Orbital mass as manifestation of Wegener's granulomatosis: an ophthalmologic diagnostic approach

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ABSTRACT

Objective. *Orbital manifestation of Wegener's granulomatosis is diverse and diagnosis is often difficult. This study aims to improve the diagnostic strategy in orbital Wegener.*

Methods. *A review of the diagnostic process in patients in whom a diagnosis of orbital WG was considered.*

Results. *Thirty-three patients were analysed, consisting of 15 patients with orbital WG, 11 with idiopathic orbital inflammation, 6 with orbital sarcoidosis and one with aspergillosis. Diagnostic findings indicating orbital WG were ear/nose/throat involvement, multiple organ system involvement, a positive ANCA, and on histology vasculitis, whereas granulomatous inflammation without signs of vasculitis was more indicative of another orbital disease.*

Conclusion. *The diagnostic process of orbital WG should include CT scanning of the orbit and sinuses, ANCA blood testing, consultation of a rheumatologist, an ophthalmologist, and an ear-nose-throat specialist, and biopsy of an easily accessible, active inflammatory lesion.*

Introduction

To diagnose orbital Wegener's granulomatosis (WG) is a challenge. WG is a relapsing multi-organ disease most often affecting the kidneys and respiratory tract. If untreated, the disease can result in renal failure and death (1-3). Ophthalmic involvement is quite diverse as it may include scleritis, corneal melting, uveitis, lacrimal duct obstruction and orbital mass (4).

The diagnostic process in orbital WG is complicated by negative and aspecific findings in blood tests (5, 6), imaging (7) and biopsy (8-12). As a result, the diagnostic process takes longer. This may harm the patient as inflammation continues, causing irreversible damage. To improve our diagnostic strategy, we reviewed patients with an orbital mass in whom WG was in the differential diagnosis. Our aim is to shorten the diagnostic process in WG by identifying diagnostic features that differentiate orbital WG from other orbital inflammatory diseases.

Materials and methods

At the University Medical Centre Utrecht, the Netherlands, patients were collected with a new orbital mass in which WG was in the differential diagnosis between 1992 and 2007. These patients had been referred to the orbital clinic either by other ophthalmologists or rheumatologists. Patients were identified searching the diagnosis, radiology and pathology databases for orbital masses in which Wegener was in the differential diagnosis. A history of systemic WG was not an exclusion criterion.

Information was collected on sex, age at diagnosis, race, final diagnosis, organ system inflammation reported by other physicians, ocular involvement, past medical history, symptoms at presentation to the orbital clinic, laboratory findings, radiologic imaging, and biopsy of orbital inflammation. The data used for analysis included only information gathered during the diagnostic process and not thereafter. ANCA was considered positive when before or during the diagnostic process an elevated C- or P-ANCA level was found using immunofluorescence, mostly with confirmation of PR3- or MPO- ANCA using ELISA.

The final diagnoses of the orbital lesions were: WG, idiopathic orbital inflammation (IOI), sarcoidosis and aspergillosis. The diagnosis WG was made according to the American College of Rheumatology (ACR) criteria (13) with two or more of the following criteria 1) nasal or oral inflammation, 2) abnormal chest radiograph showing nodules, fixed infiltrates, or cavities, 3) abnormal urinary sediment, and 4) granulomatous inflammation on biopsy of an artery or perivascular area. Sarcoidosis was

Table I. Characteristics of 32 patients in whom a diagnosis of orbital Wegener's granulomatosis (WG) was considered.

	Orbital WG (n=15) n. observed (%)	Idiopathic orbital inflammation (n=11) n. observed (%)	Sarcoidosis (n=6) n. observed (%)	Aspergillosis (n=1) n. observed
Demographics				
Sex male	8 (53)	4 (36)	3 (50)	0
Race Caucasian	15 (100)	11 (100)	5 (83)	0
Age mean in years (min-max)	47 (12–70)	39 (1–61)	45 (22–72)	25
Organ inflammation				
Kidneys	3 (20)	0 (0)	0 (0)	0
Lungs	5 (33)	0 (0)	2 (33)	0
Skin	1 (7)	0 (0)	0 (0)	0
Joints	3 (20)	0 (0)	0 (0)	0
Ear, nose throat*	11 (73)	1 (9)**	0 (0)	1
Nervous system	3 (20)	1 (9)**	0 (0)	0
Gastro intestinal	1 (7)	0 (0)	0 (0)	0
Median number of organs involved (min-max)*	3 (1–5)	1 (1–2)	1 (1–2)	1
Ocular involvement				
Intraocular	1 (7)	1 (9)	0 (0)	0
Sclera	4 (27)	1 (9)	0 (0)	0
Cornea	1 (7)	0 (0)	0 (0)	0
Orbit	15 (100)	11 (100)	6 (100)	1
Lacrimal duct	3 (20)	0 (0)	0 (0)	1
Median number of eye structures involved (min-max)	1 (1–3)	1 (1–3)	1 (1–1)	2

*Significantly deviating between Wegener's granulomatosis and the group of other diagnoses at the p=0.05 level.
** by extension from orbital lesions.

diagnosed after work-up by a pulmonologist. A diagnosis of idiopathic orbital inflammation was made, after exclusion of other diseases and biopsy showing non-specific orbital inflammation. Aspergillosis was diagnosed by fungus stain and culture.

Statistical analysis was performed using SPSS 15.0 for Windows. Diagnostic features were compared between WG and the combined group of IOI, sarcoidosis, and aspergillosis. Student's *t*-test was used for normal distributed, continuous data, Mann-Whitney test for non-parametric distributed data, and chi-square tests for frequencies. This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Results

Thirty-three patients were identified in whom a diagnosis of orbital WG had been seriously considered. The final diagnoses were: WG in 15 cases, idiopathic orbital inflammation in 11, orbital sarcoidosis in 6, and aspergillosis in 1.

In the patients with orbital WG, 5 had systemic involvement and 8 were limited to the respiratory tract. Another two patients did not fulfil the ACR criteria, but were considered WG and treated as such. Of these two, one patient was considered ocular limited WG because of a biopsy showing granulomatous vasculitis and a history of recurrent sinus disease, but with a negative sinus mucosa biopsy (14-16). The other presumed WG had a positive ANCA, necrosis on biopsy, and arthralgias and skin lesions suggestive of WG.

Table I "patient characteristics" shows that patients with WG more often have other organ system inflammation (median number of organs involved in WG 3 *versus* 1 for the other diagnoses p<0.001). Especially ear/nose and throat symptoms were more frequently encountered in orbital WG patients (11/15 in WG *versus* 2/18 in other diagnoses p<0.001). Table II "diagnostic data" shows that ANCA testing was found to be positive only in WG (10/11 p<0.001). Biopsy sites for the orbital WG group were eyelid 1, lacrimal gland 2, orbit 8, and paranasal sinus 2; for the IOI group extraocular muscle 2 and orbit 9; for the sarcoidosis group lacrimal gland 2 and orbit 4; for the aspergillosis patient the paranasal sinus. Granuloma on biopsy was found in many patients, but mostly in sarcoidosis, whereas vasculitis was found more in WG (5/10 in WG *versus* 1/18 in other diagnoses p=0.013). Granuloma without vasculitis was found less in WG (1/10 in WG *versus* 13/18 in other diagnoses p=0.004).

Nine patients had already been diagnosed as WG of another organ system at first presentation to the orbital clinic. The group with and without prior WG diagnosis were similar in most aspects. The group without prior WG diagnosis presented more often with periorbital swelling (5/6 *versus* 3/9 p=0.084) but had fewer ocular structures involved (median number structures involved 1 *versus* 2 in prior WG diagnosis p=0.088).

Table III "treatments and clinical course" highlights the serious course of orbital WG with more aggressive therapies applied and poorer outcome compared to idiopathic orbital inflammation, and sarcoidosis.

Discussion

This study was aimed to shorten the diagnostic process in orbital WG by

Table II. Diagnostic data of symptoms, signs, laboratory, imaging, and biopsy.

	Orbital WG n. observed / n. total (%)	Idiopathic orbital inflammation n. observed / n. total (%)	Sarcoidosis n. observed / n. total (%)	Aspergillosis n. observed / n. total
Symptoms				
vision loss	4 / 15 (27)	1 / 11 (9)	0 / 6 (0)	1 / 1
swelling	8 / 15 (53)	5 / 11 (45)	6 / 6 (100)	1 / 1
proptosis	4 / 15 (27)	1 / 11 (9)	0 / 6 (0)	1 / 1
eye motility disturbances	1 / 15 (7)	2 / 11 (18)	0 / 6 (0)	1 / 1
diplopia	3 / 15 (20)	5 / 11 (45)	1 / 6 (17)	1 / 1
median duration of symptoms in days (min-max)	73 (10-600)	60 (7–700)	105 (15–360)	14
Past medical history				
Wegener's granulomatosis	9 / 15 (60)	0 / 11 (0)	0 / 6 (0)	0 / 1
Other autoimmune diseases	0 / 15 (0)	1 / 11 (9)	0 / 6 (0)	0 / 1
Signs				
Mass	7 / 14 (50)	2 / 11 (18)	4 / 6 (67)	1 / 1
Proptosis	8 / 14 (57)	5 / 11 (45)	3 / 6 (50)	1 / 1
Limited eye movements	5 / 15 (33)	7 / 11 (64)	1 / 6 (17)	1 / 1
Bilateral	2 / 15 (13)	2 / 11 (18)	0 / 6 (0)	0 / 1
Laboratory				
Thyroid dysfunction	0 / 3 (0)	0 / 8 (0)	0 / 3 (0)	0 / 0
ACE raised	2 / 6 (33)	0 / 6 (0)	2 / 6 (33)	0 / 0
ANCA*	10 / 11 (91)	0 / 5 (0)	0 / 2 (0)	0 / 0
Radiologic imaging				
Anterior orbit involved	8 / 14 (57)	7 / 11 (64)	3 / 5 (60)	1 / 1
Intermediate orbit involved	9 / 14 (64)	5 / 11 (45)	2 / 5 (40)	0 / 1
Apex involved	3 / 14 (21)	2 / 11 (18)	0 / 5 (0)	0 / 1
Extraocular muscle involved	8 / 11 (73)	7 / 9 (78)	1 / 4 (25)	0 / 1
Lacrimal gland involved	5 / 11 (45)	3 / 9 (33)	2 / 4 (50)	0 / 1
Discrete mass	1 / 11 (9)	0 / 5 (0)	1 / 3 (33)	0 / 1
Bone erosion	5 / 11 (45)	2 / 7 (29)	0 / 2 (0)	1 / 1
Mucosal swelling in sinuses	10 / 13 (77)	6 / 6 (100)	2 / 3 (67)	1 / 1
Biopsy				
Inflammation	8 / 10 (80)	9 / 11 (82)	6 / 6 (100)	1 / 1
Granuloma*	3 / 10 (30)	6 / 11 (55)	6 / 6 (100)	1 / 1
Vasculitis*	5 / 10 (50)	1 / 11 (9)	0 / 6 (0)	0 / 1
Necrosis	3 / 10 (30)	0 / 11 (0)	3 / 6 (50)	0 / 1
Granuloma without vasculitis*	1 / 10 (10)	6 / 11 (55)	6 / 6 (100)	1 / 1

*Significantly deviating between Wegener's granulomatosis and the group of other diagnoses at the p=0.05 level WG Wegener's granulomatosis.

identifying diagnostic features that differentiate WG from other orbital inflammatory diseases. Of all considered diagnostic features, ear/nose/throat involvement, a positive ANCA, multiple organ system involvement and vasculitis are most indicative of WG, whereas granulomatous inflammation without signs of vasculitis is more suggestive of sarcoidosis, IOI or aspergillosis.

In WG, ninety percent of active, generalised diseases are ANCA positive (17). However, ANCA is less often present in limited WG and can become negative after treatment (15, 18). A positive ANCA has been reported by Woo and Perry in about 2 out of 3 cases of orbital WG (8, 9). Absence of ANCA does not rule out WG, but was a strong predictor of Orbital WG in this study. Current evidence suggests a pathogenetic role for ANCA in the development of vasculitides including Wegener (19).

As the name implies, Wegener's granulomatosis is a granulomatous disease and "granulomatous inflammation on biopsy of an artery or perivascular area" is one of the ACR criteria for WG. However, on orbital biopsy granulomatous inflammation is a nonspecific finding and in the absence of vasculitis more indicative of sarcoidosis, idiopathic orbital inflammation, or aspergillosis. This implies that orbital biopsy often does not make the diagnosis of WG, but can be helpful in ruling out other diseases. The difficult interpretation of orbital biopsy in suspected WG has been pointed out by others. WG lesions are thought to evolve from extravascular granuloma to granulomatous vasculitis to systemic vasculitis, making the findings on biopsy dependent on the timing of biopsy in the clinical course of the disease (20). The classic triad of necrosis, granuloma and vasculitis is only present in a minority of cases, and more often one or two features are present, with vasculitis reported most frequently (8-12). It is known that biopsy of an active site gives the best di-

Table III. Treatment and clinical course of 15 orbital Wegener, 11 idiopathic orbital inflammation and 6 sarcoidosis patients.

	Orbital n. observed / n. total (%)	Idiopathic orbital Wegener's n. observed / .n total (%)	Sarcoidosis inflammation n. observed / n. total (%)
Treatment			
None	1 / 15 (7)	3 / 11 (27)	4 / 6 (67)
Corticosteroids	14 / 15 (93)	7 / 11 (64)	2 / 6 (33)
Cyclophosphamide or azathioprine	14 / 15 (93)	0 / 11 (0)	0 / 6 (0)
Radiotherapy	2 / 15 (13)	1 / 11 (9)	0 / 6 (0)
Surgery	3 / 15 (20)	1 / 11 (9)	0 / 6 (0)
Maintenance therapy	12 / 15 (80)	0 / 11 (0)	0 / 6 (0)
Course			
Regression	2 / 15 (13)	6 / 11 (55)	6 / 6 (100)
Stabilisation	6 / 15 (40)	4 / 11 (36)	0 / 6 (0)
Progression	7 / 15 (47)	1 / 11 (9)	0 / 6 (0)
Outcome			
Visual acuity loss	6 / 15 (40)	1 / 11 (9)	0 / 6 (0)
Persistent eyeball motility disturbances	6 / 15 (40)	4 / 11 (36)	0 / 6 (0)
Visual field loss	4 / 15 (27)	1 / 11 (9)	0 / 6 (0)
Loss of eye	2 / 15 (13)	0 / 11 (0)	0 / 6 (0)
Median follow-up in years (min-max)	3 (1–13)	4 (0–7)	2 (0–4)

agnostic yield in WG. Therefore, biopsy of other sites of involvement should be included in the diagnostic work-up. Because the upper respiratory tract is often involved and is easy accessible, this can be a good site for biopsy by the ear/nose/throat (ENT) specialist.

WG of the orbit often occurs together with WG of the nose and paranasal sinuses. Orbital manifestations mostly occur in limited WG. This high co-occurrence of ocular and nasal/sinusoidal WG, and the combination of limited WG with ocular disease were also found by others (8-10).

Radiologic imaging, although helpful for localising the orbital mass, did not help to differentiate the nature of the inflammatory process in this study. Tarabishy *et al*. have shown that magnetic resonance imaging with gadolinium is able to differentiate between orbital WG, Graves', IOI, and lymhoma based on different T1 and T2 intensities (21). In selected patients with an established diagnosis of systemic WG, a radiologic scan highly suggestive of orbital WG may yield an orbital biopsy unnecessary. Bone erosion and sinus lesions are frequently reported in WG (7, 9). In this series, these lesions were found in both WG and other inflammatory diseases.

In summary: ear/nose/throat involvement, a positive ANCA, multiple organ system involvement and vasculitis are most indicative of WG, whereas granulomatous inflammation without signs of vasculitis is more suggestive of another orbital inflammatory disease. In an orbital lesion where WG is in the differential diagnosis, we recommend a CT/MRI scan of the orbit and sinuses, ANCA testing, systemic evaluation by a rheumatologist, consultation of an experienced ENT specialist with biopsy of inflammatory nasal lesions, and biopsy of easy accessible active orbital lesions. If the aforementioned workup does not make a diagnosis, less accessible or nonactive orbital lesions should be biopsied (Fig. 1).

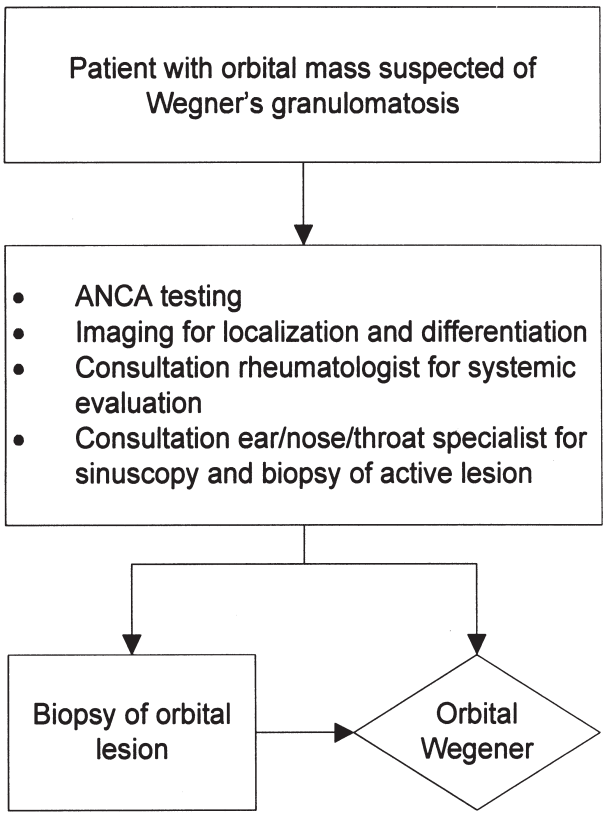

Fig. 1. Flowchart of diagnostic process for orbital Wegener's granulomatosis.

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