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Sarcoidosis and membranous glomerulonephritis: a significant association

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Abstract

Three patients were seen who had sarcoidosis associated with glomerulonephritis. Subsequent review of published reports of cases in which the two conditions occurred simultaneously showed a pattern of histological type of glomerulonephritis different from that seen in patients without associated disease. In sarcoidosis with glomerulonephritis there appeared to be a dearth of minimal-change disease and an excess of membranous glomerulonephritis compared with the prevalence that would be expected if the renal disease was merely a chance occurrence.

These findings may provide evidence for an important relation between sarcoidosis and glomerulonephritis.

Introduction

Several mainly isolated cases have been reported of sarcoidosis and glomerulonephritis occurring in the same patient. Some workers consider this relation to be significant, particularly with respect to membranous glomerulonephritis,[1] but others regard it as a chance occurrence.[2] We recently saw three patients with histologically proved sarcoidosis and glomerulonephritis. The possibility of an association between the two diseases prompted us to review reports of similar cases.

Case reports

Case 1—A 24-year-old man presented in November 1973 with the nephrotic syndrome and normal creatinine clearance. Percutaneous renal biopsy disclosed membranoproliferative glomerulonephritis with reduplication of the glomerular capillary basement membrane. Hypocomplementaemia was noted on several occasions. A chest *x*-ray film was normal in March 1979, but three months later he developed wheezing and was found to have bilateral hilar lymphadenopathy. A Kveim test yielded positive results. Serum calcium concentration and activity of angiotensin-converting enzyme were normal. Tests for circulating immune complexes by C1q binding were negative. His renal function and serum albumin concentration remained normal, though he continued to have heavy proteinuria and developed hypertension requiring treatment. The bilateral hilar lymphadenopathy persisted.

Case 2—In 1977 a 32-year-old man with longstanding epilepsy was found to have persistent haematuria and proteinuria, with granular casts in the urine and normal renal function. Histological appearances of a renal biopsy specimen obtained in January 1978 were those of segmental proliferative nephritis. In February 1980 he developed acute arthritis of both knees and ankles, erythema nodosum, and increased haematuria and proteinuria. Percutaneous renal biopsy confirmed the previous findings and indicated mesangial IgA disease. A Kveim test gave a positive result. A chest *x*-ray film was normal, as were the serum calcium concentration and angiotensin-converting enzyme activity. Circulating immune complexes as estimated by the polyethylene glycol precipitation method amounted to 152 mg/l IgG (upper limit of normal 100 mg/l IgG).

Case 3—In June 1980 a 36-year-old man received penicillin as treatment for a tooth abscess. Proteinuria and haematuria were found a week later, and after a further two weeks he developed erythema nodosum. Creatinine clearance and serum calcium concentration and angiotensin-converting enzyme activity were normal. Percutaneous renal biopsy disclosed membranous glomerulonephritis. The overall appearances and the predominantly intramembranous distribution of the immune complexes were not entirely characteristic of an idiopathic membranous nephropathy but were not those of poststreptococcal glomerulonephritis. Serum complement concentration and the concentration of circulating immune complexes (polyethylene glycol precipitation method) were both normal. A chest *x*-ray film showed bilateral hilar lymph-node enlargement. Histology of a paratracheal lymph-node biopsy specimen showed typical sarcoid granulomas, and a Kveim test gave a positive result. His renal function remained normal, though proteinuria persisted.

Review of literature

We found 30 reports of cases of sarcoidosis and glomerulonephritis occurring in the same patient and examined critically the renal histo-

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logical evidence provided by the authors. We believe that one case,[3] which was not categorised, was one of membranous glomerulonephritis and that another case,[4] described as being of membranous glomerulonephritis, was one of proliferative glomerulonephritis. Two other cases,[5 6] described as cases of proliferative and mesangioproliferative glomerulonephritis respectively, were, we believe, probably membranoproliferative glomerulonephritis. Table I compares the distribution of renal histological diagnoses in the 33 cases of glomerulonephritis associated with sarcoidosis with the distributions in two apparently non-selected series from Guy's Hospital[7] and Newcastle.[8] Membranous disease was significantly more common in the patients with sarcoidosis than in those in the Guy's series and considerably more common but not significantly so in the patients with sarcoidosis compared with the Newcastle series. We were unable to find a single case of minimal-change disease in the patients with sarcoidosis, the prevalence of such disease in the control groups being significantly higher.

TABLE I—*Histology of glomerulonephritis in sarcoidosis and in primary glomerular disease. (Figures are numbers (%) of patients)*

	Sarcoidosis (n = 33)	Guy's series[7] (n = 433)	Newcastle series[8] (n = 143)
Minimal-change		22 (5·1)*	15 (10·5)*
Membranous[1 3 9-14]	12 (36·4)	66 (15·2)**	28 (19·6)***
Proliferative[4 13 15-18]	8 (24·2)	145 (33·5)	
Focal (including IgA)[19-22]†	6 (18·2)	81 (18·7)	
Chronic[13]	2 (6·1)		
Total	16 (48·5)	226 (52·2)	80 (55·9)
Membranoproliferative[5 6 23]†	5 (15·2)	119 (27·5)	20 (14·0)

Comparison of control groups with group with sarcoidosis: *$p < 0.01$ (Fisher's exact probability test); **$p < 0.05$ (χ^2 test with Yates's correction); ***$p < 0.10$ (χ^2 test with Yates's correction).
†E R Randall, unpublished observations.

Table II compares the distribution of histological diagnoses in those patients with sarcoidosis who had the nephrotic syndrome with that in a survey of the nephrotic syndrome in adults from Guy's Hospital.[24] Membranous glomerulonephritis was responsible for 60% of the cases of the nephrotic syndrome in sarcoidosis compared with 12% in the adults with primary glomerular disease.

TABLE II—*Histology in the nephrotic syndrome in sarcoidosis and in primary glomerular disease. (Figures are numbers (%) of patients)*

	Sarcoidosis (n = 15)	Guy's series[24] (n = 213)
Minimal-change		70 (33)
Membranous	9 (60)*	25 (12)
Proliferative	6 (40)	118 (55)

*$p < 0.001$ (χ^2 test with Yates's correction).

The temporal relations between the two diseases differed greatly. In 10 cases sarcoidosis was diagnosed up to 18 years before glomerulonephritis, and in four cases the renal disease presented up to 10 years before the sarcoidosis. Of the 28 patients whose sex was given, 19 were men. The mean age of these men at the time of diagnosis of the sarcoidosis was 28 (SD 7·9) years, compared with 41·3 (SD 12·6) years in the women ($p < 0.01$). In several cases, as in two of our patients, haematuria and proteinuria increased temporarily in association with erythema nodosum. The clinical range of sarcoidosis described with glomerulonephritis did not, however, appear in any way to be exceptional.

Discussion

Published reports and the experience of individual observers (D G James, unpublished observations) do not give any indication of a higher prevalence of glomerulonephritis in patients with sarcoidosis compared with the general population. Comparisons such as we made in this study are fraught with many sources of error. We believe, nevertheless, that there is a higher than expected prevalence of membranous glomerulonephritis in patients with sarcoidosis, with perhaps a reduced prevalence of minimal-change disease. Minimal-change disease is responsible for only about 5-10% of cases of adult primary glomerular disease. Although no case of minimal-change disease has to our knowledge been reported in sarcoidosis, at most no more than three in 33 cases of primary glomerular disease could be expected. The figures for membranous glomerulonephritis are, however, striking, and confirm the views of several workers who include sarcoidosis as one of the "causes" of membranous glomerulonephritis.

The altered immunological background of sarcoidosis[25] may be relevant in modifying the histological expression of another group of immunologically determined diseases, glomerulonephritis.

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