

Purpura hyperglobulinaemia in association with rheumatoid arthritis and ulcerative colitis

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Summary

Five patients with purpura hyperglobulinaemia are reviewed. One patient developed ulcerative colitis; female members of this patient's family suffered from rheumatoid arthritis. The family showed immunoglobulin abnormalities.

Although the clinical picture of purpura hyperglobulinaemia and Henoch-Schönlein purpura can show some common features, the former may well be separated as a 'disturbed-tolerance' disease with a different prognosis.

Introduction

Five patients with the rare condition of purpura hyperglobulinaemia have attended this department during the last 10 years; I wish to draw attention to the development in one patient of ulcerative colitis and to the occurrence of rheumatoid arthritis in that patient's family; in a second patient rheumatoid factor was found in the serum.

Waldenström (1943) described purpura hyperglobulinaemia as an unexplained chronic relapsing purpura associated with normal platelets but an increased capillary fragility and a raised serum globulin, later shown to be electrophoretically characterized by a broad gamma peak. The purpura occurs mainly on the legs and there is resulting residual brown pigmentation. In general the bleeding tendency is limited to the skin; it is suggested (Schmergler & Esser, 1952) that the capillary damage is the direct result of the abnormal globulin damaging the capillary wall. The coagulation mechanism is normal and there are no cryoglobulins. Marrow smears may show an increase of reticulum cells (Horster, 1950), marrow hypoplasia (Taylor & Battle, 1954) or a lymphocyte infiltration (Waldenström, 1954). Strauss (1959) in a review of seventy-two cases points to the association with unexplained

enlargement of the liver and spleen, with arthritis and Sjögren's syndrome and with intestinal symptoms, but so far there has been no report of the occurrence of ulcerative colitis. Birch *et al.* (1964) reported a case with a benign thymoma, removal of which resulted in remission of the purpura but the latex fixation and Rose-Waaler tests then became positive.

Case reports

Case 1 E.R., female, age 53—Patient with ulcerative colitis

This lady first attended early in 1952 complaining that for 4 years she had pains and stiffness of the muscles of the arms and legs together with recurrent purpura. She was noted to look well but to have petechiae on the legs and a positive Hess test. The joints and fundi were normal and she was normotensive. At that time her platelet count was 245,000/mm³, haemoglobin 15.1 g/100 ml and WBC 10,850/mm³. Six months later at the time of an exacerbation she had a skin biopsy that showed fresh blood in the sub-epithelial tissue surrounding small blood vessels which appeared normal. Her albumin was 4.6, globulin 3.9 g/100 ml and liver function tests normal.

In 1955 she had an attack of cystitis, of which she has had several recurrences over the years. Renal function is normal. Then in 1956 after a sore throat she had a severe attack of purpura together with a conjunctivitis that was slow to resolve. At that time her albumin was 4.4 and globulin was 3.6 g/100 ml and ESR 150 mm/hr.

Again in 1961 after a sore throat she had more purpura and for 2 months had diarrhoea with pale, bulky stools. Full investigation at the time revealed no cause. The year after she had not only purpura but also erythema multiforme.

In 1964 she had more cystitis and later developed a right episcleritis that only slowly responded to hydrocortisone drops. Her

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albumin was 4.2 g, globulin 4.0 g/100 ml and the antinuclear factor test negative.

She continued to have recurrent purpura and then in 1966 was readmitted for investigation of the complaint that she was passing blood in her motions.

Examination revealed, as before, a fit normotensive lady with purpura on the shins. This time she was noted to be tender in the left iliac fossa, the caecum was palpable and sigmoidoscopy showed the typical appearance of ulcerative colitis, as did the barium enema. For the first time she was anaemic, Hb 11.8 g/100 ml WBC, 12,900/mm³ and platelets 183,000/mm³. The serum iron was 80 µg/100 ml the albumin 3.4 (lower than before), globulin 3.9 g/100 ml and the alkaline phosphatase raised at 37 KA units. Liver biopsy was normal. The fibrinogen was 520 mg/100 ml, the cryofibrinogen (heparin) 65 mg/100 ml and plasminogen normal. There was no Bence Jones proteinuria but electrophoresis showed a broad gamma band and on ultracentrifuge analysis the 7S fraction was increased. Serum viscosity was 1.5 units, compared with a value of 1.2 for normal serum. The ANF, latex and SCAT titres were negative. The bone marrow was normal but electron microscopy of a bone marrow trephine showed some activity of the plasma cells and there were some transitional lymphoblasts characterized by an increased amount of endoplasmic reticulum. The reticulum cells were not hypertrophied. She responded well to Predsol retention enemas.

Enquiry about her family revealed that on her mother's side two aunts had died with rheumatoid arthritis, a living aunt has suffered for years with rheumatoid arthritis and has large nodules, and three other aunts are well. She herself has four brothers and three sisters and three sons, all of whom are quite well. The sera of the members of the family were further investigated.

Case 2. Female, age 23—Patient with rheumatoid factor

At the age of 10 she developed recurrent purpura which has persisted for over 10 years. At the outset she was found to have a platelet count of 258,000/mm³, a positive Hess test and a raised γ-globulin on electrophoresis. The initial albumin was 4.3 g, globulin 4.7 g/100 ml.

At the age of 12 she had had an attack of hepatitis but recovery was complete. The raised γ-globulin persists.

Her relatives are all quite well; she herself has a SCAT titre 1/128 and latex 1/10,240.

Case 3. Female, age 61—Patient with nephropathy

For 20 years she has had periodic episodes of purpura of the legs, sometimes associated with urticaria, with joint pains and with ankle oedema. Her platelets are 252,000/mm³. Hess test positive, ESR 53 mm/hr and she has a raised γ-globulin. Albumin 4.3, globulin 4.9 g/100 ml.

In 1957 she developed small intestinal obstruction; the ileum was found to be covered by petechial haemorrhages. Shortly after this she developed thirst and polyuria with tetany and flaccid paralysis. Potassium-losing nephropathy was confirmed and she has been maintained on oral potassium supplements since.

Case 4. Female, age 67—Patient subjected to splenectomy

For over 30 years she has bruised easily. For 20 years she has had recurrent purpura on the arms and legs. In 1953 she was admitted with melaena and after this splenectomy was performed. The spleen weighed 143 g and histology showed fibrinoid necrosis of the arterioles. At that time the sternal marrow was hypoplastic but there was an increase of reticulum cells. After the splenectomy she continued to have purpura and she was then put on a small dose of corticosteroids but she continued to show a raised 7S gamma-globulin and to suffer recurrent purpura. Her family are quite well: she herself is unmarried.

Case 5. Female, age 57—Typical uncomplicated presentation

Since 1943 she has had recurrent purpura on the legs. The Hess test is persistently positive, her platelets are 200,000/mm³ and the ESR is 50–70 mm/hr. There is increased γ-globulin of 7S-type, but liver function tests are normal. Renal function is normal. Her family is normal.

Investigation of the sera of the relatives of Case 1

Immunoglobulins were estimated by the immunodiffusion method of Fahey & McKelvey (1965) using dilutions of pooled normal serum as the reference. Normal values of immunoglobulin G (IgG) were taken to be 1.0 (0.8–1.5) of IgA 0.12 (0.056–0.193) and of IgM 0.08 g/100 ml (0.039–0.117).

The SCAT and latex titres were kindly estimated by Dr J. Ball of the Rheumatism Research Unit. The SCAT is performed as described by Kellgren & Ball (1959) and the latex according to the method of Singer & Plotz (1956). In addition to the standard SCAT used for routine work. SCAT titres were also estimated using 1/8000, 1/20,000 and 1/40,000 sensitization of the red cells.

TABLE 1
Results for the family of Case 1 giving the serum proteins, the immunoglobulins, the sheep-cell agglutination at four levels of sensitization and the latex titres

		Serum albumin (g/100 ml)	Serum globulin (g/100 ml)	Ig G (g/100 ml) relative to 0.8-1.5	Ig M (g/100 ml) pooled 0.039-0.117	Ig A (g/100 ml) normal serum 0.056-0.193	Sheep-cell agglutination titre			Latex titre	
							Standard	1/8000	1/20,000		1/40,000
Normal											
proposita	A	3.4	3.9	2.0	0.096	0.096	1/4	1/16	1/4	—	1/20
Aunt	B	6.0	2.8	0.68	0.08	0.144	1/64	1/2048	1/2048	1/32	1/5120
Brother	C	4.5	2.9	0.8	0.042	0.096	1/4	1/16	1/4	—	1/20
Brother	D	4.4	2.8	1.0	0.048	0.288	1/4	1/32	1/4	—	1/1280
Brother	E	4.3	2.3	1.0	0.08	0.192	1/4	1/64	1/16	—	1/160
Brother	F	4.5	3.1	2.0	0.042	0.048	1/4	1/8	1/4	—	1/160
Sister	G	4.4	2.8	1.38	0.08	0.096	1/4	1/16	1/4	—	1/20
Sister	H	5.2	3.6	2.0	0.08	0.07	1/4	1/64	1/4	1/4	1/20
Sister	J	4.7	2.8	1.0	0.11	0.12	1/4	1/16	1/4	—	1/20
Son	K	4.4	2.8	1.0	0.08	0.096	1/4	1/16	1/4	—	1/20
Son	L	4.9	2.5	1.0	0.042	0.096	1/4	1/32	1/4	—	1/20
Son	M	5.0	3.5	1.5	0.024	0.096	1/4	1/32	1/4	—	1/20

The results are given in Table 1, where it will be seen that the proposita (A) has a raised IgG but insignificant latex and SCAT titres, whereas the live aunt (B) who has rheumatoid arthritis has the expected high titres. Raised total globulins occur in one sister (H) who is quite well, in one brother (F) and in one son (M). Raised IgG values were found in these three (H, F, M). One brother has a raised IgA (D).

The routine standard SCAT and latex titres of the family are unremarkable: only the aunt with rheumatoid arthritis shows a raised titre but two other aunts had died with this condition. However, it will be seen that by raising the degree of sensitization of the sheep cells (particularly with a sensitization titre of 1/8000 at which the international standard gives a titre of 1/4096) a slight degree of positivity is revealed in some members of the family. There are no control studies at this degree of sensitization for valid comparisons. The latex titre is also seen to give raised levels in some family members, albeit there is no correspondence.

Estimation of anti-colon antibodies in the family produced negative results in all members of the family, including the proposita with ulcerative colitis.

Discussion

If purpura hyperglobulinaemia is a 'disturbed-tolerance' disease, as is rheumatoid arthritis, it is perhaps not surprising to find the development

in our patient of another autoimmune disorder, namely ulcerative colitis. The fact that disease in this family is confined to the female members, and the evidence of protein and immunoglobulin abnormalities together with the possible tendency to raised titres of rheumatoid factor, support the 'disturbed-tolerance' supposition.

Hyperglobulinaemia is known to be common in relatives of patients with SLE. Both Leonhardt (1964) and Waldenström (1961) describe purpura hyperglobulinaemia in the spectrum of SLE-like syndromes and mention family cases. There is also a high incidence of rheumatoid factor in relatives of patients with acquired agammaglobulinaemia (Fudenberg, German & Kunkel, 1962).

Lagercrantz *et al.* (1966) in a study of anti-colon antibodies in ulcerative colitis found that over the age of 25 titres were higher in female patients and they mention elevated anti-colon antibody titres in certain families. They incline to the opinion that the antibodies are primary and not merely the secondary result of the colon lesions. In none of the members of this family could anti-colon antibodies be detected. The association of true rheumatoid arthritis with ulcerative colitis, as distinct from colitic arthritis has been reported, although Wright & Watkinson (1965) in 269 cases of ulcerative colitis found only four cases of rheumatoid disease, and this is no greater than that expected in the general population.

Samitz & Greenberg (1951) have reviewed the skin lesions that appear as a result of ulcerative

colitis. They found ninety-three instances of skin complications in sixty-five of 189 patients. Petechial haemorrhages were found in only three cases. In the present case there is no doubt of the dissociation in time between the purpura and the ulcerative colitis.

Few authors attempt any distinction between purpura hyperglobulinaemia and Henoch-Schönlein purpura. Thus Case 3 in our series has features that are more commonly attributed to Henoch-Schönlein disease. Bernard, Mathé & Israel (1957) were able to classify cases of Henoch's purpura into three groups: allergic purpura, 'rheumatoid purpura' and chronic idiopathic hyperglobulinaemic purpura which, although it readily progressed into subacute nephritis, they thought to be indistinguishable from Waldenström's disease. Undoubtedly the skin lesions are histologically the same. In Henoch's purpura the γ -globulin is only expected to be raised during the attack. Henoch's purpura is acknowledged to be predominantly a male condition and, perhaps in keeping with the frequency of preceding infection (Kreidberg, Dameshek & Latarroea, 1955) often of streptococcal type, all authors are now agreed that nephritis occurs in 40–60% of cases (Heptinstall, 1960) and furthermore that this condition may be a generalized vasculitis. Apart from the possibility of acute tubular necrosis in purpura hyperglobulinaemia as in the case of Birch *et al.* (1964) and, as reported by Waldenström (1961), acute renal failure in a patient whose condition progressed into an SLE-like condition, other authors do not mention a glomerulo-nephritis associated with purpura hyperglobulinaemia. This may merely be a reflection of the paucity of cases for both Henoch-Schönlein purpura and purpura hyperglobulinaemia might be expected to be conditions in which there are at times circulating antigen-antibody complexes. However, there may well be a case for distinguishing purpura hyperglobulinaemia, as a 'disturbed-tolerance' condition, from Henoch-Schönlein disease as a similar type of hypersensitivity phenomenon often associated with streptococcal infection.

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