# THE AMERICAN COLLEGE OF RHEUMATOLOGY 1990 CRITERIA FOR THE CLASSIFICATION OF HYPERSENSITIVITY VASCULITIS

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**Criteria for the classification of hypersensitivity vasculitis were developed by comparing 93 patients who had this disease with 714 control patients with other forms of vasculitis. For the *traditional format classification*, 5 criteria were selected: age >16 at disease onset, history of taking a medication at onset that may have been a precipitating factor, the presence of palpable purpura, the presence of maculopapular rash, and a biopsy demonstrating granulocytes around an arteriole or venule. The presence of 3 or more of these 5 criteria was associated with a sensitivity of 71.0% and a specificity of 83.9%. A *classification tree* was also constructed. The criteria appearing in the tree structure were the same as for the traditional format, except there were 2 pathology criteria: one required the presence of granulocytes in the wall of an arteriole or venule, and the other required the presence of eosinophils in the inflammatory exudate. The classification tree was associated with a sensitivity of 78.5% and a specificity of 78.7%.**

The concept that inflammatory vascular disease secondary to allergic or hypersensitivity mechanisms should exist as a distinct nosologic entity was first proposed by Zeek and colleagues in 1948 (1). The rationale for this concept was based upon a series of clinical and experimental observations that suggested a difference between hypersensitivity vasculitis and other forms of vasculitis that were recognized at that time. Distinguishing features included prominent involvement of the skin and the observation that the condition frequently appeared to be precipitated by use of serum or drugs, and hence, the prefix "hypersensitivity" (2). Pathologically, the disease tended to involve the small blood vessels, with infiltration of polymorphonuclear leukocytes and leukocytoclasia (nuclear fragmentation). All lesions tended to be about the same age, having occurred around the same time. Experimentally, a similar disease could be produced in animals by sensitization with a variety of nontoxic antigens.

Unfortunately, despite these distinguishing features, difficulties have arisen in defining hypersensitivity vasculitis (HSV) as a distinct illness. These difficulties include the observations that in many patients with both the clinical and pathologic picture of HSV, no inciting antigen or stimulant can be found (3). Furthermore, in patients with vasculitis secondary to recognized diseases or mechanisms other than hypersensitivity to exogenous antigens, a clinical and pathologic picture similar to that of hypersensitivity vascu-

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**Table 1.** Comparison of the sensitivity and specificity of potential criteria variables for hypersensitivity vasculitis*

| Criterion | No. of cases (n = 93) | No. of controls (n = 714) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| History | | | | |
| 1. Medications at onset†‡§ | 89 | 762 | 52.8 | 83.7 |
| 2. Age >16†‡§ | 93 | 708 | 94.6 | 10.7 |
| Physical | | | | |
| 3. Maculopapular rash†‡§ | 93 | 705 | 53.8 | 79.1 |
| 4. Palpable purpura†‡§ | 92 | 711 | 63.0 | 77.4 |
| 5. Petechiae | 92 | 711 | 38.0 | 88.0 |
| 6. Cutaneous ulcers | 91 | 709 | 30.8 | 90.4 |
| Biopsy | | | | |
| 7. Granulocytes in periarteriolar location | 73 | 418 | 28.8 | 88.3 |
| 8. Granulocytes in extraarteriolar location | 72 | 417 | 16.7 | 92.6 |
| 9. Granulocytes in perivenular location | 84 | 384 | 38.1 | 86.2 |
| 10. Granulocytes in extravenular location | 84 | 385 | 27.4 | 91.2 |
| 11. Eosinophils in periarteriolar location | 73 | 418 | 11.0 | 92.8 |
| 12. Eosinophils in arteriolar wall | 74 | 419 | 12.2 | 94.7 |
| 13. Eosinophils in extraarteriolar location | 72 | 420 | 15.3 | 94.3 |
| 14. Eosinophils in perivenular location | 85 | 384 | 16.5 | 94.5 |
| 15. Eosinophils in extravenular location | 84 | 385 | 21.4 | 95.6 |
| 16. Eosinophils in venular wall | 85 | 385 | 17.6 | 96.6 |
| 17. Granulocytes in arteriolar wall | 73 | 420 | 31.5 | 86.7 |
| 18. Granulocytes in venular wall | 84 | 384 | 45.2 | 85.9 |
| 19. Biopsy variables 17 or 18 "wall granulocytes"†§ | 79 | 387 | 55.7 | 77.5 |
| 20. Abnormal biopsy variables 7, 8, 9, or 10†‡ | 82 | 385 | 53.7 | 76.4 |
| 21. Abnormal biopsy variables 11–16, eosinophils in any location†§ | 76 | 380 | 34.2 | 85.8 |

* 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 one of the final "short list" of variables (n = 7) (see text).
‡ Criterion is used for the traditional format classification.
§ Criterion is used for the tree classification.

litis can also be observed. Such conditions include certain cases of vasculitis associated with connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome), malignancies, Henoch-Schönlein purpura, the presence of mixed cryoglobulins with unknown antigens, and, occasionally, patients with polyarteritis nodosa, Churg-Strauss syndrome, and "polyangiitis" (4–7).

Despite these limitations, the concept of hypersensitivity vasculitis has endured and, generally, has been believed to be clinically useful, as demonstrated by its retention in recent classification schemes of systemic vasculitis (5,6,8). This study represents an attempt to more clearly delineate and separate the syndrome of hypersensitivity vasculitis from other recognized forms of systemic vasculitis.

For a description of the patient selection and evaluation methods, see the articles by Bloch et al (9) and Hunder et al (10), which appear elsewhere in this issue of *Arthritis and Rheumatism.*

Table 2. 1990 criteria for the classification of hypersensitivity vasculitis (traditional format)*

| Criterion | Definition |
|---|---|
| Age at disease onset >16 years | Development of symptoms after age 16 |
| Medication at disease onset | Medication was taken at the onset of symptoms that may have been a precipitating factor |
| Palpable purpura | Slightly elevated purpuric rash over one or more areas of the skin; does not blanch with pressure and is not related to thrombocytopenia |
| Maculopapular rash | Flat and raised lesions of various sizes over one or more areas of the skin |
| Biopsy including arteriole and venule† | Histologic changes showing granulocytes in a perivascular or extravascular location |

* For purposes of classification, a patient shall be said to have hypersensitivity vasculitis if at least 3 of these 5 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 71.0% and a specificity of 83.9%.
† This is criterion 20 from Table 1.

## RESULTS

**Patient population.** From among the 807 patients with definite vasculitis who were entered into the study, 93 had a diagnosis of hypersensitivity vasculitis. Among these patients, 46% were male, and the mean age at onset of HSV was 47.3 years (95% were older than age 16).

After review of the results of univariate analyses of the items on the data collection form, the subcommittee selected variables that they considered potentially useful discriminators between HSV and other forms of vasculitis (Table 1). The number of cases and controls (those in whom a particular variable was determined), the sensitivity (percentage of cases in whom the variable was present or abnormal), and the specificity (proportion of controls in whom the variable was absent or normal) for each potentially useful discriminator are shown in Table 1.

A number of potentially important criteria were combined in a way that favorably influenced the sensitivity and/or specificity. Four single items and 3 combined items were selected from among those listed in Table 1 as a "short list" of criteria that would have the greatest power to separate patients with HSV from those with other forms of vasculitis.

**Traditional format classification.** Approximately 30 combinations of the 7 variables in the "short list" were tested before a final set was chosen to classify hypersensitivity vasculitis in the traditional format.

Table 2 lists the final criteria selected for the traditional format and their definitions. From among these 5 variables, the presence of 3 or more of any of them yields a sensitivity of 71.0% and a specificity of 83.9%. The selection of these final criteria was influenced by a variety of factors, including a search for sensitivity and specificity levels of at least 70%, as well as the inclusion of criteria that were recorded for as many cases as possible. Using this strategy, 105 of 715 controls did not have sufficient variables recorded to classify them as a case or a control. In these instances, the missing values were assigned a "control" value.

**Tree classification.** Figure 1 and Table 3 display and define the best of several classification trees derived using the computer program CART (9). The use of this tree allows the classification of an individual case of vasculitis as either HSV (case) or non-HSV (control), with a sensitivity of 78.5% and a specificity of 78.7%. As can be observed in Figure 1, the presence of palpable purpura most effectively separated the cases from the controls. The tree classification complements the traditional classification format (Table 2) by offering a somewhat higher sensitivity at the cost of some specificity. The tree also allows classification of the majority of cases (59 of 93) without requiring a biopsy. This may be useful in epidemiologic surveys or other studies in which it is difficult to obtain a biopsy. For different investigative purposes, dependent upon the reason one uses disease classification criteria, there are times when an enhanced degree of either sensitivity or specificity may be more desirable.

The classification tree contains 4 subsets (numbers 2, 4, 6, and 7) in which subjects are to be classified as having HSV, and 3 subsets (numbers 1, 3, and 5) in which subjects are to be classified as having other forms of vasculitis (Table 4).

## DISCUSSION

In view of the previous and current ambiguities about hypersensitivity vasculitis and its relationship to other, similar forms of vasculitis, as reviewed above, it is not surprising that the criteria for hypersensitivity

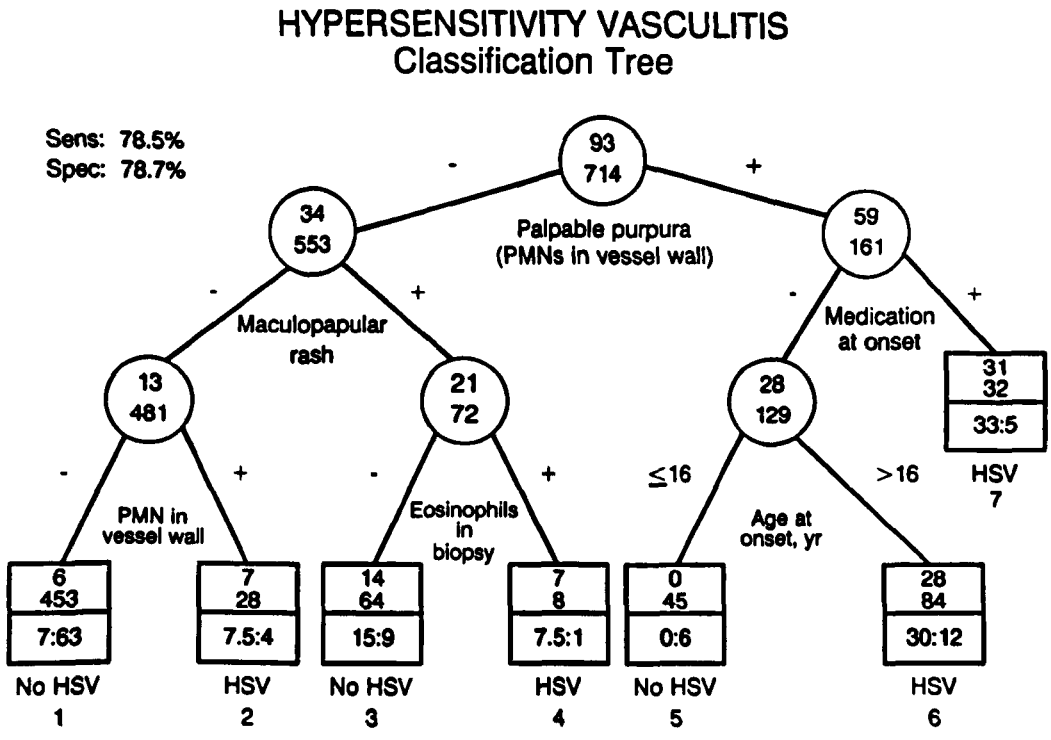


**Figure 1.** Classification tree for hypersensitivity vasculitis (HSV). The circles and boxes contain the number of patients with HSV (top number) and the number of control patients with other forms of vasculitis (bottom number). The bottom half of the boxes shows the percentage of patients with HSV (out of all HSV cases) (left number) and the percentage of controls (out of all controls) (right number). Boxes specify whether subjects are classified as having HSV or not having HSV (No HSV); the numbers under these specifications are the subset numbers (see Table 3 for definitions of criteria and Table 4 for explanations of subsets). Parentheses indicate the surrogate variable "polymorphonuclear neutrophils (PMNs) in vessel wall" to be used when "palpable purpura" is not defined.

vasculitis yielded the lowest sensitivity and specificity values among the vasculitic conditions that were studied by the subcommittee. There are several factors that may have contributed to the limits of these sensitivities and specificities.

The final criteria yielded a sensitivity of 71.0% for the traditional format and 78.5% for the tree structure. Failure of these criteria to identify almost 3 of 10 patients entered by the traditional format and 2 of 10 patients by the tree classification may be best understood by examining the classifying subsets of the tree structure (Figure 1). Cases of HSV not correctly

**Table 3.** Criteria and definitions used for the classification of hypersensitivity vasculitis (tree format)

| Criterion | Definition |
|---|---|
| 1. Age at disease onset >16 years | Development of symptoms after age 16 |
| 2. Medication at disease onset | Medication was taken at the onset of symptoms that may have been a precipitating factor |
| 3. Palpable purpura | Slightly elevated purpuric rash over one or more areas of the skin; does not blanch with pressure and is not related to thrombocytopenia |
| 4. Maculopapular rash | Flat and raised lesions of various sizes over one or more areas of the skin |
| 5. Polymorphonuclear neutrophils in vessel wall* | Biopsy demonstrating granulocytes in the wall of a venule or arteriole |
| 6. Eosinophils in biopsy† | Biopsy demonstrating eosinophils in a venule or arteriole at any location |

* This is criterion 19 from Table 1.
† This is criterion 21 from Table 1.

Table 4. 1990 classification tree criteria for hypersensitivity vasculitis (HSV)*

| HSV subsets | No. of patients HSV/non-HSV | % correctly classified | % HSV patients in subset | Non-HSV subsets | No. of patients HSV/non-HSV | % correctly classified | % non-HSV patients in subset |
|---|---|---|---|---|---|---|---|
| 7. Purpura; history of medication at disease onset | 31/32 | 49 | 33 | 5. Palpable purpura without medication at disease onset, age ≤16 at disease onset | 0/45 | 100 | 6 |
| 6. Purpura; no history of medication at disease onset; age >16 at disease onset | 28/84 | 25 | 30 | 1. No purpura or maculopapular rash; no granulocytes in vessel wall | 6/453 | 99 | 63 |
| 4. Maculopapular rash and biopsy demonstrating eosinophils in a venule or arteriole; no purpura | 7/8 | 47 | 7.5 | 3. Maculopapular rash; no purpura; no eosinophils in venule or arteriole | 14/64 | 82 | 9 |
| 2. Biopsy demonstrating granulocytes in the wall of a venule or arteriole; absence of purpura and maculopapular rash | 7/28 | 20 | 7.5 | | | | |

* The subset numbers also appear below the subset boxes in Figure 1. The classification tree yields a sensitivity of 78.5% and a specificity of 78.7%. See Table 3 for definitions of criteria.

classified by the tree (false negatives) were found exclusively in the group of patients without palpable purpura, thus reaffirming that while this physical sign is a most sensitive finding in hypersensitivity vasculitis, a variety of other dermatologic manifestations may predominate. Those cases misclassified by the tree structure lacked 1 of 2 specified histopathologic findings, probably reflecting the known problem of sampling and timing of skin biopsies (11).

The specificity achieved by classification using the traditional format (83.9%) and that achieved by using the tree classification (78.7%) were good, considering that the traditional clinicopathologic picture of HSV is seen in a variety of conditions. Table 5 lists those conditions, along with the numbers of patients who would be misclassified as having HSV by the traditional format and by the tree classification. As expected, the single most difficult disorder to differentiate from HSV was Henoch-Schönlein purpura, which is characterized by palpable purpura (also the most sensitive finding in HSV) and a histopathologic picture that is indistinguishable from that of HSV. Points of clinical differentiation that are supported by the criteria are the generally younger age of the patient with Henoch-Schönlein purpura (mean age 17.4 years versus 47.3 years for HSV patients) and the characteristic target-organ distribution of this disease (i.e., gastrointestinal tract and renal organs). While some have questioned whether these disorders deserve to be distinct nosologic entities and have suggested they merely represent different pictures of hypersensitivity to various foreign antigens (12), the results of more recent immunopathologic studies, such as the demon-

Table 5. Cases of vasculitis misclassified by proposed criteria for hypersensitivity vasculitis

| Diagnosis | No. of cases misclassified: Traditional format | No. of cases misclassified: Tree classification |
|---|---|---|
| Henoch-Schönlein purpura | 31 | 35 |
| Polyarteritis nodosa | 23 | 30 |
| Wegener's granulomatosis | 12 | 23 |
| Cryoglobulinemic vasculitis* | 9 | 13 |
| Unspecified type of vasculitis | 8 | 14 |
| Churg-Strauss syndrome | 9 | 11 |
| Malignancy-associated vasculitis† | 2 | 4 |
| Cutaneous polyarteritis | 4 | 4 |
| Giant cell (temporal) arteritis | 0 | 3 |
| Leukocytoclastic vasculitis | 5 | 4 |
| Takayasu arteritis | 2 | 2 |
| Miscellaneous vasculitis‡ | 10 | 9 |
| Total misclassified | 115 | 152 |

* Includes cryoglobulinemic vasculitis with urticaria (5 patients), essential cryoglobulinemia (6 patients), cryoglobulinemia associated with hepatitis B (2 patients).
† Includes vasculitis associated with breast cancer (1 patient), myeloproliferative disease (1 patient), myeloma (1 patient), unspecified (1 patient).
‡ Includes single case reports of vasculitis with diverse associations.

stration of circulating IgA immune complexes and IgA deposits in vascular lesions of Henoch-Schönlein purpura, support their distinction (13). These 2 variables were not assessed completely in this study, but they may serve as important points of differentiation in future studies. Polyarteritis nodosa, Churg-Strauss syndrome, and Wegener's granulomatosis were also frequently misclassified as hypersensitivity vasculitis, reflecting the presence of a small-vessel component of the systemic process in these disorders (7). The remaining clinical and pathologic features of these disorders generally serve to readily differentiate them from HSV.

The differentiation of vasculitis with cryoglobulinemia from hypersensitivity vasculitis poses both practical and theoretical problems. The syndrome of essential cryoglobulinemia is also characterized by vasculitis of small vessels, palpable purpura, and leukocytoclasia, but is generally a chronic illness, whereas hypersensitivity vasculitis usually runs a more limited course (14). By definition, cryoglobulinemic vasculitis is not associated with a known antigenic stimulus, although rheumatoid factor is present in the majority of patients. It is possible that essential cryoglobulinemia with vasculitis is the result of an ongoing reaction to an unidentified antigenic stimulus and, thus, may represent a chronic form of HSV in a broad sense. Alternatively, small amounts of cryoglobulins are frequently found in HSV. This is not totally unexpected, since cryoglobulins occur as part of an immune complex reaction; indeed, they were detected in 26% of the entire study group, although their concentrations were generally low.

The remaining, sizable group of miscellaneous disorders that were misclassified as hypersensitivity vasculitis reflect the known association of a wide variety of conditions with the clinicopathologic picture outlined by the criteria and emphasize the importance of a careful search for infections, malignancies, and a variety of systemic disorders when the presence of HSV is a clinical possibility. Further differentiation of these disorders will await an increased understanding of their etiopathogenesis. The classification criteria, including the traditional and tree formats, can be applied without subjecting the patient to biopsy in the majority of cases. The addition of a punch biopsy of involved skin for routine histologic examination will increase the yield of successfully classified cases.

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