

ASSOCIATION BETWEEN SADDLE NOSE DEFORMITY AND RETRO-ORBITAL MASS IN WEGENER'S GRANULOMATOSIS

Guilherme Laranja Gomes*, Ari Stiel Radu Halpern*,
Fernando Henrique Carlos de Souza*, Samuel Katsuyuki Shinjo*

Abstract

Objectives: The relationship between saddle nose deformity (SND) in Wegener's granulomatosis (WG) and other clinical features, including retro-orbital mass formation (ROM), has been poorly described. Therefore, this relationship was analyzed retrospectively from 2000 to 2010.

Patients and Methods: Eighteen consecutive WG patients with SND diagnosed by computed tomography were matched to 36 WG patients without SND (control group) for gender, age at WG diagnosis and disease duration.

Results: No difference was found between the two groups in relation to WG type (limited and systemic forms), ethnicity, laboratory features, constitutional symptoms or clinical manifestations, including upper respiratory tract, and treatment, except for ROM (33.3 *vs.* 2.8% in SND(+) and SND(-) groups, respectively; $p=0.004$) and subglottic stenosis (22.2 *vs.* 2.8%; $p=0.038$). However, on multivariate analysis, only ROM (OR 17.15; 95% CI 1.11-265.52) was statistically associated to SND. In addition, in more than half of the cases, SND manifested prior to ROM.

Conclusions: Results of this prospective analysis showed that SND was strongly associated to ROM in WG. Since early diagnosis and aggressive treatment of orbital involvement could lead to better prognosis, the presence of SND warrants additional vigilance.

Keywords: Subglottic Stenosis; Wegener's Granulomatosis; Retro-orbital Mass; Saddle Nose; Systemic Vasculitis.

Introduction

Wegener's granulomatosis (WG) is a systemic disease characterized by necrotizing granulomatous vasculitis, affecting mainly the upper airways, lungs and kidneys¹⁻³.

The incidence of WG ranges from 3 to 9.7 cases per million / year⁴. The disease is more prevalent in the Caucasian population and the average age of involvement is about 40 years^{2,5,6}.

Eye/nose/throat (ENT) involvement in WG occurs in more than 75% of cases, reaching 90-100% during disease evolution^{2,5,7-24}. It is responsible for considerable morbidity and chronic damage in WG^{2,5,7-24}.

Ophthalmologic involvement is also prominent consisting of episcleritis, scleritis, lacrimal gland obstruction, ptosis, ocular pain, diplopia, amaurosis, periorbital cellulitis and retro-orbital mass (ROM) formation¹⁴⁻²⁰. The latter occurs in 15-50% of WG cases and can represent an isolated manifestation of WG or as a consequence of adjacent paranasal sinuses inflammation^{11,18-23}. However, this association has not yet been well established in the literature. In addition, the early ROM diagnosis could be important, when there is predominance of granulomatous inflammation and focal vasculitis, instead of irreversible fibrosis²⁴, allowing appropriate treatment meant to keep a good prognosis.

Sinonasal manifestations described include epistaxis, nasal crusting, smell disturbances, nasal congestion, purulent rhinorrhea, and nasopharyngeal ulceration^{2,10,11}. During the evolution of the disease the submucosa and mucosa areas become more involved causing ulcerations, chronic sinusitis, nasal septal perforations, paranasal sinus mucocele formation from chronic outflow tract obstruction, and nasal bone destruction with classic presentation of saddle nose deformity (SND) which occurs in 10-25% of cases⁹⁻¹³. Despite the importance of sinonasal findings in WG, there are relative few studies on sinonasal profile in WG, mainly SND.

*Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, Brazil

Therefore, in the present study we analyzed the relationship between SND and other systemic features in WG, including possible ROM formation.

Patients and Methods

The present study was based on a single center retrospective cohort that spanned from January 2000 to January 2010 and where the patients were prospectively studied. Eighteen consecutive WG patients with SND were followed at Division of Rheumatology, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil.

For each patient, two other WG patients without SND (control group) were randomly selected and matched for age, gender, age at WG diagnosis, and disease duration.

All patients fulfilled at least two of the five modified American College of Rheumatology (ACR) criteria for the classification of WG (in the modified ACR criteria, a positive serum enzyme immunoassay for antibodies against proteinase 3 (ELISA) was added to the original four criteria²⁴. For the limited form of WG, diagnosis was based on the modified ACR criteria for the classification of WG, in the absence of disease features that posed immediate threats to either a critical individual organ or to the patient's life^{2,25,26}.

ROM was diagnosed by computed tomography made as a routine evaluation of WG patients in our service. All patients were also analyzed for nasal sinus involvement, mainly, nasal septum destruction and saddle nose deformity.

All information regarding demographic, clinical and laboratory features were extensively reviewed and obtained from the patients' medical files. The following variables over the first three years of follow up were recorded: age, sex, ear/nose/ / throat (ENT) involvement (defined as rhinorrhea, epistaxis, oral or nasopharyngeal ulceration, chronic sinusitis, saddle nose deformity, mastoiditis), pulmonary involvement (subglottic stenosis, hemoptysis, or abnormal thoracic imaging in the absence of concomitant infectious pneumopathy such as pulmonary infiltrate and/or nodules or cavitations, respiratory failure, alveolar hemorrhage), renal involvement (glomerulonephritis: microscopic hematuria or red cell casts in the urinary sediment with either proteinuria >0.5 mg/day or serum creatinine >1.8 mg/dL; chronic renal), joint involvement (arthralgias or arthri-

tis), cutaneous involvement (petechiae or purpura, cutaneous vasculitis, skin ulcers), ophthalmologic involvement (episcleritis, scleritis, amaurosis), neurologic involvement (peripheral: mononeuritis multiplex or cranial neuropathy, cranial vasculitis), cardiac involvement (cardiomyopathy), gastrointestinal involvement (intestinal perforation or bleeding). An organ or system was also deemed to be affected when a biopsy contained granulomatous inflammation or vasculitis or, in the case of the kidneys, segmental glomerular necrosis or pauci-immune extracapillary glomerulonephritis.

The extent of organ damage secondary to vasculitis was assessed by means of the Vasculitis Damage Index (VDI)²⁷. This score ranges from 0 to 64, with higher scores indicating more severe damage.

The classic therapeutic regimen with corticosteroids and immunosuppressive agents was given to all patients. Cyclophosphamide was used either in an oral daily schedule of 2 mg/kg or every three weeks intravenous pulse therapy (doses ranging between 0.5 and 1.0 g/m²). The choice between oral and parenteral treatment was based on access to medication and patient adherence to treatment. Oral prednisone, starting with 1mg/kg/day, was maintained for at least 2 months before gradual reduction for the next 6 months. In cases of immediate threat to either a critical organ or to the patient's life, corticosteroid was given as intravenous pulse therapy (methyl prednisolone 1 g + saline solution 0.9% 500 mL in 4 h, once day, three consecutive days) followed by the oral regimen described above. Other immunosuppressive agents such as methotrexate, azathioprine, and mycophenolate mofetil were used in selected cases due to intolerance to cyclophosphamide. Refractory patients received additional intravenous human immunoglobulin (2 g/kg). Cotrimoxazol (800+160 mg, twice per day, oral) was used in all patients.

Statistical analysis. Continuous variables are shown as means plus standard deviation (SD) and categorical variables as percentages. Fisher's exact test was used for comparisons between both groups when applicable. The 95% confidence interval (95% CI) of percentage was calculated by a binomial distribution. *p* values < 0.05 were considered to be statistically significant. Evaluation was performed using the computer program STATA version 7.0 software (STATA, College Station, TX, USA).

Results

Eighteen WG patients with SND were analyzed and matched for gender, age at WG diagnosis and duration of disease with 36 control subjects.

The demographic, clinical and laboratory features of all patients are shown in Table I. No difference was detected between the two groups in relation to WG form (limited form 0 *vs.* 8.3%; $p=0.543$), ethnicity (white, respectively, 83.3 *vs.* 86.1%; $p=0.651$) and laboratorial characteristics (cytoplasmatic ANCA, respectively, 72.2 *vs.* 55.6%; $p=0.375$). The VDI value was also similar to both groups (respectively, 6.3 ± 2.0 *vs.* 6.3 ± 2.5 ; $p=0.966$).

In general, constitutional symptoms and clinical manifestations were also similar in both groups, except for predominance of ROM (33.3 *vs.* 2.8%; $p=0.004$) and subglottic stenosis (22.2 *vs.* 2.8%; $p=0.038$) in patients with SND. In 6 out of 18 patients, ROM manifested prior to SND (Figure 1).

Therapy was also comparable in both groups and comprised glucocorticoid (100.0 *vs.* 94.5%; $p=0.547$) and cyclophosphamide (72.2 *vs.* 83.3%; $p=0.475$). Others drugs that were used include methotrexate (33.3 *vs.* 27.8%; $p=0.756$), azathioprine (16.7 *vs.* 19.5%; $p=1.000$), mycophenolate mofetil (27.8 *vs.* 8.3%; $p=0.100$), cotrimoxazol (77.8 *vs.* 55.6%, $p=0.142$) and human intravenous immunoglobulin (27.8 *vs.* 13.9%; $p=0.273$).

Comorbidities were also found equally in both groups consisting of systemic arterial hypertension (50.0 *vs.* 33.3%; $p=0.384$) and non-glucocorticoid related diabetes mellitus (11.1 *vs.* 13.9%; $p=1.000$).

Both ROM (33.3 *vs.* 2.8%, $p=0.004$) and subglottic stenosis (22.2 *vs.* 2.8, $p=0.038$) were associated to SND on univariate analysis, while multivariate analysis, showed association only with ROM (Table II).

Discussion

SND occurs in 10-25% of WG cases⁹⁻¹³ and despite the importance of sinonasal findings in WG, relatively few studies have investigated the relationship between SND and other WG profiles. In the present study, a large retrospective analysis was conducted that found SND to be strongly associated with ROM in WG and therefore reinforcing the possibility of inflammatory extension from adjacent areas. Moreover, SND showed a tendency to

manifest earlier than ROM.

Orbital mass is the most common form of ophthalmologic involvement later in the disease course and may be contiguous, secondary to spread of granulomatous disease from the nasal passages or paranasal sinuses, or focal, arising primarily within the orbit^{2,9,18-24,28-33}. However, this hypothesis has not yet been verified in a large sample^{31,33}.

Rasmussem *et al*⁸ analyzed the distribution of ENT involvement in a sample of 124 patients from the European vasculitis study group (EUVAS), but did not focus on their correlations. Cannady *et al*¹¹ observed sinonasal involvement in 89% of cases, manifesting as nasal crusts (56%), nasal obstruction (54%), epistaxis (50%), sinusitis (33%) and orbital lesions (2.5%). Woo *et al*²⁹ studied the main ophthalmologic manifestations in WG, and examined the simultaneous involvement of eyes and chronic sinusitis. However, these authors did not report the frequency of ROM or its relationship with other sinonasal manifestations. On the other hand, Kwan and Rose³³ reported a patient case with limited WG who developed an orbital inflammatory mass as a direct extension of nasal inflammatory disease through a rhinostomy formed during lacrimal drainage surgery.

There is a significant difference in outcomes between orbital and sinonasal disease in WG³¹. The former often progresses in spite of systemic treatment and is generally acknowledged as one of the most refractory components of WG³¹. Orbital granulomas in WG present variable histopathology features of inflammation, fibrinoid necrosis, fibrosis and vasculitis²⁴. During natural disease progression, fibrous tissue may replace areas of acute inflammation and necrosis. Consequently, granulomatous lesions in the orbit can diminish in response to immunosuppressive treatment but subsequently become fibrotic. Thus, early orbital disease diagnosis and its treatment may slow progression and reduce sequelae. In this context, it is important to identify laboratory and/or clinical features associated to orbital lesion to allow early intervention, for example with more aggressive drugs.

The association between SND and subglottic stenosis has not yet been described in the literature. This association was confirmed in the present study, but only on univariate analysis. Subglottic stenosis may arise either as a presenting feature or as a late-stage manifestation of the disease and it

Table I. Demographic, clinical and laboratory features of Wegener's Granulomatosis patients

	Saddle nose+ (N=18)	Saddle nose- (N=36)	p
Mean age at onset WG diagnosis \pm SD	41.3 \pm 15.6	41.1 \pm 16.5	0.967
Time duration of WG \pm SD	8.4 \pm 6.4	8.9 \pm 6.6	0.805
Gender male (%)	5 (27.8)	16 (44.4)	0.505
Ethnicity white (%)	15 (83.3)	31 (86.1)	0.651
Limited form of WG (%)	0	3 (8.3)	0.543
cANCA (%)	13 (72.2)	20 (55.6)	0.375
pANCA (%)	3 (16.7)	6 (16.7)	1.000
Constitutional symptoms (%)	9 (50.0)	17 (47.2)	1.000
Ophthalmologic involvement			
Episcleritis / escleritis (%)	8 (44.4)	12 (33.3)	0.552
Retro-orbital mass (%)	6 (33.3)	1 (2.8)	0.004
Ductal lacrimal obstruction (%)	1 (5.6)	2 (5.6)	1.000
Renal involvement			
Glomerulonephritis (%)	10 (55.6)	25 (69.5)	0.372
ENT involvement			
Sinusitis (%)	14 (77.8)	27 (75.0)	1.000
Rhinorrhea (%)	12 (66.7)	20 (55.6)	0.560
Epistaxis (%)	12 (66.7)	20 (55.6)	0.560
Subglottic stenosis (%)	4 (22.2)	1 (2.8)	0.038
Mastoiditis (%)	1 (5.6)	2 (5.6)	1.000
Hearing loss (%)	2 (11.1)	5 (13.9)	1.000
Pulmonar involvement			
Hemoptisis (%)	5 (27.8)	15 (41.7)	0.381
Alveolar hemorrhage (%)	1 (5.6)	5 (13.9)	0.651
Pulmonary infiltrate (%)	2 (11.1)	14 (38.9)	0.057
Pulmonary nodules (%)	8 (44.4)	12 (33.3)	0.552
Cavitations (%)	5 (27.8)	6 (16.7)	0.475
Cutaneous involvement			
Skin ulcers (%)	2 (11.1)	3 (8.3)	1.000
Purpura or petechiae (%)	3 (16.7)	8 (22.2)	0.733
Neurological involvement			
Peripheral (%)	2 (5.6)	3 (16.7)	0.319
Cranial (%)	0	2 (11.1)	0.107
Central (%)	0	0	1.000
Cardiac involvement			
Cadiomyopathy (%)	0	0	1.000
Gastrointestinal tract involvement			
Intestinal bleeding (%)	0	2 (2.8)	1.000
Intestinal perforation (%)	1 (5.5)	3 (8.3)	1.000
Joint involvement			
Arthralgia or arthritis (%)	2 (11.1)	5 (13.9)	1.000

ANCA: anti-neutrophil cytoplasmic antibody; ENT: eye, nose, throat; SD: standard deviation; WG: Wegener's granulomatosis

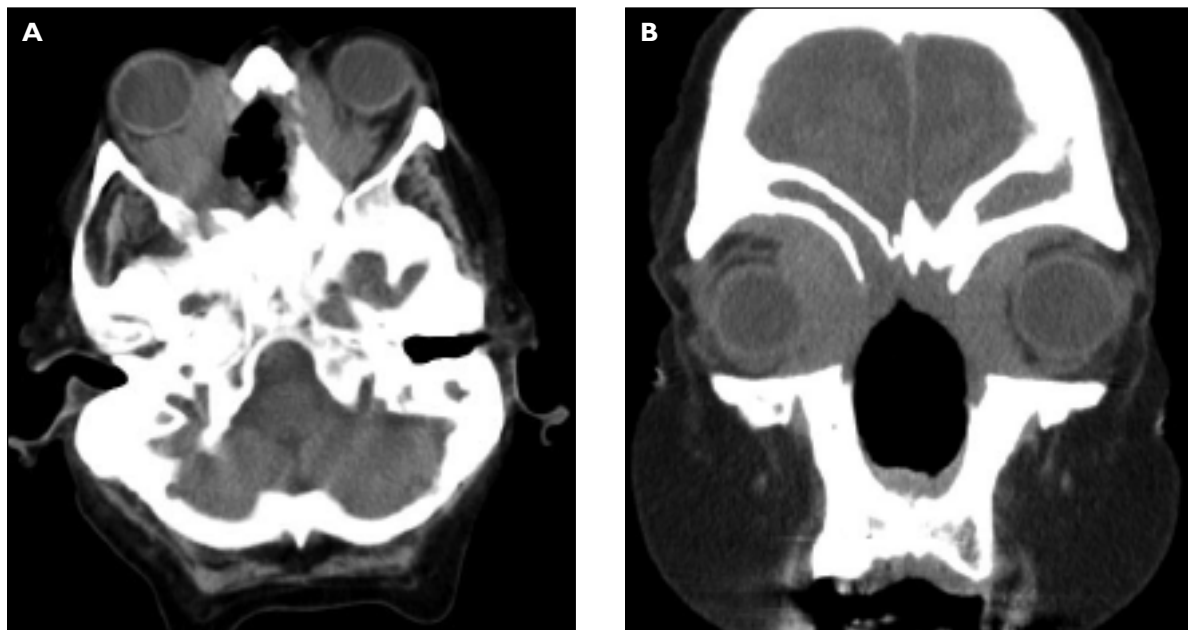


Figure 1. Wegener's granulomatosis patient with retro-orbital mass formation and adjacent paranasal involvement (nasal septal destruction) at computed tomography

Table II. Multivariate analysis

	OR	95% CI
Sex (male)	0.32	0.07-1.44
Age	1.02	0.98-1.06
Retro-orbital mass	17.15	1.11-265.52
Subglottic stenosis	2.14	0.11-41.13

CI: confidence interval; OR: odds ratio.

is an important complication occurring in 10-16% of WG^{1,9,10,34-37}. In this case, an inflammatory process occurs in the walls of these structures causing air tract stenosis and subglottic stenosis, considered a catastrophic manifestation with acute respiratory insufficiency³⁴⁻³⁷.

The possible association between ROM and subglottic stenosis has been previously described³⁰ only in small samples (6 out of 51 patients with WG). In this same study, it was reported the presence of SND in two patients with subglottic stenosis although ROM was not described.

In conclusion, SND was strongly associated to ROM and had a tendency to manifest earlier than did ROM in WG. This finding indicates a need for increased vigilance among this group of WG patients.

Correspondence to

Samuel Katsuyuki Shinjo
Av. Dr. Arnaldo, 455, 3º andar, Sala 3190,
CEP 01246-903, São Paulo, Brazil.
Phone: +55-11-3061-7492.
Fax: +55-11-3061-7490.
E-mail: samuel.shinjo@gmail.com

References

- Godman GC, Churg J. Wegener's granulomatosis: pathology and review of literature. *Arch Pathol Lab Med* 1954; 58: 533-553.
- Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener's granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; 116: 488-498.
- Kornblut AD, Wolff SM, deFries HO, Fauci AS. Wegener's granulomatosis. *Laryngoscope* 1980; 90: 1453-1465.
- Nolle B, Specks U, Ludemann J, Rohrbach M, DeRemee RA, Gross WL. Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener granulomatosis. *Ann Intern Med* 1989; 111: 28-40.
- Cotch ME, Hoffman GS, Yerg DE, Kaufman GI, Targonski P, Kaslow RA. The epidemiology of Wegener's granulomatosis. Estimate of the five year prevalence, annual mortality and geographic disease distribution from population-based data sources. *Arthritis Rheum* 1996; 39: 87-92.
- Bajema IM, Hagen EC, van der Woude FJ, Bruijijn JA. Wegener's granulomatosis: a meta-analysis of 349 literary cases reports. *J Lab Clin Med* 1997; 129: 17-22.

7. D'Cruz DP, Baguley E, Asherson RA, Hughes GR. Ear, nose and throat symptoms in subacute Wegener's granulomatosis. *BMJ* 1989; 299: 419-422.
8. McDonald TJ, DeRemee RA. Head and neck involvement in Wegener's granulomatosis. *Adv Exp Med Biol* 1993; 336: 309-313.
9. Rasmussen N. Management of the ear, nose and throat manifestations of Wegener granulomatosis: an otorhinolaryngologist's perspective. *Curr Opin Rheumatol* 2001; 13: 3-11.
10. Langford CA, Hoffman GS. Wegener's granulomatosis. *Thorax* 1999; 54: 629-637.
11. Cannady S, Barra PS, Hoffman GS. Sinonasal Wegener Granulomatosis: A single institution experience with 120 cases. *The Laryngoscope* 2009; 119: 757-761.
12. McDonald T, DeRemee RA. Wegener's granulomatosis. *Laryngoscope* 1983; 93: 220-231.
13. McDonald TJ, DeRemee RA, Kern EB, et al. Nasal manifestations of Wegener's granulomatosis. *Laryngoscope* 1974; 84: 1201-1213.
14. Fauci AS, Wolff SM. Wegener's granulomatosis: studies in eighteen patients and a review of the literature. *Medicine (Baltimore)* 1973; 52: 535-561.
15. O'Devaney K, Ferlito A, Hunter BC, et al. Wegener's granulomatosis of the head and neck. *Ann Otol Rhinol Laryngol* 1998; 107: 439-445.
16. Pakrou N, Selva D, Leibovitch I. Wegener's granulomatosis: ophthalmic manifestations and management. *Semin Arthritis Rheum* 2006; 35: 284-292.
17. Jabs DA. Ocular manifestations of the rheumatic diseases. In: Tasman W, Jaeger EA, editors. *Duane's clinical ophthalmology*. Philadelphia: Jb Lippincott. 1992; p. 1-33.
18. Fauci AS, Haynes BF, Katz P, Woff SM. Wegener's granulomatosis: Prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; 98: 76-85.
19. Haynes BF, Fishman ML, Fauci AS, Woff SM. The ocular manifestations of Wegener's granulomatosis: Fifteen years of experience and review of the literature. *Am J Med* 1977; 63: 131-141.
20. Bullen CL, Liesegang TJ, McDonald TJ, DeRemee RA. Ocular complications of Wegener's granulomatosis. *Q J Med* 1993; 90: 279-290.
21. Thorne JE, Jabs DA. Ocular manifestations of vasculitis. *Rheum Dis Clin North Am* 2001; 27: 761-779.
22. Stavrou P, Deutsch J, Rene C, Laws DE, Luqmani RA, Murray PI. Ocular manifestations of classical and limited Wegener's granulomatosis. *Q J Med* 1993; 86: 719-725.
23. Simmons JT, Leavitt R, Kornblut AD, Fauci AS. CT of the paranasal sinuses and orbits in patients with Wegener's granulomatosis. *Ear Nose Throat J* 1987; 66: 134-140.
24. Talar-Williams C, Sneller MC, Langford CA, Smith JA, Cox TA, Robinson MR. Orbital socket contracture: a complication of inflammatory orbital disease in patients with Wegener's granulomatosis. *Br J Ophthalmol* 2005; 89: 493-497.
25. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's Granulomatosis. *Arthritis Rheum* 1990; 33: 1101-1107.
26. Rasmussen N. Consensus Therapeutic regimens for ANCA-associated systemic vasculitis: The European Community Systemic Vasculitis Study Group. *Lancet* 1997; 349: 1029-1030.
27. The WGET Research Group. Design of the Wegener's granulomatosis Etanercept Trial. *Control Clin Trials* 2002; 23: 450-468.
28. Exley AR, Bacon PA, Luqmani RA, et al. Examination of disease severity in systemic vasculitis from the novel perspective of damage using the vasculitis damage index (VDI). *Br J Rheumatol* 1998; 37: 57-63.
29. Woo TL, Francis IC, Wilcsek GA, Coroneo MT, McNab AA, Sullivan TJ. Australasian orbital and adnexal Wegener's granulomatosis. *Ophthalmol* 2001; 108: 1535-1543.
30. Solans Laqué R, Bosh Gil J, Canela M, Lorente J, Pallisa E, Vilardell-Tarrés M. Clinical features and Therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. *Lupus* 2008; 17: 832-836.
31. Juri J, Neda S. Review and new insights on Wegener granulomatosis. *Coll Antropol* 2005; 29: 159-162.
32. Fechner FP, Faquin WC. Wegener's granulomatosis of the orbit: a clinicopathological study of 15 patients. *The Laryngoscope* 2002; 112: 1945-1950.
33. Kwan ASL, Rose G. Orbital Wegener's granuloma resulting from direct extension of nasal disease through a surgical rhinostomy. *Br J Ophthalmol* 1998; 82: 198.
34. Waxman J, Bose WJ. Laryngeal manifestations of Wegener's granulomatosis: case report and review of the literature. *J Rheumatol* 1986; 13: 408-411.
35. Langford CA, Sneller MC, Hallahan CW, et al. Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. *Arthritis Rheum* 1996; 39: 1574-1560.
36. Gluth MB, Shinnars PA, Kasperbauer JL. Subglottic stenosis associated with Wegener's granulomatosis. *Laryngoscope* 2003; 113: 1304-1307.
37. McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. *Medicine (Baltimore)* 1976; 55: 193-215.