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Wegener's Granulomatosis vasculitis and granuloma

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ABSTRACT

Wegener's Granulomatosis (WG) is an autoimmune disease with manifestations in different organ systems. The hallmark of WG is a necrotizing granulomatous inflammation of the upper and/or lower respiratory tract and systemic small vessel vasculitis which can involve multiple organ systems. The treatment of WG has evolved over the last decades. Steroid, cytotoxic and biologic therapies have been used leading to great improvements in outcome. However, still mortality is high and relapses are a major cause of mortality and morbidity.

Despite intensified maintenance regimens and new possibilities of biologic therapies in WG the relapse rate is high. Even patients treated with high dose cytotoxic therapies in autologous stem cell treatment protocols have shown relapses in the course of disease. Increasing knowledge of the pathophysiology of granuloma in WG and new biologic therapies might be of great importance for future treatment of WG.

Contents

1. Introduction

WG is an autoimmune disease of unknown etiology. Major progress unraveling the pathophysiology of WG has been made since the first diagnosis by Friedrich Wegener in 1939. The identification of anti-neutrophil cytoplasmic antibodies (ANCAs) in the 1980s has led to enhanced diagnosis of WG and recently to the understanding of the pathogenic role of proteinase 3 ANCA (PR3-ANCA) in small vessel vasculitis.

The observation of germinal center-like formations in granuloma, suggesting antigen-driven autoantibody production has led to the hypothesis of granuloma functioning as ectopic lymphoid tissue maintaining ANCA production [1]. Although great progress has been made regarding the knowledge of the underlying pathophysiological process still the initiating event or aberrant immunological responses leading to granuloma formation and vasculitis currently have not been identified. There is increasing evidence that *S. aureus* plays a role in the pathogenesis of WG, the mechanism however is not clarified as yet [2].

WG is a rare disease with a prevalence ranging from 5 to 16 per 100,000 in Northern Europe [3] to 3 per 100,000 in the United States of America [4]. The clinical course of WG is characterized by an initial or localized phase, usually followed by a generalized or systemic phase.

In the initial phase of WG symptoms arise from granulomatous inflammation of the upper and/or lower respiratory tract. Patients may present with hearing loss, recurrent otitis media, recurrent mastoiditis and sinusitis, recurrent epistaxis, nasal septum perforation and saddle nose deformity. Granulomatous masses can be found along the upper and lower respiratory tract. Parenchymal lung nodules are most frequently seen, but also intraorbital masses leading to proptosis or diplopia or granulomatous masses involving the kidney can be seen. In this phase ANCA positivity is found in only 50% of the cases, in generalized or systemic WG, ANCA positivity is seen in more than 90%

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of the patients [5]. Approximately 80% of the patients with localized or initial disease progress to generalized or systemic WG [6].

Generalized or systemic WG is characterized by clinical signs of small vessel vasculitis. In this phase general symptoms like malaise, fever and weight loss are usually seen. The clinical spectrum includes the life threatening pulmonary-renal syndrome, but also less dramatic signs of systemic vasculitis. In the pulmonary-renal syndrome patients can present with severe dyspnea, hemoptysis and renal insufficiency as a result of necrotizing alveolar vasculitis and rapidly progressive necrotizing glomerulonephritis.

Other manifestations of systemic vasculitis include corneal ulceration, (epi)scleritis or retinal vasculitis in ocular involvement, pericarditis, myocarditis and conduction abnormalities in cardiac involvement and mucosal ulceration in gastrointestinal involvement. Cutaneous manifestations comprise of a diverse spectrum of hemorrhagic, vesicular lesions and palpable purpura to ulcerative, pyoderma gangrenosum like lesions. In nervous system involvement, mononeuritis multiplex, cranial nerve abnormalities and cerebral vasculitis can all be seen, leading to detrimental morbidity. If untreated, systemic WG leads to more than 90% mortality in the first two years [7].

Current remission induction treatment protocols in systemic WG consist of cyclophosphamide and corticosteroids, supported by plasma exchange in case of severe renal vasculitis or pulmonary hemorrhage. Optimization of treatment protocols has led to remission rates of 70–90% in the first year and early mortality rates of 5–12% [8,9]. Despite optimization of treatment protocols 10% of the patients are refractory to treatment [10]. Relapses still occur in approximately 10% of the patients in the first year [11], in 18–40% of the patients in the second year and in up to 66% of the patients during long-term follow-up [12].

This review will discuss the current opinion on the pathophysiology of WG and new treatment options.

2. Pathophysiology of vasculitis in WG

PR3-ANCA positivity is seen in 90–95% of the systemic WG cases. Recent evidence suggests a central role for PR3-ANCA in the pathophysiology of systemic vasculitis in WG [13] (Fig. 1).

The serine proteinase 3 (PR3) is the major autoantigen in WG and is stored in the azurophilic granules of neutrophils. In patients with WG increased neutrophil membrane expression of PR3 has been demonstrated [14] and, in another study, increased neutrophil membrane expression of PR3 was found to be related to relapse in PR3-ANCA associated vasculitis [15].

Priming neutrophils with pro-inflammatory cytokines as TNFα was shown to increase expression of PR3 on the outer membrane of the neutrophils [16]. Translocation of PR3 from the azurophilic granules to the surface of the neutrophil makes PR3 available for PR3-ANCA binding. Binding of PR3-ANCA to both PR3 and Fcγ-receptors was shown to cause activation of the neutrophil, via the FcγRIIa signal transduction system [17]. TNFα primed neutrophils activated by PR3-ANCA were shown to induce a respiratory burst and degranulate, resulting in the release of pro-inflammatory cytokines, proteases and reactive oxygen species [18], leading to vascular damage.

In vitro studies have shown that TNFα can up regulate adhesion molecules on endothelial cells [19] and primed, PR3-ANCA activated neutrophils are able to adhere to activated endothelium and display direct cytotoxicity towards endothelial cells [20].

The ability of neutrophils to become activated in response to cytokine exposure and PR3-ANCA binding, and the capacity of cytokines such as TNFα to up regulate the expression of adhesion molecules has led to the understanding of the pathogenic role of PR3-ANCA in small vessel vasculitis and the understanding of the interplay between PR3-ANCA, neutrophils, cytokines (TNFα) and the endothelium.

Biologic therapies aiming at interference of the interaction between cytokines (TNFα), PR3-ANCA and neutrophils, and the production of autoantibodies might be of great promise. Of particular interest might be the use of biologic therapies in the initial phase of life threatening systemic vasculitis, refractory disease and relapsing WG.

3. Treatment of vasculitis in WG

The importance of PR3-ANCA in the pathophysiology of vasculitis in WG is supported by results of clinical studies on the value of plasma

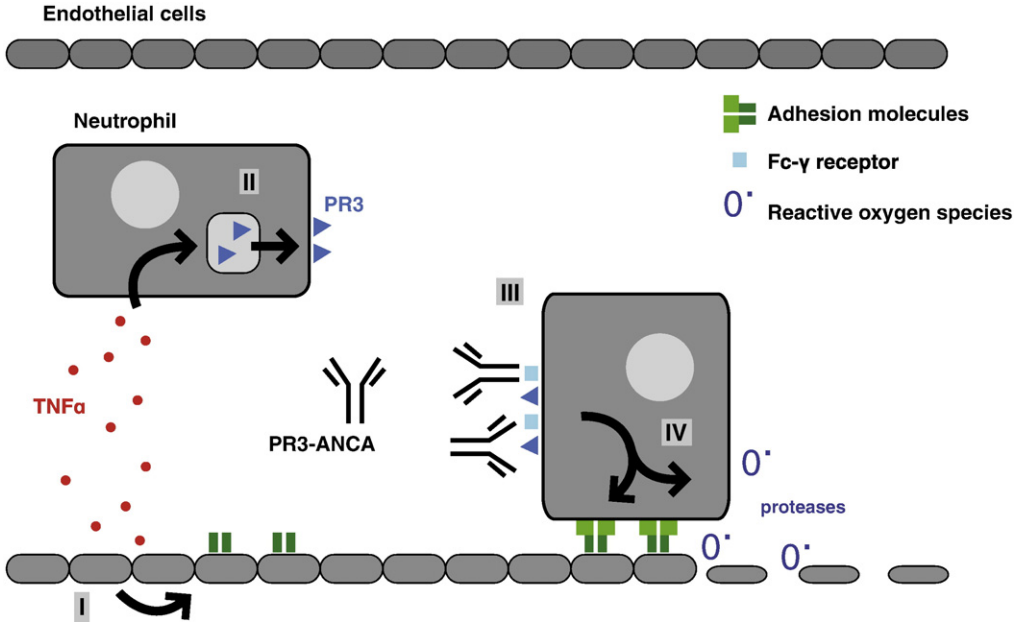

Fig. 1. Pathophysiologic mechanism of PR3-ANCA associated vasculitis. (I) TNFα induces increased expression of adhesion molecules on endothelial cells. (II) TNFα priming of neutrophils leads to migration of proteinase 3 (PR3) from the azurophilic granula to the cell membrane. (III) Interaction of circulating PR3-antineutrophil cytoplasmic antibodies (PR3-ANCA) with PR3 and Fcγ-receptor on the surface of the neutrophil leads to neutrophil activation. (IV) Neutrophil activation by PR3-ANCA leads to a change in neutrophil rheology, arrest in diapedesis and adhesion to the TNFα primed endothelium. PR3-ANCA induces release of reactive oxygen species and proteolytic enzymes resulting in damage of the endothelium.