THE AMERICAN COLLEGE OF RHEUMATOLOGY 1990 CRITERIA FOR THE CLASSIFICATION OF WEGENER'S GRANULOMATOSIS

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Criteria for the classification of Wegener's granulomatosis (WG) were developed by comparing 85 patients who had this disease with 722 control patients with other forms of vasculitis. For the *traditional format classification*, 4 criteria were selected: abnormal urinary sediment (red cell casts or >5 red blood cells per high power field), abnormal findings on chest radiograph (nodules, cavities, or fixed infiltrates), oral ulcers or nasal discharge, and granulomatous inflammation on biopsy. The presence of 2 or more of these 4 criteria was associated with a sensitivity of 88.2% and a specificity of 92.0%. A *classification tree* was also constructed with 5 criteria being selected. These criteria were the same as for the traditional format, but included hemoptysis. The classification tree was associated with a sensitivity of 87.1% and a specificity of 93.6%. We describe criteria which distinguish patients with WG from patients with other forms of vasculitis with a high level of sensitivity and specificity. This distinction is important because WG requires cyclophosphamide therapy, whereas many other forms of vasculitis can be treated with corticosteroids alone.

Wegener's granulomatosis (WG) was first described in the 1930s (1,2), and since that time, the disorder has been recognized as a distinct type of systemic vasculitis (3–8). It is a disease of unknown etiology that is characterized by the clinicopathologic complex of necrotizing granulomatous vasculitis of the upper and lower respiratory tract, glomerulonephritis, and variable degrees of small vessel vasculitis (3–8). A limited form of WG, without glomerulonephritis, has been described (9). Wegener's granulomatosis is a rare disease, the incidence of which is not known. We have established classification criteria for WG by comparing 85 patients who have the disease with 722 control patients who have other forms of vasculitis (10).

Patients with Wegener's granulomatosis often present with nonspecific signs and symptoms of a systemic illness, such as fever, malaise, weight loss, arthralgias, and myalgias (8). Upper airways disease manifested by sinus pain, purulent nasal discharge, epistaxis, nasal mucosal ulceration, and otitis media are common (8). The majority of patients present with pulmonary disease manifested by nodular infiltrates seen on chest radiograph (8,11). Renal disease is frequently seen and can be severe, leading to renal failure (8). Wegener's granulomatosis can affect any organ system including the skin, eye, trachea, nervous

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system, heart, gingiva, breast, prostate, gastrointestinal tract, vulva, and cervix (8,11).

Laboratory findings are generally nonspecific, and indicate a systemic inflammatory illness such as anemia, thrombocytosis, elevated erythrocyte sedimentation rate, and elevated C-reactive protein (8). Abnormalities of renal function, such as an elevated blood urea nitrogen level, serum creatinine level, creatinine clearance, and an active urinary sediment, may be seen (8).

Recently, antineutrophil cytoplasmic antibodies (ANCA or ACPA) have been reported to be both sensitive and specific for Wegener's granulomatosis (12,13). However, the sensitivity varies with disease activity, and the specificity depends on the nature of the controls chosen for analysis. In addition, the test still requires skilled personnel for proper interpretation and is not yet standardized. At this point in time, the test for antineutrophil cytoplasmic antibodies needs to be studied further to carefully determine its usefulness for differentiating among the various vasculitides. It is likely to be valuable in the diagnosis of WG and should be included in future classification studies. Many of the cases in the present study, however, were submitted prior to the description of this test.

As mentioned previously, Wegener's granulomatosis is a clinicopathologic diagnosis. The characteristic histopathology is a necrotizing granulomatous vasculitis, which may be found in any affected organ but is most predictably found in lung tissue (8,11). Although granulomatous vasculitis can be found in renal biopsy tissues from these patients, it is extremely rare. Instead, a focal, segmental glomerulonephritis, which is nondiagnostic, is often seen. In evaluating pulmonary infiltrates in patients suspected of having WG, it is important that infectious agents that can elicit a similar histopathologic picture be ruled out with appropriate cultures and special stains (8,11). In particular, acid-fast bacilli, fungi, and helminths can cause a systemic illness with pulmonary infiltrates and biopsy evidence of granulomatous vasculitis (8,11).

The nonspecific findings of inflammation and/or vasculitis that are associated with other, more typical features of WG (8) can be demonstrated in many organs. For example, leukocytoclastic vasculitis is commonly seen in skin lesions from patients with WG, but sinus, retroorbital, and tracheal tissues may demonstrate only acute and chronic inflammation (8,14).

Corticosteroids in combination with cyclophosphamide are extremely effective therapy for Wegener's granulomatosis; complete remission of disease activity occurs in more than 90% of WG patients treated with this regimen (8). Because of the potential for irreversible end organ system damage, it is important to identify this disorder and institute appropriate immunosuppressive therapy early. However, the therapy is associated with numerous potential side effects and should not be started unless the patient has an appropriate clinicopathologic picture and other disorders have been ruled out. This is especially important in patients with disease limited to the lungs and/or upper airways. It is therefore important to distinguish WG from other forms of vasculitis, since patients with WG require cyclophosphamide therapy and those with other forms of vasculitis can be treated with corticosteroids alone (15).

Table 1. Demographic characteristics of patients with Wegener's granulomatosis (WG)

	WG patients (n = 85)	Control patients (n = 722)
Age at disease onset (mean ± SEM)	45.2 ± 1.8	48.2 ± 0.9
% male	63.5	40.9
% female	36.5	59.1
% white	91	81
% black	7	9
% other race	2	10

For a description of patient selection and evaluation, see the article by Bloch et al (10), which appears elsewhere in this issue of *Arthritis and Rheumatism*.

RESULTS

Patient population. Eighty-five patients with the diagnosis of Wegener's granulomatosis were entered into this study. The classification criteria were selected by comparing findings in these patients with those in the other 722 patients with other forms of vasculitis. The age, sex, and race distribution of the 85 patients with WG are shown in Table 1. The male: female ratio was 1.7:1. The race distribution reflected that in the control population.

Table 2 lists the 11 variables that were chosen as potentially important discriminators against other forms of vasculitis. This "short list" of potential criteria included 2 single items and 9 combined items. The individual items in Table 2 were selected from inspection of the results of univariate analysis of all items on the data collection sheet. Combined items

were derived by selecting the best combination of individual variables. In Table 2, the number of patients indicates those who had the particular variable determined. Sensitivity indicates the percentage of cases in whom the variable was present and abnormal. Specificity indicates the proportion of controls in whom the variable was absent or normal.

Traditional format classification. Approximately 30 combinations of the "short list" of 11 variables in Table 2 (from sets of 3 criteria to a set using all 11) were tested before a final set was chosen to classify Wegener's granulomatosis. Table 3 lists the final criteria set chosen; it is made up of 4 of the original 11 criteria selected. A patient with vasculitis will be classified as having WG if at least 2 of the 4 criteria listed in Table 3 are present. The presence of any 2 of the 4 criteria is associated with a sensitivity of 88.2% and a specificity of 92.0%. Some other criteria lists (not shown) also had sensitivities and specificities which approached those of the criteria set chosen.

With this traditional format, 10 (11.8%) of the subjects entered as WG cases were not classified as having the disease. Criteria (Table 3) present in the misclassified patients were an abnormal urinary sediment in 1, nasal or oral inflammation in 2, and an abnormal chest radiograph result in 2. The criterion requiring histopathology (granulomatous inflammation on biopsy) was not present in any of the misclassified patients (5 patients had negative biopsy findings, and the other 5 patients were not examined). Other additional variables from Table 2 were present in the misclassified patients, including hemoptysis in 2, sinus pain in 1, abnormal sinus radiographic findings in 2, elevated serum creatinine level in 4, eye inflammation in 3, ear inflammation in 3, and small vessel vasculitis demonstrating predominantly polymorphonuclear mixed infiltrates on biopsy in 2.

In addition, 58 (8%) of the 722 controls were misclassified as having WG because they had 2 or more of the criteria in Table 3. Entry diagnoses in these cases included polyarteritis nodosa in 10, Churg-Strauss syndrome in 6, hypersensitivity vasculitis in 11, Henoch-Schönlein purpura in 7, giant cell (temporal) arteritis in 6, Takayasu arteritis in 2, lymphomatoid granulomatosis in 2, leukocytoclastic vasculitis in 2, cryoglobulinemia in 2, vasculitis associated with malignancy in 2, necrotizing vasculitis of the kidney in

Table 2. Comparison of the sensitivity and specificity of potential criteria variables for Wegener's granulomatosis ("short list")*

Criterion	No. of patients (n = 85)	No. of controls (n = 722)	Sensitivity (%)	Specificity (%)
1. Hemoptysis†	83	719	30.1	97.4
2. Paranasal sinus pain or tenderness	84	716	48.8	95.1
3. Abnormal sinus radiographic findings (opacification or bony destruction)	77	290	61.0	88.6
4. Serum creatinine >1.5 mg/dl	85	687	42.4	84.7
5. Urinary sediment†‡	84	685	53.6	80.0
6. Eye inflammation (scleritis, episcleritis, or proptosis)†‡	84	713	27.4	96.9
7. Otitis media (purulent or granulomatous) or unilateral or bilateral deafness	78	709	39.7	94.4
8. Nasal or oral inflammation†‡	85	712	72.9	88.2
9. Abnormal chest radiograph†‡	84	675	65.5	88.6
10. Granulomatous inflammation on biopsy†‡	71	359	74.6	89.1
11. Biopsy showing predominantly granulocytes in wall of arteriole or venule	64	414	42.2	61.4

* Values are the number of cases or controls with the variable described or tested. The sensitivity is the proportion of cases positive for the variable tested or described. The specificity is the proportion of controls negative for the variable tested or described.
† Criterion is used for the traditional format classification.
‡ Criterion is used for the tree classification.

Table 3. 1990 criteria for the classification of Wegener's granulomatosis (traditional format)*

Criterion	Definition
1. Nasal or oral inflammation	Development of painful or painless oral ulcers or purulent or bloody nasal discharge
2. Abnormal chest radiograph	Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
3. Urinary sediment	Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
4. Granulomatous inflammation on biopsy	Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)

* For purposes of classification, a patient shall be said to have Wegener's granulomatosis if at least 2 of these 4 criteria are present. The presence of any 2 or more criteria yields a sensitivity of 88.2% and a specificity of 92.0%.

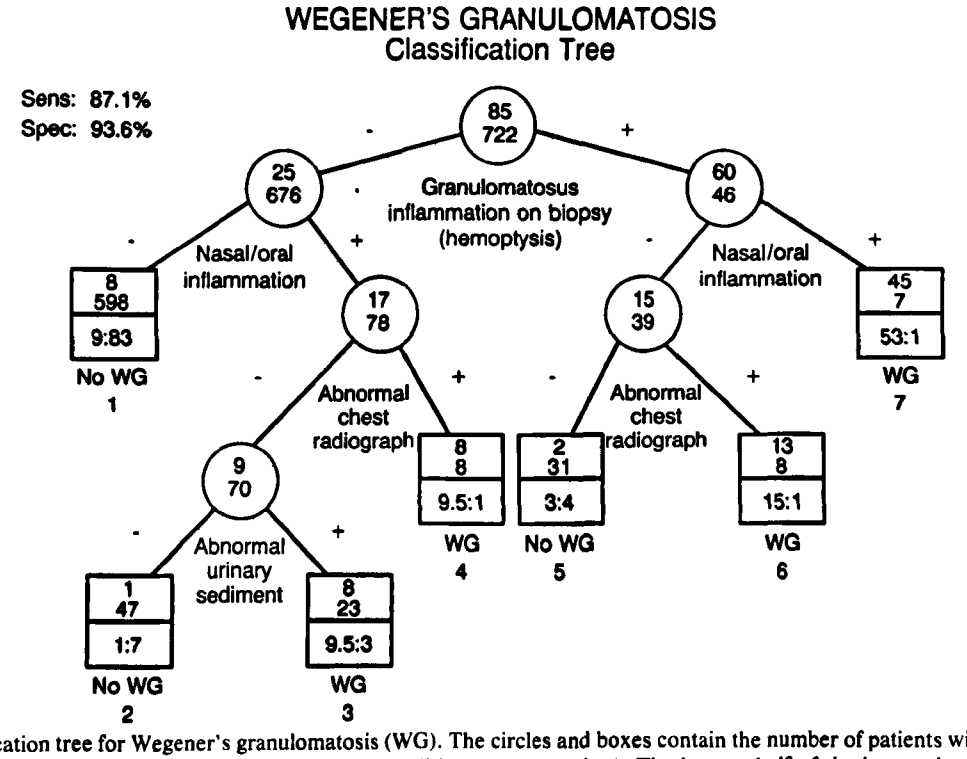

Figure 1. Classification tree for Wegener's granulomatosis (WG). The circles and boxes contain the number of patients with WG (top number) and the number of control patients with other forms of vasculitis (bottom number). The bottom half of the boxes shows the percentage of patients with WG (out of all WG cases) (left number) and the percentage of controls (out of all controls) (right number). Boxes specify whether patients are classified as having WG or not having WG (No WG); the numbers under these specifications are the subset numbers (see Table 4 for definitions of criteria and Table 5 for explanations of subsets). Parentheses indicate the surrogate variable "hemoptysis" to be used when "granulomatous inflammation on biopsy" is not defined.

Table 4. Criteria and definitions used for the classification of Wegener's granulomatosis (tree format)

Criterion	Definition
1. Nasal or oral inflammation	Development of painful or painless oral ulcers or purulent or bloody nasal discharge
2. Hemoptysis*	Hemoptysis during illness
3. Abnormal chest radiograph	Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
4. Urinary sediment	Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
5. Granulomatous inflammation on biopsy	Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)

* Used as a surrogate if biopsy data are not available.

1, unspecified vasculitis in 6, and overlap vasculitis in 1. Criteria from Table 3 that were present in these patients were abnormal urinary sediment in 42, nasal or oral inflammation in 37, abnormal chest radiographic findings in 27, and granulomatous inflammation on biopsy in 15. In addition, misclassified controls had other manifestations listed in Table 2, including hemoptysis in 6, sinus pain in 10, abnormal sinus radiographic findings in 6, eye inflammation in 7, ear inflammation in 8, and small vessel vasculitis on biopsy in 29.

Tree classification. Figure 1 shows the best of several tree classifications derived using the computer program CART. Although all 11 variables listed in Table 2 were included as potential criteria, only 5 criteria were used (Table 4). In the classification tree, the presence of granulomatous inflammation on biopsy separated the cases from the controls better than any other criterion. As defined in Table 4, granulomatous

Table 5. 1990 classification tree criteria for Wegener's granulomatosis (WG)*

WG subsets	No. of patients WG/non-WG	% correctly classified	% WG patients in subset	Non-WG subsets	No. of patients WG/non-WG	% correctly classified	% non-WG patients in subsets
3. Nasal or oral inflammation and active urinary sediment; absence of granulomatous inflammation and normal chest radiograph	8/23	23	9.5	1. Absence of granulomatous inflammation and absence of nasal or oral inflammation	8/598	99	83
4. Abnormal chest radiograph and nasal or oral inflammation; absence of granulomatous inflammation	8/8	50	9.5	2. Nasal or oral inflammation; negative findings for biopsy, chest radiograph, and urinary sediment	1/47	98	7
6. Granulomatous inflammation on biopsy and abnormal chest radiograph; absence of nasal or oral inflammation	13/8	62	15	5. Granulomatous inflammation on biopsy; absence of nasal or oral inflammation and normal chest radiograph	2/31	94	4
7. Granulomatous inflammation on biopsy and nasal or oral inflammation	45/7	87	53				

* The subset numbers also appear below the subset boxes in Figure 1. Missing data rule: If biopsy is not defined, substitute hemoptysis. The classification tree yields a sensitivity of 87.1% and a specificity of 93.6%. See Table 3 for definitions of criteria.

inflammation could be present in the vessel wall or in a perivascular or extravascular area. When this information was not available, hemoptysis was used as a surrogate variable, since on computer analysis, it divided the cases in a manner that best approximated the "granulomatous inflammation on biopsy" criterion (10). The classification tree resulted in an overall sensitivity of 87.1% and a specificity of 93.6%.

The classification tree contains 4 subsets (numbers 3, 4, 6, and 7) in which subjects are to be classified as having Wegener's granulomatosis, and 3 subsets (numbers 1, 2, and 5) in which subjects are to be classified as having other forms of vasculitis (Table 5). All WG cases that were correctly classified had 2 positive criteria. Thus, in subset 7, these criteria were granulomatous inflammation on biopsy (39 cases) or the surrogate of hemoptysis (6 cases) and nasal or oral inflammation (45 cases). Thirteen additional cases of WG were correctly classified in subset 6 by the presence of an abnormal chest radiograph result. In addition, these patients all had granulomatous inflammation on biopsy, but no nasal or oral inflammation. Eight WG patients were correctly classified in subset 4 based on nasal or oral inflammation and an abnormal chest radiograph. The remaining 8 cases were correctly classified in subset 3 by having nasal or oral inflammation and abnormal urinary sediment, while having negative findings on biopsy and chest radiograph.

In the classification tree, 11 patients (12.9%) with an entry diagnosis of Wegener's granulomatosis were misclassified. These 11 had the manifestations listed in Table 4, including hemoptysis in 1, abnormal urinary sediment in 3, nasal or oral inflammation in 1, abnormal chest radiograph results in 3, and granulomatous inflammation on biopsy in 1, as well as the following manifestations given in Table 2: sinus pain in 2, abnormal sinus radiographic findings in 3, elevated serum creatinine level in 4, eye involvement in 3, ear inflammation in 2, and biopsy showing small vessel inflammation in 1.

Forty-six control cases (6.4%) were misclassified as having Wegener's granulomatosis by the tree method. Entry diagnosis in these included: polyarteritis nodosa in 7, Churg-Strauss vasculitis in 4, hypersensitivity vasculitis in 11, Henoch-Schönlein purpura in 7, giant cell (temporal) arteritis in 5, Takayasu arteritis in 1, leukocytoclastic vasculitis in 1, unspecified vasculitis in 5, overlap vasculitis in 1, cryoglobulinemia in 2, vasculitis associated with malignancy in 1, and lymphomatoid granulomatosis in 1. Criteria

from Table 4 manifested by these controls included hemoptysis in 5, abnormal urinary sediment in 29, nasal or oral inflammation in 37, abnormal chest radiograph results in 18, and biopsy showing granulomatous inflammation in 11. Other manifestations given in Table 2 included sinus pain or tenderness in 6, abnormal sinus radiograph results in 5, elevated serum creatinine level in 16, eye involvement in 6, ear inflammation in 7, and biopsy showing small vessel inflammation in 24.

DISCUSSION

Criteria for the classification of Wegener's granulomatosis were developed by comparing 85 patients who had this disease with 722 control patients who had other forms of vasculitis. No criteria sets previously described have been derived by analysis of cases.

Wegener's granulomatosis is a clinicopathologic complex of necrotizing granulomatous vasculitis of the upper and lower respiratory tract and glomerulonephritis (3–8). The validity of this definition is reflected by the identification of a traditional format criteria set (Table 3), with both sensitivity and specificity approaching 90%, requiring only 4 criteria, which distinguishes patients with WG from other patients with vasculitis. This criteria set includes pulmonary, renal, nasal, or oral inflammation and granulomatous inflammation on biopsy. The classification tree for WG (Figure 1) also provides high sensitivity and specificity values. The surrogate of hemoptysis allows classification when biopsy data (granulomatous inflammation) are not available. However, it is important to realize that our control group consisted of patients with documented vasculitis, and tissue or angiographic demonstration of vasculitis is therefore generally a prerequisite for our controls.

The demographic profile of our 85 patients with Wegener's granulomatosis (in Table 1) is similar to that described in the literature (3,8). In this series, approximately 65% of the patients had abnormal chest radiograph results, showing nodules, cavities, or infiltrates, over 50% had abnormal urinary sediment, and 75% had biopsy-demonstrated granulomatous inflammation.

Both the traditional and tree formats have sensitivities and specificities of approximately 90%, misclassifying between 6% and 13% of cases and controls, respectively. As emphasized in the tree structure, the presence of granulomatous inflammation on biopsy is the best single discriminator between patients with WG and controls. In the traditional format, misclassified WG cases averaged less than 1 criterion per patient (5 criteria for 10 patients) (see Table 3). In the tree format, misclassified WG patients also had less than 1 criterion per patient (9 criteria for 11 patients) (see Table 4). Since each format required at least 2 positive criteria, these patients were misclassified. However, other features listed in Table 2 were present in these patients.

It is striking that only 1 of all the misclassified WG patients had a biopsy demonstrating granulomatous inflammation. However, 70% of the correctly classified patients with Wegener's granulomatosis, and 75% of the 85 cases entered in the study, fulfilled this criterion. The misclassified WG patients had disease manifestations that were not selected for either format (Tables 3 and 4) because these manifestations did not significantly improve the sensitivity and specificity of the format. This is illustrated by the number of variables from Table 2 that were demonstrated in the WG patients who were misclassified: 10 misclassified patients in the traditional format had 22 manifestations (2.2 per patient), and 11 patients in the tree format had 24 criteria (2.2 per patient).

The items in Table 2 were selected by the vasculitis subcommittee members with the aid of analyses of items on the data collection sheet (10).

Other parameters, less sensitive or specific for classification purposes, may nevertheless be helpful in establishing a diagnosis. For example, in the appropriate clinical setting, nonspecific findings such as leukocytoclastic vasculitis of the skin or mononeuritis multiplex can help establish a diagnosis in any given patient.

Misclassified controls had many different entry diagnoses within the spectrum of vasculitis. Many of these controls had biopsies demonstrating granulomatous inflammation (25% of misclassified controls). In this regard, it is often difficult to distinguish Wegener's granulomatosis from Churg-Strauss syndrome because of the presence of nasal, sinus, and pulmonary involvement in both diseases (16). In addition, the histopathology in lung tissue can show granulomatous vasculitis in either disorder. Therefore, it is interesting that a large number of misclassified controls had Churg-Strauss syndrome; in the traditional format, 6 of 58 misclassified controls (10%) had Churg-Strauss syndrome as an entry diagnosis, and this was also true for 4 of 46 controls (9%) misclassified in the tree format, which is a high percentage, considering that all

Churg-Strauss syndrome patients accounted only for 2.8% of the control group (20 of 722).

Other variables which may be specific for Wegener's granulomatosis are not included for several reasons. For example, one finding that is virtually diagnostic for Wegener's granulomatosis in a patient with systemic vasculitis is a saddle-nose deformity (8). This finding represents inflammation and collapse of the nasal cartilage. Information on this item was not collected in this data set. Yet, although saddle-nose deformity may be very specific, its sensitivity would be too low (rare event) to be of value. Another finding which may be important is the presence of antineutrophil cytoplasmic antibodies, but this test was not available when our data were collected (12,13), and its value in classification has yet to be established.

This data set confirms that laboratory parameters such as the erythrocyte sedimentation rate may be elevated in patients with Wegener's granulomatosis, but that the finding lacks specificity.

The use of either criteria set is relatively straightforward. Biopsy is the only invasive test, and an open-lung biopsy is often required in order to obtain adequate tissue for examination. Although routine histologic staining is sufficient for the determination of granulomatous inflammation, cultures and special stains must be done to rule out an infectious cause. There are no exclusions other than the presence of a connective tissue disease. In the tree classification, the surrogate of hemoptysis provides greater flexibility for the use of these criteria when biopsy data indicating granulomatous vasculitis are not available.

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