Glomerulonephritis in sarcoidosis: causal relationship unproven

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Summary: Two patients with sarcoidosis and glomerular mesangial proliferative lesions are described. Although a causative relationship between sarcoidosis and glomerulonephritis has been suggested, critical review of the literature fails to confirm this.

Introduction

The most common cause of renal involvement in sarcoidosis is hypercalcaemia which may predispose to nephrocalcinosis, nephrolithiasis and renal tubular abnormalities.^{1–5} Less frequently described is interstitial granulomatous nephritis.^{6–12} Glomerulonephritis has also been reported in association with sarcoidosis but a causal relationship has never been established.

Patients

Patient 1

A 41 year old Pakistani man visited his home country after living in Britain for 11 years. He developed a fever and on investigation bilateral hilar lymphadenopathy was found. A 30 month course of anti-tuberculous chemotherapy was given. In early 1981 he returned to England where, on chest X-ray, sarcoidosis was diagnosed and chemotherapy was discontinued. Fever recurred two years later and hepatosplenomegaly with generalized sarcoid skin lesions over the trunk and legs were noted. Investigations revealed normal chest X-ray and respiratory function tests; proteinuria of 2 g daily, hypercalcaemia of 8.9 mmol/day and serum angiotensin converting enzyme (SACE) 3 times the upper limits of normal. Skin biopsy showed non-caseating epithelioid and giant cell granulomas. A Kveim test was positive. Sym-

toms subsided without treatment but returned after 6 months when there was bilateral parotid and submandibular gland enlargement and hepatosplenomegaly. The proteinuria had doubled, creatinine clearance was 80 ml/min, SACE activity unchanged and the complement profile was normal.

Renal biopsy showed mild diffuse increase in mesangial matrix with some focal and segmental mesangial proliferation. There were multiple interstitial non-caseating epithelioid and giant cell granulomas. Immunoperoxidase studies showed diffuse mesangial IgM, IgG, C1q and C3. Electron microscopy confirmed the light microscopic findings and demonstrated incomplete foot process obliteration of visceral epithelial cells. There were no electron-dense deposits.

A 2 year course of prednisolone began in November 1983 and he showed considerable improvement. When last seen in March 1989 he was clinically well, his proteinuria had resolved, serum creatinine was 85 µmol/l and SACE was normal.

Patient 2

A 50 year old Ghanaian woman presented in 1982 with a maculopapular eruption around the chin and right nasolabial fold. Biopsy showed lupus pernio. There were no other systemic symptoms and chest X-ray was normal. Six months of methotrexate led to considerable resolution of the lesions. In February 1985 the lupus pernio recurred. Routine urine examination showed proteinuria of 1.3 g/day with a creatinine clearance of 55 ml/min. Chest X-ray was normal, serum IgG was elevated at 15.3 g/l, the complement profile showed mild elevation of haemolytic and C4 activity but C3 was normal. Renal histology

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showed a segmental increase in mesangial cells and an increase in mesangial matrix. In two glomeruli segmental thickening of the capillary walls and Bowman's capsule was present. The interstitium showed small scattered foci of fibrosis with moderately dense mononuclear cell infiltration. Immunoperoxidase showed scattered fine granular localization of IgM +, C1q +, C3 + and IgG ± in the mesangium. Electron microscopy confirmed the light microscopic findings; there were electron-dense deposits in the mesangial matrix and focal loss of foot processes of some visceral epithelial cells.

She was treated with prednisolone 5 mg, azathioprine 50 mg and cyclophosphamide 50 mg daily. When last seen in March 1990 she was clinically well and renal function had become normal with a serum creatinine of 108 µmol/l and a 24 h urine protein of 0.8 g/day.

Discussion

Glomerulonephritis has occasionally been reported in association with sarcoidosis. The most common abnormal glomerular morphologies are membranous, mesangiocapillary, focal sclerosis, IgA nephropathy, chronic and non-specific glomerulonephritides.¹³⁻³¹ In one patient crescentic proliferative glomerulonephritis recurred following transplantation.²⁴

Several authors (D.G. James, unpublished observations cited in References 22 and 24) have noted that the relative infrequency of glomerulonephritis as a manifestation of sarcoid causes uncertainty as to whether the coincidence of the two conditions is fortuitous or causally related. Many serious criticisms may be levelled at sporadic case reports purporting to suggest a causal relationship but without providing any aetiopathological evidence.

In a number of earlier case reports the renal pathology was inadequately studied, poorly documented^{28,32} or obtained from post mortem tissues³³ making interpretation of glomerular change difficult. We agree with Taylor *et al.*²² that in several publications the descriptions of renal morphology

are apparently at variance with the claims of the authors, the appearances described being more suggestive of membranoproliferative rather than proliferative and mesangioproliferative glomerulonephritis.^{18,30} In other reports abnormalities such as hypercalcaemia, nephrolithiasis or nephrocalcinosis often co-existed with minor glomerular changes.^{19,32,34} Further, prolonged periods often existed between the development of active sarcoid and the glomerulonephritis and vice versa.^{15,19,22,23} Of the 33 cases reported and reviewed by Taylor *et al.*,²² 10 patients developed sarcoidosis up to 18 years before the glomerulonephritis and in 6 patients the renal disease presented up to 10 years before the sarcoid. In many of the reported cases there is little or no evidence of active sarcoid at the onset of glomerulonephritis.^{16,22} Also, critical review of the histology in a number of early papers^{2,3,21,25,27-29,33,35-39} is impossible because renal morphology was in the process of development, details of glomerular change are too sparse, immunofluorescent or immunoperoxidase studies were not reported and electron microscopy was not performed. Without these complementary techniques an adequate analysis of a renal biopsy is not possible.⁴⁰ Perhaps one centre should collect blocks of tissue from the various reporting laboratories to provide an overall uniform histological diagnosis and immunoperoxidase studies.⁴¹

Both of our patients presented with sarcoidosis, had proteinuria of presumed glomerular origin and had IgM associated mesangioproliferative lesions. This glomerular histology is not uncommon, the aetiology is unknown and not linked to any recognized clinical picture.⁴² Therefore, in our patients, as in those previously reported, it is impossible to establish a causal relationship between sarcoid and glomerulonephritis.

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