Review

Meningeal involvement in Wegener's granulomatosis is associated with localized disease

G. Di Comite, E.P. Bozzolo, L. Praderio, M. Tresoldi, M.G. Sabbadini[1]

Clinical Immunology and Rheumatology Unit, H. San Raffaele Scientific Institute; [1]Vita-Salute San Raffaele University, Milan, Italy.

Gabriele Di Comite, MD; Enrica P. Bozzolo, MD; Luisa Praderio, MD; Moreno Tresoldi, MD; Maria Grazia Sabbadini, MD.

Please address correspondence to: Gabriele Di Comite, Division of Internal Medicine 1° A, IRCCS H. San Raffaele, via Olgettina 60, 20132, Milan, Italy. E-mail: dicomite.gabriele@hsr.it

Received on May 24, 2005; accepted in revised form on September 22, 2005.

Clin Exp Rheumatol 2006; 24 (Suppl. 41): S60-S64.

Key words: Wegener's granulomatosis, meningitis, vasculitis, ANCA.

ABSTRACT

Meningeal involvement is a rare occurrence in Wegener's Granulomatosis (WG). A Medline search uncovered only 48 previously reported cases.

Here we describe the clinical features of meningeal involvement in WG and to evaluate the association with systemic disease extension.

Through a systematic literature review of papers concerning meningeal involvement in WG, we collected and analysed data about sex, age, disease extension, symptoms, cerebrospinal fluid examination, imaging, ANCA and histology about previously reported patients.

Headache is almost always the first symptom of meningeal involvement in WG. Later in the course of the disease other abnormalities may develop. Among them cranial nerve palsy, seizures and encephalopathy are the most frequent. Diagnosis is obtained by neuroimaging, which may disclose two distinct patterns of meningeal thickening: diffuse or focal. 62.9% of patients tests positive for ANCA. Histology typically shows necrotizing granulomatosis. Meningeal involvement is by far more frequent in the setting of localized WG.

Meningitis is a rare complication of WG. It usually develops in patients with localized disease who are more likely to have destructive lesions of the upper airways. It may be recognized by a constellation of clinical and radiological findings and by histological signs of necrotizing granulomatosis, with little or no vasculitis.

Introduction

Wegener's granulomatosis (WG) almost always begins with a granulomatous reaction over the upper and lower airways toward an undefined agent (1). In some patients, after a period ranging from a few months to many years, systemic vasculitis develops affecting potentially any other organ system. In this setting, the kidney is the most commonly involved organ (2).

In the mid-1960s Carrington and Liebow observed that, in certain patients, disease remains confined to the airways and that only direct extension to contiguous structures, such as the orbit, develops. They addressed this condition as limited WG (3). Since then, the definitions of different subsets of WG have varied in the medical literature (4-8) and a general consensus has not been achieved yet. Recently, two main classification systems have been adopted, respectively by the European Vasculitis Study Group (EUVAS), which identified different subgroups of patients according to the stage of disease, and by the Wegener's Granulomatosis Etanercept Trial Research Group (WRG), which made a distinction according to disease activity. In the former system, 'localized' WG was defined as disease restricted to the respiratory tract. 'Early systemic' WG included other organ involvement without renal involvement or threat to vital organ function. Finally, 'generalized' WG included glomerulonephritis or imminent vital organ failure (8). The WRG differentiated two subgroups of patients, according to the absence or presence of an immediate threat to vital organ function, respectively referred to as 'limited' and 'severe' WG (2).

According to these classifications, patients with neurological involvement are classified as having generalized or severe disease.

In the cohort of patients from the WRG, more than 90% of patients with severe WG had anti-neutrophil cytoplasmic antibodies (ANCA), more likely with a diffuse cytoplasmic (cANCA) staining at indirect immunofluorescence. On the other hand, 78% of patients in the limited disease subgroup

tested positive for ANCA and the peripheral staining (pANCA) was common (2).

In 2003 Fam *et al.* reported 1 patient with WG and biopsy-proven cranial pachymeningitis (9). They found other 14 previously reported biopsy-proven cases. Interestingly, they noted that 95% of patients developed meningeal disease in the setting of active localized disease.

During the past 20 years we have been following 60 patients with WG. Two of them developed meningeal involvement, both in the setting of WG restricted to the respiratory tract. One of them tested negative for ANCA and the other 1 had pANCA (10).

Our own experience with this rare condition and the observations reported by Fam *et al.*, rouse questions about the clinical features of patients with meningeal involvement and the pathogenetic implications of the association between meningitis and disease extension to other organs. With this aim, we performed a systematic review of the literature.

Methods

We searched 3 electronic bibliographic databases (EMBASE, MEDLINE, CINAHL) from inception to date, to find articles concerning neurological involvement in WG and case reports of meningeal localization. We found additional papers by searching the references of retrieved articles and of previous systematic reviews concerning WG. We also reviewed papers describing large cohorts of patients with WG. Search was restricted to English language papers only.

In all patients, diagnosis of WG was established according to the 1990 American College of Rheumatology (11) or to the 1976 ELK criteria (4). Patients were considered to have meningeal involvement if they had documentation on Magnetic Resonance Imaging (MRI) of new onset enhancing diffuse or focal meningeal hypertrophy. Histological confirmation was not considered necessary for diagnosis.

We extracted data about sex, age at diagnosis, systemic disease extension, neurological symptoms, cerebrospinal fluid (CSF) examination, ANCA, imaging and histology about patients with meningeal involvement.

In order to evaluate the correlation of meningeal disease with systemic vasculitis, we classified patients into subgroups according to the EUVAS classification system (8). Thus, disease is referred to as 'localized' when it is restricted to the upper and/or lower airways; 'early systemic' when any other organ is involved, without renal involvement or threat to vital organ function; 'generalized' in the presence of glomerulonephritis or imminent vital organ failure.

Results

Chronic meningitis is a rare complication in WG. It was detected in 2 of 324 WG patients from the Mayo Clinic in Rochester (12, 13) and in none of the patients described in other large series in the English medical literature (2, 14-16). A search for single reports disclosed 46 more patients with meningeal involvement in WG.

Epidemiology: the male/female ratio was 9/8, or 1.13. The mean (± SD) age at diagnosis of meningitis was 48.2 ± 15.1, range 16-75 (Table I).

We know that in 32/48 patients the mean time between the onset of WG first symptoms and the onset of meningitis was 34.87 ± 59.35 months (range 0-240). Among patients with localized, early systemic and generalized WG the mean time was respectively 30.9 ± 59.8 (range 0-240), 32.2 ± 49.9 (range 8-155) and 49.5 ± 73.8 (range 0-180).

In 13 patients the onset of the meningeal manifestations was not preceded by other signs of WG.

Disease extension: detailed clinical data were available for 37 of the 48 patients (regarding the other 11 patients, only a description of the radiological features was provided) (17). Twenty-six patients were classified as having localized WG (70.3%) before the onset of meningitis, 4 as having early systemic disease (10.8%) and the remaining 7 as having generalized WG (18.9%).

Among the 26 patients with localized WG, sinusitis and/or nasal mucosa inflammation was present in 22 cases (84.6%). In 2 patients mastoiditis was observed and in 2 patients saddle-nose developed. Two patients (7.7%) had sub-glottic stenosis. In 9 cases (34.6%) the disease was restricted to the ENT (Ear/Nose/Throat) system, while 8 patients (30.8%) had also lung involvement. Four patients (15.4%) presented proptosis due to extension of sinus granulomas to the orbital space. In 3 patients (11.5%) WG was restricted to meninges only. All of them had a typical histological picture.

Four patients were classified as having early systemic disease. All of them had sinusitis and/or nasal involvement and cutaneous vasculitis. One of them developed monolateral scleritis and another one had sub-glottic stenosis. Two patients presented concomitant lung involvement.

Among the 7 patients with generalized WG, renal and ENT-system involvement were always present. In all but 1

Table I. Clinical features of 37 patients with meningeal involvement in WG.

Characteristic	
Age (years) at meningitis onset (SD years)	48.2 ± 15.1
Months between first WG symptoms and meningitis onset	34.9 ± 59.4
	% of pts
Sex	
Male	52.9
Female	47.1
ENT	89.1
Limited WG	84.6
Early Systemic WG	100
Generalized WG	100
Lung	37.8
Limited WG	30.8
Early Systemic WG	50
Generalized WG	85.7
Kidney	18.9
Eye	13.5
Limited WG	15.4
Early systemic WG	25
Generalized WG	-
Skin	16.2
Early systemic WG	15.4
Generalized WG	28.6
Joints (arthritis)	5.4
Peripheral nervous system	2.7
ANCA	62.9
cANCA	37.1
pANCA	14.3
Unidentified pattern	11.4

patient, the lungs were also affected. Two patients developed arthritis and 2 developed cutaneous vasculitis. In 1 case, peripheral nervous system involvement coexisted. The overall rate of the different organs involvement among these 37 patients is shown in Table I.

Neurological symptoms: a detailed clinical description is available for 37 patients (Table II). Chronic headache was the most common (72.3%) and almost always the first symptom of meningeal localization of WG. Additional abnormalities developed later in the course of the disease. Cranial nerve palsy has been reported in 32.4% of cases, with III, VI, VII and X nerves most commonly involved. Any other cranial nerve might be affected and multiple palsies were common. Seizures have been described in 13.5% of patients and encephalopathy in 10.8%. Monolateral proptosis, due to an orbital mass, was observed in 10.8% of patients; ataxia, due to cerebellar meninges involvement, and blurred vision in 5.4%. We found single reports (2.7%) of transient ischaemic attacks, personality changes/hallucinations and paresthesia. Patients with spinal cord involvement (18.9%) presented with neck pain or backache. Spastic paraparesis might also be present.

Table II. Clinical features of chronic meningitis in 37 patients with WG.

Characteristics	Pts (%)
Symptoms	
Headache	72.3
Cranial nerve palsy	32.4
Seizures	13.5
Encephalopathy	10.8
Proptosis	8.1
Ataxia	5.4
Blurred vision	5.4
Ischaemic attacks	2.7
Personality changes	2.7
Paresthesia	2.7
CSF examination	
Pleocytosis	41.2
High protein count	41.2
High pressure	17.6
Normal	29.4
Pathology	
Necrotizing granulomatosis	61.5
Small vessel vasculitis	7.7
Granulomatosis + vasculitis	15.4
Lymphocytic inflammation	11.5
Fibrous thickening	3.8

Table III. Radiological features of chronic meningitis in 48 patients with WG.

Characteristics	Pts (%)
Localization	
Brain	87.5
Spinal cord	14.6
Involved meninges	
Dura	81.2
Leptomeninges	27.1
MRI thickening pattern	
Diffuse	72.9
Focal	27.1

Imaging: data are shown in Table III. MRI with gadolinium contrast or Computed Tomography (CT) typically showed dural thickening on the contrast-enhanced phase (81.2%). Leptomeninges involvement was found less commonly (27.1%). In 10.8% of cases dural and leptomeningeal thickening coexisted.

Brain meninges were affected in 87.5% of cases (42/48 patients) and spinal cord meninges in 14.6% (7/48). Two distinct MRI patterns were described in 1999 by Murphy *et al.*: a) diffusely abnormal meninges unrelated to sinus or orbital disease; b) focal enhancing thickening adjacent to sinus or orbital disease (17). 72.9% of patients presented the former pattern of distribution and 27.1% the latter one. In 4 patients white matter lesions, adjacent to meningeal thickening, have been described. Tentorium was affected in 31.3% of cases. Spinal cord involvement always consisted of dural thickening.

CSF examination: lumbar puncture was performed in 17 patients (Table II). In 41.2% of cases a mild pleocytosis, mainly consisting of lymphocytes and monocytes, and a high protein concentration were found. 17.6% of patients had elevated pressure. CSF was normal in 29.4% of cases. In 1 patient with pulmonary and renal disease, ANCA were found in the CSF and were used as a marker for disease activity. ANCA disappeared when remission was achieved (18).

Histology: meningeal biopsy was performed in 26 patients (Table II). The most common finding was necrotizing granulomatous inflammation, with little or no signs of vasculitis (61.5%). In 7.7% of cases small vessel vasculitis was the main feature and in 15.4% granulomatosis and vasculitis coexisted. 11.5% of patients presented an aspecific lymphocytic inflammatory pattern. Autopsy of 1 patient with generalized disease disclosed dural fibrous thickening.

ANCA: ANCA were tested in 35 patients and were found positive in 22 (62.9%). Six out of 7 patients (85.7%) with generalized WG had ANCA, with a cytoplasmic staining at indirect immunofluorescence in 4, a peripheral pattern in 1 and an undefined pattern in the remaining case. Thirteen out of 25 patients (52%) with localized WG tested positive for ANCA: 8 had cANCA, 4 pANCA and in 1 patient the staining was not specified. Three out of 4 patients with early systemic disease were tested for ANCA: one stained positive for cANCA and the remaining two patients were negative (Table I).

Treatment: Few details about treatment and follow-up have been reported. We know that 24 patients were treated with corticosteroids, in association with oral or intravenous pulse cyclophosphamide (1.5-2 mg/Kg) in 17 cases. One patient was treated with monthly infusions of 10 mg intrathecal methotrexate and 2 with weekly 15-20 mg oral methotrexate. Treatment achieved a complete clinical response in all patients but 1, who died 1 month after starting oral cyclophosphamide, because of interstitial pneumonia. In 14 patients follow-up MRI was performed and showed a complete resolution of the radiological abnormalities in 11 patients. In 3 cases residual persistent enhancing thickening was observed, despite apparent remission of disease. It is not clear whether this represents active disease or residual fibrosis (19).

Discussion

WG is characterized by granulomas of the respiratory tract and systemic necrotizing vasculitis, commonly in association with ANCA directed to a defined target antigen, proteinase 3, a protein present within granules of neutrophils and translocated to the surface upon priming of the cell (20). The interaction between ANCA and neutrophils

induces the respiratory burst and release of proteolytic enzymes, which sustain a state of chronic inflammation (21). The etiology of WG appears multifactorial and bacterial infections of the respiratory tract have been proposed as initiators of the disease. Whereas granulomatous lesions express predominantly T helper type 1 cytokines in localized WG, a shift towards stronger T helper type 2 cytokine expression is found in granulomatous lesions of the respiratory tract in generalized WG. Thus, the shift in the cytokine profile in granulomatous lesions of the respiratory tract might be of importance for the direction and the extension of disease progression (21, 22).

Neurological involvement is not uncommon in WG, with central nervous system (CNS) affected in 3-23% of cases (2, 15, 23). Three alternative mechanisms have been proposed for the pathogenesis of the different CNS manifestations in WG: a) vasculitis of the nervous system; b) direct granulomas extension from contiguous affected structures (sinus or orbit); c) granulomas remote from involved nasal or paranasal structures (23, 24).

Meningeal involvement has been rarely observed in patients with WG. We found only 2 cases among large cohorts of patients and 46 single case reports. Review of those reports reveals interesting features.

Headache is the most common symptom associated with chronic meningitis. Headache is a common symptom in WG, due to chronic sinusitis or orbital disease, therefore meningeal involvement may remain unrecognized for a long time. Most patients develop, later in the course of the disease, additional neurological abnormalities. Multiple cranial nerve palsy is frequent, most commonly with III, VI, VII and X nerves affected. Less frequently seizures, encephalopathy, monolateral proptosis, ataxia or blurred vision develop. We found single reports of transient ischaemic attacks, psychiatric syndromes or paresthesia. Spinal cord involvement usually presents with neck pain or backache and with unsteady gait, typically due to spastic paraparesis. MRI with gadolinium contrast is the most useful diagnostic technique to detect meningeal disease, as computed tomography (CT) sensitivity is lower (17, 24). The most commonly observed finding on MRI is diffuse dural enhancing thickening, followed by focal dural thickening. Tentorium involvement is quite common. Only in a minority of cases the leptomeninges are affected. 62.9% of patients test positive for ANCA, with a cytoplasmic staining in only 37.1% of cases.

Histological examination most commonly shows necrotizing granulomatosis. The finding of prominent small vessel vasculitis in the specimen from 2 patients and the presence of sub-dural haematoma in another patient, suggest that, in a minority of cases, vasculitis is the pathogenetic factor of meningitis.

Patients with meningeal involvement in WG were treated with high-dose corticosteroids, in association with immunosuppressants in the majority of cases. Cyclophosphamide was the most commonly adopted drug and both cyclophosphamide and methotrexate provided successful results. There is a general consensus concerning the fact that vital organ involvement in WG should be treated promptly and aggressively. Thus, accordingly with the data from the literature, we suggest the administration of high-dose corticosteroids in association with cyclophosphamide or methotrexate for the treatment of meningitis in WG.

The most striking data resulting from our analysis is the strong association of meningeal disease with active localized disease, which was observed in 70.3% of patients, compared with 10.8 and 18.9% of patients with early systemic and generalized disease respectively.

The WRG reported in 2003 that patients with localized WG are more likely to have a higher rate of sinus involvement and of upper airway destructive lesions (2). We wonder whether this might be the reason why meningitis in WG is strongly associated with localized disease.

It could be argued that, in patients with localized WG, diagnosis is often delayed, compared with patients with early systemic and generalized disease, due to the paucity of symptoms, and that this, in the absence of an adequate treatment, may favour spreading to meninges. We noted, however, that the mean time between the onset of the first symptoms of WG and the development of meningitis was not different between patients in the localized-disease group and patients in the other two groups. Furthermore, in 13 patients with localized disease, meningitis was not preceded by other signs of WG and in 3 of them meninges seemed to be the only organ affected.

In 2001, Reinhold-Keller *et al.* observed that the English language literature had previously described only 12 patients with generalized ANCA-negative WG and that 10 of them had cerebral and/or meningeal involvement (25). We wonder whether those patients could have developed CNS disease in the setting of localized WG, through direct extension of granulomas from the upper airways structures, since ANCA are much less common among patients with localized disease compared with patients with generalized WG. Accordingly, in the cohort of patients we considered, 52% of patients with localized disease and 86% of patients with generalized disease respectively stained positive for ANCA.

All the above-mentioned considerations and the observation that granulomatous inflammation is more prominent in the respiratory tract lesions, whereas the kidneys are principally affected by widespread vasculitis (26, 27), seem to suggest that the spreading of granulomas from contiguous or remote paranasal or orbital affected structures could be the major mechanism of meningeal disease development (23, 24).

Definitions of different WG subgroups is still hampered by an imprecise understanding of the factors that influence the type of response in a given individual. Recently some authors suggested that the severity of WG might have to be considered in terms of 'granulomatous-vasculitic activity', rather than in terms of 'limited-generalized' or 'renal-nonrenal' (26, 27).

Further advances in this direction will help to clarify the factors underlying the development of CNS involvement in WG.

References

1. PAPADIMITRAKI ED, KYRMIZAKIS DE, KRITIKOS I *et al*.: Ear-nose-throat manifestations of autoimmune rheumatic diseases. *Clin Exp Rheumatol* 2004; 22: 485-94.
2. THE WEGENER'S GRANULOMATOSIS ETANERCEPT TRIAL RESEARCH GROUP: Limited versus generalized Wegener's Granulomatosis. Baseline data on patients in the Wegener's Etanercept trial. *Arthritis Rheum* 2003; 48: 2299-309.
3. CARRINGTON CB, LIEBOW AA: Limited forms of angiitis and granulomatosis of Wegener's type. *Am J Med* 1966; 41: 497-527.
4. DEREMEE RA, MCDONALD TJ, HARRISON EG JR, COLES DT: Wegener's granulomatosis. Anatomic correlates, a proposed classification. *Mayo Clin Proc* 1976; 51: 777-81.
5. LUQMANI RA, BACON PA, BEAMAN M *et al*.: Classic versus non-renal Wegener's granulomatosis. *Q J Med* 1994; 87: 161-7.
6. MACFARLANE DG, BOURNE JT, DIEPPE PA, EASTY DL: Indolent Wegener's granulomatosis. *Ann Rheum Dis* 1983; 42: 398-407.
7. STEGEMAN CA, BOOMSMA MM, COHEN TERVAERT JW: Trimethroprim-sulfamethoxazole monotherapy for active loco-regional or limited Wegener's granulomatosis. *Arthritis Rheum* 2001; 44 (Suppl. 9): S55.
8. JAYNE D: Update on the European Vasculitis Study Group trials. *Curr Opin Rheumatol* 2001; 13: 48-55.
9. FAM AG, LAVINE E, LEE L, PEREZ-ORDONEZ B, GOYAL M: Cranial pachymeningitis: an unusual manifestation of Wegener's granulomatosis. *J Rheumatol* 2003; 30: 2070-4.
10. DI COMITE G, BOZZOLO E, BIANCHI S, SABBADINI MG: Two cases of meningeal involvement in Wegener's granulomatosis. *Rheumatology* (*Oxford*) 2004; 43: 1459-60.
11. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990; 33: 1101-7.
12. NISHINO H, RUBINO FA, DEREMEE RA, SWANSON JW, PARISI JE: Neurological involvement in Wegener's Granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. *Ann Neurol* 1993; 33: 4-9.
13. NISHINO H, RUBINO FA, PARISI JE: The Spectrum of Neurological Involvement in Wegener's Granulomatosis. *Neurology* 1993; 43: 1334-7.
14. FAUCI AS, HAYNES BF, KATZ P, WOLFF SM: Wegener's Granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; 98: 76-85.
15. HOFFMAN GS, KERR GS, LEAVITT RY *et al*.: Wegener's Granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; 116: 488-98.
16. LANGFORD CA, TALAR-WILLIAMS C, BARRON KS, SNELLER MC: Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's Granulomatosis: extended follow-up and rate of relapses. *Am J Med* 2003; 114: 463-9.
17. MURPHY JM, GOMEZ-ANSON B, GILLARD JH *et al*.: Wegener's Granulomatosis: MR imaging findings in brain and meninges. *Radiology* 1999; 213: 794-9.
18. SPRANGER M, SCHWAB S, MEINCK HM *et al*.: Meningeal involvement in Wegener's granulomatosis confirmed and monitored by positive circulating antineutrophil cytoplasm in cerebrospinal fluid. *Neurology* 1997; 48: 263-5.
19. MURPHY JM, BALAN KK, TOMS A, GOMEZ-ANSON B, LOCKWOOD M: Radiolabeled leucocyte imaging in diffuse granulomatous involvement of the meninges in Wegener's granulomatosis: scintigraphic findings and their role in monitoring treatment response to specific immunotherapy (humanized monoclonal antilymphocyte antibodies). *Am J Neuroradiol* 2000; 21: 1460-5.
20. BORGMANN S, HAUBITZ M: Genetic impact of pathogenesis and prognosis of ANCA-associated vasculitides. *Clin Exp Rheumatol* 2004; 22: S79-86.
21. MUELLER A, HOLL-ULRICHK, FELLER AC *et al*.: Immune phenomena in localized and generalized Wegener's granulomatosis. *Clin Exp Rheumatol* 2003; 21: S49-54.
22. LAMPRECHT P, ERDMANN A, MUELLER A *et al*.: Heterogeneity of CD4 and CD8$^+$ memory T cells in localized and generalized Wegener's granulomatosis. *Arthritis Res Ter* 2003; 5: R25-31.
23. DRACHMAN DD: Neurological complications of Wegener's Granulomatosis. *Arch Neurol* 1963; 8: 145-155.
24. SCULLY RE, MARK EJ, MCNEELY WF, EBELING SH: Case Records of the Massachusetts General Hospital. *N Eng J Med* 1999; 340: 945-53.
25. REINHOLD-KELLER E, DEGROOT K, HOLL-ULRICH K *et al*.: Severe CNS manifestations as the clinical hallmark in generalized Wegener's Granulomatosis consistently negative for antineutrophil cytoplasmic antibodies (ANCA). A report of 3 cases and a review of the literature. *Clin Exp Rheumatol* 2001; 19: 541-9.
26. BLIGNY D, MAHR A, LETOUMELIN P, MOUTHON L, GUILLEVIN L: Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. *Arthritis Rheum* 2004; 51: 83-91.
27. BAJEMA IM, HAGEN EC, FERRARIO F *et al*.: Renal granulomas in systemic vasculitis. EC/BCR project for ANCA-assay standardization. *Clin Nephrol* 1997; 48: 16-21.