Wegener's Granulomatosis Strictly and Persistently Localized to One Organ Is Rare: Assessment of 16 Patients from the French Vasculitis Study Group Database

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ABSTRACT. ***Objective.*** To study the frequency and characteristics of patients with Wegener's granulomatosis (WG) strictly and persistently localized to one organ.

Methods. Retrospective analysis of the French Vasculitis Study Group (FVSG) WG cohort.

Results. Sixteen patients (3.2% of the cohort) were identified who had isolated lung nodules, ear-nose-throat, or ocular involvement that did not progress to systemic disease (median followup, 58 mo) over the period of observation. Ten received first-line therapy with cyclophosphamide, which was effective in 4. Cotrimoxazole alone achieved remission in one, combined with corticosteroids in 3. Eight required subsequent treatments because of first-line failure or relapse.

Conclusion. Strictly and persistently localized WG is uncommon. Optimal treatment remains to be determined. (First Release Dec 1 2010; J Rheumatol 2011;38:475–8; doi:10.3899/jrheum.100518)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS TREATMENT LOCALIZED FORMS

Two phenotypes of Wegener's granulomatosis (WG) have been described, but their definitions are still debated. One, systemic or severe, is associated with potentially life-threatening manifestations, and the other is more limited[1,2,3,4]. It remains unclear whether patients with WG limited to one organ or system are just diagnosed at an early phase or represent a distinct subset.

We conducted a retrospective study on the patients with WG in the French Vasculitis Study Group (FVSG) database, to estimate the frequency and analyze the characteristics of those with strictly localized disease that did not progress to more generalized forms throughout their followup.

MATERIALS AND METHODS

Since 1982, clinical data from patients with WG, enrolled in therapeutic trials or referred, at least once, to the Department of Medicine in Avicenne Hospital (Bobigny) until 2003, then in Cochin Hospital (Paris), have been systematically compiled in the FVSG database. For this study, patients had to meet the WG classification criteria of the American College of Rheumatology[5] and/or the Chapel Hill criteria[6], and have histological findings consistent with WG diagnosis and/or positive testing for antineutrophil-cytoplasm antibody (ANCA), performed on stored blood samples for those diagnosed prior to the availability of these tests. Alternative diagnoses for WG had to be excluded, especially infections, using appropriate investigations.

Among the patients with WG, we identified those with disease localized to one organ, i.e., with isolated ear, nose, and throat (ENT) manifestations (such as crusting rhinitis, sinusitis, and/or otitis), ocular involvement (e.g., scleritis or orbital pseudotumor), or lung nodules. Patients with subglottic stenosis were excluded if associated with nasal, sinus, or ear manifestations. To ascertain the diagnosis of strictly localized WG, followup exceeding one year was also required for eligibility.

Mild constitutional symptoms, e.g., weight loss < 5 kg, fever < 38°C, or arthralgias (without synovitis or arthritis), were not considered exclusion

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Accepted for publication October 5, 2010.

criteria. Patients with kidney-limited disease or glomerular involvement (microscopic hematuria, serum creatinine rise > 10%, and/or a documented biopsy), or isolated alveolar hemorrhage (diffuse ground-glass opacities on lung computed tomography scans and/or hemorrhagic bronchoalveolar lavage fluid) were not included, because no consensus exists on whether those patients have WG, microscopic polyangiitis, or a separate vasculitis entity (kidney-limited vasculitis for the former).

Disease activity was assessed at diagnosis using the original version Birmingham Vasculitis Activity Score (BVAS), and calculated retrospectively for those patients diagnosed before its creation[7]. Complete remission (CR) was considered when BVAS was 0 for at least 6 months. Partial remission (PR) was defined as a BVAS decrease (> 50%) but with persistent symptoms, potentially attributable to low-grade disease activity. For persistent lung nodules or retroorbital pseudotumors, size reduction was considered PR, because there is no means to ascertain whether those lesions are scars or low-grade active lesions. Diagnosing relapse required the recurrence or first appearance of one or more BVAS items attributable to active vasculitis after a period of remission.

RESULTS

Among the 494 patients with WG extracted from the database in January 2009, and satisfying our selection criteria, we identified 16 (3.2%) with limited disease that did not progress during their followup (median time from diagnosis, 58 mo; Figure 1, Table 1).

Median age at diagnosis was 47 years. Six (37.5%) patients had nasal and sinus involvement, including 2 with saddle-nose deformity and 1 with otitis media. Six (37.5%) had isolated pulmonary nodules. Four (25%) had isolated orbital pseudotumors with exophthalmia, bilaterally for 2 and with necrotizing scleritis for one. Median BVAS was 7 (range 3–11). Only one had nonspecific arthralgias. Thirteen (81.3%) were ANCA-positive. Twelve had biopsies, with 7 showing findings compatible with WG, including the 3 ANCA-negative patients (granulomatous vasculitis for 2; necrotizing and granulomatous inflammation for one with ENT disease). All stained negative for mycobacteria and fungi.

Eight patients (50%) achieved remissions (4 PR, 4 CR) with only one line each of remission-induction therapy consisting of corticosteroids (CS) and intravenous (IV) cyclophosphamide (CYC) for 4 patients, followed by maintenance with azathioprine; or cotrimoxazole alone for one, and combined with CS for 3. None of these 8 patients relapsed during followup.

The 8 remaining patients (50%) failed to achieve remission with first-line therapy (CS alone for one, combined with oral CYC for 2, IV CYC for one, or azathioprine for one) or relapsed after IV CYC + CS induction (n = 3) and required subsequent line(s) of treatment. Such treatment failures were not associated with a specific organ and none of these patients had other organ involvement throughout followup.

At the last evaluation, 6 patients were in CR and 8 in PR (4 had grumbling ENT manifestations, 1 residual orbital pseudotumor, 3 lung sequelae). Only 2 were off-treatment.

DISCUSSION

Our results emphasize the rarity (3.2%) of patients with WG strictly localized to one organ at diagnosis and who remained so throughout their entire followup. Holle, *et al*[8] recently reported a similar 5% of WG localized to one organ/system. The strict definitions of localized WG probably explain the difference with earlier reported frequencies of 15%[9] to 29%[2,3,10]. Notably, like Holle, *et al*[8], we included only patients with a followup exceeding 1 year, thereby excluding those whose initial localized disease rapidly progressed to more generalized WG, and almost certainly those with alternative diagnoses, such as infections, cancers, or

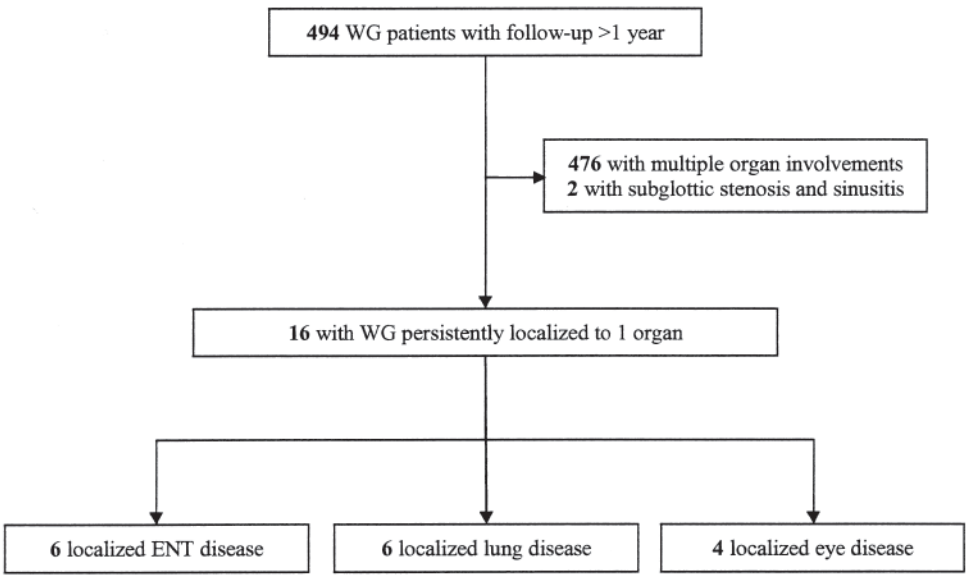

Figure 1. Location of disease in study patients with Wegener's granulomatosis (WG) strictly and persistently localized to one organ. ENT: ear/nose/throat.

Table 1. Main characteristics, treatments, and outcomes of the 16 patients with Wegener's granulomatosis that was strictly and persistently localized to one organ.

Sex/Age at Diagnosis, yrs	ANCA IF	ANCA ELISA	Organ	Followup, mo	No. of Courses	Treatment First-line*	Treatment Subsequent Courses* (Rescue or After Relapse)	Last Evaluation Outcome	Last Evaluation Status	Last Evaluation Treatment
M 51	C-ANCA	PR3	Nose & sinus	39	3	CS	IV CYC+CS; Oral CYC+CS/AZA/MTX	PR	Grumbling disease	MTX+CS
M 38	C-ANCA	PR3	Nose & sinus	35	2	Oral CYC+CS/MTX	IV CYC+CS/AZA	CR	Asymptomatic	AZA+CS
F 17	P-ANCA	MPO	Nose & sinus, saddle-nose deformity	38	1	IV CYC+CS/AZA	—	CR	Grumbling disease	AZA+CS
M 29	C-ANCA	PR3	Nose + sinus	238	1	Oral CYC+CS/CTX	AZA	PR	Grumbling disease	AZA
F 33	P-ANCA	MPO	Nose & sinus	143	1	CTX+CS		CR	Asymptomatic	CTX+CS
M 47	Neg	Neg	Nose & sinus, otitis	163	1	CTX+CS	—	PR	Grumbling disease	CTX
F 31	C-ANCA	PR3	Bilateral orbital pseudotumors	63	4	CS/AZA	IV CYC+CS; Oral CYC+CS/AZA; **RTX/CTX**	CR	Asymptomatic	None
F 47	P-ANCA	MPO	Orbital pseudotumor	72	2	IV CYC+CS/AZA	**IV CYC+CS**†	Relapse	Scleritis of the right eye and bilateral ulcerative keratitis	IV CYC+CS†
F 39	P-ANCA	MPO	Orbital pseudotumors & scleritis	13	1	CTX	—	PR	Persistent unilateral exophthalmia	CTX
F 49	Neg	Neg	Orbital pseudotumor	137	1	CTX+CS	—	PR	Blurred vision	CTX+CS
M 52	C-ANCA	PR3	Lung nodules	95	2	IV CYC+CS/MTX	IVIG/AZA	PR	Asymptomatic, fibrous remodeling of lung apexes on CT scan	AZA
M 51	C-ANCA	PR3	Lung nodules	51	1	IV CYC+CS/AZA	—	CR	Asymptomatic, normal CT scan	None
F 53	C-ANCA	PR3	Lung nodules	52	1	IV CYC+CS/AZA/CTX	—	CR	Asymptomatic, normal CT scan	CTX
M 59	C-ANCA	PR3	Lung nodules	123	2	IV CYC+CS/MTX	**MMF**	PR	Asymptomatic, residual nodular scars on CT scan	MMF
F 22	Neg	Neg	Lung nodules	12	1	IV CYC+CS/AZA	—	PR	Asymptomatic, residual nodular scars on CT scan	AZA
M 52	Neg	PR3	Lung nodules	41	3	IV CYC+CS/AZA	**Oral CYC+CS/MTX; RTX**†	Relapse	Asymptomatic, increased size of lung nodules on CT scan	RTX†

* "/" separates sequential induction/maintenance drugs, and ";" separates subsequent replacement regimens, after failure to achieve remission (rescue treatment) or relapse (in boldface type).† Started because of relapse. ANCA: antineutrophil-cytoplasm antibodies; AZA: azathioprine; CR: complete remission; CS: corticosteroids; CT: computed tomography; CTX: cotrimoxazole; CYC: cyclophosphamide; IF: immunofluorescence-labeling pattern (P: perinuclear; C: cytoplasmic); IV: intravenous; IVIG: intravenous immunoglobulins; MMF: mycophenolate mofetil; MPO: antimyeloperoxidase; MTX: methotrexate; NEG: negative; PR: partial remission; PR3: antiproteinase 3; RTX: rituximab.

other systemic diseases. However, some lymphomas may still mimic WG with ANCA-positivity[11]. Our study's retrospective design prevented unbiased determination of the frequency of patients whose localized WG progressed to a generalized form, before or after 1 year postdiagnosis. Holle, *et al* found that only 10% of their patients progressed to the systemic form, after a median of 6 years[8].

While our patients had some characteristics similar to those in previous studies, e.g., their relatively younger age[2,12], most of them were ANCA-positive (83%), close to the 78% of the patients with limited disease observed in the Wegener's Granulomatosis Etanercept Trial[4], but higher than the 46% reported by Holle, *et al*[8]. Notably, the majority of our patients had granulomatous-type manifestations, such as orbital granulomas, ENT disease, or isolated lung nodules.

Previous studies suggested that patients with initially limited/early WG could achieve remission with less aggressive therapy[10,13,14]. However, Holle, *et al*[8] found that cotrimoxazole alone was "not sufficient" for 73% of their patients, with 64% requiring methotrexate and 50% CYC at some time. Similarly, most of our patients required corticosteroids and immunosuppressant(s). However, because of the small number of patients identified with persistently localized WG, it would be premature to advance any therapeutic recommendations.

A prospective multicentric registry is needed to better study this patient subset with persistently localized WG, and to help optimize their therapeutic strategy.

ACKNOWLEDGMENT

We thank Janet Jacobson for editorial assistance, and the past and current members of the FVSG who followed several of the patients described here and/or included them in the database.

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