Polyarteritis nodosa associated with streptococcus

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Abstract

Twelve children are described with an essentially benign vasculitic illness in association with streptococcal infection. They demonstrated characteristic clinical features of nodular cutaneous polyarteritis with fever. Laboratory findings showed an acute phase response associated with raised antistreptolysin and antihyaluronidase titres in all patients and a positive throat culture for β haemolytic streptococcus in three patients. Ten required corticosteroids. Two patients had systemic involvement with abnormal arteriography; both had appreciably raised white cell counts ($>40 \times 10^9/l$). They may represent a subset of poststreptococcal vasculitis, requiring cytotoxic treatment for effective disease control.

(Arch Dis Child 1993; 69: 685-688)

Polyarteritis nodosa is an inflammatory disease affecting the small and medium sized arteries. It is distinct from other arteritides of childhood such as mucocutaneous lymph node syndrome (Kawasaki disease) and the arteritides of Wegener and Churg-Strauss, which affect small vessels with granulomata and have a predilection for the respiratory tract, in addition to renal vasculitis.

There is a limited form of polyarteritis nodosa in which the disease is confined to the skin, muscles, and peripheral nerves.¹ Fink described the recurrent, painful skin nodules and the livido reticularis in children with cutaneous polyarteritis.² Diaz-Perez and Winklemann have suggested that cutaneous polyarteritis nodosa should be separated from the systemic form of the disease.³

This report describes 12 children with vasculitis in association with streptococcal infection. Nine followed a benign course and one, a more indolent relapsing disease, but nevertheless confined to the skin; the other two

were systemically unwell and had visceral microaneurysms.

Patients and methods

Between 1971 and 1990, 12 children were seen in our department at Northwick Park Hospital in whom the diagnosis was made of cutaneous polyarteritis nodosa in association with streptococcal infection. Eight were boys and four girls; their mean age at onset was 8 years (range 4-11 years).

The diagnosis of cutaneous polyarteritis nodosa was based on a characteristic rash and, in six, histological examination. There was a preceding streptococcal upper respiratory tract infection and/or sore throat with raised antistreptolysin O and antihyaluronidase titres and/or positive throat swab for β haemolytic streptococcus. Vasculitic illnesses such as Wegener's, Churg-Strauss, Kawasaki disease, systemic lupus erythematosus, and Henoch-Schönlein purpura were excluded. No patient had liver disease or exposure to hepatitis B.

The following laboratory tests were obtained: full blood count, erythrocyte sedimentation rate, antistreptolysin O titre, antihyaluronidase titre, hepatitis B surface antigen, serum electrolytes, glutamic oxaloacetic transaminase, albumin, total protein, creatine phosphokinase, urine microscopy, and 24 hour urinary protein and creatinine clearance. Standard tests for antinuclear antibodies were performed by immunofluorescence using a rat liver substrate. Rheumatoid factor was tested by the latex fixation method (Behring Rapi Tex RF). Serum immunoglobulin was determined by laser nephelometry, as were C3 and C4 and C reactive protein. Total haemolytic complement was measured by standard haemolytic assay. Antibodies to neutrophil cytoplasmic antigen (ANCA) were sought in six patients by the method of immunofluorescence to myeloperoxidase and antiglomerular basement membrane (aGBM) antibodies were sought in the same six patients by radioimmunoassay.

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Accepted 4 August 1993

Table 1 Clinical signs on presentation

Case No	Sex/age in years	Oedema		Cutaneous vasculitis				Arthritis
		Muscle	Periorbital	Instep	Limbs	Trunk	Face	
1	F/6	+	+	+	+	-	+	+
2	M/5	-	-	+	+	+	-	+
3	M/5	-	-	+	+	+	-	+
4	M/11	+	+	+	+	+	-	+
5	M/8	-	-	+	+	+	-	+
6	F/10	+	+	+	+	-	+	+
7	M/9	+	-	+	+	+	-	+
8	M/7	+	+	+	+	-	-	+
9	M/11	-	-	+	+	-	-	+
10	F/9	+	+	+	+	+	-	+
11	F/4	+	-	+	+	-	-	+
12	M/8	+	+	+	+	+	+	+

Present = +, absent = -.

Results

CLINICAL DETAILS

The duration of disease, between the onset of symptoms and diagnosis, was 1-12 weeks. Eleven of the 12 patients had been referred to Northwick Park Hospital for a second opinion. All patients had a preceding sore throat and there was an associated upper respiratory tract infection in nine (75%). All had malaise, a recurrent fever of 38-39°C, weight loss of up to 10% body weight, and 10 (83%) had non-specific central abdominal pain. Table 1 outlines the clinical signs present.

Figure 1 Erythematous nodular vasculitic lesions on sole and medial aspect of foot.

In all patients painful erythematous nodules occurred on the medial aspect of the foot and sole (fig 1). All patients had a livido rash on the arms and/or shins (fig 2). Seven patients (58%) had lesions on their trunk and three (25%) on their face. The rash on the limbs was associated with 'brawny' oedema of muscles in seven out of 12; six patients had periorbital oedema. An evanescent arthritis, most commonly affecting the ankles and knees, was present in all patients. In six, muscle pain was severe enough to cause immobilisation. All the children were unwell and highly irritable.

Three patients gave a history of rheumatic fever, although none had a documented carditis. All patients had normal electrocardiograms. Digital desquamation was not present. One child developed gangrene of a terminal digit (case 4) and one child had an acute anterior iritis (case 2) on presentation. Neither Raynaud's phenomenon nor hypertension were seen. There were no deaths in this series.

LABORATORY FEATURES

All patients had an acute phase response with erythrocyte sedimentation rate of >50 mm in first hour and increased C reactive protein, mean 55 mg/l (15–112 mg/l). Table 2 outlines the haematological findings on presentation. All patients had a leucocytosis of greater than $11.0 \times 10^9/l$. Peripheral eosinophilia was not present in any patient. The mean haemoglobin concentration was 102 g/l (range 77–123) with a normochromic normocytic picture and platelet count of 698 ($455\text{--}1188 \times 10^9/l$). Immunoglobulin profile showed hypergammaglobulinaemia in all patients with IgG >15 g/l. IgA, IgM, and IgE were normal. C3 was raised

Figure 2 Wasted forearm of case 8 with vasculitic livido rash.

Table 2 Haematological findings on presentation

Case No	Haemoglobin (g/l)	White cell count ($\times 10^9/l$)	Neutrophils ($\times 10^9/l$)	Platelets ($\times 10^9/l$)
1	77	23.2	17.4	1188
2	99	21.0	14.7	1030
3	120	12.2	NK	455
4	116	90.0	72.1	505
5	100	25.6	19.9	924
6	123	11.5	4.8	680
7	101	24.5	NK	570
8	85	65.0	60.0	800
9	93	11.0	NK	499
10	112	15.9	14.0	635
11	105	15.5	14.0	500
12	100	40.1	34.0	NK

NK=not known.

in four patients and hypocomplementaemia was not seen. Liver function tests were normal, although four patients had hypoalbuminaemia on presentation (albumin <24 g/l). Creatine phosphokinase was normal on presentation. Two patients had hyponatraemia (sodium <125 mmol/l) and a further two patients had hypokalaemia (potassium <3 mmol/l). None had renal disease and urine microscopy and urinalysis for protein were negative in all cases.

The antistreptolysin O titre was raised at 1060 U in all patients (normal range <200 U). Antihyaluronidase titre was raised (256 U) in all six patients in whom it was measured. Three patients had β haemolytic streptococcus grown on throat swab. Routine autoantibody screen was negative in all. All patients were negative for hepatitis B surface antibody. The six patients who were tested for ANCA and aGBM were negative to both.

Figure 3 Skin biopsy specimen demonstrating inflammatory infiltrate around the vessels of the deep dermis. There are no giant cells or granulomata seen (haematoxylin and eosin stain).

PATHOLOGICAL FINDINGS

Six patients had biopsies of the skin lesions. In all a necrotising vasculitis was seen involving the vessels of the deep dermis, with no giant cells or granulomata (fig 3).

TREATMENT

All were treated with oral penicillin and nine with a non-steroidal anti-inflammatory drug. Ten patients required oral corticosteroids (prednisolone). The mean starting dose was 2 mg/kg/day which was reduced to 1 mg/kg/day within 14 days. The fever regressed within one day of steroid treatment and the acute phase reactants (erythrocyte sedimentation rate and C reactive protein) subsided within 14 days. A prophylactic dose of penicillin was continued long term (up to 15 years).

OUTCOME

Seven patients ran a chronic relapsing course and had recurrent vasculitic lesions on steroid reduction. Five recovered fully with no exacerbation on drug withdrawal. Mean follow up was 8 years (range 1–19 years).

One patient (case 8) was free of disease for eight years and then stopped penicillin prophylaxis. Within six months he developed tonsillitis and a severe vasculitic illness followed. He had swinging fever and a widespread vasculitic rash, in particular on the medial aspect of his feet. He developed bilateral peroneal nerve palsies, confirmed on nerve conduction studies. His neutrophil count was $65 \times 10^9/l$, haemoglobin 78 g/l, erythrocyte sedimentation rate 100 mm/hour, and C reactive protein 16 mg/l. Visceral arterial imaging was performed. Figure 4A and B demonstrate the microaneurysms of his hepatic and renal arteries. He was given parenteral steroids (methylprednisolone 20 mg/kg on three consecutive days) and cyclophosphamide (0.5 g/m^2 intravenously every three weeks for six doses). A further patient, case 9, who also had severe recurrent disease, underwent visceral arteriography that

demonstrated renal microaneurysms. His urinalysis and renal function was entirely normal. He, too, was treated with parenteral cyclophosphamide in addition to corticosteroid therapy. Case 1, who had severe chronic relapsing disease, had normal arteriography. Her recurrent episodes followed non-specific infections and occurred when the steroid dose was reduced to below 12.5 mg prednisolone/day. She subsequently responded to oral azathioprine (2.5 mg/kg/day). Recurrence of disease in all three patients was associated with an increase of the antistreptolysin O titre ($>1060 \text{ U}$), although β haemolytic streptococcus was not isolated from throat swabs.

Discussion

The 12 patients described had a characteristic illness after a sore throat. All were unwell with fever, arthralgia or arthritis, myalgia, and vasculitic rashes. The distribution of the nodular rash was predominantly on the limbs and more especially, the instep of the foot. The oedema of the shins and around the elbows and forearms might have led to an erroneous diagnosis of arthritis.

The association with streptococcal infection was demonstrated by recent infection confirmed by either a positive throat swab and/or a significant increase of antistreptolysin O and antihyaluronidase titres. Although the latter may be part of a general anamnestic immunoglobulin response, serial measurements correlated with clinical progression more closely than total IgG, and decreased on treatment. Interestingly, two patients had been diagnosed previously with rheumatic fever. Rose and Spencer noted, in their review of 111 patients with polyarteritis, that concomitant rheumatic fever was found in 12.5% of their patients.⁴ This association had also been made in a necropsy series by Freidberg and Gross.⁵ Fordham, in addition, described polyarteritis and acute poststreptococcal glomerulonephritis in three patients,⁶ but glomerulonephritis was not a feature in our patients.

Figure 4 (A) Arteriogram of coeliac axis of case 8 with relapse of cutaneous polyarteritis showing multiple aneurysms. (B) Arteriogram of renal artery of the same child showing peripheral aneurysms.

Three patients in our series developed a subsequent recurrent vasculitic illness, one in association with cessation of penicillin prophylaxis. Microaneurysms were demonstrated on angiography in two of them. The microaneurysms suggest that cutaneous polyarteritis nodosa is part of a continuum of polyarteritis nodosa and can occur after streptococcal infections. Most cases of cutaneous polyarteritis nodosa have a benign course.⁷ In contrast, Magilavy *et al* reported nine patients with a chronic course with evidence of systemic vasculitis on angiography, but without renal deterioration.⁸ Although Fisher and Orkin suggest that cutaneous involvement is inversely related to the degree of systemic involvement,⁹ and Sack *et al* observed that cutaneous involvement in polyarteritis nodosa was a pointer that the disease would follow a more benign course,¹⁰ we believe that arteriography should be performed in systemically ill patients or patients with relapsing cutaneous lesions as described in this report, as they require more

aggressive cytotoxic treatment for effective disease control.

The authors wish to thank Dr John Loftus for his help in documenting some of the clinical details and Mrs Geraldine Brown and Mrs Hilary Cook for their secretarial help.

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