Relapsing polychondritis with crescentic glomerulonephritis

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British Medical Journal, 1978, **1**, 743-745

Summary and conclusions

Relapsing polychondritis is rare and its cause is unknown. The tissues affected are those with a high glycosaminoglycan content, such as cartilage, the aorta, the sclera and cornea, and parts of the ear. Symptoms can usually be controlled with oral steroids, but when there is coexistent progressive crescentic glomerulonephritis quadruple chemotherapy may be used.

Three cases of the clinical syndrome of relapsing polychondritis were studied in which rapidly progressive crescentic glomerulonephritis developed. In two the patients appeared to respond to aggressive treatment with immunosuppressive agents and anticoagulants. The multisystemic nature of the disease, the renal lesions, and the response to treatment all suggested that the condition might be related to periarteritis nodosa.

Introduction

Although the first documented case of relapsing polychondritis was described in 1923,[1] the disease was not named until 1960.[2] Additional cases were later described,[3] the most notable series being that of McAdam *et al*,[4] which included 23 new cases. McAdam *et al* established empirically six clinical diagnostic criteria, and the presence of three or more of these together with histological evidence of chondritis confirmed the diagnosis. The criteria were (1) recurrent chondritis of both auricles; (2) nonerosive inflammatory polyarthritis; (3) chondritis of nasal cartilages; (4) inflammation of ocular structures, including conjunctivitis, keratitis, scleritis or episcleritis, and uveitis; (5) chondritis of the respiratory tract affecting laryngeal or tracheal cartilages or both; and (6) damage to cochlea or vestibule or both manifest by neurosensory hearing loss and tinnitus or vertigo or both.

The mortality of patients with relapsing polychondritis after five years is 25%, upper-airway collapse and cardiovascular complications being the most common causes of death. There have been reports of specific organs such as eyes and ears being affected, but few have mentioned renal complications. Early reports commented on mildly abnormal urine sediments in up to 25% of cases[5] but details were vague. The single case of proliferative glomerulonephritis with crescents reported by Hughes *et al*[3] is one of the cases included here. Only one other case of severe azotaemia has been described,[6] and no deaths have been ascribed to renal failure, emphasising the rarity of severe renal complications.

Case reports

CASE 1

In May 1975 a 43-year-old housewife developed chondritis of both ears and bilateral iritis (table I). Within four weeks she had arthralgia of both knees. She was admitted with low-grade fever, effusion into the left knee, and subsiding chondritis of both pinnae. Biopsy of the abnormal nasal mucosa showed dense inflammatory granulation tissue with massive plasma-cell infiltration but no vasculitis. Haemoglobin was 10·5 g/dl and erythrocyte sedimentation rate (ESR) 67 mm in the first hour. Plasma urea and creatinine concentrations were normal. Her symptoms responded to aspirin 900 mg four times daily, and the iritis cleared with betamethasone drops. Three weeks after discharge she was readmitted with a low haemoglobin concentration and proteinuria and haematuria. Results of investigations are given in table II. Renal biopsy showed segmental necrotising glomerulonephritis, 73% of all glomeruli having crescents (table III). She was treated with prednisolone 60 mg and azathioprine 100 mg daily and dipyridamole 200 mg three times daily. In view of her slow improvement heparin was added but was later changed to warfarin. With this regimen her creatinine concentration returned to normal within two months.

Over the next year the prednisolone dosage was gradually reduced to a minimum of 20 mg daily and the azathioprine continued. When the joint pains recurred, however, azathioprine was stopped and levamisole 50 mg three times daily prescribed on two days of each

TABLE I—*Presence of symptoms and systems affected during course of illness in each of the three cases*

	Case 1	Case 2	Case 3
Ears (external)	+	+	
Ears (internal)		+	+
Nose	+	+	+
Eyes	Bilateral anterior uveitis	Bilateral anterior uveitis	Bilateral conjunctivitis
Joints	Arthritis of left knee		
Polyarthralgia	+	+	+
Skin			
Myalgia		+	+
Pleurisy			+
Neuropathy	Mild right ulnar neural palsy	Left sixth-nerve palsy and Horner's syndrome	
CNS		Vasculitis	
Heart	Soft extrasystolic murmur		
Lung opacities		+	
Retinal exudates		+	
Sore throat			+
Blood pressure (mm Hg)	125/85	130/70	200/90
Oedema	+		

TABLE II—*Results of clinical investigations*

	Case 1	Case 2	Case 3
Haemoglobin (g/dl)	8·4*	11·9	10·9
White cell count ($\times 10^{-9}$/l)	5·2	14·2	15·0
Eosinophils ($\times 10^{-9}$/l)	0·1	1·3	
Erythrocyte sedimentation rate in first hour (min)	100	115	140
C3 as % of reference normal serum	85	ND	ND
C4 as % of reference normal serum	86	ND	ND
Antistreptolysin O titre	625	100	200
Antinuclear factor	Negative†	Negative	Negative
DNA binding (%)	14	ND	ND
Rheumatoid factor	Negative	Positive	Negative
Hepatitis B surface antigen	Negative	Negative	Negative
Plasma urea concentration (mmol/l)	15	22	53
Plasma creatinine concentration (μmol/l)	290	430	845
Creatinine clearance (ml/min)	25	16	
Glomerular filtration rate (^{51}Cr-EDTA) (ml/min)	15	4	ND
Total protein (g/l)	67	48	63
Albumin (g/l)	33	29	31
Urinary protein (g/day)	1·6	0·9	ND
Urinary red cell count ($\times 10^{-9}$/l)	0·32	Macroscopic haematuria	+ + +

*Serum iron concentration 4·1 μmol/l (23 μg/100 ml); hypochromic, microcytic film.
†Positive for thyroid antibodies on autoantibody screen.
ND = Not done.
Conversion: SI to traditional units—Plasma urea: 1 mmol/l ≈ 6 mg/100 ml. Plasma creatinine: 1 μmol/l ≈ 0·01 mg/100 ml.

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TABLE III—*Results of biopsy*

	Case 1	Case 2	Case 3
Time from apparent onset (weeks)	10	30	5
No of glomeruli	33	54	16
No (%) sclerosed	4 (12)	5 (9)	2 (13)
No (%) with crescents major*	18 } 73%†	36 } 81%	9 } 88%†
No (%) with crescents minor	6 }	8 }	5 }
No (%) normal	5 (15)	5 (9)	
Mesangial proliferation	+	+	+
Polymorph neutrophils			+
No with fibrinoid necrosis	8	50	14
Interstitial infiltrate	+ +	+	+
Oedema	+	+	+ +
Fibrosis	+	+	+
Tubules	Early atrophy	Patchy atrophy	Early atrophy
Vasculitis			
Immunofluorescence	Negative	ND	ND

*Crescents covering more than 60% of Bowman's capsule.
†% of all glomeruli; percentages of unsclerosed glomeruli were 83, 90, and 100 for cases 1, 2, and 3 respectively.
ND = Not done.

week. This was also withdrawn after a brief period because of recurrent fever. Two years after the clinical onset of her illness she was symptom free; her urine was free of protein, glomerular filtration rate (GFR) 28 ml/min, plasma creatinine concentration 96 μmol/l (1·1 mg/100 ml), and ESR 7 mm in the first hour. She was still taking prednisolone 20 mg daily, dipyridamole 200 mg twice daily, and warfarin and guanethidine 25 mg twice daily for persisting hypertension.

CASE 2

In October 1970 a 49-year-old man had an attack of otitis media with deafness but no pain or discharge. Myringotomy was performed and mucoid sterile fluid obtained. He then developed mastoiditis and in December underwent left radical mastoidectomy. In January he had transient arthralgia in both shoulders, hands, feet, and jaw. In February his nose became inflamed and he had a brief illness with malaise, shivering, generalised myalgia, nausea, and vomiting. Diplopia developed in March and lasted three weeks. Left lateral rectus weakness, bilateral conjunctivitis, and left Horner's syndrome were found. Radiography disclosed small opacities in the apices of both lungs. Haemoglobin and plasma urea concentrations were normal, and his ESR was 75 mm in the first hour.

By April he had lost 10 kg and developed transient pain and tenderness in the lower costal margin and inflammation of the right pinna. He was pale and ill on admission, with partial left ptosis and myosis and mild bilateral anterior uveitis. There was one small exudate in the left retina. Results of investigations (table II) were otherwise normal except for a soft, apical, mid-systolic murmur. Renal biopsy showed segmental necrotising glomerulonephritis, 90% of the unsclerosed glomeruli having crescents (table III). Biopsy of the right pinna showed typical chondritis, but this and the iritis rapidly improved with prednisolone 80 mg daily. His renal function continued to deteriorate, with a fall in creatinine clearance from 16 to 8 ml/min, but improved when azathioprine and heparin were added to the treatment. He was discharged in June receiving prednisolone 25 mg and azathioprine 150 mg daily and subcutaneous heparin 11 000 units thrice daily. By August the apical opacity in the left lung was much smaller, his ESR was 40 mm in the first hour, creatinine clearance 26 ml/min, and GFR 18 ml/min. In December he developed neurological symptoms suggesting cranial arteritis, which resolved when the steroid dose was increased. In March 1972 the heparin was replaced by warfarin and dipyridamole 200 mg thrice daily was added. His renal function remained stable until September when it started to decline. The steroid dosage was increased with some improvement but he died in September 1973 in uraemia. Necropsy showed healed necrotising arteritis in both cranial and renal arteries.

CASE 3

In December 1971 a 67-year-old man developed myalgia, polyarthralgia, a tender nose, conjunctivitis, and deafness. Bilateral myringotomies were performed but two weeks later he developed a sore throat and right-sided pleuritic pain. On admission to hospital four weeks after onset of the initial symptoms his serum urea concentration was 25 mmol/l (151 mg/100 ml). The urea concentration rose rapidly and he became oliguric. Blood pressure was 200/90 mm Hg. Results of investigations are given in table II. After renal biopsy, which showed glomerulonephritis with segmental fibrinoid necrosis and crescents in all unsclerosed glomeruli (table III), he was discharged home for terminal care and treatment with prednisolone 30 mg daily.

Results

All three patients fulfilled the clinical criteria for diagnosing relapsing polychondritis. Case 2 also showed clinical evidence of generalised vasculitis with multiple cranial nerve palsies and lung granuloma. All three patients had bilateral conjunctivitis or anterior uveitis or both and polyarthralgia. The patient in case 1 had arthritis of the knee, and the other two had prominent myalgia. Each patient presented with mild anaemia (haemoglobin 8·4-11·9 g/dl), an increased ESR (100-140 mm in the first hour), and a variable leucocytosis ($5{\cdot}2 \times 10^9$-$15{\cdot}0 \times 10^9$/l). The patient with vasculitis had eosinophilia, with $1{\cdot}3 \times 10^9$ eosinophils/l.

All patients had a nephritic onset to their renal disease with profuse microscopical haematuria and mild proteinuria (up to 1·6 g a day). Renal failure varied from a creatinine clearance of 25 ml/min to oliguria. Only one patient was hypertensive at presentation, with a blood pressure of 200/90 mm Hg.

The histological findings on renal biopsy were uniform. In each case more than 80% of the unsclerosed glomeruli were covered by epithelial crescents, and although glomerular tuft proliferation was mild, segmental fibrinoid necrosis of the tufts was extensive. No vasculitis was seen. The extent of tubular atrophy, interstitial fibrosis, and oedema was variable, and there was diffuse round-cell infiltration of the interstitium.

Discussion

The cause of relapsing polychondritis is unknown. The tissues affected are those with a high glycosaminoglycan content —for example, cartilage, aortic wall, sclera, cornea, and inner-ear components.[3] The absence of familial history, the peak incidence in middle age, and the patchy nature of cartilage disease suggest an acquired disorder. Anticartilage antibodies and lymphocytes sensitised to chondromucoproteins are not constant findings and are commonly found in rheumatoid arthritis.[3] Twenty-five per cent of the 159 patients reviewed by McAdam *et al*[4] had associated rheumatic or autoimmune disease. These included rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus (SLE), systemic sclerosis, Reiter's syndrome, psoriatic arthritis, thyroid disease, ulcerative colitis, and dysgammaglobulinaemias.

All the features of relapsing polychondritis apart from chondritis occur in the various types of necrotising vasculitis. Certain parallels also exist between it and dermatomyositis. In this disease the characteristic target organs are skin and muscle, and the cellular infiltrate and perivascular cuffing with lymphocytes is similar to that seen in cartilage in relapsing polychondritis. In both conditions scleritis and episcleritis are common, and overt arteritis may occur. Lymphocytes in dermatomyositis are cytotoxic to cultured fetal muscle cells.[7]

McAdam *et al* commented on the high incidence (56%) of medium- and large-artery damage in their series. When aortic regurgitation occurs in relapsing polychondritis the histological appearance of the aortic wall is indistinguishable from that in ankylosing spondylitis or Reiter's disease.

Relapsing polychondritis is rare, although chondritis coexistent with systemic vasculitis is probably sometimes overlooked. It has been questioned whether a specific pathological diagnosis is important, for the pathological subclassification of periarteritis is difficult and rarely helpful clinically. Two conditions in which a specific diagnosis is therapeutically important, however, are cranial or giant-cell arteritis and Wegener's granulomatosis. The segmental necrotising glomerulonephritis with relapsing polychondritis reported here was indistinguishable from that seen in periarteritis nodosa and Wegener's granulomatosis. These diseases are further characterised by negative glomerular

immunofluorescence (IF). Focal segmental glomerulonephritis with fibrinoid necrosis but varying glomerular IF may also be seen in other forms of glomerulonephritis, such as Goodpasture's syndrome (linear IgG), subacute bacterial endocarditis (IgG, C3, Clq), SLE (all immunoglobulins and C3, C4, Clq), Henoch-Schönlein purpura (mesangial IgA), and IgA nephritis (mesangial IgA). Although we did not look for soluble antigen-antibody complexes or cryoglobulins, such complexes have been implicated in this type of renal disease.[8 9] Rheumatoid factor was present in one of our patients, possibly as an indirect marker of circulating immune complexes. The reported incidence of rheumatoid factor in relapsing polychondritis is 18%.[1]

Since 1971 we have treated 28 cases of rapidly progressive crescentic glomerulonephritis with quadruple therapy of prednisolone, azathioprine, anticoagulants, and dipyridamole.[10] In case 1 the GFR improved with treatment from 15 to 28 ml/min and the patient's renal function remained steady for at least two years. In case 2 the patient initially appeared to respond to treatment, with a rise in GFR from 3·5 to 19 ml/min and a steady renal function for 12 months, but died in renal failure after two years.

Acute symptoms have a variable response to oral steroids but can usually be controlled. Only one death with severe azotaemia has previously been reported. The patient also had scleroderma, and renal histology showed the changes of malignant hypertension.[6] In relapsing polychondritis associated with rapidly progressive crescentic glomerulonephritis aggressive treatment may be lifesaving.

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(*Accepted 5 January 1978*)

Growth hormone, prolactin, and corticosteroid responses to insulin hypoglycaemia in alcoholics

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British Medical Journal, 1978, **1**, 745-748

Summary and conclusions

Plasma growth hormone (GH), prolactin, and corticosteroid responses to insulin-induced hypoglycaemia were studied in 24 men with progressive alcoholism who had been abstinent for two to seven days. Ten normal healthy subjects (five men, five women) served as controls for comparing GH and prolactin responses, while cortisol responses were studied in a further six male controls. Blood samples were taken at intervals after an injection of soluble insulin (0·1 U/kg body weight). All patients developed adequate hypoglycaemia (blood glucose <2·2 mmol/l (<39·6 mg/100 ml)) and nine had impaired GH responses (peak concentration <10 mU/l). Prolactin concentrations fell or remained unchanged in nine patients, eight of whom also had impaired GH responses. In seven patients corticosteroid concentrations decreased from basal concentrations, and six of these patients had impaired GH responses. All three hormone responses were impaired in several patients, and significant correlations were found between the GH and prolactin responses at 45 and 60 minutes. GH response was not correlated with age, duration of drinking, duration of alcoholism, or admitted alcohol intake. GH responses were significantly lower in patients who had the most severe withdrawal symptoms. Our observations of impaired stress responses in some recently abstinent alcoholics may have important implications for the management of alcohol withdrawal syndrome.

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Introduction

Chronic alcohol consumption has several important effects on the endocrine system.[1] In particular, some alcoholics have an impaired cortisol response to oral alcohol and hypoglycaemia,[2] and shortly after withdrawal of alcohol some may also have an impaired growth-hormone (GH) response to hypoglycaemia.[3] We decided to extend these studies by investigating GH, prolactin, and corticosteroid responses to insulin-induced hypoglycaemia in a larger group of patients. Relations between the hormone responses and relevant features of the patient's clinical history were also examined.

Patients

Twenty-four men with progressive alcoholism (mean age 45 years; range 25-65) were investigated two to seven days after they had stopped drinking. All had given informed consent to the study. Only patients with symptoms of physical dependence on alcohol were studied, patients with hepatic cirrhosis, hypokalaemia, or