Granulomatosis with Polyangiitis

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Core Messages

- Wegener's granulomatosis (WG), or the recently proposed terminology "granulomatosis with polyangiitis (GPA)", is a potentially lethal systemic vasculitis classically involving the upper (sinuses) and lower respiratory tracts and kidneys, with orbital or ocular involvement in over 50 % of cases.
- Limited forms of the disease (typically without renal involvement) and supported by the presence of positive antineutrophil cytoplasmic antibodies (ANCA) occur and may progress to the more recognizable pattern of disease.
- The common ophthalmic findings include orbital inflammation and necrosis, episcleritis, scleritis, and peripheral ulcerative keratitis and may be a presenting or possibly the only initially apparent clinical feature.

71.1 Definition

Wegener's granulomatosis (WG) or granulomatosis with polyangiitis (GPA) is a rare and potentially lethal systemic necrotizing granulomatous vasculitis of the small- and medium-sized arteries and veins classically involving the upper

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M. Zierhut et al. (eds.), *Intraocular Inflammation*,
DOI 10.1007/978-3-540-75387-2_71, © Springer-Verlag Berlin Heidelberg 2016

and lower respiratory tract with frequent involvement of the kidneys [9, 31, reviewed in 24]. However, limited or incomplete forms (typically without renal involvement) are common. Although first described by Klinger as a form of polyarteritis nodosa in 1931 [17], it is named after the German pathologist Friedrich Wegener, who recognized the unique nature of the condition and established Wegener's granulomatosis as a distinct clinicopathologic entity [3]. The average age of onset is around 40 years [31]. Recently, three professional bodies proposed to change the honorific eponym of Wegener's granulomatosis to the more descriptive term "granulomatosis with polyangiitis" (GPA) [30]. The new name recognizes the main pathologic feature (granulomatous inflammation) and reflects the frequent vasculitic involvement of multiple types of vessels (polyangiitis). It is expected that the parenthetical reference to Wegener's will gradually be phased out as the new terminology becomes accepted [30]. This chapter acknowledges the proposed change [27a, 32].

71.2 Clinical Manifestations

71.2.1 General Disease

GPA is a potentially lethal systemic vasculitis classically involving the upper and lower respiratory tracts and kidneys (complete form). However, GPA is a continuum of disease, which can involve any single or combination of organs, including commonly the eyes, nerves, skin, and joints. In the incomplete or limited form of GPA, the kidneys are typically spared [2, 5].

The disease can be present with limited or single organ involvement for months or even years, with nonspecific signs and symptoms of a systemic illness, such as fever malaise, weight loss, arthralgias, and myalgias, before evolving to a more generalized and clinically recognizable pattern. The earliest and most common symptoms and findings are usually referable to the upper respiratory tract (up to 90 % of patients) [12], with glomerulonephritis developing ultimately in 77–85 % of untreated patients, usually within the first 2 years of disease onset [7, 12].

71.2.2 Ocular Disease

Ocular involvement may occur in about 50 % of patients with GPA but may only be noted in up to 15 % at presentation [1, 12, 28]. However, ocular disease may be a presenting or even the only clinically apparent manifestation of GPA, especially in the limited form of the disease (reviewed in [1, 8, 24, 25]).

Any ocular tissue may be involved, with orbital involvement being one of the most frequently reported ocular findings, usually due to contiguous extension from sinus or nasal disease. Painful proptosis, pseudotumor, orbital abscess, or orbital mass with cranial nerve involvement or muscle entrapment resulting in diplopia are common ophthalmic findings [1, 12, 24, 28]. Vision loss may occur from a compressive optic neuropathy [12, 24, 28].

Recurrent conjunctivitis and episcleritis are frequent ocular findings but are relatively benign. In contrast, scleritis (diffuse, nodular, or and especially necrotizing) and peripheral ulcerative keratitis (Fig. 71.1), occurring alone or in combination with scleritis, can lead to significant ocular morbidity with vision loss and even blindness, if

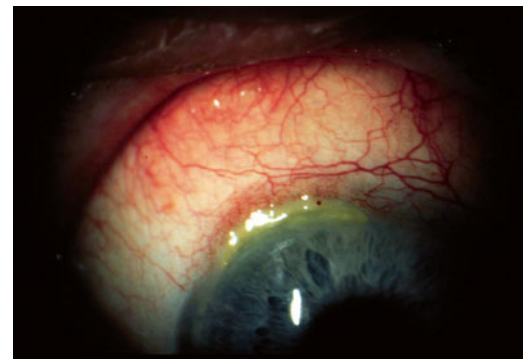

Fig. 71.1 A 53-year-old male presenting with fatigue, fever, weight loss, microscopic hematuria, and peripheral ulcerative keratitis. cANCA was positive. Patient was ultimately diagnosed with GPA and treated with systemic cyclophosphamide

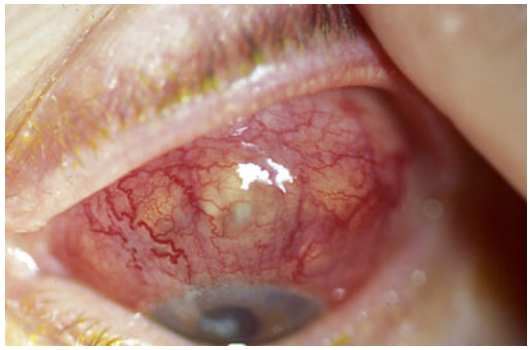

Fig. 71.2 A 72-year-old female referred for necrotizing scleritis refractory to oral corticosteroids. Patient was cANCA positive and diagnosed with cANCA-positive limited GPA. Treatment with systemic cyclophosphamide controlled scleritis

inadequately treated [8, 25, 28]. Scleritis, with or without peripheral ulcerative keratitis, can be a presenting or at times the only apparent clinical feature of GPA. Necrotizing scleritis appears to correlate best with systemic involvement, and the onset of scleritis may portent the development of systemic disease (Fig. 71.2) [3, 7].

Uveitis occurs in about 10 % of cases, is usually a nonspecific anterior uveitis, and is frequently associated with anterior scleritis or peripheral ulcerative keratitis [1, 2, 24, 28]. Intermediate and posterior uveitis are uncommon features of GPA [1] and usually seen in established disease. Retinal vasculitis, retinitis, and vascular occlusions have been reported with hemorrhages in the posterior or peripheral retina being the most common finding [24]. Choroidal folds and infarcts have been reported with some findings due to hypertensive retinopathy.

71.3 Etiology and Pathogenesis

The cause of GPA is unknown. A hypersensitivity phenomenon to airborne substances initially in the upper and lower airways and the possible role of infectious agents and microbial superantigens in disease pathogenesis have been proposed but remain conjectural [4, 28]. To date, no offending antigen, microbe, chemical, or noxious agents have been isolated. However, the role of the immune system is evident by the presence of granulomas (suggesting a delayed-type hypersensitivity (DTH) reaction), activated T cells in tissue, and elevated soluble IL-2 receptor levels during active disease with overproduction of cytokines such as IFN-gamma and TNF-alpha resulting in a predominantly Th1-type profile [19, 23].

A novel group of autoantibodies termed ANCA (antineutrophil cytoplasmic antibody) may not only be a marker for GPA and help support the diagnosis but also play a direct pathologic role (reviewed in [13, 16]). Cytokine-primed neutrophils in patients with GPA express increased amounts of surface serine proteinases and myeloperoxidase, which are the targets of ANCA. ANCA can activate primed neutrophils to generate reactive oxygen species and release lytic enzymes capable of damaging vascular endothelial cells and enhance the recruitment of more inflammatory cells to the site of active inflammation [13, 16]. However, they may not be essential for disease pathogenesis since not all patients are ANCA positive.

71.4 Diagnosis

The wide range of clinical presentations including those cases with mild and indolent disease may often delay diagnosis. Establishing the diagnosis of GPA is essential since therapy with cyclophosphamide is frequently required, whereas many other forms of vasculitis may be treated with corticosteroids alone [7].

The diagnosis of GPA can most securely be made by suggestive clinical features combined with histopathologic findings consisting of the triad of vasculitis, necrosis, and granulomatous inflammation (usually from large biopsy specimens such as an open lung biopsy) [7, 9]. Frequently, less than three pathologic features are present. This is evident in the early stages where clinical findings are evolving, in limited forms where the characteristic organs, especially the kidney, are not involved, or when a single site, such as the eye, may be the only clinically apparent site of involvement at presentation [25].

Antineutrophil cytoplasmic antibodies (ANCA) have become an invaluable adjunct in helping support or establish the diagnosis of GPA and related forms of vasculitis [13]. ANCAs are antibodies directed against cytoplasmic enzymatic granules of neutrophils and monocytes and produce two different fluorescence staining patterns. The granular, centrally accentuated, cytoplasmic pattern termed cANCA is sensitive and highly specific for active GPA and is almost always produced by antibodies against a serine proteinase 3 (PR3) [13, 15]. This is the common type of ANCA seen in patients with GPA. However, a perinuclear staining fluorescence pattern, called pANCA, is produced by antibodies against a variety of target antigens. Only when the target antigen is myeloperoxidase (MPO) is it associated with GPA, microscopic polyangiitis, Churg-Strauss syndrome, and pauci-immune glomerulonephritis [20]. Some patients with rheumatoid arthritis, inflammatory bowel disease, or systemic lupus erythematosus have *atypical* pANCA, likely due to autoantibodies directed against other neutrophil constituents, such as lactoferrin.

Although cANCA specificity is about 98 %, the sensitivity depends on disease activity and extent. For patients with active generalized disease, it is about 95 % sensitive but decreases to only 41 % when the disease is in remission [20]. The sensitivity for active limited disease is about 65 % but only 35 % when in remission [20]. A relationship between ANCA titers and disease activity is reported but is not universal [24]. With contiguous orbital involvement, ANCA sensitivity and specificity are similar to that reported for limited GPA. A positive ANCA associated with scleritis appears to be both sensitive and very specific for GPA and thus, an ANCA test is mandatory in any scleritis workup [11, 25]. However, the specificity of a positive ANCA is less clear in patients with isolated uveitis or retinal vasculitis, and thus, other clinical findings and usually a supportive biopsy are required for the diagnosis to be established [10].

Most other laboratory findings are generally nonspecific and indicate a systemic inflammatory process. Additional testing should also include blood urea nitrogen and creatinine, urine analysis and chest radiograph, and occasionally sinus radiographs or a sinus CT scan.

Thus, suggestive clinical findings supported by a positive cANCA help establish the diagnosis of GPA.

71.5 Differential Diagnosis

The differential diagnosis of granulomatosis with polyangiitis includes systemic inflammatory and vasculitic conditions that may produce similar ocular disease, including rheumatoid arthritis, relapsing polychondritis, polyarteritis nodosa, systemic lupus erythematosus, Churg-Strauss syndrome, Crohn's disease, and other systemic disorders. At onset, the differentiation may be difficult but may become evident as the more characteristic local and systemic features develop, thus highlighting the importance of continued surveillance. Primary or secondary ocular and orbital infectious processes, such as orbital cellulitis, should be excluded. However, at times, the presence of a characteristic feature, such as scleritis, combined with a positive ANCA is the only way to differentiate limited forms of GPA from other inflammatory conditions [25].

71.6 Treatment

Systemic treatment is required for GPA. Steroids alone may prolong survival by months. Therapy has traditionally included a combination of daily, oral cyclophosphamide, 2 mg/kg body weight, and prednisone, 1 mg/kg body weight, with higher doses in patients with more rapidly progressive disease [7, 24] (Fig. 71.3). Six to 12 months following cyclophosphamide-induced remission, a combination of azathioprine and prednisone can be successfully used as maintenance therapy, to minimize potential cyclophosphamide-induced side effects [18]. Azathioprine, although not as

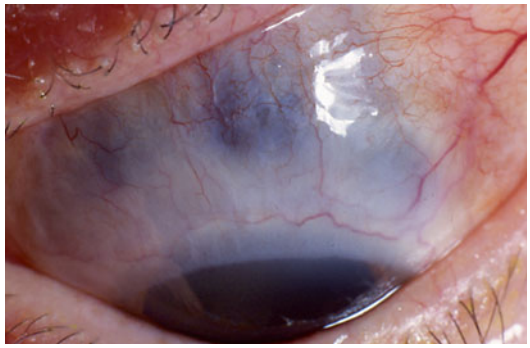

Fig. 71.3 Same patient as in Fig. 71.2, following treatment with cyclophosphamide. Scleral inflammation is controlled, although there is residual scleral thinning

effective, may be used as second-line induction therapy as well [24]. Low-dose weekly methotrexate has also been used successfully for non-life-threatening GPA, as either primary therapy or when cyclophosphamide therapy was not effective, had caused significant toxicity, or for the maintenance of cyclophosphamide-induced remission [27]. Relapse rate may be higher with methotrexate; thus, close monitoring is mandatory.

Trimethoprim-sulfamethoxazole (T/S) has been reported to be of benefit where there is no renal involvement, but the mechanism of action is unclear and either an antimicrobial effect, which would prevent infections that would trigger relapses, or an anti-inflammatory/immunosuppressive effect is theorized [14].

More recent therapeutic modalities using biological agents including TNF-alpha blockade with infliximab have shown promising results in limited case series and single case reports, and B-cell depletion with anti-CD20 monoclonal antibody rituximab has been shown to be as effective as cyclophosphamide, in a multicenter, randomized clinical trial, for induction of remission and possibly superior in relapsing disease and has received FDA approval for the treatment of GPA [6, 18, 19a, 21, 27a, 29]. However, these therapies have not been vigorously studied to date, have an unknown long-term safety profile, and continue to be evaluated. Intravenous immunoglobulin (IVIg) has been utilized with some benefit, but cost, limited availability, and inability to maintain a sustained effect limit its use [18]. Alternative treatments, with T-cell depletion using the humanized monoclonal anti-CD52 antibody alemtuzumab, gusperimus, a synthetic analogue of the antibiotic spergualin which suppresses lymphocyte and macrophage function, autologous stem cell transplantation, and newer B-cell targeted therapies, are being evaluated [23a].

Conjunctivitis and episcleritis, which are usually non-vision threatening, may initially be treated with local corticosteroid therapy with careful monitoring for the development of more severe ophthalmic disease. T/S may be considered, with the reservations noted above [26]. However, severe vision-threatening ophthalmic disease such as orbital inflammation, scleritis especially necrotizing, peripheral ulcerative keratitis, uveitis, and retinal and optic nerve vasculitis require the use of systemic cytotoxic immunosuppressive therapy with the adjunctive use of systemic as well as local/regional corticosteroids.

Surgical intervention may be required in patients with orbital disease (decompression and drainage). Tectonic scleral grafting may rarely be required when globe perforation from necrotizing scleritis is imminent.

71.7 Prognosis

Untreated, the prognosis is dismal [12]. The outcome of GPA has dramatically improved with the introduction of daily cyclophosphamide combined with glucocorticosteroids [7, 12]. The prognosis for limited GPA is better than with the complete form of the disease. Patients with severe renal disease have a higher mortality with a guarded prognosis even with cytotoxic immunosuppressive therapy.

The visual prognosis depends on the severity and chronicity of the eye disease and in general is good when treated appropriately with systemic cytotoxic therapy when necessary. But vision loss or total blindness may be seen if the disease has been long-standing and inadequately treated or when there has been a delay in diagnosis.

Take-Home Pearls

- GPA must be considered in the differential diagnosis of any patient presenting with scleritis or peripheral ulcerative keratitis, especially when associated with upper or lower respiratory symptoms or renal disease.
- A positive ANCA test is helpful to establish the diagnosis of GPA. This marker is essential in the workup of patients with scleritis and peripheral ulcerative keratitis.
- Systemic immunomodulatory therapy is required for the treatment of most manifestation of GPA.
- The ocular and systemic prognosis depends on early recognition and aggressive immunosuppressive therapy.

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