the first patient with this condition. Later, in 1931, Klinger [(1)] reported a case of this disease, a 70-year-old physician with constitutional symptoms, inflammation of the upper respiratory tract leading to saddle nose deformity, glomerulonephritis and pulmonary lesions. In 1936, the German pathologist, Friedrich Wegener [(2)] published three cases with similar clinical features. Goodman and Churg, in 1954, described a triad of pathological features of the disease: 1) systemic necrotizing angiitis, 2) necrotizing granulomatous inflammation of the respiratory tract, and 3) necrotizing glomerulonephritis.
WG is an uncommon disease with an estimated prevalence, in the United States, of 3 per 100,000 [(3)]. The incidence and prevalence of WG in the United Kingdom is estimated at 10,2 cases and 250 cases per million population, respectively. It is extremely rare in blacks compared with whites; the male-to-female ratio is 1:1 and, although the disease can be seen at any age, the mean age of diagnosis is 40 years [(3, 4)].

3. Pathology and pathogenesis

The histopathologic characteristics of WG are necrotizing vasculitis of small- and medium-sized blood vessels with granuloma formation, with an important triad of granulomatous inflammation, vasculitis and necrosis.
Lung biopsy shows the typical necrotizing granulomatous vasculitis, almost always with multiple and bilateral nodules (50% are cavitated) or diffuse infiltrates, composed of neutrophils, lymphocytes, plasma cells, histiocytes and eosinophils.

Upper respiratory tract tissue reveals acute and chronic inflammation, necrosis and granulomatous lesions, with or without vasculitis [4], being the triad of pathological features present in only about 15% of cases.

Renal involvement is manifested by segmental and focal necrotizing glomerulonephritis, often with crescents and mononuclear tubulointerstitial infiltrates, without evidence of immune complex deposition (pauci-immune on immunofluorescence or electron microscopy). However granulomas are infrequently found in renal biopsy specimens [5].

The immunopathogenesis of this disease is still unclear, although the knowledge has suffered substantial progress in recent years, with both cellular and humoral immunity thought to be involved. Also, genetic background and environmental factors may play an important role in WG.

Autoimmune responses to PR3 (Wegener autoantigen) plays a central role in disease development, according to in vitro and in vivo experimental data [6]. Activated PMNs release PR3, which interacts with dendritic cells and induces their maturation into antigen-presenting cells, able to induce an unbalanced Th1 response, and leading to granuloma formation [7]. Nowadays, the latter is accepted to be the place of ANCA production, essential to the onset of vasculitis, since PR3-ANCA activates PMNs and monocytes to develop a respiratory burst, adhere and migrate across the endothelium. The activated PMN and monocytes release pro-inflammatory mediators, such as TNF-α, IL-1, IL-8 [8]. This process is reinforced by activation of the alternative complement pathway [6]. The presence of ANCAs suggests the role of humoral autoimmunity (Figure 1).

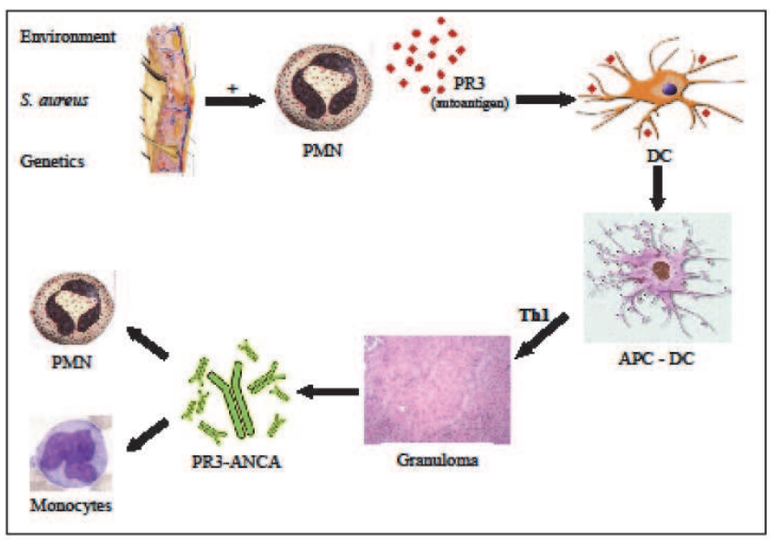

Fig. 1. Pathogenesis of WG. PMN: polymorphonuclear DC: Dentric cell; APC: Antigen-presenting cell

It is common to see WG progressing from a localized stage, restricted to the respiratory tract, to a systemic disease (generalized), and this transition may be influenced by a number of genetic risk factors. There is evidence that the human leukocyte antigen (HLA) system is involved both in WG development [9, 10], and other ANCA-positive vasculitides. Research is being carried out to confirm this association, for instance, to confirm the possible relation between WG and a region on chromosome 6p21.3 [11], although further investigation is needed. Indeed, this autoimmune disease is genetically associated with the class II region of the major

histocompatibility complex (MHC), such as HLA-DPB1*0401 allele [12, 13]. Similarly to other autoimmune diseases, the functional polymorphism, 620W, in the intracellular tyrosine phosphatase gene PTPN 22, is a predisposing factor for WG in the presence of ANCA. This is due to loss of function of the PTPN 22 protein, which is important in T-cell receptor (TCR) signaling, via inhibition of key molecules in the receptor pathway, resulting in activation and proliferation of T cells and, subsequently, in humoral alterations [14]. Another genetic risk factor for WG is the CTLA-4 (cytotoxic T-lymphocyte antigen 4) polymorphism [15].
Environmental exposure to solvents or silica, farming and living in northern latitudes has been associated to the development of this autoimmune disease [16].
The relationship between WG and infectious diseases was first described by Friedrich Wegener in 1936 in its original descriptions, when he proposed that infectious agents are implicated in the disease pathogenesis [17]. Chronic nasal carriage of *Staphylococcus aureus* (the frequency in a healthy population varies from 20-35%) has been associated with a higher relapse rate of WG, suggesting a role of these bacteria in its pathophysiology [18]. Several toxins of this pathogen stimulate B-cell and probably T-cell activity. Also, direct stimulation of neutrophils in vitro has been documented [19], with *Staphylococcus aureus* producing proteinases with activity against human proteinase inhibitors, like α_1-antiprotease, which is the main inhibitor of proteinase-3, resulting in persistent inflammatory activity [20]. Additionally, several reports have noted that antibiotic therapy with sulfamethoxazole-trimethoprim has been beneficial in the treatment of refractory or limited WG localized to the respiratory tract [21].

4. Clinical manifestations

WG has a spectrum of clinical presentations. While the disease is active, most patients have nonspecific symptoms and signs such as malaise, weakness, migratory arthralgias, anorexia, weight loss, night sweats and fever. It is important to exclude secondary infection when fever is present. These constitutional symptoms may last for weeks to months without evidence of specific organ involvement.
Ear, nose and throat (ENT) manifestations are frequent in WG [22]. Involvement of the upper airways occurs in 95% of the patients, being chronic sinusitis the most common initial complaint (67%). Other frequent manifestations include saddle nose deformity by collapse of nasal support with bone and cartilage destruction, subglottic tracheal stenosis (16%) causing stridor, rhinitis, epistaxis, oral and/or nasal ulcers, serous otitis media, otorrhea and hearing loss (conductive and neurosensorial) [23].
Lung involvement is also common and may be manifested as asymptomatic diffuse pulmonary infiltrates (71%), nodules, atelectasis, consolidation and/or pleural effusion or may be clinically expressed as cough (34%), hemoptysis (18%) due to bronchiectasis, cavitated pulmonary parenchymal lesions or diffuse alveolar hemorrhage (DAH), dyspnoea (7%), pleuritic pain and chest discomfort (8%) [24]. The development of pulmonary fibrosis and pulmonary arterial hypertension may also occur. Chest radiography and computerized tomography (CT) scan are important investigations that must be included in the workup of these patients.
WG can also be recognized as tumor-like masses outside the lung, being the breast and kidney the most common extra-thoracic locations, although such cases are rare [25].
Another typical complication is **renal disease**, which is present in 17% at initial diagnosis and in 77% throughout the course of the disease, manifesting itself with acute renal failure, hematuria, red blood cell casts and proteinuria.

Eye involvement (52%) is manifested as conjunctivitis, dacryocystitis, keratitis, uveitis, scleritis, optic nerve vasculitis, retinal artery occlusion, diplopia and proptosis caused by retroorbital mass [26].

Cutaneous manifestations, present in 45% of patients, are nonspecific findings and usually affect the lower extremities. Palpable purpura, papules, subcutaneous nodules, ulcerations, livedo reticularis and urticaria are frequent, being leukocytoclastic angiitis (purpura, focal necrosis and ulceration) the most common skin lesion [27].

Musculoskeletal system is also often involved by the vasculitic process, with myalgias, polyarticular and symmetric arthralgias, and non-deforming arthritis of the large joints, being present in 32% of patients at initial diagnosis and in 67% throughout the course of the disease.

Cerebral manifestations (23%) include cranial nerve neuropathy, cerebral vasculitis, mononeuritis multiplex, pachymeningitis, central nervous system mass lesions, among other less frequent manifestations. Peripheral neuropathy is, however, more common than central nervous system involvement.

In patients with WG has been documented a high incidence of venous thrombotic events (VTEs). According to WeCLOT study [27] the incidence of VTEs was 7/100 person-years, but rotine anticoagulation for all patients is not recommended. Antiplasminogen antibodies were higher in PR3-ANCA patients than healthy control subjects (five in nine patients with VTE were positive for antiplasminogen antibodies) [28].

Less frequently, involvement of the heart (present in 6-44% of the patients with pericarditis, myocarditis, conduction system abnormalities and coronary vasculitis) [29]; gastrointestinal tract (splanchnic vasculitis, abdominal pain); oral cavity ("strawberry gingival hyperplasia"); lower genitourinary tract (urethra, ureters, cervix, vagina, testicular and prostate), parotid glands, thyroid gland (hyperthyroidism), liver or breast is seen.

Organ involvement	Percent at initially of the disease	Percent during the course of disease
ENT	73	92
Lung	45	85
Kidney	18	77
Ocular	15	52
Skin lesions	13	46

Table 1. Percent of organ involvement in WG [22]

5. Laboratory findings

Characteristic laboratory findings are nonspecific and include elevated sedimentation rate and C-reactive protein, mild normocitic, normochromic anemia (50%), leukocytosis with neutrophil predominance, thrombocytosis (>400,000/microL) as an acute phase reactant, elevated blood urea nitrogen and creatinine levels, hypoalbuminemia, hypergammaglobulinemia (essentially of the IgA class), antinuclear antibody may be positive and slightly elevated rheumatoid factor levels. Patients should have a urinalysis, including microscopic analysis of urinary sediment, to determine the presence of hematuria and proteinuria.

Almost 90% of the patients with active WG have a positive anti-PR3 ANCA and only a small percentage of patients may have anti-myeloperoxidase (anti-MPO) ANCA.

ANCAs can be detected by two methods: immunofluorescence (IF) and enzyme-linked immunosorbent assay (ELISA). The former is a qualitative ANCA assay and there are three IF patterns recognized: cytoplasmic (C-ANCA), perinuclear (P-ANCA) and atypical. However, this technique has significant inter-reader variability unlike ELISA. The latter provides target antigen-specific characterization of ANCA. Only ANCA directed against PR3 or MPO have been associated with primary vasculitic syndromes. False positive ANCA titers appear in certain infectious and neoplastic diseases. Together, IF and ELISA confer 96% of sensitivity and 98,5% of specificity for the diagnosis of WG [30].

C-ANCA directed against PR3 is most specific for WG, especially if active glomerulonephritis is present. Rising C-ANCA titers may herald a relapse in some patients with WG, but this relationship is unreliable [31].

The measurement of PR3 membrane expression on neutrophils by flow cytometry (an increase is predictive of relapse) is a promissory marker for the activation of WG, but more research is needed [30].

6. Diagnosis

In a patient with the clinical features described above, the diagnosis of WG requires the demonstration of necrotizing granulomatous vasculitis on tissue biopsy, often from a site of active disease, being lung and kidney biopsies the most specific (lung biopsy is performed in the absence of renal involvement).

WG can be classified according to the nomenclature of the Chapel Hill Consensus (CHC) Conference for primary systemic vasculitis (table 2) [32] and according to the classification criteria defined by the American College of Rheumatology (ACR) (table 3) in 1990 [33].

- Granulomatous inflammation involving the respiratory tract and
- Necrotizing vasculitis affecting small- to medium-sized vessels (capillaries, venules, arterioles and arteries)
- Necrotizing glomerulonephritis is common
- Cytoplasmic pattern ANCAs (C-ANCA) with antigen specificity for proteinase 3 (PR3) are a very sensitive marker for WG

Table 2. Definition of WG according to the Chapel Hill Consensus Conference

1. Nasal or oral inflammation: oral ulcers or purulent or bloody nasal discharge
2. Abnormal chest radiograph: nodules, fixed infiltrates or cavities
3. Nephritic urinary sediment: microhematuria or red blood cells casts
4. Granulomatous inflammation on biopsy
5. For the diagnosis of WG the patient must have, at least, 2 or more of these 4 criteria (sensitivity of 88,2% and specificity of 92%)

Table 3. American College of Rheumatology Classification Criteria

The European Vasculitis Study Group (EUVAS) has developed a definition of the disease stage including localized disease (table 4) [34]. WG can also be divided in limited (absence of disease features that pose immediate threats to either a critical individual organ or to the patient's life) or severe disease.

Disease Stages	Organ involvement	Detection of ANCA
Localized	Upper and lower airways	- / +
Early systemic	Any, but no imminent organ failure, creatinine < 150µmol/L	+
Generalized	Any, creatinine < 500µmol/L	+
Rapid progressive GN	Creatinine > 500µmol/L	+
Refractory	Progress in spite of therapy	+

Table 4. Disease stages according to the European Vasculitis Study Group (EUVAS)

7. Differential diagnosis

The differential diagnosis includes pathologies with related clinical features, mainly lung - kidney syndrome, or with similar laboratory findings (ANCA positive). The following table lists the most relevant disorders (table 5).

Churg - Strauss Syndrome	NK nasal type lymphoma
Microscopic polyangiitis	Cocain induced
Goodpasture's syndrome	Lymphomatoid granulomatosis (EBV)
Relapsing polycondhritis	Hemolytic- Uraemic syndrome
Upper airways or lung tumors	Infective endocarditis
Glomerulonephritis	Polyarteritis nodosa
Histoplasmosis	Sarcoidosis
Rhinoscleroma	Systemic Lupus Erythematosus

Table 5. WG´s differential diagnosis

8. Treatment

Therapy is adapted according to disease stage and activity [35] and requires remission induction with initial immunosuppressive therapy, followed by maintenance immunosuppressive therapy to prevent relapse and control the disease.

8.1 Remission induction

Patients with **limited disease** (localized/early systemic) should be treated with oral steroids 1mg/Kg/day in combination with oral or subcutaneous methotrexate (20-25mg/week), according to the NORAM study [36]. Daily folic acid 1mg/day is recommended. In these cases cyclophosphamide should be avoided due to associated toxicity. Methotrexate is equal to cyclophosphamide in inducing remisson [36], although the former was associated with more relapses at 18 months, compared to cyclophosphamide, 69,5% vs 46,5% , respectively.

Patients with **generalized disease or severe disease** (threatened vital organ function) should be treated with cyclophosphamide in combination with steroids (FAUCI scheme, introduced in 1970s).

Cyclophosphamide can be given orally (2mg/Kg/day and the maximum dosage is 200mg/day) or intravenously (15mg/Kg every 2 weeks for the first 3 pulses, then every 3 weeks for the next 3-6 pulses, being the maximum dose 1500mg) and must be adjusted to renal function and age (table 6). The total duration of treatment should not exceed 6 months

[37]. Pulsed cyclophosphamide has fewer side effects (lower rate of leucopenia) than oral doses, with equal efficacy [38] for remission induction. However, higher relapse rates in the maintenance phase, following the pulsed scheme, have been reported, and more studies are needed to assess this [35].

Age (years)	Creatinine 150-300μmol/l	Creatinine 300-500μmol/l
< 60	15mg/Kg/pulse	12,5mg/Kg/pulse
> 60 and <70	12,5mg/Kg/pulse	10mg/Kg/pulse
>70	10mg/Kg/pulse	7.5mg/Kg/pulse

Table 6. Pulsed cyclophosphamide reductions for renal function and age

Steroids were always considered the cornerstone of therapy. Although their use has not been evaluated in randomized controlled trials, every clinical trial has used this therapy in combination with another immunosuppressant. The ideal dose and duration of steroid therapy is unknown and further studies are needed. They are usually given orally (1mg/Kg/day of prednisolone during 1 month and then tapering slowly), but in the set of rapidly progressive glomerulonephritis and/or alveolar hemorrhage intravenous pulse methylprednisolone (0,5-1g/day for 3 consecutive days) can be used. In these two settings, plasma exchange can also be considered as adjuvant, although it has not been shown to improve overall survival.

Patients treated with cyclophosphamide and corticosteroids should receive prophylaxis against *Pneumocystis jiroveci* pneumonia with trimethoprim/sulfamethoxazole 960mg 3 times per week or, in cases with allergy to this antibiotic, dapsone 100mg daily.

8.2 Remission maintenance

In order to minimize exposure to the side effects of treatment with cyclophosphamide, alternative therapies have been proposed in recent years.

In the remission maintenance three agents can be used: azathioprine (2mg/Kg/day), methotrexate (20-25mg/week) and leflunomide. According to the CYCAZAREM trial [40], the former is safer than and as effective as cyclophosphamide. In a trial published in New England Journal of Medicine in December 2008, methotrexate has been shown to be similar to azathioprine in security and efficacy in maintaining remission [41]. Leflunomide was compared with methotrexate in a small trial and the results showed a trend to lower relapse rates with the first agent, but with more adverse effects [42]. In this study the dose of leflunomide was 30mg/day.

Mycophenolate mofetil (2g/day) can also be considered for maintenance therapy when there is intolerance or lack of efficacy with azathioprine or methotrexate, although more studies are needed.

8.3 Alternative therapies

Alternative therapies have increasingly been investigated, some of them with promise results.

Several studies showed clinical improvement or remission with **rituximab** (375mg/m^2 per week for four weeks). This data was confirmed by two recent trials, RAVE [43] and RITUXVAS [44], which showed non inferiority of rituximab compared with cyclophosphamide for induction of remission for the first study and remission of severe disease (renal involvement) for the second trial, with the former study reporting a possible superiority of rituximab in relapsing disease and in the RITUXVAS trial the rituximab group was associated with high rate of severe adverse events.

Etanercept studies, namely the Wegener´s granulomatosis etanercept (WGET) trial [45] didn´t find improvement in the maintenance of remission, with either severe or nonlifethreatening disease activity, when added to standard therapy, with a possible risk to increase infections and malignancies. This study didn´t evaluated this drug per se.
Infliximab, antithymocyte globulins and alentuzumab (CAMPATH-1H study) [46] are under investigation and further studies are needed to define their role in therapy.
Some studies suggest the use of intravenous immunoglobulin for refractory vasculitis, when conventional therapy is contra-indicated or for relapsed disease. However more studies are needed.

9. Prognosis

Patients with WG should have a closely follow-up, with regularly visits to her/his physician, involving multidisciplinary approach, and frequents exams to monitored the disease.
Relapse is common (50% within 5 years), being ANCA status at diagnosis, target organ involvement (lung, renal, heart and chronic nasal carriage of *Staphylococcus aureus*) and treatment with <10g of cyclophosphamide in the first 6 months, maintaining prednisone >20mg/day for <2, 75 months and/or goal of zero dose of glucocorticoids factors associated to high risk of relapse [47].
Untreated generalized or severe disease has a poorer prognosis, with a mortality rate up to 90% within 2 years, but the introduction of immunosuppressive therapy increases the lifelong of these patients, being the overall 10-year survival rate 75-88% [48]. Renal involvement is associated with a bad prognosis.
The leading causes of death are infection, respiratory and renal failure, malignancy and cardiovascular disease, being the first one the major responsible for the mortality and morbidity in WG.

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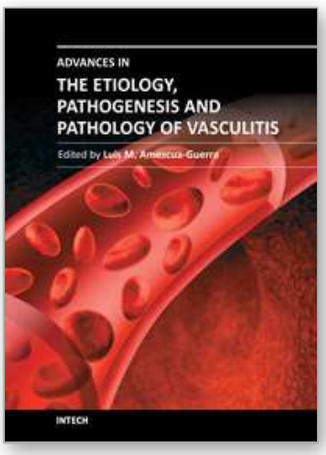

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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to devote their work to this book by keeping both the text and the accompanying figures and tables lucid and memorable. Here, you will find an amalgam between evidence-based medicine to one based on eminence, through an exciting combination of original contributions, structured reviews, overviews, state-of the-art articles, and even the proposal of novel pathogenetic models of disease. The book contains contributions on the etiology and pathology of vasculitis, the potential role of endothelial cells and cytokines in vascular damage and repair as well as summaries of the latest information on several primary and secondary vasculitis syndromes. It also covers selected topics such as organ-specific vasculitic involvement and quality of life issues in vasculitis. The editor and each of the authors invite you to share this journey through one of the most exciting fields of the medicine, the world of Vasculitis.

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