

## NON-THROMBOCYTOPENIC PURPURAS

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**Abstract.** 88 cases of microscopical diapedesis of the red blood cells in the superficial blood vessels of the skin were investigated clinically, histologically and immunohistologically. Polymorphonuclear vasculitis (PMNV) was found in 27 cases, 18 of which also demonstrated immunoglobulins (mostly IgM) in the vessel walls. Complement (C<sub>3</sub>) was found in 16 cases. The cases with PMNV formed a uniform group as regards preceding infections, drug consumption, clinical features, and pathological urinalysis and laboratory data. The second group consisted of 21 cases of lymphocytic perivasculitis with immunoglobulins and/or complement (LP+ig/C<sub>3</sub>). It clearly differed clinically from the former group in three respects: urinalysis was normal, a slowing of the venous outflow was found in more than half of the cases and the duration of the disease was longer. The biggest group consisted of 40 cases of lymphocytic perivasculitis without detectable immunoglobulins in the vessel walls (LP). In this group the duration of the disease was shortest. The capillary resistance was lower than in the other groups. The results of this investigation indicate that there are at least three pathogenetically differing groups among the clinical purpuric conditions.

**Key words:** Polymorphonuclear vasculitis; Lymphocytic perivasculitis; Non-thrombocytopenic purpura; Direct immunofluorescence

Non-thrombocytopenic purpura is not a single entity. It is frequently a sign of systemic disease but very often a solitary finding. It cannot be equated with vasculitis as histological vasculitis with necrosis or damage to the vascular wall and infiltration of polymorphonuclear leukocytes is not always found in purpura. In fact purpuric conditions with lymphocytic perivasculitis form an even larger group. The purpose of the present study was to distinguish between these two conditions by using histopathological and immunohistological methods and to determine underlying and concomitant diseases.

### PATIENTS AND METHODS

Over a period of one year (1975-76) records were kept of all patients with visible purpuric lesions visiting the Department of Dermatology of Helsinki University. Of these

patients all those with microscopically determined superficial diapedesis of the red blood cells and a normal thrombocyte count were included in the series. Cases involving medium-sized or large vessels, definite disease entities and syndromes in which the diapedesis of red blood cells is an established and frequent if not regular histological feature were excluded from the series.

Records of 46 male and 42 female patients were included. The ages of the patients ranged from 8 to 81 years; 20 were under 30 years of age.

**Laboratory examinations.** The following examinations were made: white blood cell count, haemoglobin, ESR, urinalysis, serum creatinine, serum aspartate aminotransferase and alanine aminotransferase. Immunological studies included the Waaler-Rose and latex test for rheumatoid factor, antinuclear factors (ANF-FA), direct Coombs, antistreptolysin titre and cryoglobulin determination. The ability of serum to cause platelet aggregation was measured for detection of IgG-containing immunocomplexes (8).

**Tissue examination.** One-half of the skin biopsy from affected skin was studied using routine histological techniques and the following stainings: hematoxylin and eosin, iron stain for hemosiderin, Unna-Pappenheim for pyroninophilic cells, toluidine blue for mast cells and PAS. The other half of the biopsy was examined using direct immunofluorescence with specific antisera for IgG, IgM, IgA, C<sub>3</sub> and fibrinogen as described previously (9). A renal biopsy was performed in 7 cases and examined as described above.

**Capillary resistance** was determined using a suction cup in the subclavicular area. The test was considered positive if petechiae appeared within one minute with less than 150 mmHg suction.

**Follow-up** of the patients varied from 2 months to 4 years, being 1 year on average. Only 7 patients had only one recorded visit, and there were clinical data from previous consultations for several patients.

### RESULTS

**Histological and immunohistological study.** Two different histological reaction patterns were found. The first pattern showed mainly neutrophil infiltration and damage to the vascular wall, varying from oedema to fibrinoid necrosis in 27 cases (Fig. 1). It is referred to here as polymorphonuclear vasculitis (PMNV) (syn: fibrinoid, leukoclastic, necrotizing, hypersensitivity vasculitis).

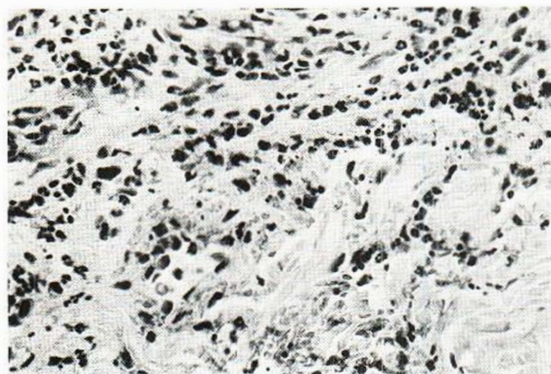


Fig. 1. Polymorphonuclear vasculitis. The neutrophils are the main cell type in the infiltration. The blood vessels are completely destroyed, whereas the endothelial cells are unrecognizable. HE, 12.5×40.

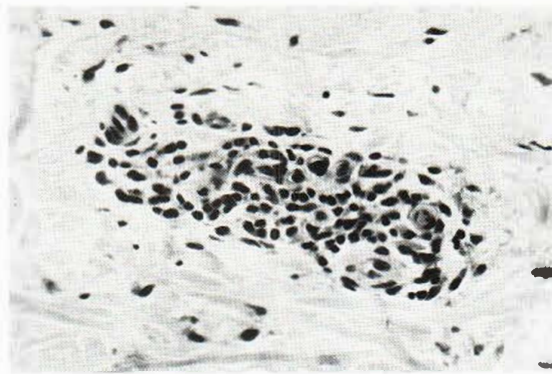


Fig. 2. Lymphocytic perivasculitis with immunoglobulins. Extravasation of red blood cells from an undamaged blood vessel surrounded by a few lymphocytes. HE, 12.5×40.

The second pattern showed mainly mononuclear perivascular cell infiltration with little or no involvement of the vascular wall of the superficial blood vessels. In this study the reaction is termed lymphocytic perivasculitis and was found in 61 cases (Fig. 2).

In the PMNV group immunoglobulins were found in the vessel walls in 18 of the 27 cases (Table I). Complement ( $C_3$ ) was present in the same location in 16 cases. Fibrinogen was found in almost all cases irrespective of the presence of Ig or complement.

In the lymphocytic perivasculitis group, immunoglobulins and/or complement was present in the vessel walls in 21 cases (LP+ig/ $C_3$ ). The presence of  $C_3$  was the most frequent finding, occurring in 20 cases (Table I). In 40 cases neither immunoglobulins nor complement were found (LP).

*Clinical data.* The mean age was 50 years in group PMNV, 44 years in the LP group with immunoglobulins and 45 years in the LP group without immunoglobulins. Three patients in the LP group with immunoglobulins and 4 patients in the LP

group without immunoglobulins were under 20 years of age; none in the PMNV groups was under 20.

At the end of the follow-up period the mean duration of the disease was 2 years in the PMNV group, 2 years and 7 months in LP with immunoglobulins and 1 year in LP without immunoglobulins.

In the PMNV group, purpura disappeared in 11 patients, persisted in 14 patients, relapsed once and one patient died of cardiac failure during the observation period.

In LP with immunoglobulins, purpura disappeared in only 5 patients, persisted in 14 patients, relapsed in one patient and one patient was no longer under observation.

In LP without immunoglobulins the purpura disappeared in 19 patients, persisted in 14 patients, had relapsed in 4 patients and 3 patients were absent from the follow-up.

Purpuric lesions were localized symmetrically on the skin, predominantly on the legs. Bullous lesions were seen only once and necrotic lesions in the form of multiple ulcers on the legs in 4 patients in

Table I. Immunoglobulins, complement and fibrinogen found on the vessel wall in neutrophilic vasculitis and lymphocytic perivasculitis

Category	No. of patients	IgG	IgM	IgA	$C_3$	Negative	Fibrinogen
PMNV	27	2	11	8	16	9	23
LP	61	1	8	5	20	40	45

Table II. *Preceding infections possibly associated with purpura*

Infection	Patient category		
	PMNV	LP+ig/C <sub>3</sub>	LP
Streptococcal	2	—	—
Gonococcal	1	—	—
Influenza	3	2	1
Pyelonephritis	1	—	4
Gastrointestinal	1	—	—
Tuberculous	—	—	2

the PMNV group and in 3 patients in the LP groups. Purpura was accompanied by arthralgia in 4 patients in the PMNV group and in one patient in the LP group. It was preceded by symptoms resembling influenza in 3 patients in each group. Other infections preceding the onset of purpura are presented in Table II.

Those conditions and diseases which retard the blood flow in the periphery of the body are presented in Table III. Varices, deep venous thrombosis or sudden immobilization, as in one young patient after a broken leg, were found in 13 patients with lymphocytic perivascularitis and immunoglobulins. The number was much higher than in the two other groups; the difference is statistically highly significant ( $p < 0.001$ ). Other conditions assumed to aggravate retrograde haemodynamic pressure, such as heart failure and diabetes, were found with about equal frequency in all groups. Arterial hypertension was found more often in the LP group without immunoglobulins, but it may also be associated with the consumption of hypertensive drugs, as is shown in Table IV.

*Drug consumption.* All the drugs known to be used before or at the onset of the purpura are listed in Table IV. An evident relationship with drug ingestion was confirmed by oral challenge in only 5 cases. The triggering drugs were carbamazepine, phenylbutazone, methyl dopa+chlorothiazide, clonidine+pindolol and ferrous sulphate. Ten patients were submitted to oral challenge with 22 drugs, with negative results. These drugs are recorded in Table IV, as the negative result of exposition does not always exclude the triggering effect of the drug.

The number of patients using drugs is slightly higher in LP, as also is the number of eligible drugs per patient in contrast to the other two categories.

*Laboratory features.* The most important laboratory data of the patients are given in Table V. An elevated sedimentation rate and pathological urinalysis were more frequently found in the PMNV group than in the other groups; the differences were statistically significant ( $p < 0.001$ ) in both respects. Cryoglobulins, positive platelet aggregation test, rheumatoid factor, elevated hepatic transaminases, porphyrins, antinuclear antibodies, and an elevated antistreptolysin titre were frequently found in the same group.

A positive capillary resistance test was found more often in the group LP than in other groups; the difference was not statistically significant. In the LP group the number of patients with normal values in laboratory tests was higher than in other groups; the difference was statistically significant ( $p < 0.01$ ).

Renal biopsy was performed in 7 patients with haematuria and albuminuria. Six of these patients had purpura with polymorphonuclear cell vasculitis. The results of this study are given in Table VI, in which the immunofluorescence study is compared with that of the skin. The immunoglobulin class M found most regularly in the skin was missing in renal tissue. The occurrence of complement was alike in both tissues. Immunoglobulins and/or complement were mostly found in mesangial areas, in some cases also on the vascular walls and on the glomerular basement membrane, and twice in tubular areas. In every case impairment of renal function was minimal, although it persisted in 4 patients after the skin lesions had been completely cured, during the follow-up period. In addition to the 7 patients with a renal biopsy, transient

Table III. *Disorder affecting the inflow and/or outflow of blood*

Underlying conditions	Category		
	PMNV (27)	LP+ig/C <sub>3</sub> (21)	LP (40)
Varicosities	3	10	2
Thrombosis or immobilization	1	3	1
Heart failure	4	2	6
Diabetes	5	2	6
Pregnancy	1	—	2
Transient rise in pressure (vomiting)	—	—	1
Arterial hypertension	3	—	8
Normal values of above	17	6	26

Table IV. List of drugs possibly responsible for purpura

\* = no other drugs eligible, e = positive exposition, N = negative exposition

	PMNV	LP+ ig/C <sub>3</sub>	LP		PMNV	LP+ ig/C <sub>3</sub>	LP
No. of drug consumers/ total no. of patients	14/27	9/21	28/40	Spirinolactone	2	-	-
<i>Anti-inflammatory drugs</i>				Amiloride	1 <sup>N</sup>	-	1
Salicylate	3 <sup>N</sup>	7 <sup>****</sup>	9 <sup>*****NN</sup>	<i>Hypotensive</i>			
Phenazone	1	-	2 <sup>N</sup>	Rauwolfia alkaloids	-	-	3 <sup>*NN</sup>
Phenylbutazone	2 <sup>*e</sup>	-	1	Clonidine	2	-	2 <sup>e</sup>
Ibuprofen	1	-	-	Methyldopa	3 <sup>eN</sup>	-	-
Indomethacin	-	1 <sup>*</sup>	1	Hydralazine	-	-	1
<i>Anti-infectious drugs</i>				Timolol	1	-	-
Amoxicillin	1 <sup>*</sup>	-	-	Pindolol	1 <sup>N</sup>	-	2 <sup>e</sup>
Cephalosporin	-	-	1	Propranolol	-	-	1
Streptomycin	-	-	1	<i>Miscellaneous</i>			
Tetracycline	1	1	1	Ephedrine	-	-	2
Rifampicin	-	-	2	Ergotamine	-	-	2
Sulphonamide	-	1	1	Quinine	1	-	2 <sup>*</sup>
Ethambutol	-	-	2	Atropine	1	-	-
Isoniazid	-	-	1 <sup>N</sup>	Phenobarbital	1	-	2
PAS	-	-	1	Pentymal	-	-	1 <sup>N</sup>
Nitrofurantoin	1	1	1 <sup>N</sup>	Codein	-	-	1 <sup>N</sup>
Methenamin	-	1	1	Meprobamate	1	-	1
Trimethoprim	-	1	1	Diazepam	2 <sup>*</sup>	-	1
Kloromycetin	-	-	1 <sup>N</sup>	Brompheniramine	-	-	1
Nalidixin	-	-	1 <sup>N</sup>	Carbromal	-	-	1
<i>Antidiabetic</i>				Carbamazepine	-	-	1 <sup>*e</sup>
Chlorpropamide	1 <sup>*</sup>	-	1	Promethazine	-	-	1
Carbutamide	-	-	1	Ferrous sulphate	-	-	1 <sup>*e</sup>
Phenformin	-	-	3	Warfarin	2 <sup>*</sup>	-	2
<i>Diuretic</i>				Metamitsol	-	-	1 <sup>N</sup>
Chlorothiazide	2 <sup>eN</sup>	-	6 <sup>NN</sup>	<i>Local</i>			
Frusemide	2	1	2 <sup>NN</sup>	Resorcinol	-	1 <sup>*</sup>	-

haematuria and/or proteinuria were also seen in 12 cases (Table V).

## DISCUSSION

A histological picture, with mainly polymorphonuclear leukocytes and a more or less damaged superficial vessel wall, was found in 27 cases out of 88 patients with clinical purpura. In the immunofluorescence study, immunoglobulins and/or complement were found in 18 cases. This is in accordance with Cream et al. (4), who showed that the detection of immunoglobulins depends on the timing of the biopsy. At least in the guinea pig, immunoglobulins had disappeared as early as within 18 hours after a single antigenic challenge. In this group of 27 patients, elevated sedimentation

Table V. Laboratory features of patients and capillary resistance

	PMNV	LP+ ig/C <sub>3</sub>	LP
Patients, no.	27	21	40
Elevated sedimentation rate	17	6	4
Platelet aggregation test, pos.	5	5	3
Cryoglobulins (semiquantita- tion)	5	2	-
Rheumatoid factor	2	-	-
Elevated transaminases	4	4	4
Porphyrins	-	2	-
Antinuclear factor	5	1	-
Elevated antistreptolysin titre	4	1	1
Pathological urinalysis	15	2	2
Capillary resistance $\leq 150$	6	5	15
Normal values of the above	1	6	19

Table VI. Immunofluorescence study of the skin and renal tissue of patients with glomerulonephritis and purpura

TBM=tubular basement membrane, GBM=glomerular basement membrane

Skin	IgG	IgM	IgA	C <sub>3</sub>	Renal tissue	IgG	IgM	IgA	C <sub>3</sub>	Serum creatinine
Leg	+	+	+	+	Mesangium	-	-	-	+	75
					TBM	-	-	-	+	
Forearm	-	-	-	+	Arterioles	-	-	-	+	77
					Mesangium	+	-	+	+	
					Arterioles	-	-	-	+	
Shin	+	-	+	+	Tubular cells	-	-	-	+	66
					Mesangium	-	-	+	+	
Leg	+	+	+	+	GBM	+	-	-	-	86
Leg	-	+	-	-	Mesangium	-	-	-	+	155
					Capillaries	+	-	+	+	
Leg	-	+	+	+	Mesangium	+	-	+	-	160
					GBM	+	-	+	-	
Leg	-	-	-	-	GBM	+	-	+	+	62

rates, cryoglobulins, antinuclear factor, elevated antistreptolysin titre and pathological urinalysis were found more often than in the other groups, suggesting a pathogenic role of immunocomplexes in polymorphonuclear vasculitis, as has been emphasized by previous authors (1, 2, 5, 11, 12, 13).

The smallest group consisted of 21 cases with immunoglobulins and/or complement on the vessel wall but without visible morphological damage to it and without polymorphonuclear leukocytes but with a lymphocytic cuffing along the blood vessels. Our immunofluorescence finding is in complete agreement with that of Parish (7) who has also extended his studies to consider lymphocytic vasculitis. The main characteristic of this group was a slowing of the outflow of the blood for various reasons. In 10 cases the main cause was varicose veins in the legs. According to Copeman (3), immune complexes would be expected to lodge in that part of the cutaneous circulation where the blood flows more slowly because of retrograde intraluminal haemodynamic pressure. In this group, pathological values in the laboratory tests were found less often than in the previous group.

The largest group of patients in our study suffered from clinically similar purpuric eruptions, differing from the other patients on the basis of a negative immunohistological finding and falling histologically under the heading lymphocytic perivasculitis. Illig (6) recently grouped this type of purpura under the heading purpura pigmentosa progressiva. He emphasizes the feasibility of de-

tecting in the future unusual drug-induced reactions in this group. In our study this group shows a slight preponderance of patients consuming drugs compared with the other groups. The obvious causal relationship to drug ingestion could be proved only in a few cases.

Ever since time of Rüter (10) primary emphasis has been placed on the bacterial origin of vascular lesions; especially in the works of Parish (7) complexes of bacterial antigens have been shown to induce cutaneous vasculitis in some cases. In the present series bacterial infections do not seem to have played a central role in triggering either a neutrophilic or a lymphocytic vascular lesion, even if "flu" pyelonephritis or gastrointestinal infections sometimes preceded the purpura. Pyelonephritis was treated with drugs, which might have caused the purpuric lesions.

The mean duration of the disease differed considerably in these three groups. The duration was shortest (about 1 year) in the group with lymphocytic vasculitis without immunoglobulins. The immunological reaction may be the delayed type of reaction, against a background of drug consumption or infection. The longest duration (almost 3 years, on average) was found in the group with lymphocytic perivasculitis with immunoglobulins. This group was often associated with chronic venous disease, which by retarding the blood flow might contribute to the attachment of immunoglobulins and complement. The immunological explanation is probably that there is an insufficient release of tissue or

microbial antigens to induce polymorphonuclear chemotaxis in antibody excess.

The mean duration of the disease in the PMNV group was 2 years, which might indicate a faster elimination of immunocomplexes from the circulation by means of polymorphonuclear leukocytes. The release of tissue or microbial antigens is sufficient and continuous enough to induce polymorphonuclear chemotaxis in antigen excess.

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