Acta Derm Venereol (Stockh) 1995; 75: 125–129

Henoch-Schönlein Purpura: Clinicopathologic Correlation of Cutaneous Vascular IgA Deposits and the Relationship to Leukocytoclastic Vasculitis

STEVEN D. HELANDER, FERNANDO R. DE CASTRO and LAWRENCE E. GIBSON

Department of Dermatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

Significant cutaneous vascular IgA deposits are common in Henoch-Schönlein purpura but not in other vasculitides. The specificity for IgA vascular deposits for Henoch-Schönlein purpura is not well defined. To examine the specificity of IgA vascular deposits for this disease, we compared clinicopathologic features of 92 cases with IgA vascular deposits and a direct immunofluorescence impression of vasculitis with 90 similar cases without IgA deposits. Henoch-Schönlein purpura was diagnosed in 24% of cases with vascular IgA deposits on direct immunofluorescence examination. IgA deposits were frequent in erythema nodosum and venous stasis-related problems and in cryoglobulinemia, coagulopathic vasculopathies, and livedoid vasculitis. Of our cases, 78% exhibited vascular fluorescence with multiple conjugates. No histologic or immunofluorescence pattern alone was specific. The diagnostic specificity for Henoch-Schönlein purpura is improved if gastrointestinal involvement, upper respiratory infection, or age < 20 years is present. We propose diagnostic criteria for Henoch-Schönlein purpura incorporating clinical findings yielding sensitivity and specificity > 90%. ***Key word: direct immunofluorescence.***

(Accepted July 15, 1994.)

Acta Derm Venereol (Stockh) 1995; 75: 125–129.

L. E. Gibson, Department of Dermatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

The cutaneous direct immunofluorescence (DIF) finding of IgA deposits on vessel walls is relatively uncommon. When this is seen, the question of Henoch-Schönlein purpura (HSP) is frequently raised. Schönlein (1) and Henoch (2) separately described a striking syndrome, mainly in children, characterized by palpable purpura on the extremities and buttocks in association with renal, gastrointestinal, and joint involvement. The existence of IgA was unknown, and yet the presence of such deposits has come to be regarded by many clinicians as an essential part of the syndrome. Whereas the presence of vascular immune deposits of IgA is clearly established in most cases of HSP, the predictive value of these DIF findings for this diagnosis has not been determined (3–5). Also, the broader question of the significance of IgA vascular deposits in the context of vasculitis needs to be addressed. This is of particular interest because of recent work regarding the role of IgA in the pathogenesis of other neutrophilic dermatoses, such as dermatitis herpetiformis, linear IgA bullous disease, and the intraepidermal bullous neutrophilic dermatoses.

We attempted to address these issues by examining the clinicopathologic correlation of the DIF finding of IgA on vessel walls.

MATERIALS AND METHODS

We reviewed the records of 5,000 DIF studies performed in the Mayo Clinic immunodermatology laboratory during the last 7 years. The only selection criteria for our study group were that the studies were conducted on patients seen at the Mayo Clinic, they have IgA deposits on vessel walls, and the overall DIF findings be sufficient at least to suggest a diagnosis of vasculitis. In our laboratory, we require vascular deposits with at least one immunoglobulin conjugate in addition to C3 or two immunoglobulin conjugates for a diagnosis of vasculitis, and we take into account fluorescence intensity and biopsy site. We added this last selection requirement to screen out the many cases of non-specific, weak, focal vascular fluorescence encountered with this highly sensitive technique. A control group of similar size was then defined by selecting the first 90 studies performed after an arbitrary date in which a DIF diagnosis of vasculitis, as defined above, was made in the absence of IgA vascular deposits.

Among the 92 cases of vasculitis with IgA, information on the site of biopsy was available for 84 (91%). Of the 84 specimens, 74 (88%) were from involved skin, 6 (7%) from perilesional skin, and 4 (5%) from uninvolved skin. Of 90 control cases of vasculitis without IgA deposits, 84 (93%) had information on biopsy site available: 74 were from lesional sites, 7 from perilesional skin, and 3 from uninvolved skin.

All biopsy specimens were immediately snap-frozen in liquid nitrogen. Cryostat sections were stained with FITC-tagged polyclonal antisera directed against IgG, IgM, IgA, C3, and fibrinogen. The specimens were examined with a Zeiss fluorescence microscope. The examination was performed without knowledge of the clinical details.

The site and findings for each conjugate were recorded for each selected case. The medical histories were then reviewed and specific data, including prodrome, dermatologic findings, systemic involvement, results of investigations, complications, course, and outcome, were extracted. A final diagnosis, made on the basis of the overall clinical picture, the results of all investigations, and, in some cases, years of follow-up, was used as an end point to avoid bias. To make the diagnosis of HSP, we used the strict set of criteria outlined in Table I. This set is based on the American College of Rheumatology (ACR) criteria (6), with the additional criterion of renal biopsy findings of mesangioproliferative glomerulonephritis with or without IgA. To avoid problems of circular logic, we did not use the presence of IgA in skin or kidney as a criterion. The diagnosis of HSP is suggested by two or more of the remaining four criteria.

Table I. *Diagnostic criteria used for a final diagnosis of Henoch-Schönlein purpura*[a]

Palpable purpura
Age ≤ 20 at onset
Abdominal pain and/or hematochezia
Leukocytoclastic vasculitis in skin biopsy
Renal biopsy showing mesangioproliferative glomerulonephritis with or without IgA deposits

[a] Diagnosis of Henoch-Schönlein purpura requires at least three of the five criteria.

Data from Mills et al. (6). By permission of the American College of Rheumatology.

 ISSN 0001-5555

Table II. *The predictive value of a direct immunofluorescence interpretation suggestive of vasculitis*

	IgA present 92 cases		IgA absent 90 cases		Total 182 cases	
	No.	%	No.	%	No.	%
Clinically confirmed vasculitis	67	73	50	56	117	64
No vasculitis	25	27	40	44	65	36

Table III. *Disease spectrum of vasculitis cases*

Disease	IgA present 67 cases		IgA absent 50 cases	
	No.	%	No.	%
Henoch-Schönlein purpura	16	24	1	2
Livedoid vasculitis	10	15	5	10
Cryoglobulinemia	6	9	1	2
Coagulopathic vasculopathies:				
Lupus anticoagulant	4	6	2	4
Hypergammaglobulinemic purpura	2	3	0	

For cases in which the final diagnosis was vasculitis, histologic material was retrieved and reviewed without prior knowledge of the diagnosis by a dermatopathologist (L.E.G.). We used a histologic grid to examine in detail the size and site of the vessels affected, the composition of the infiltrate, the nature of the vascular destruction, and the associated changes in the epidermis, the dermis, and, where included, the panniculus. Findings were rated on a scale of 0 to 4+, from least to greatest degree of change.

All the data were coded and loaded into a flat-file data base to facilitate multiple variable cross-searches. Calculations of sensitivity and specificity were made according to standard formulae:

$$\text{Sensitivity} = \frac{\text{no. of true positives}}{\text{no. of true positives} + \text{no. of false negatives}}$$

$$\text{Specificity} = \frac{\text{no. of true negatives}}{\text{no. of true negatives} + \text{no. of false positives}}$$

RESULTS

Of 5,000 DIF records reviewed, we found only 92 biopsy specimens that met the clinical and routine histopathologic criteria for vasculitis as defined above. We obtained 90 control studies in which the impression was vasculitis without IgA deposits. The predictive value of the DIF impression for a final diagnosis of vasculitis is shown in Table II. Vasculitis would be falsely diagnosed using DIF alone in 27% of cases with IgA deposition. The range of diagnoses among these false-positive diagnoses was broad. Venous stasis-related problems and erythema nodosum were the most frequent diagnoses in both groups. Neutrophilic dermatoses, urticaria, dermatitis, drug reactions, and purpura simplex were other entities that caused confusion (Table III).

With the modified ACR diagnostic criteria (Table I), we diagnosed Henoch-Schönlein purpura in only 17 cases: 24% of the cases with IgA vascular deposits and 2% of the cases without these deposits. Typical DIF findings for HSP are shown in Fig. 1. Coagulopathic vasculopathy and cryoglobulinemia (Fig. 2) together accounted for an additional 18% of the IgA-positive cases but only 6% of the control cases. Livedoid vasculitis was seen in 15% of cases with IgA and in 10% of cases without IgA. IgA vascular deposits were seen occasionally in

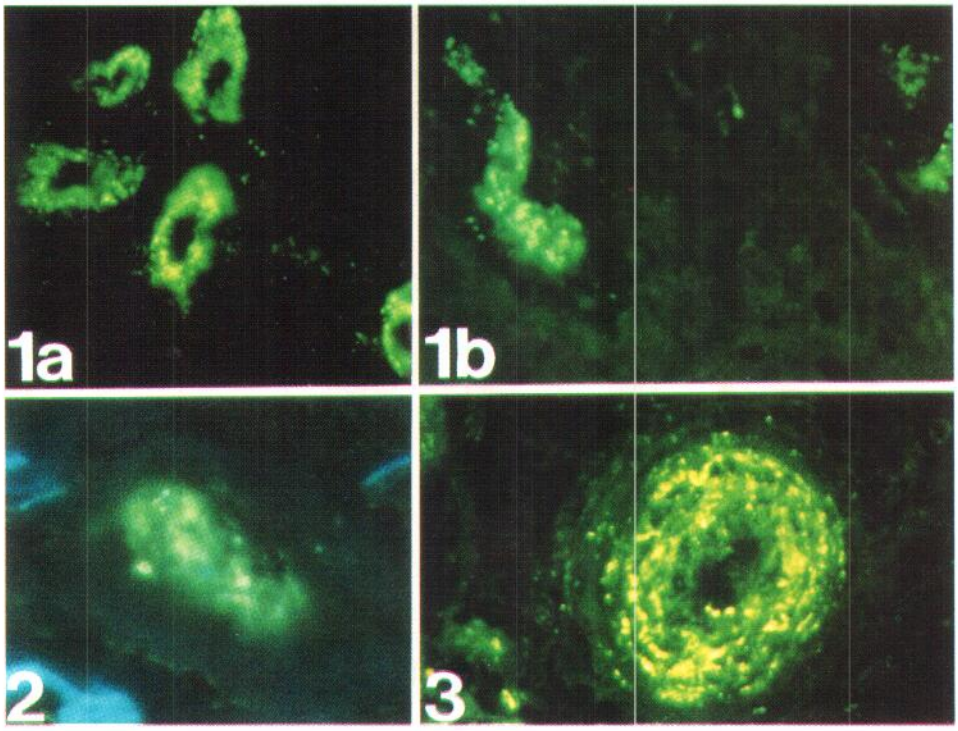


Fig. 1. Henoch-Schönlein purpura (HSP). Direct immunofluorescence with IgA. (*a*) Intense fluorescence of small dermal vessels. (×400.) (*b*) Vascular fluorescence confined to the papillary dermis. Although this pattern is common, it is not always seen, nor is it specific to HSP (×400).

Fig. 2. Cryoglobulinemia. Intense vascular fluorescence with IgA indistinguishable from that of Henoch-Schönlein disease (×400).

Fig. 3. Degos' disease. Intense vascular fluorescence of an arteriole with IgA in deep dermis. Smaller superficial vessels may also be involved. It is an important differential diagnostic consideration for the direct immunofluorescence finding of cutaneous vascular IgA, since these patients also have gastrointestinal symptoms (×400).

Table IV. *Systemic involvement in cases of small vessel vasculitis*

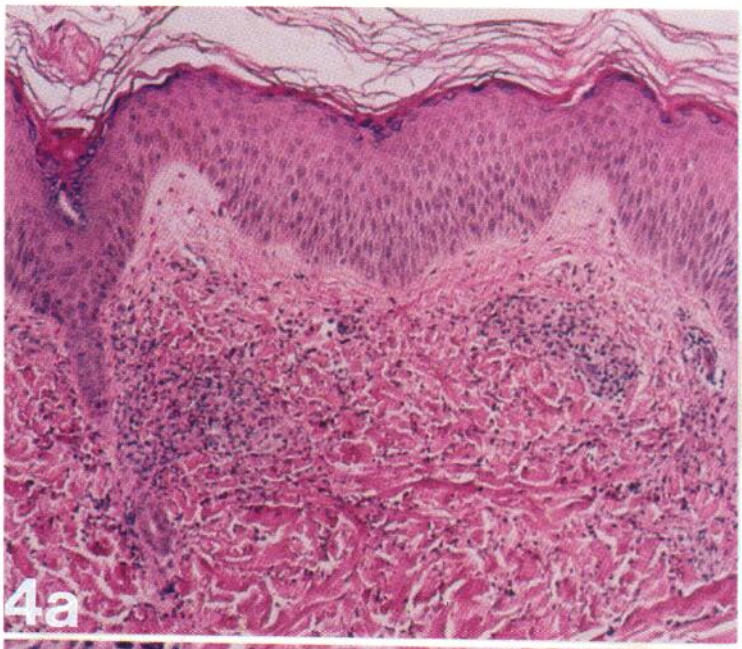
System	IgA present 67 cases		IgA absent 50 cases	
	No.	%	No.	%
Gastrointestinal	17	25	5	10
Renal	29	43	11	22
Musculoskeletal	18	27	17	34
No gastrointestinal, renal, or musculoskeletal involvement	3	4	17	34

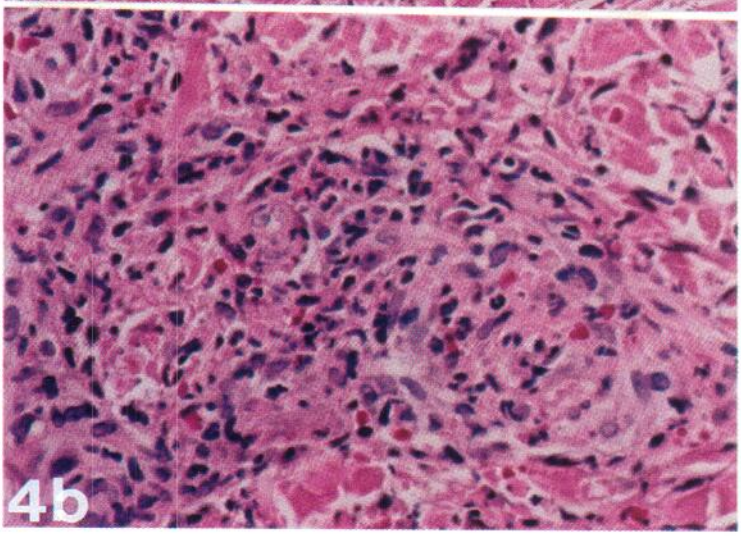
various other vasculitic disorders, including urticarial vasculitis, granulomatous vasculitis, and Degos' disease (Fig. 3).

Systemic involvement in the cases with and without IgA deposits is compared in Table IV. Gastrointestinal involvement (defined by colicky pain or hematochezia or both) and renal involvement were significantly more common in the group with IgA deposits. Again, the differences were solely due to the HSP cases in the IgA group; there was no difference between the group with IgA deposits and the group without IgA deposits if the HSP cases were removed from the analysis. Musculoskeletal problems were seen with similar frequency in both groups.

Palpable purpura was seen in 94% of the HSP cases but was also the commonest lesion in both groups in patients with vasculitis. Distinctive urticated plaques, previously reported (3), were not seen in any of the 17 HSP cases. There was no difference in distribution of cutaneous lesions between patients with HSP and those with other forms of small vessel vasculitis. Buttock lesions were seen in 22% of cases in both groups.

Of the patients with vasculitis, a respiratory tract infection prodrome was seen in 17% of those with IgA deposits but in only 2% of those without IgA deposits. Again, the differences disappeared after the HSP cases were removed. Less than half of the respiratory infections in the HSP patients were shown to be streptococcal by positive culture results.





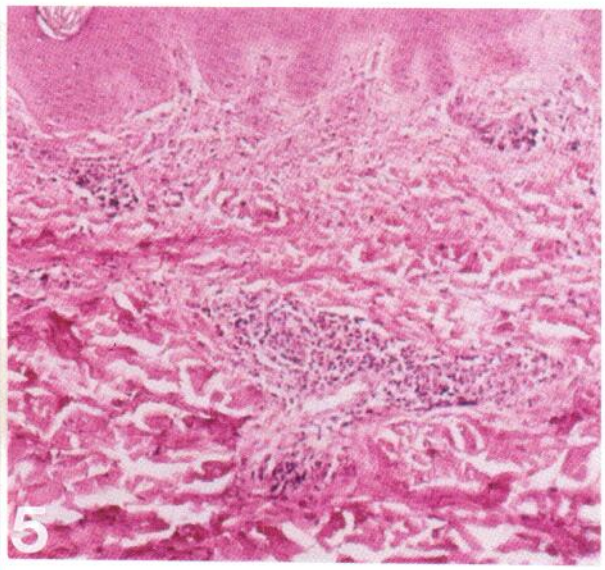


Fig. 4. Henoch-Schönlein purpura. Leukocytoclastic vasculitis indistinguishable from other causes of small vessel vasculitis. (Hematoxylin and eosin; (*a*) ×100; (*b*) ×400).
Fig. 5. Henoch-Schönlein purpura. Non-specific perivascular lymphocytic infiltrate. An adjacent biopsy sample submitted for direct immunofluorescence showed vascular fluorescence with IgA. (Hematoxylin and eosin; ×100).

Table V. *Direct immunofluorescence findings in 17 cases with a final diagnosis of Henoch-Schönlein purpura*

	No. of cases
IgA plus	
IgG	0
IgM	8
C3	14
Fibrinogen	13
3 or more conjugates	13
4 or more conjugates	6
No IgA	1

Slides were available for blinded review in 33 cases of IgA vasculitis and in 35 of the control cases. By using strict criteria for the diagnosis of vasculitis – the presence of either fibrinoid necrosis or thrombus in association with an inflammatory infiltrate involving the vessel wall – we managed to achieve a high specificity (99%) but poor sensitivity (49%) for a final diagnosis of vasculitis. Sensitivity was somewhat better in the IgA group (61%) compared with the control group (43%), again only because of the HSP cases in the former group. Histologically, there were no significant differences between the two groups. We also compared patients with HSP with patients with other forms of vasculitis. Five further cases of HSP not included in our main study were added blindly to the histologic review but only analyzed for this comparison to avoid skewing the data. We could find no significant difference between the histologic pattem seen in HSP and that seen in other small vessel vasculitides (Fig. 4).

Because of this low specificity of IgA vascular fluorescence for making the diagnosis of HSP, we attempted to define DIF findings that might distinguish the HSP cases from those with other diagnoses (Table V). In all 16 of the 17 HSP cases with IgA deposits, vascular fluorescence was seen with additional conjugates. Most showed C3 or fibrinogen staining, or both, and 8 had vascular IgM deposits. In 78%, vascular fluorescence was seen in three or more conjugates and 6 stained with at least four conjugates. There were no additional DIF features specific to the HSP cases.

Because it was not possible to improve the specificity of DIF study for a diagnosis of HSP on the basis of DIF criteria, we examined the diagnostic performance of several clinical and histologic findings in combination with these DIF findings. The sensitivity/specificity compromise for each was ranked in terms of diagnostic performance (Fig. 5). The implications of these findings are discussed below.

DISCUSSION

The ready availability of cutaneous DIF examination has helped greatly in correctly diagnosing and in understanding the immunopathogenesis of several disorders.

Vascular immune deposits with IgA are uncommon in the context of vasculitis (7) and in clinically normal skin (4). It has been reported that the immunofluorescence patterns in HSP characteristically show deposits confined to IgA and C3 (8) or with fibrinogen (9). Moreover, it has been suggested that the presence of additional vascular deposits with IgG and IgM favors a diagnosis other than HSP (5). Our data do not support these views. IgM vascular deposits were frequently present, and in several quite typical childhood cases of HSP, we saw vascular fluorescence with multiple conjugates (Table V). Although deposits were confined to the papillary dermis in 78% of cases, this was also common in other forms of vasculitis. Thus, we conclude that criteria related to the depth of vessel involvement or to findings in conjugates other than IgA are of no use in improving the accuracy of the diagnosis of HSP.

False-positive diagnoses frequently are made when vascular immune deposits are interpreted as vasculitis. Non-specific deposition of immune complexes in vessel walls is particularly common in the lower extremities because of the hemodynamics. However, pathologic immune complexes preferentially lodge here for the same reasons. Thus, although a biopsy specimen from the lower extremities is undesirable, it may be unavoidable. We saw an equal number of true– and false-positive diagnoses made on the basis of biopsy specimens from the lower extremities. The frequency of diseases with venous pathology, including stasis and erythema nodosum (in which venulitis is found), is indicative of how difficult it may be to identify the type of vessel affected when interpreting DIF material. DIF studies were positive in many cases in which histologic examination of the same site showed only non-specific changes (Fig. 6). DIF evaluation remains an important adjunct to histologic examination in the diagnosis of HSP because of sensitivity. Because it is not possible to discriminate between HSP and

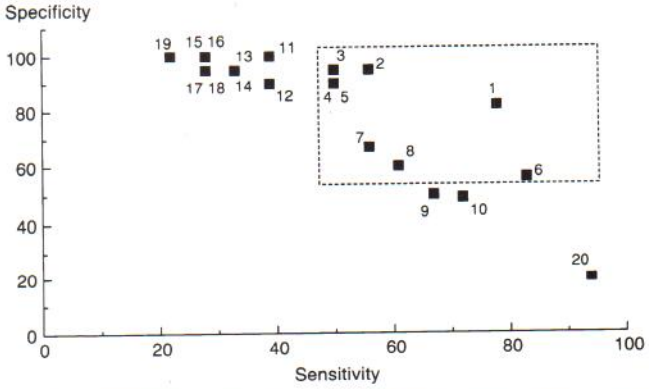


Fig. 6. Performance of individual and combinations of criteria for the diagnosis of Henoch-Schönlein purpura. *Boxed area* defines area of optimal sensitivity/specificity compromise. Combinations of criteria ranked by performance are as follows: *1*, IgA deposits + GI manifestations; *2*, IgA deposits + GI manifestations + renal involvement; *3*, IgA deposits + GI manifestations + vasculitis on histology; *4*, purpura + GI manifestations + vasculitis on histology; *5*, IgA deposits + URI prodrome; *6*, IgA deposits + purpura; *7*, IgA deposits + renal involvement + vasculitis on histology; *8*, purpura + renal involvement + vasculitis on histology; *9*, IgA deposits + vasculitis on histology; *10*, IgA deposits + renal involvement; *11*, IgA deposits + age ≤ 20 + renal involvement; *12*, IgA deposits + age ≤20; *13*, IgA deposits + vasculitis on histology + URI prodrome; *14*, purpura + vasculitis on histology + URI prodrome; *15*, IgA deposits + age ≤ 20 + vasculitis on histology; *16*, GI manifestations + vasculitis on histology + URI prodrome; *17*, IgA deposits + age ≤ 20 + GI manifestations; *18*, renal manifestations + vasculitis on histology + URI prodrome; *19*, renal manifestations + GI manifestations + URI prodrome; *20*, IgA deposits alone. *GI*, gastrointestinal; *URI*, upper respiratory tract infection.

Table VI. *Criteria[a] for the diagnosis of Henoch-Schönlein purpura in patients with vasculitic skin lesions (including vasculitic ulcers) or histologic evidence of leukocytoclastic vasculitis (or both)*

Direct immunofluorescence study suggesting vasculitis, with IgA vascular deposits
Age ≤ 20 years at onset
Gastrointestinal involvement (colicky pain and/or hematochezia)
Upper respiratory tract infection prodrome
Renal biopsy finding of mesangioproliferative glomerulonephritis with or without IgA deposition

[a] Three or more criteria required for sensitivity and specificity in excess of 90%.

other forms of small vessel vasculitis by histologic criteria alone, DIF studies add specificity to the diagnosis of HSP.

Evidence is accruing to suggest that HSP is an immune complex hypersensitivity disorder (9). Since vascular immune deposits in vessel walls correlate with circulating immune complexes (5), the DIF patterns seen in HSP may be an important clue to the pathogenesis. The similarity of the histologic findings in HSP to those of the Arthus reaction further suggests an immune-complex pathogenesis. It has been shown that IgA-containing immune complexes are present in HSP but are uncommon in other forms of small vessel vasculitis (10), in keeping with the low overall incidence of IgA deposits in vasculitis. In addition, plasmapheresis, which removes immune complexes, may be an effective therapy in some cases (11).

The high incidence of IgA deposits in cases with cryoglobulinemia is interesting. Cryoglobulins have been described previously in HSP. Of 44 HSP patients, 47% with acute disease and 64% with chronic nephritis had detectable cryoglobulins, some containing IgA (12). IgA-containing immune complexes are seen in cryoglobulinemia but are uncommon. The class of immunoglobulin in cutaneous vessel walls correlates with that of the circulating cryoglobulin (13). Vascular IgA deposits are also frequent in systemic lupus erythematosus and antinuclear antibody-positive connective tissue diseases.

We have attempted to improve the diagnostic specificity of the DIF findings for a diagnosis of HSP by combining them with clinical and histologic findings. We did not find the morphology and distribution of the cutaneous eruption to have any discriminatory value. As shown in Fig. 5, gastrointestinal involvement in the context of IgA vascular deposits was the only combination that gave a satisfactory compromise between sensitivity and specificity. An upper respiratory tract infection prodrome was also a useful finding. The criterion of age ≤ 20 years is probably more useful than our data suggest. For reasons of selection bias stated above, we think that our incidence for HSP in adults does not reflect that in the general population. Because no one combination of criteria is ideal, we conclude that an algorithmic set of diagnostic criteria modified from that suggested by the ACR is the best approach. Our proposed criteria are shown in Table VI. We have removed palpable purpura and leukocytoclastic vasculitis from the original criteria, because some clinical or histologic evidence (or both) of cutaneous vasculitis is a prerequisite to enter the algorithm, and they do not differentiate HSP from other forms of cutaneous vasculitis. We have added the cutaneous DIF finding of vasculitis with IgA vascular deposits, upper respiratory tract infection prodrome, and renal biopsy evidence of mesangioproliferative glomerulonephritis (with or without IgA deposits).

In conclusion, we have examined the clinicopathologic correlation of the uncommon DIF finding of vasculitis with IgA vascular deposits. This finding is sensitive but not specific for the diagnosis of HSP; it may be seen in various vasculitic and non-vasculitic disorders. No additional immunofluorescence or histologic features improved specificity. We have identified three useful clinical criteria and incorporated them into a diagnostic algorithm that permits diagnosis of HSP with sensitivity and specificity in excess of 90% for our data. The criteria proposed were developed in a study population of mainly adults. Whether these criteria would perform as well in a mainly pediatric population is not known.

REFERENCES

1. Schönlein H. Allgemeine und spezielle Pathologie und Therapie. 3rd edn., vol 2, Wurzburg: 1837, Herisau.
2. Henoch EH. Über ein eigenthumliche form von Purpura. Berl Klin Wochenschr 1874; 11: 641–643.
3. Piette WW, Seabury Stone M. A cutaneous sign of IgA-associated small dermal vessel leukocytoclastic vasculitis in adults (Henoch-Schönlein purpura). Arch Dermatol 1989; 125: 53–56.
4. Hené RJ, Velthuis P, van de Wiel A, Klepper D, Dorhout Mees EJ, Kater L. The relevance of IgA deposits in vessel walls of clinically normal skin: a prospective study. Arch Intern Med 1986; 146: 745–749.
5. Herrmann WA, Kauffmann RH, van Es LA, Daha MR, Meijer CJLM. Allergic vasculitis: a histological and immunofluorescent study of lesional and non-lesional skin in relation to circulating immune complexes. Arch Dermatol Res 1980; 269: 179–187.
6. Mills JA, Michel BA, Bloch DA, Calabrese LH, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. Arthritis Rheum 1990; 33: 1114–1121.
7. Schroeter AL, Copeman PWM, Jordon RE, Sams WM Jr, Winkelmann RK. Immunofluorescence of cutaneous vasculitis associated with systemic disease. Arch Dermatol 1971; 104: 254–259.
8. Golitz LE. The vasculitides and their significance in the pediatric age group. Dermatol Clin 1986; 4: 117–125.
9. Hall RP III. Henoch-Schönlein purpura. In: Jordon RE, ed. Immunologic diseases of the skin. Norwalk, Connecticut: Appleton & Lange, 1991: 451–460.
10. Tappeiner G, Jordon RE, Wolff K. Circulating immune complexes in necrotizing vasculitis. Major Probl Dermatol 1980; 10: 68–75.
11. Kauffmann RH, Houwert DA. Plasmapheresis in rapidly progressive Henoch-Schönlein glomerulonephritis and the effect on circulating IgA immune complexes. Clin Nephrol 1981; 16: 155–160.
12. Garcia-Fuentes M, Chantler C, Williams DG. Cryoglobulinaemia in Henoch-Schönlein purpura. BMJ 1977; 2: 163–165.
13. Gianetti A, Serri F, Bernasconi C. Immunofluorescent studies of the skin in mixed cryoglobulinemia and Schönlein-Henoch purpura. Acta Derm Venereol (Stockh) 1976; 56: 211–216.