IMMUNOSUPPRESSIVE TREATMENT OF 34 PATIENTS WITH MICROSCOPIC POLYARTERITIS

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Summary

Microscopic polyarteritis is a systemic vasculitis of unknown aetiology which predominantly affects small arterioles supplying kidneys, skin, joints and musculature. Pathologically, a focal segmental necrotizing glomerulonephritis is present and arterioles within the kidney and elsewhere show patchy fibrinoid necrosis. We have described 34 such patients, all of whom had renal impairment and evidence of a systemic vasculitis. Thirty-three patients were treated with prednisolone, cytotoxic drugs and plasma exchange in various combinations. The resultant five year actuarial patient and kidney survival rates were 65 per cent and 55 per cent respectively, suggesting that aggressive immunosuppressive treatment improves the outlook of such patients, compared with previous reports of the outcome of patients with renal vasculitis [1].

Introduction

In 1948, Davson, Ball and Platt [2] drew attention to a sub-group of patients with polyarteritis in whom a primary systemic vasculitis was accompanied by a focal segmental necrotizing glomerulonephritis, itself a manifestation of vasculitis since the glomerulus may be regarded as a differentiated blood vessel [3]. Over the years the condition has received little attention. We have used the term 'microscopic polyarteritis' to describe patients with histological or clinical evidence of a non-granulomatous primary systemic small vessel vasculitis accompanied by focal segmental necrotizing glomerulonephritis who do not have evidence of Wegener's granulomatosis, neoplasia, relapsing polychondritis, rheumatoid arthritis or other diseases which may be associated with vasculitis and focal segmental necrotizing glomerulonephritis. This is a more restricted use of the term 'microscopic polyarteritis' than was recently proposed by Serra et al [1] who included any patients with focal segmental necrotizing glomerulonephritis.

Patients

We have reviewed the records of 34 patients with microscopic polyarteritis (22 men and 12 women with a mean age of 50 years, range 14–74 years) who presented to the renal unit of Hammersmith Hospital between July, 1974 and June, 1984.

Clinical features

Twenty-nine per cent of the patients experienced prodromal symptoms comprising a sore throat or flu-like illness prior to the onset of other systemic features. Patients were unwell for a mean of 3.7 months (range 2 weeks to 22 months) prior to presentation. The major clinical features at presentation are shown in Table I.

TABLE I. Clinical features of 34 patients with microscopic polyarteritis at presentation

	Percentage
General	
Constitutional upset	76
Hypertension (diastolic >95mmHg)	29
Musculoskeletal	
Arthralgic/arthritis	71
Myalgia/muscle weakness	65
Vasculitic skin lesions	56
Episcleritis	24
Pulmonary haemorrhage	29
Gastrointestinal	
Pain	32
Diarrhoea	21
Gastrointestinal bleeding	29
Peripheral neuropathy	27
Cerebral (headache, convulsions)	9
Cardiovascular	9
Ear, nose, throat	
Sinusitis	9
Deaf at onset	3
Epistaxis	6

Laboratory findings

General No single investigation was diagnostic of microscopic polyarteritis. All patients had an elevated erythrocyte sedimentation rate and normochromic normocytic anaemia (mean 9.4g/dl). An acute phase response was suggested by thrombocytosis (41%), raised C-reactive protein (88%) or raised $\alpha 1$ and

α2 globulins (73%). Abnormal immunological investigations included circulating immune complexes by C1q binding assay or rheumatoid factor binding assay (45%), hypercomplementaemia with C_3>135 per cent or C_4>120 per cent normal human serum (27%), positive rheumatoid factor by latex test (41%), antinuclear antibodies (21%) and hypergammaglobulinaemia (14%). Cryoglobulins, anti-DNA antibodies and hepatitis B surface antigenaemia were not found.

Renal Plasma creatinine was elevated (>120μmol/L) in all patients at the time of referral to our care (mean 574μmol/L, median 578μmol/L). Proteinuria was present in 91 per cent (>3g/24hrs in 41%) and microscopic haematuria in 100 per cent.

Pulmonary Seven patients had definite and three had suspected alveolar haemorrhage on the basis of haemoptysis, elevated KCO (diffusing capacity for carbon monoxide corrected for alveolar volume) and radiological findings. The use of these criteria in diagnosis of lung haemorrhage is described elsewhere [4].

Angiography

Twelve patients underwent visceral angiography to exclude polyarteritis nodosa and no aneurysms were found.

Renal histology

Renal biopsy specimens were obtained from 32 patients and post-mortem examinations were performed on six. A focal segmental necrotizing glomerulonephritis was found in all instances, with crescents in 88 per cent of biopsies (affecting >60% glomeruli in 56%). Vasculitis was seen in 19 per cent of renal biopsies. Direct immunofluorescence showed granular deposits of IgA, IgG or IgM in the minority of biopsies (<30%) and the pattern was variable; granular C_3 was present in 50 per cent in mesangium or capillary loops.

Treatment

All patients were treated except for one who died from septicaemia within five days. Thirty-two patients received prednisolone (usually commencing at 60mg/day), 27 received cyclophosphamide (3mg/kg/day for 8 weeks), 20 received azathioprine (1mg/kg/day for 8 weeks if aged under 55 years) and 18 patients received daily 4 litre plasma exchanges for plasma protein fraction (mean of 7 exchanges per patient).

Response to treatment

Response to treatment in the first two months At the end of two months when cyclophosphamide was normally discontinued, 27 patients had improved symptomatically and their nephritis had been controlled, including five of eight patients

who had required dialysis at presentation for oliguric renal failure. The presenting plasma creatinine did not predict the response of renal function to therapy at two months, since there were no differences in the creatinines at two months between those patients who had presented with a creatinine above 500μmol/L (n=14) and those who had presented with a creatinine below 500μmol/L (n=13), (Mann-Whitney U test).

Of the 10 patients with pulmonary haemorrhage, a life threatening manifestation of microscopic polyarteritis, four required ventilation. Three patients died from hypoxia within 4–14 days, but the other seven responded to treatment.

During the first two months, seven patients died: five within 14 days of diagnosis (3 lung haemorrhage, 1 myocardial infarction, 1 infection) and two from infection at one and two months.

Long-term follow-up The 27 patients who survived longer than two months have been followed for a mean of 47 months. The actuarial patient survival rates at one and five years are 70 per cent and 65 per cent. Twenty-two patients are still alive and have been followed for a mean of 59 months.

Renal function Actuarial kidney survival rates at one and five years are 65 per cent and 55 per cent. The renal function in the 22 long-term survivors, together with the percentage of crescents in initial renal biopsies and number of disease relapses is shown in Table II. The progression to end-stage renal failure was shown by renal biopsy in four patients to be due to progressive scarring; a fifth patient had continuing low grade disease activity and four relapses. During follow-up 18 of 22 patients required treatment for hypertension (diastolic >95mmHg). At initial presentation 10 of 34 patients were hypertensive (diastolic 95–110mmHg).

TABLE II. Long-term follow-up of 23 patients

Plasma creatinine (μmol/L)	Number of patients	Crescents >60% glomeruli	Relapses
<120	5	0	2
>150	13	6	6
Dialysis dependent	5	5	1

Relapses There were 19 relapses in 12 patients. Six patients were on no medication and five of these required further treatment. In six other patients, relapses occurred while still on therapy: four who were on prednisolone and cyclophosphamide relapsed when the cyclophosphamide was reduced in dosage or withdrawn. Nine patients are still alive (4 are still on treatment) and two patients died following disease relapse.

Mortality There have been five late deaths between 3 and 43 months. Two were from unrelated causes and at post-mortem no evidence of disease activity

was found, one was from infection whilst the patient was still on immunosuppressive therapy, and two occurred following disease relapse from a subarachnoid haemorrhage and a brain-stem stroke.

Discussion

Microscopic polyarteritis is primary systemic vasculitis of unknown aetiology which, in this study, was shown to have a propensity to affect middle-aged males, although both sexes and a wide age range (13–73 years) may be affected. Clinically, non-specific constitutional symptoms are followed within weeks or months by vasculitic rashes and musculoskeletal symptoms and eventually culminate in the onset of renal failure. Such a presentation is similar to that recently described in another group of patients with renal vasculitis [1]. The vasculitic process may also involve the lungs, causing pulmonary haemorrhage, the gastrointestinal tract, eyes and neurological system. Unfortunately, as yet, there is no laboratory investigation which is diagnostic for the disorder, although evidence of an acute phase response (raised C-reactive protein, platelets, $\alpha 1$ and $\alpha 2$ globulins) and immune aberration (rheumatoid factor, antinuclear antibody and immune complexes) are found in some patients. Pathologically, a segmental necrotizing glomerulonephritis and arteritis with fibrinoid necrosis, are characteristic but again, not diagnostic. So, whilst clinical, immunological and pathological data suggest a primary vasculitis which can be distinguished from other types of primary vasculitis such as Wegener's granulomatosis, Henoch-Schönlein purpura, polyarteritis nodosa, Churg-Strauss syndrome, temporal arteritis and giant cell arteritis, only delineation of aetiology and pathogenesis will support this.

The rapid response to immunosuppressive treatment in this group of patients with severe renal and systemic vasculitis is of great interest. Comparison must be made with historical controls which comprise groups of patients with polyarteritis [5,6] (both polyarteritis nodosa and microscopic polyarteritis were probably included), severe systemic vasculitis with or without renal involvement [7] or renal vasculitis. In a recently reported group with renal vasculitis [1] which most resembled our own group, the five year actuarial survival was 34 per cent. In our group, 79 per cent initially responded to treatment and the five year actuarial survival rate was 65 per cent. Aggressive immunosuppressive treatment which includes steroids and cyclophosphamide is not without risk: 3 of 12 deaths were due to infection which could have been exacerbated by such therapy; nevertheless the high overall patient and kidney survival rates reported here would appear to justify this approach.

References

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