Wegener's granulomatosis: prevalence of the initial clinical manifestations – report of six cases and review of the literature

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ABSTRACT

Objectives: To describe the initial clinical manifestations of Wegener's Granulomatosis (WG) in Brazil. **Patients and Methods:** Retrospective analysis of six medical records of WG patients followed-up at the Rheumatology Department of Hospital Geral of Fortaleza (HGF), as well as a bibliographic survey of cases of WG in Brazil on LILACS, SciELO, and MEDLINE databases. **Results:** The study identified 49 patients, 15 (31%) males and 34 (69%) females. Systemic disease was observed in 35 patients (73%): 28 adults, 5 children, and 2 teenagers. Limited disease was observed in 13 adults and 1 child. The average age of onset in adults was 42.2 years (18 to 65 years). Acute clinical manifestations, with the onset of symptoms less than three months before the diagnosis, were observed in 41% (20/49) of the patients, and the insidious presentation in 59% (29/49) of the patients. The prevalence of the initial clinical manifestations in adults with systemic disease (n = 28) was 64% (18/28), upper airways, 36% (10/28), lungs, 18% (5/28), kidneys, 25% (7/28), eyes, 11% (3/28) skin, 25% (7/28), musculoskeletal, and 7% (2/28), neurological. In adults (n = 13) with limited disease, prevalent symptoms included: upper airway, 84% (10/13), eyes, 23% (3/13), and lungs, 15% (2/13). **Conclusion:** The prevalence of the initial clinical manifestations of WG in Brazil was similar to that reported in the literature. The lack of specific symptoms may delay diagnosis cases with insidious presentation of the disease and increase the morbidity and mortality in acute disease.

Keywords: Wegener´s granulomatosis, prevalence, clinical manifestations, Brazil.

INTRODUCTION

Wegener's Granulomatosis (WG) is a necrotizing vasculitis that affects small and medium-size blood vessels with granulomata formation.[1] It is one of the most common forms of systemic vasculitis, with a reported annual incidence of 10 cases per one million people[1]. Its causes are unknown, and it is the prototype of conditions associated with anti-neutrophilic cytoplasmic antibody (ANCA).[2] It affects mainly Caucasian individuals, without gender predilection, with a mean age of onset of 41 years.[3] Its clinical presentation is divided in limited and systemic;[1] the latter is usually associated with more severe disease, characterized by renal involvement, which is predictive of a poor prognosis.[2] The clinical presentation can vary, and it may affect several organs. The most common symptoms are related to the upper and lower airways, especially recurring bloody rhinorrhea, rhinosinusitis, and cavitary and nodular lesions in the lungs. Pulmonary manifestations are

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seen in 45% of the cases, on presentation, and 87%, during the course of the disease.[4,5] Ocular involvement in WG can be the initial presentation in 8% to 16% of the cases.[6-9]

The diagnosis is based on clinical manifestations, histopathological findings compatible with granulomatous necrotizing vasculitis,[1] and the presence of ANCA, which, after the discovery of its association with WG by van der Woude *et al*.,[10] allowed the earlier diagnosis and treatment of the disease.[11,12] Cytoplasmic ANCA pattern has specificity for WG of up to 98% in the acute phase,[13,14] and it seems that its titer is related with disease activity.[15-17] Note that, despite of the clinical characteristics and immunopathologic findings, a small percentage of patients with WG can be ANCA negative.[18]

Due to the small number of Brazilian studies on the initial manifestations of WG, the authors conducted an extensive review of the literature, along with the experience of the Rheumatology Department of HGF in the clinical management of six patients who received the diagnosis of this disorder from June 2005 to August 2008.

PATIENTS AND METHODS

Patients

This is a descriptive, transversal study carried out at the Rheumatology Department of Hospital Geral de Fortaleza, through the retrospective analysis of the medical records of six patients with the diagnosis of WG, according to the 1990 criteria of the American College of Rheumatology (ACR).[9] Those patients were identified among 535 patients hospitalized over a three-year period.

Review of the literature

Reports of cases of WG in Brazilian patients were searched in the SciELO (1998-2009), LILACS (1985-2009), and Medline (1966-2009) databases. Reports that included the initial clinical manifestations of WG were selected by type of publication (case reports and original studies), language (Portuguese and English), keywords (Wegener's Granulomatosis and clinical manifestations), and country of origin (Brazil). The following parameters were evaluated: gender, age, onset of clinical disease, characterized as acute (less than three months before the diagnosis) or insidious, and type of disease presentation (systemic or limited). Limited disease was defined by the absence of renal involvement. This study was approved by the Ethics Committee of the Institution, under research in humans protocol number 231946.

RESULTS

Table 1 shows the demographic and evolutive (gender, age, duration of the disease, and deaths), clinical, and therapeutic characteristics of the six WG patients seen at HGF. Table 2 shows the main results of laboratorial, radiological, and histopathological exams.

The number of WG patients corresponded to approximately 1% of the total number of patients admitted to the Rheumatology Service of HGF in three years. Five female and one male patients with ages between 16 and 55 years were included. Two patients evolved to death. Patient number two was being investigated for bilateral exophthalmia at the Endocrinology Department, with a diagnostic hypothesis of Grave's disease, and had been examined by an ophthalmologist who suspected of orbital pseudotumor (Figure 1A). The patient with the earlier diagnosis (after 10-day evolution) had vasculitis of the lower limbs and pulmonary bleeding (Figure 1 B). Figure 1C shows vasculitis and necrosis of the right hand of patient number one. The type of disease presentation, along with 43 Brazilian patients identified in the literature search, is listed.

Literature search identified 30 studies that reported initial manifestations of the disease[19-48] (Table 3). Forty-nine WG patients, 15 (31%) males and 34 (69%) females, were diagnosed in Brazil; 35 (73%) patients, 28 adults, five children, and two adolescents, had systemic manifestations; limited disease was diagnosed in 13 adults and one child; the mean age of onset of the disease in adults was 42.2 years, ranging from 18 to 65 years. Acute clinical onset, with symptomatology for less than three months before the diagnosis, was observed in 41% (20/49) of the patients; insidious disease affected 59% (29/49) of the patients. In adults with systemic disease (n = 28), the main clinical manifestations, before and at the time of the diagnosis, are shown in Figure 2. Predominant clinical manifestations in patients with limited disease (n = 13) were related to the upper airways in 76% (10/13), eyes in 23% (3/13), and lungs in 15% (2/13) of the cases. Table 4 shows the initial presentation of WG in adults by organs and systems, comparing two Brazilian studies and an international reference.[2,19-30,32,35,38-40,42,44,49,50]

Some particularities of the patients seen at HGF should be mentioned: 1) the first patient developed paresthesia in the lower limbs with electroneuromyography showing axonal mononeuropathy of the posterior tibial nerve, a rare symptom in the initial phase of WG. 2) The diagnosis of patient number two was delayed, evolving from limited to systemic disease, with indolent evolution.[11]This patient has saddle-nose deformity, which is seen in 3.5 to 7% of the cases.[26-30] 3) Patient number

Table 1
Patients with Wegener's Granulomatosis at HGF (n = 6)

Patient	Gender	Age	Duration symptoms	Clinical picture			Treatment
				Onset	Evolution	Hospitalization	
1	F	55	5m	Nasal pain and edema, bloody rhinorrhea, dysphonia, and tinnitus	Fever, odinophagia, arthritis in knees and elbows. Erythematous plaques, purpura on LL, and distal necrosis of 2nd right finger	Pallor, loss of weight of 13 kg; paresthesia LL; proteinuria, hematuria	Prednisone, pulse solu-medrol and CF
2	F	35	16y	Bilateral ocular pain, tearing, and hyperemia	Progressive ocular proptosis; total loss of vision in the right eye, and episodes of epistaxis and hemoptysis for 1 year	Saddle-nose, bilateral ocular proptosis, purpuric lesion on the palate, arthritis right knee and ankle, proteinuria, hematuria	Prednisone, pulse solu-medrol and CF
3	F	28	18m	Bilateral nodular episcleritis, loss of visual acuity, nasal obstruction	Six months: bilateral neurosensorial hearing loss; arthralgia in hands and feet	Arthritis hands, purpura on LL, nodule right elbow, hematuria	Prednisone, pulse solu-medrol and CF
4	F	39	10y	Fever, asthenia, purpura, subcutaneous nodules, arthritis, coughing, and bloody sputum; Treated for TB for 6 m	Fever, arthritis, hemoptysis; renal failure and hypertension. Treatment for WG for 5 years (oral corticosteroids, CF, and AZA)	Worsening renal function, orbital pseudotumor, proteinuria, hematuria	Prednisone, pulse solu-medrol and CF, AZA, rituximab
5	F	16	10d	Dry cough, dyspnea, hemoptysis, oliguria, and purpura in LL	Respiratory failure, hematuria, proteinuria	Pulmonary hemorrhage, mechanical ventilation, and death	Prednisone, pulse solu-medrol, Immunoglobulin
6	M	29	30d	Fever, hemoptysis, and migratory polyarthritis in LL	Respiratory discomfort	Pulmonary hemorrhage, nephrotic-range proteinuria, hematuria, and death	Prednisone, pulse solu-medrol and CF, plasmapheresis, hemodialysis

F: female; M: male; m: months; y: years; TB: tuberculosis; LL: lower limbs; WG: Wegener's Granulomatosis; CF: cyclophosphamide; AZA: azathioprine; kg: kilogram.

Table 2
Laboratorial, radiological, and histopathological exams of six patients with Wegener's Granulomatosis seen at the Rheumatology Service of HGF (n = 6)

Patient	ESR (mm)	Hb (g/dL)	Proteinuria (mg/24h)	Hematuria	ANCA		Chest X-ray	Tomography		Biopsy
					C	P		Chest	Sinuses	
1	94	7.7	1078	Yes	1/40	—	Abnormal	DM and GGO	Abnormal	Kidney: DPGN
2	63	10.9	511	Yes	—	1/640*	Normal	Normal	Abnormal	Kidney: ATN
3	90	12.0	< 200	Yes	1/640	—	Normal	BM	Abnormal	Cutaneous nodule: CSG
4	80	10.4	900	Yes	1/320	—	Abnormal	ND	ND	Nasal septum: granuloma
5	100	6.7	NR	Yes	1/320	—	Abnormal	ND	ND	Skin: LV
6	93	7.7	26.356	Yes	1/80	—	Abnormal	ND	ND	Lung: granuloma

ANCA: anti-neutrophilic cytoplasmic antibody; C: cytoplasmic pattern; P: perinuclear pattern; ATN: acute tubular necrosis BM: bibasilar micronodules; CSG: Churg-Strauss Granuloma DM: diffuse micronodules; DPGN: diffuse proliferative glomerulonephritis; ESR: erythrocyte sedimentation rate; GGO: ground-glass opacities; Hb: hemoglobin; LV: leukocytoclastic vasculitis; ND: not done. *Positive anti-proteinase 3.

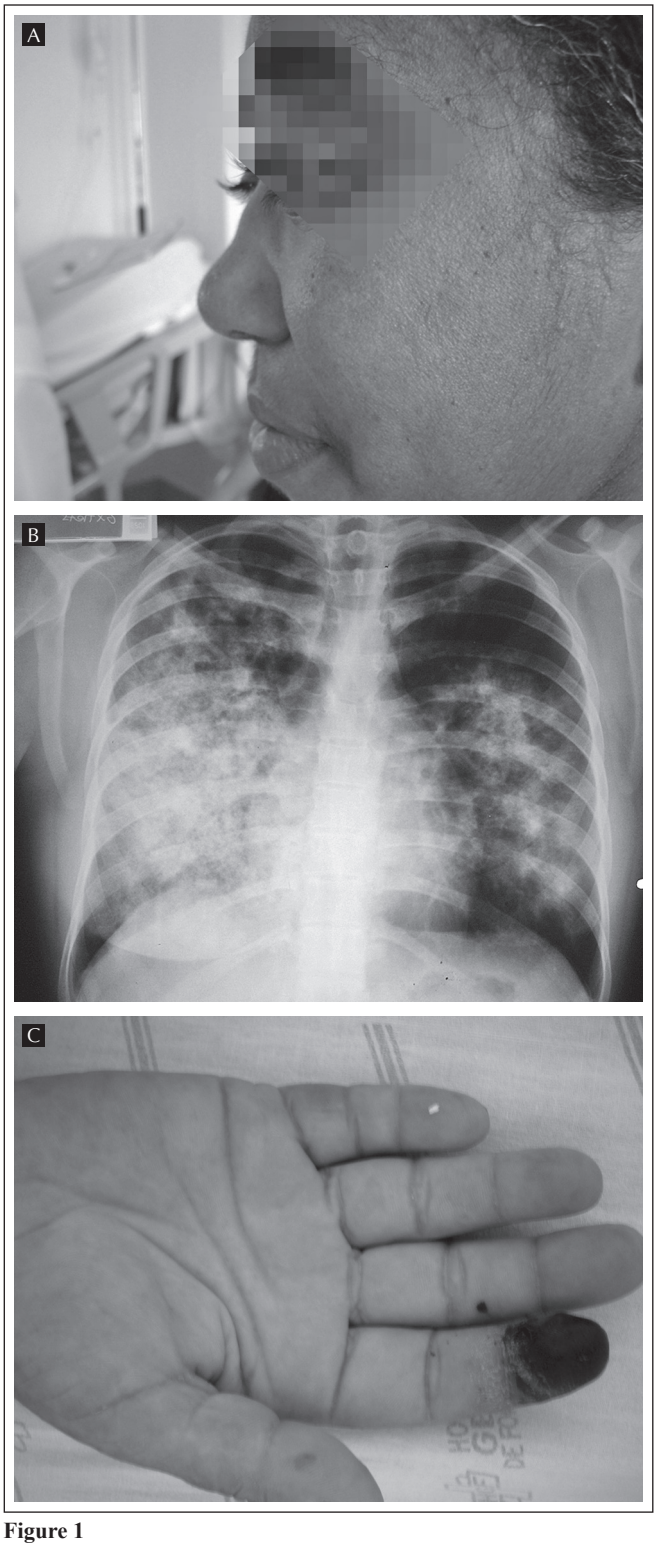

Figure 1
Clinical and radiographic manifestations of WG; A) Ocular proptosis and saddle-nose deformity in patient number two; B) Cotton-like, reticulo-nodular infiltrate, especially in the right hemithorax; C) Necrosis of the distal phalange of the right second finger.

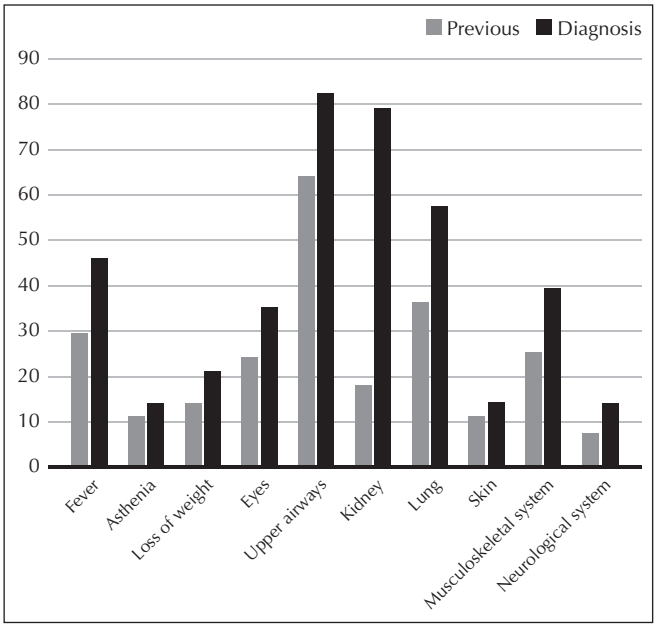

Figure 2
Constitutional symptoms and organs involved in systemic WG in adults (n = 28). *Symptoms for more than three months before the diagnosis.

three was being investigated for six months for hearing loss, had indication for a cochlear implant. The patient developed a granular lesion in the extensor surface of the elbow with a biopsy report compatible with Churg-Strauss granuloma. 4) Patient number four, treated initially for tuberculosis (TB), was being followed-up for five years for WG with several acute relapses. The patient had a new relapse and, based on the small international experience,[51,52] she was treated empirically with a biological agent (rituximab). Note that the diagnostic confusion with TB in patients with Wegener's Granulomatosis with pulmonary manifestations is frequently reported in areas endemic for TB.[6,30] 5) The last two patients had pulmonary hemorrhage, and kidney and respiratory failure, evolving to death. This illustrates the elevated morbimortality of this disease, especially in cases of systemic disease and acute presentation.[53]

On the evaluation of pediatric WG, which affects patients from one to 18 years of age, three cases had insidious disease, with onset of the initial symptoms more than three months before the diagnosis; two were acute cases; and the last case evolved to death five days after the onset of pulmonary-renal symptoms and positive p-ANCA, without a biopsy to confirm the diagnosis of WG or microscopic polyangiitis. A teenager had polyarthritis and purpura on the hands and sole of the feet for three years, receiving a diagnosis of leukocytoclastic vasculitis before the diagnosis of WG; the patient developed

Table 3
Summary of cases of Wegener's granulomatosis in Brazil, published in journals (n = 49)

Author, year	Case #	Age	Gender	Type	Clinical picture	
					Acute	Insidious
Correa *et al.*, 1985[19]	1	65	M	S	x	
	2	49	F	S	x	
Azevedo *et al.*, 1985[20]	1	22	M	S		x
Santiago *et al.*, 1987[21]	1	19	M	S	x	
Pedrini *et al.*, 1988[22]	1	23	F	S	x	
Pacheco *et al.*, 1988[23]	1	64	F	S		x
Fernandes *et al.*, 1992[24]	1	64	F	S		x
	2	40	F	S		x
	3	58	M	S		x
Fernandes *et al*, 1994[25]	1	39	M	S		x
Esteves *et al.*, 1994[26]	1	62	M	S	x	
Nascimento *et al.*, 1997[27]	1	31	F	S		x
Furtado *et al.*, 1997[28]	1	43	F	S	x	
Skare *et al.*, 1998[29]	1	25	M	S	x	
Matozo *et al.*, 1998[30]	1	51	M	S		x
Fernandes *et al.*, 1998[31]	1	63	M	L		x
Cachapuz *et al.*, 1999[32]	1	40	M	L		x
	2	40	F	S	x	
Azevedo *et al.*, 2001[33]	1	65	F	L		x
Neviani *et al.*, 2002[34]	1	42	F	L	x	
Rezende *et al.*, 2003[35]	1	18	F	S	x	
Souza *et al.*, 2003[36]	1	48	F	L		x
Gomides *et al.*, 2004[37]	1	30	M	L	x	
Guidolin *et al.*, 2004[38]	1	31	F	S	x	
Ghanem *et al.*, 2004[39]	1	35	F	S		x
Larrubia *et al.*, 2004[40]	1	39	F	S	x	
Monteiro *et al.*, 2005[41]	1	32	M	L		x
Schmidt *et al.*, 2007[42]	1	43	M	S		x
Gomides *et al.*, 2006[43]	1*	30	M	L	x	
	2	42	F	S		x
	3	50	F	L	x	
Pereira *et al.*, 2007[44]	1	40	F	L		x
	2	60	F	L		x
	3	46	M	S		x
	4	32	F	L		x
Scalcon *et al.*, 2008[45]	1	21	F	L		x
Rodrigues *et al.* **	1	55	F	S		x
	2	35	F	S		x
	3	28	F	S		x
	4	39	F	S		x
	5	29	M	S	x	
Vecchi *et al.*, 2001[46]	1	10y and 4m	F	S		x
	2	10y and 10m	F	S		x
	3	10y and 9m	F	S		x
	4	10y and 4m	F	L	x	
	5	6y and 2m	F	S	x	
Blanco *et al.*, 2001[47]	1	10y	F	S	x	
Machado *et al.*, 2003[48]	1	15y	F	S		x
Rodrigues *et al.***	1	16y	F	S	x	

Acute: symptomatology for up to three months; insidious: symptomatology for more than three months; M: male; S: systemic; F: female; L: limited; *: mentioned before; **: present study; y: years; m: months.

Table 4
Initial involvement of organs and systems in systemic Wegener's Granulomatosis in the studies analyzed

	Morrow *et al*.[49], 1999	Antunes e Barbas, 2005[2] (n = 50)	fernandes e Samara, 1991[50] (n = 10)	Rodrigues *et al*.* (n = 28)
Ear, nose and throat	70	80	50	64
Lungs	45	60	40	36
Kidney	18	45	10	18
Eyes	NR	45	30**	25
Skin	25	40	30	11
Musculoskeletal	NR	40	50	25
Nervous system	Raro	30	30**	7

* = present study; ** = reported as a group; NR = not reported.

subglottic stenosis and chronic renal failure and remission of the disease after classical WG treatment for one year; the other teenager, seen at HGF, developed pulmonary hemorrhage and died 30 days later.

DISCUSSION

Wegener's Granulomatosis has been rarely described in Brazil. The six cases of WG diagnosed at HGF in approximately three years motivated this study.

The literature review revealed a small number of publications, encompassing only 109 Brazilian patients, demonstrating how rare this disorder is in our country; 50 of those cases were reported by the Medical School of USP (from 1985 to 2000), 10 cases by the School of Medical Sciences of UNICAMP (from 1982 to 1991), and 49 patients in this review, included in reports from 1966 to 2009. Their cases were documented in thesis, series of cases, and individual reports.

The investigation of the initial clinical manifestations of WG allowed the following observations: renal involvement, which characterizes systemic disease, has high morbimortality. The lack of specificity of the initial clinical manifestations of WG with insidious presentation gave patients enough time to seek tertiary hospitals for proper investigation, which occurred only in 29/49 (59%) patients in this study. Establishing an adequate diagnosis was difficult in the remaining patients, who had more acute presentations.

The prevalence of upper airways, pulmonary, and kidney symptoms in the initial presentation of systemic WG in adult patients was similar to that of the international literature summarized by Morrow *et al*.[49] in 1999. In a Brazilian study by Antunes & Barbas,[2] in 2005, with 50 patients followed-up from 1985 to 2000, symptoms were evaluated at the time of the diagnosis, demonstrating higher prevalence of all clinical manifestations investigated. The report of neurological symptoms in the initial phases of WG in three Brazilian adults could reflect a populational peculiarity, delayed diagnosis in Brazil, or a bias in reporting only cases considered relevant. The incidence of cutaneous manifestations (Table 4) of WG was lower in this cohort than in that of two other Brazilian studies and in the international literature. Musculoskeletal symptoms showed lower frequency, reported in less than 32% of the cases, the lower frequency in the literature. Ocular manifestations at the onset of the disease in 25% of the patients was similar to the reports of the two Brazilian studies and higher than reported by Duna *et al*.,[6] which ranged from 8 to 16%. Those results could also reflect a bias in the documentation of Ophthalmology Departments.

Over a period of seven years, Vecchi *et al*.[46] evaluated five Brazilian children, females, with the diagnosis of WG, demonstrating that the presentation of WG is more severe in this age group due to the high incidence of renal involvement and failure. Hypertension was seen in all five patients, and pneumopathy and hematuria were present from the onset of the symptoms in four children with systemic disease. The time between the onset of the symptoms and diagnosis ranged from 15 days to three years (mean of 18 months). Those results are similar to those reported by Akikusa *et al*.,[54] who evaluated 25 patients with pediatric WG over a 21-year period and observed a male/female ratio of 1:4 and mean duration of symptoms before the diagnosis of two years. Constitutional symptoms were present in 100% of the patients at the onset of the disease. Glomerulonephritis was seen in 88% of the cases, upper airways involvement in 84%, pulmonary symptoms in 80%, and lung nodules and hemorrhage in 44% of the patients.

The diversity of clinical manifestations and type of disease onset (indolent or fulminant) represents a constant diagnostic challenge for rheumatologists. We observed that the prevalence of the initial clinical manifestations of WG in Brazil was similar to that reported in the literature. Note that the lack of specificity of the symptoms could delay the diagnosis, in cases with insidious presentation, and increase morbimortality, in

acute presentations. This indicates the importance of further studies on rare rheumatic diseases, such as WG and other systemic vasculitis, in Brazil. Those studies could facilitate the knowledge of populational peculiarities in each region of the country and compare them to data in the international literature.

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