Wegener's Granulomatosis: A View from the Granulomatous Side of the Disease

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Key words: Wegener's granulomatosis, granuloma, vasculitis, localized, orbita

Abstract

Although the airway granulomata in Wegener's granulomatosis were stressed initially by Friedrich Wegener himself, in the last few decades systemic lesions mainly caused by acute vasculitis have received the most attention. However, recently, the implication of granulomatous manifestations in WG has raised much interest. The present data suggest that an aberrant Th1-type response might play a role in the initiation of WG, clinico-pathologically characterized by granulomatous inflammation rather than vasculitis. Disease progression to generalized WG with the predominance of vasculitic manifestations is associated with a "switch" or further complexity of the collective T cell response with the appearance of another subset of Th2-type cells and a less prominent Th1-type cytokine production in the granulomatous lesions of the upper respiratory tract. However, the clinical significance of the granulomatous inflammation is not yet completely understood. Further research will also have to focus on the role of the granulomata during relapsing disease. We review present knowledge of granulomatous inflammation in WG. Morphologic aspects, the scale of cytokine alterations as well as the variety of clinical manifestations are discussed.

IMAJ 2005; 7: 768–773

A key question for understanding chronic inflammatory and autoimmune diseases is where the disease actually begins. Wegener's granulomatosis is a potentially life-threatening chronic inflammatory disease of as yet unknown etiology, characterized by granuloma formation, vasculitis, and an autoimmune response to "Wegener's autoantigen" proteinase 3, a 29 kD neutrophil- and monocyte-derived serine protease [1,2]. Antineutrophil cytoplasmic autoantibodies specific for proteinase 3 are detected in about 95% of patients with generalized WG, but only in about half of those presenting with early localized WG restricted to the respiratory tract. Apart from their diagnostic value and correlation with disease activity, PR3-ANCA play a direct pathogenic role in inducing systemic vasculitis by interacting with PR3 on the surface of cytokine primed neutrophil granulocytes, as suggested by numerous *in vitro* and several *in vivo* studies. The interaction of ANCA and neutrophils results in premature neutrophil activation, subsequent endothelial cell damage, and further leukocyte recruitment [reviewed in 2]. However, it is not clear whether PR3-ANCA give rise to pathogenic granulomatous inflammation – a defining feature of WG. Instead, there is increasing evidence that WG may start as granulomatous disease in the respiratory tract and ANCA vasculitis may develop subsequently [2,3]. Moreover, WG relapses are related to granuloma formation and persistence of granulomata [2]. In this article, we review current clinical and experimental data on aspects of the "granulomatous side" of WG.

WG = Wegener's granulomatosis

PR3-ANCA = antineutrophil cytoplasmic autoantibodies specific for proteinase 3

Morphologic spectrum of granulomatous lesions

The granulomatous lesions seen in WG have a wide morphologic spectrum. Therefore, and due to an often irregular pattern, this form of tissue injury is usually referred to as "granulomatous lesion" rather than "granuloma." The lesions display different morphologies, such as neutrophilic microabcesses, necrotizing palisading granulomas, and sometimes epithelioid cell granulomas. Granulomatous lesions of the respiratory tract consist of CD4+ T cells, CD8+ T cells, histiocytes, clusters of CD20+ B cells, neutrophil granulocytes, CD68+ macrophages, and CD68+ multinucleated giant cells. Scattered eosinophil granulocytes may be interspersed, making the differential diagnosis of Churg-Strauss syndrome occasionally difficult. The central necrosis may be confluent or may show an irregular serpiginous pattern known as "geographic" necrosis. A palisade of epithelioid histiocytes may arrange around the necrotic foci. The center of the necrosis is acellular or in some instances contains polymorphonuclear leukocytes [4]. The morphologic triad of granuloma formation, "geographic" necrosis, and small vessel vasculitis is found in about one-third of biopsies, while two-thirds display two or only one of the features of the morphologic triad. One biopsy series in a study showed differences in the morphologic findings in localized WG and generalized WG [Table 1] [5]. Disease progression from early, localized WG to generalized WG is associated with a "switch" or increasing complexity of the cytokine and cellular profile, as discussed below [6,7]. Rarely, granulomatous lesions may be found in an organ other than the respiratory tract, e.g., kidney, parotid gland, retro-orbital tissues, or meninges [4].

Fienberg`s hypothesis: WG starts as granulomatous disease

American pathologist R. Fienberg studied open lung biopsies of WG patients and described the evolution of granulomatous

Table 1. Granuloma formation, geographic necrosis, and Th1-type response is more frequent and stronger, respectively, in localized WG compared to generalized WG

Morphologic and immunohistochemical findings	Localized WG	Generalized WG
Granuloma	5/5	3/5
Vasculitis	2/5	3/5
Geographic necrosis	3/5	0/5
IFN-γ	↑↑↑	↑↑
TNF-α	NA	↑↑
CD26+ cells	↑↑↑	↑
CD4+ CD28- T cells	NA	↑↑
CCR5+ cells	↑↑↑	↑

Synopsis of biopsy findings of three studies on morphologic aspects [5] and immunohistochemical characterization of granulomatous lesions in localized and generalized WG (n=5 per group) [6,7].
CD26 = optional Th1-type marker, CD4+ CD28- T cells = effector memory T cells, CCR5 = Th1-type CC chemokine receptor 5, NA = not analyzed.

lesions in WG. He claimed that the earliest lesions in the lung are foci of swollen collagen fibers representing apparent tissue injury and/or necrosis. Next, mononuclear histiocytes migrate to the vicinity of the necrosis. Neutrophil granulocytes, lymphocytes, epithelioid cells and multinucleated giant cells appear subsequently. Finally, the histiocytes become oriented in a pallisading manner around the central necrosis area. Granulomatous lesions in the lung can be found in proximity to inflamed vessels, but also at extravascular sites. Therefore, Fienberg suggested that WG starts as granulomatous disease in the respiratory tract and systemic vasculitis develops subsequently [4]. However, early foci of fibrinoid necrosis could also be a consequence of initial necrotizing capillaritis. Thus, it is speculation whether PR3-ANCA could give rise to granulomatous lesions or whether granulomatous lesions represent ectopic lymphoid-like structures, in which immunity to "Wegener's autoantigen" PR3 is sustained [8].

Recently published data from autoimmune animal models underscore the importance of inflammation of the target organ, in which co-stimulatory molecules, cytokines, and the formation of ectopic lymphoid-like tissue sustain autoantigen presentation and autoimmune disease [9–11]. The initiating mechanisms driving granuloma formation and inducing a sustained autoimmune response to PR3 are still obscure [2,8]. Chronic nasal carriage of *Staphylococcus aureus* is a risk factor for exacerbation of WG [12]. *Staph. aureus* produces a number of superantigens and serine proteases, some of which are strong T cell activators. Other potential inducing agents of ANCA could be drugs, in particular antithyroid drugs, and inorganic chemicals such as hydrocarbons and especially silica [2]. Since interferon-gamma and T cells play a pivotal role in granuloma formation, alterations in the T cell response and anomalous autoantigen presentation in ectopic lymphoid-like structures could create immunity to PR3 [8,13]. A greater abundance of neutrophils and monoctyes as a potential source of PR3 was demonstrated years ago in WG compared to other granulomatous diseases [14]. Under conditions where local neoformation of lymphatic tissue can occur, autoantigens could maintain immunopathologic and autoimmune responses, as long as the autoantigen is available [15]. Anomalous sustained presentation, recognition, and immune response to PR3 by ectopic lymphoid-like tissue formation in granulomatous lesions could explain the clinical observation of a link between relapses and persistence of granulomata [2,8].

Alterations in the cytokine and T cell response

Abundant IFN-γ, CD26 (optional Th1-type marker), and Th1-type CC chemokine receptor CCR5 expression is seen in granulomatous lesions of the respiratory tract in localized WG, while IFN-γ expression and CD26 expression is less strong in generalized WG [6]. Another study failed to demonstrate IFN-γ expression in nasal tissues of generalized WG patients, but it was not explicitly stated whether granulomatous and/or vasculitic lesions were present [16]. Furthermore, a different antibody was used for IFN-γ staining. In generalized WG, but not in localized WG, a fraction of Th2-type CCR3+ T cells and interleukin-4 expression is seen in tissue lesions [15]. The CC chemokine RANTES is expressed in granulomatous lesions of the respiratory tract. RANTES is one of the ligands for both Th1-type CCR5 and Th2-type CCR3 and thus could favor migration of different T cell subsets into granulomatous lesions over time [17]. These data suggest that an aberrant Th1-type response might play a role during initiation of WG [3]. After a variable period, generalized PR3-ANCA-positive WG usually develops. Disease progression is associated with a "switch" or further complexity of the collective T cell response with the appearance of another subset of Th2-type cells and a less prominent Th1-type cytokine production in granulomatous lesions of the upper respiratory tract. This "switch" or increasing complexity of the cytokine profile might be a consequence of further B cell expansion and T cell-dependent PR3-ANCA production during disease progression [8].

Phenotype and function of T cells are altered in WG. Skewing of the T cell phenotype affects the whole CD4+ and CD8+ T cell population and might reflect a profound generalized alteration in T cell differentiation. A fraction of T cells lacking the co-stimulatory molecule CD28 – so-called late differentiated or effector memory T cells – is expanded in WG and some other chronic inflammatory and autoimmune diseases such as rheumatoid arthritis. The expansion of CD28- T cells starts early in the disease process and is already evident in localized WG. With disease progression to generalized WG, further expansion of CD28- T cells is seen [5]. The expansion is independent of age and immunosuppressive treatment, and it correlates with organ involvement [7,18]. CD28- T cells are enriched in bronchoalveolar fluid and are a major source of T cell tumor necrosis factor-alpha and IFN-γ production in granulomatous lesions [7,19]. Circulating CD4+ CD28- T cells express CD57 (differentiation marker), CD18 (activation marker and adhesion molecule β2-integrin), and Th1-type CCR5. They produce

IFN-γ = interferon-gamma

Th1-type cytokines TNF-α and IFN-γ, but not IL-2. Furthermore, CD4+ CD28- T cells show intracytoplasmic perforin expression, indicating a cytotoxic potential of these cells [7]. Expansion of CD28- effector memory T cells could be a consequence of cytokine effects, genetically determined, or due to an antigen-driven process; but what causes their expansion in WG remains unresolved. It has been suggested that escape of effector memory T cells from regulatory control could sustain chronic inflammation and autoimmune responses as a result of their cytokine production or bystander activation of autoreactive T and B cells [20].

WG granuloma: ectopic lymphoid tissue sustaining an immune response to PR3?

Alteration of the T cell and cytokine response and abundance of PR3 in granulomatous lesions could sustain chronic inflammation and autoimmune responses as described above, but there is scarce information on the role of antigen-presenting cells. Granulomatous lesions contain macrophages, histiocytes, and giant cells – all of which could function as (auto-)antigen-presenting cells in WG granulomatous lesions. There is some evidence that inactivation and processing of PR3 from apoptotic neutrophils via antigen-presenting cells is aberrant *in vitro* [21]. Furthermore, neutrophil granulocytes acquire characteristics of antigen-presenting cells such as HLA-DR expression in WG.

Clusters of CD20+ B cells are present in granulomatous lesions [6,22]. There is preliminary evidence of immunoglobulin heavy chain usage and affinity maturation *in loco* similar to that found in circulating PR3-ANCA-producing B cells [22]. However, it is unclear whether follicular structures are formed and plasma cells generated in granulomatous lesions in WG. Moreover, *de novo* formation of ectopic lymphoid tissue could be incomplete in the presence of a strong pro-inflammatory cytokine response. Follicular hyperplasia is seen in Hashimoto's thyroiditis, in salivary glands of patients with Sjögren's syndrome, in the thymus of patients with myasthenia gravis, and in synovitis in rheumatoid arthritis. Such structures could represent a common feature of many autoimmune diseases and a "fast track to autoimmunity" [23]. So far, the evidence that granulomatous lesions are ectopic lymphoid-like tissues in which an autoimmune response to PR3 is sustained is indirect and comes from immunhistochemical analysis and *in vitro* data. Since animal models reproducing both granulomatous lesions and vasculitis of WG are lacking, definite proof of this concept is not possible. However, this situation is not much different from that of other autoimmune diseases.

Clinico-pathologic disease stages: granulomatous inflammation vs. vasculitis

In his original report on three patients with an unknown systemic disease that would later be known as WG, Friedrich Wegener emphazised the vasculitic features of the disease, but also stressed the importance of the characteristic granuloma formation. For WG patients having a predominantly granulomatous involvement of the lungs in the absence of (renal) vasculitis, Carrington and Liebow introduced the term *limited* WG [24]. Later, Fienberg suggested the chronological sequence of initial granulomatous inflammation and subsequent development of systemic vasculitis, as discussed above [25]. Following this idea, the European Vasculitis Study Group (EUVAS) refined previous definitions and defined disease stages according to clinical and pathologic considerations [Table 2]. L*ocalized* WG has been defined as WG restricted to the upper and/or lower respiratory tract. Patients are characterized by a predominantly granulomatous inflammation of the respiratory tract in the absence of other systemic manifestations, i.e., clinically apparent vasculitis. E*arly systemic* WG includes any organ involvement except renal or imminent vital organ failure in contrast to *generalized* WG, which is characterized by renal involvement and/or imminent vital organ failure [Table 1].

Table 2. Wegener's granulomatosis as defined by EUVAS

Clinical subgroup	Constitutional symptoms	ANCA status	Threatened vital organ function
Localized	No	Negative/positive	No
Early systemic	Yes	Positive	No
Generalized	Yes	Positive	Yes
Severe renal	Yes	Positive	Yes
Refractory	Yes	Positive/negative	Yes

Definition of disease stages by the European Vasculitis Study Group (EUVAS) by clinico-pathologic criterias. It was agreed that the level of immunosuppression should reflect the severity of vasculitis.

Clinical aspects of the granulomatous inflammation in WG

Upper respiratory tract

Granulomatous ear, nose and throat manifestations represent the classic clinical symptoms of WG and are reported in more than 70% of patients as the initial symptom [26]. Later in the course of the disease, almost 100% of patients will have some manifestation of the ENT tract. Granulomatous inflammation of the nasal mucosa is often accompanied by scattered vasculitis and leads to nasal obstruction caused by diffuse mucosal swelling, crusting and bloody nasal discharge. Necrosis of the nasal cartilage may involve the entire cartilage or only parts of it. Perforation of the nasal septum or development of the typical saddle nose deformity often ensues. Frequently, perforation of the nasal septum does not become apparent until disease activity ceases and the diseased tissue is absorbed. The saddle nose deformity and perforated nasal septum are therefore not necessarily signs of active disease. Paranasal sinus involvement is another granulomatous manifestation of major importance, but it has received relatively little attention in the past decade. Headache, serosanguineous discharge and sensitive paranasal sinuses may reflect acute granulomatous inflammation. Chronic cough and nasal congestion are suggestive of chronic

TNF-α = tumor necrosis factor-alpha
IL = interleukin
ENT = ear, nose and throat

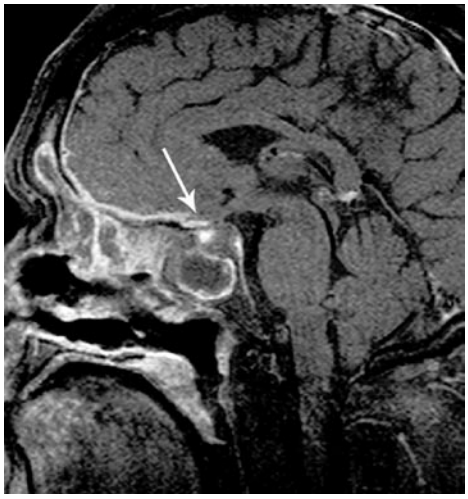

Figure 1. A 52 year old patient with known WG and new development of polyuria and polydipsia. Contrast-enhanced T1-weighted MR image shows enlarged pituitary gland and enhanced inflammatory mass in the sphenoid sinus.

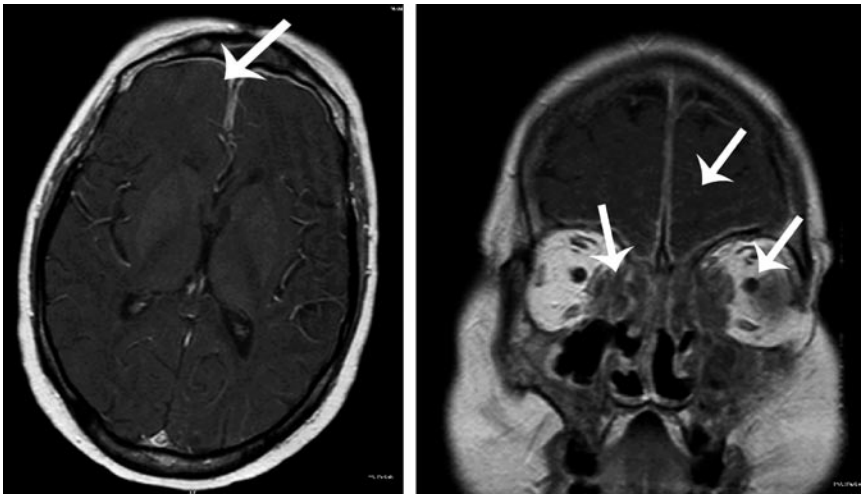

Figure 2. Patient with WG and severe frontal cephalgia due to pachymengitis and orbital granulomata with penetration from the sinus ethmoidales. T1-weighted MRI with gadolinium appears to be the most sensitive but not highly specific method for detecting thickening and enhancement of the meninges.

sinusitis [27]. Examination may reveal mucosal irregularity ("cobblestone" or "granular" appearance), ulcers, thick crusts, or friable mucosa. An excellent target for a representative biopsy is inflammation of the nose or maxillary and ethmoid cells. Granulomatous inflammation and diffuse mucosal thickening is best documented by magnetic resonance imaging, but erosions and destruction of the ethmoid sinuses or even complete bony obliteration of the maxillary, frontal or sphenoid sinuses are better illustrated by computed tomography scan. The granulomata can be detected as low signal intensity lesions on T1- and T2-weighted sequences. Granulomatous inflammation of the mastoids or, less frequently, the dacrocystitis can also be detected.

Granulomatous lesions resulting from continuous invasion from nasal or paranasal sinus may involve the orbita, meninges, brain or pituitary [Figure 1] and are present in 5–20% of patients. The development of a retro-orbital granuloma may be accompanied by symptoms such as decreased vision, diplopia or facial pain, whereas the main clinical signs are proptosis and immobility of the eyeball [28] [Figure 2]. Progression is often marked by an increased incidence of bilaterality or other systemic features. Similar to retro-orbital granulomatous inflammation, involvement of the meninges is uncommon. Interestingly, about 40% of patients with granulomatous leptomeningitis are ANCA-negative. Moreover, the majority of patients with generalized WG and a *negative* ANCA test reported in the English literature have cerebral and/or meningeal involvement [29]. Cerebrospinal fluid findings are often inconsistent, but a neuro-imaging procedure such as MRI with gadolinium appears to be the most sensitive, although not highly specific method for detecting thickening and enhancement of the meninges [30]. The differential diagnosis for diffuse symmetric linear meningeal thickening is broad and includes neurosarcoidosis. Central diabetes insipidus and hyperprolactinemia are rare complications of WG and are caused by granulomatous involvement of the pituitary gland. Typical imaging findings are pituitary enlargement and a homogenous enhancement seen in T1-weighted images [30]. Although the source of the hyperintense signal in the posterior pituitary gland on T1-weighted images remains controversial, published data suggest that it is a functional marker of the neurohypophysis and is absent in central diabetes insipidus. Histopathologic examination of invasive biopsies of the intrasellar masses were performed in two WG patients and revealed necrotic tissue containing polymorphnuclear cells with connective tissue infiltrated by lymphocytes, polymorphonuclear cells and plasma cells [31]. Usually, the introduction of immunosuppressive therapy, mainly cyclophosphamide plus glucocorticoids, results in reduction of the polyuria and polydipsia and thereby indirectly indicates the inflammatory nature of pituitary changes. The occurrence of compartmentalization with an isolated granulomatous manifestation of the meninges, the orbitae or subglottic region without active systemic disease is of particular clinical interest, but therapeutically often frustrating [32].

Lower respiratory tract

In contrast to the otorhinolarnygologic manifestations, subglottic stenosis may lead to acute respiratory failure and is an acute life-threatening disease if not treated appropriately. The incidence of subglottic stenosis ranges between 10% and 20% in WG patients [33]. Depending on the type and activity of stenosis, systemic immunosuppression may be needed. Interestingly, the clinical course of subglottic stenosis may run independent of systemic WG activity. Clinical experience has demonstrated favorable results when intervention was avoided during active disease. Only if subglottic stenosis causes severe acute respiratory failure or if scarred stenosis persists after systemic immunosuppression should intratracheal dilation be implemented.

Because of recent advances, tracheotomy is usually not required.

Granulomatous involvement of the lungs may be asymptomatic or present with unproductive cough. At the time of diagnosis, 50–70% of WG patients have abnormal chest radiographs. In the last few years the use of chest CT has revealed lesions that were undetectable on conventional X-rays. In total, more than two-thirds of patients with WG and lung disease have nodular shadows on the chest radiograph [34]. The noduli consist of round lesions with well-defined margins and are more often multiply distributed, predominantly bilateral and subpleural [35]. The granuloma size varies between 0.5 and 10 cm, but most (>65%) are small (<2 cm). Cavitation occurs in 50% of cases during the disease, frequently in the largest nodules. The cavitated noduli usually have thick to medium-sized walls and are rarely filled with fluid, but they may finally calcify after secondary infection. Open surgical biopsies of the pulmonary granuloma may reveal the characteristic triad of WG – namely, granuloma, geographic necrosis and vasculitis – that is seen less frequently in other biospy specimens [36]. For clinical management, the early detection and recognition of changes in the pulmonary granulomata is of particular significance, but the mere existence of granulomata does not automatically reflect active disease. With treatment, nodules regress without scarring in most cases, but in some patients a single granuloma may persist for years without clinical or immunologic signs of persistent disease activity.

Other rare locations of granulomatous inflammation in WG

The upper and lower respiratory tract as well as the adjacent tissues are primarily involved in WG, but granulomatous inflammation has been described in almost every organ and may also be the single manifestation of WG. Since the manifestations are rare and reported only in case reports, the diagnosis must be meticulously verified.

Salivary gland involvement is detected more frequently than other uncommon manifestations in WG. Painful unilateral or bilateral parotid swelling or submandibular salivary gland enlargement may attract attention and cause facial palsy [37]. Recurrent acute pancreatitis, histopathologically described as granulomatous pancreatitis, has been reported in WG [38]. Granulomatous inflammation of the urogenital tract has also been noted. Prostata involvement, orchitis, granulomatous inflammation of the uterus, ureteral stenosis or bladder pseudotumors may be the presenting symptoms in WG, leading to an odyssey through various medical departments for decades [39].

Conclusions

The clinical manifestations of granulomatous inflammation have a broad range in WG. In contrast to knowledge about the pathogenesis of the vasculitic component of the disease, far less is known about the granulomatous component of WG. Discovering the trigger mechanisms behind the persistence of the granulomata and the shift from localized to generalized WG will be of major interest in the future. Elucidating the mechanisms behind granulomatous inflammation in WG will help to identify new targets for more specific therapies of WG.

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