

Sarcoidosis with renal involvement

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Summary

Nine of ninety patients with sarcoidosis were found to have significant renal impairment. Epithelioid granulomata were present in five of eight patients who had renal biopsies and glomerular lesions were present in six. There was close correlation between hypercalcaemia, hyperuricaemia, nephrocalcinosis and creatinine clearance. In one patient, renal sarcoidosis complicated membrano-proliferative glomerulonephritis and one patient died in end-stage renal disease.

Introduction

Sarcoidosis has been considered a rare cause of impaired renal function and sarcoid granulomata are infrequently found in the kidneys at post-mortem (Scadding, 1967). Occasional case reports have appeared of patients dying of renal insufficiency due to diffuse interstitial granulomatous infiltration (Chanal, 1937; Rutishouser and Rwylin, 1950; Sorger and Taylor, 1961). It is only in recent years, however, that sarcoidosis has been recognized as a cause of serious renal impairment in living patients (Coburn *et al.*, 1967). Its incidence and effect on renal function are uncertain and its contribution to end-stage renal disease is unknown.

In this study ninety patients with sarcoidosis were assessed prospectively to find out the frequency and extent of renal functional impairment in this disease.

Patients and methods

The diagnosis of sarcoidosis was made by clinical examination, radiology, clinical chemistry and histology in 47 males and 43 females whose ages ranged from 10 to 66 years (Table 1). Renal disease was specifically looked for, and particular attention was paid to the presence or absence of proteinuria,

haematuria, hypertension, abnormalities of serum proteins, disturbances in serum calcium (normal range 2.1-2.6 mmol/l), phosphorus (normal range 0.8-1.4 mmol/l), and uric acid (normal range 178-416 mmol/l), calciuria in excess of 5 mmol/24 hr, impaired urine concentrating ability and impaired creatinine clearance. When these tests suggested renal disease, radiological investigations including standard pyelography, nephrotomography, and skeletal survey were carried out. Lymph glands for histology were excised in seven patients and liver biopsies were obtained in two. Renal tissue was obtained by percutaneous needle biopsy using the Menghini needle in seven patients, by open biopsy in one, and at post-mortem in one. All tissues were fixed in 10% buffered formalin and stained with haematoxylin and eosin. Renal tissue was also stained by the periodic acid-Schiff reaction and the periodic acid-Silver methenamine method.

TABLE 1. Age and sex of cases of sarcoidosis. Nine patients (10%) indicated in parentheses were found to have impaired renal function

Age (years)	0-19	20-29	30-39	40-49	50-59	Total
Male	8 (2)	19 (3)	13	5 (1)	2 (1)	47
Female	8	17 (1)	12 (1)	5	1	43

Results

Nine of the ninety patients (10%) with a diagnosis of sarcoidosis were found to have impaired renal function (Table 2). Of these, seven were male, average age 28 years, and two were female, aged 22 and 28.

Three patients had blood pressure above 150/90 mmHg; all except one had bilateral hilar lymphadenopathy. The exception (case 8) was a 54-year-old

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TABLE 2. Summary of clinical and laboratory data in nine sarcoid patients with renal involvement

Case	Age (years)	Sex	BP (mmHg)	BHL*	ESR (mm/hr)	Mantoux test	Lymph gland biopsy	Serum CaPP (mmol/l)	Serum uric acid (mmol/l)	Urinary protein (g/24 hr)	Urinary Ca++ (mmol/24 hr)	Creatinine clearance (ml/min)
1.	21	M	120/70	+	120	—	+	2.5	250	+	3.9	45
2.	22	M	125/75	+	21	—	+	2.75	464	15.0	6.2	47
3.	22	F	160/100	+	68	—	+	2.1	250	10.7	2.6	130
4.	14	M	120/80	+	40	—	+	3.1	470	0.4	3.2	30
5.	28	F	160/100	+	65	—	+	3.15	518	0.5	8.1	30
6.	28	M	120/80	+	84	+	+†	2.9	440	—	7.6	108
7.	45	M	200/130	+	124	—	+	3.5	963	+++	5.1	4.5
8.	54	M	130/90	+	47	—	+†	1.8	434	4.8	0.13	5.4
9.	14	M	130/70	+	96	—	+	2.5	0	0.57	0.26	95.6

* BHL = Bilateral hilar lymphadenopathy

† = Liver biopsy positive

+ = Positive finding

— = Negative finding

0 = Not done

Serum Ca++ (normal range 2.1–2.6 mmol/l)

Serum uric acid (normal range 178–416 μ mol/l)

Normal urinary Ca++ < 5 mmol/24 hr.

male whose chest X-ray was reported as 'suggestive of sarcoid'. All had raised ESR (average 74 mm/hr) at some stage in their illness, but usually at initial investigation.

Non-caseating epithelioid granulomata were present in excised scalene lymph glands in six patients (cases 1, 2, 3, 4, 5 and 9) and in an axillary lymph gland in one (case 7). Eight of the nine patients were anergic. The exception, case 6, a 28-year-old male telephone operator presented with erythema nodosum, chest pain and a non-productive cough. Routine chest X-ray showed bilateral hilar lymphadenopathy and hilar flare. A scalene lymph gland biopsy was negative for sarcoidosis but a needle biopsy of liver contained non-caseating epithelioid granulomata. His Mantoux test was positive at a strength of 100 old tuberculin (OT) units, nevertheless, the clinical picture was that of sarcoidosis and examination of several specimens of sputum for tubercle bacilli by Ziehl-Neelsen stain and culture was negative. He made satisfactory progress on symptomatic treatment and a short course of indomethacin. In case 8 an open biopsy of the liver showed peri-portal non-caseating epithelioid granulomata. Five of the nine patients had hypercalcaemia, transient in two (cases 2 and 5) and persistent in three (cases 4, 6 and 7) and these five also had serum uric acid levels in excess of 416 μ mol/l. There was thus a close correlation between hypercalcaemia and hyperuricaemia and both seemed to reflect the degree of renal failure. Two patients, cases 3 and 8, had initial hypocalcaemia. In case 3, a nephrotic, this was mild and transient and may have been due to hypoproteinaemia. Case 8 was hoarse and hypocalcaemic symptoms required oral calcium. The initial levels were 1.95, 2.0, 2.0 mmol/l.

His serum uric acid was slightly elevated at 434 μ mol/l. This may have been related to thiazide diuretics prescribed over a long period for hypertension. All but one patient (case 6) had proteinuria although this was mild in case 1. Urinary calcium in excess of 5 mmol in 24 hr was found in four patients (cases 2, 5, 6 and 7). It must be pointed out, however, that balance studies were not performed, and dietary intake of calcium was not controlled.

Creatinine clearance was significantly impaired in six patients (cases 1, 2, 4, 5, 7 and 8).

The main benefit of renal radiology was to demonstrate kidney size, cortical thickness, calyceal patterns and drainage.

Renal biopsies were studied in eight of the nine patients in this series. Epithelioid granulomata were present in five (cases 1, 3, 5, 8 and 9) (Fig. 1). Glomerular lesions in the form of non-specific mesangial fibrosis and focal hyaline deposits were present in six cases (cases 1, 2, 4, 6, 8 and 9) (Fig. 2). Case 3 showed membrano-proliferative glomerulonephrosis at first biopsy (1968) and diffuse basement membrane thickening 5 years later. An interstitial inflammatory infiltrate was present in five patients (cases 1, 2, 3, 8 and 9) and significant interstitial fibrosis and nephrocalcinosis in four (cases 2, 3, 4 and 5) (Fig. 3). In Table 3, an attempt has been made to correlate the histological findings with the clinical chemistry. As expected, there is close correlation between hypercalcaemia, hyperuricaemia, nephrocalcinosis and creatinine clearance. Otherwise no correlation is apparent.

Eight of the nine patients improved on treatment with corticosteroids. As already mentioned, case 6 was given indomethacin for a short period. Case 3 was given prophylactic penicillin, spironolactone and

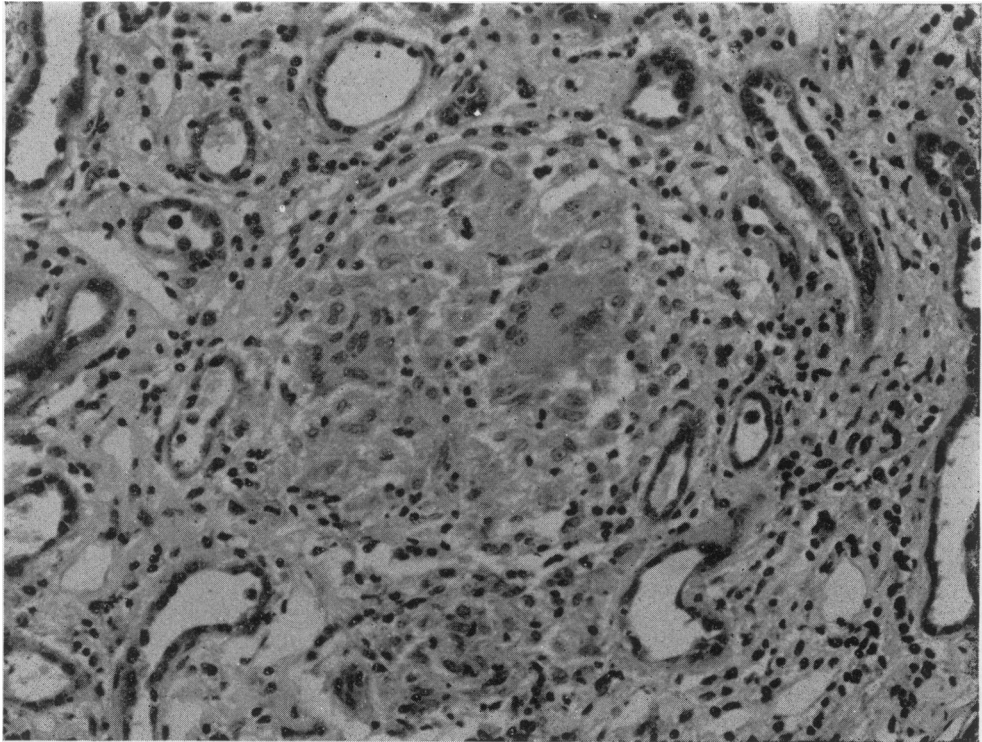


FIG. 1. A typical non-caseating epithelioid granuloma in the renal medulla (case 3). (HE, $\times 240$.)

furosemide in addition to corticosteroids and indomethacin. In case 5, corticosteroids were replaced by oxyphenbutazone when the patient became pregnant. Of the nine cases, one (1.1%) (case 7) died in end-stage renal disease with granular contracted kidneys. At post-mortem, epithelioid granulomata could not be found but there was marked nephrocalcinosis. The other eight patients all showed varying degrees of renal impairment, although this was minimal in case 6.

Discussion

The variety of ways in which the kidneys may be involved by sarcoidosis has been thoroughly reviewed by Coburn *et al.* (1967). Granulomatous infiltration, focal glomerulonephritis and capillary hyaline changes have been described (Teilum, 1951; McPhaul *et al.*, 1964) although serious renal functional impairment is usually a consequence of hypersensitivity to vitamin D, resulting in hypercalcaemia, nephrocalcinosis and nephrolithiasis. A study of the literature, however, does not reveal the frequency of renal functional impairment in this disease.

In this study the authors found that when specific-

ally looked for, histological evidence of renal disease and impaired renal function was found in nine of ninety patients (10%). Epithelioid granulomata, glomerular lesions, interstitial inflammation and fibrosis were present in a considerably higher proportion of biopsies in this series than in that of Lebacqz, Verhaegen and Desmet (1970) who examined twenty-five successful biopsies from 152 patients. In particular the finding of epithelioid granulomata in five (5.5%) and glomerular lesions in eight (8.8%) was higher than expected. Interstitial inflammation (5.5%) and interstitial fibrosis (4.4%) were also prominent histological findings.

The correlation between hypercalcaemia and nephrocalcinosis (Table 3) was predictable. Five patients (5.5%) had hypercalcaemia, persistent in three (3.3%) and transient in two (2.2%). This compares with an incidence of 2.8% for persistent hypercalcaemia in 381 patients reported by Israel and Goldstein (1970) and in 5.3% of 149 cases investigated by Mikhael (1970). Of perhaps greater interest was the presence of initial hypocalcaemia in two patients in one of whom (case 8) treatment with oral calcium was necessary to alleviate symptoms. This

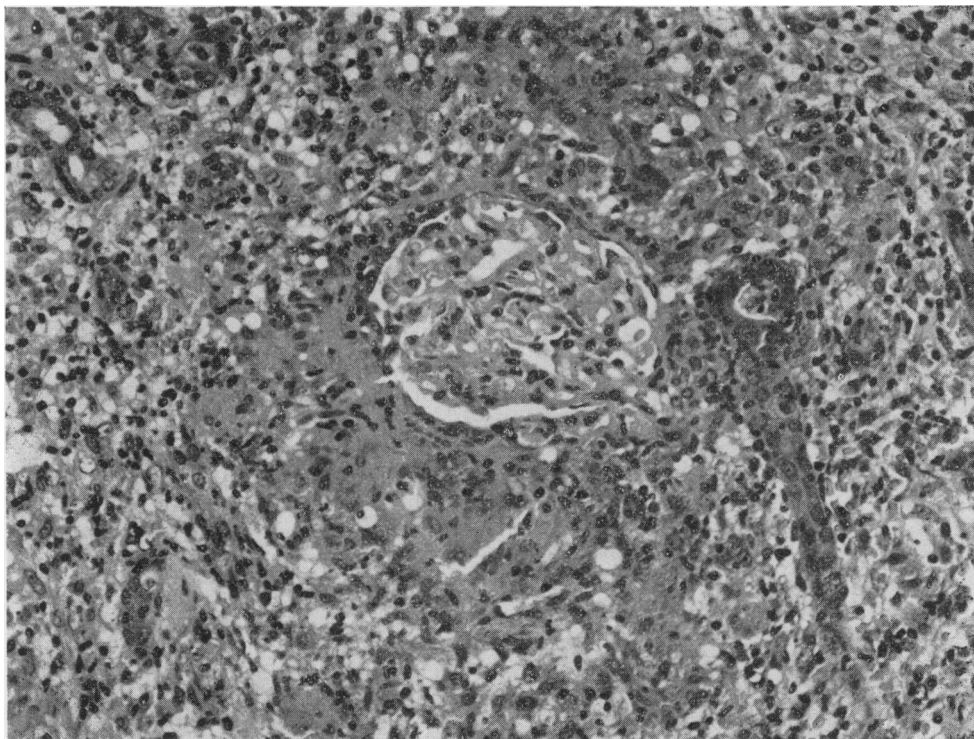


FIG. 2. Granulomatous nephritis. A glomerulus showing non-specific mesangial fibrosis surrounded by proliferating epithelioid cells and scattered lymphocytes (case 8). (HE, $\times 150$.)

TABLE 3. Renal histology and clinical chemistry in eight of nine sarcoid patients

	Cases							
	1	2	3	4	5	6	8	9
Histology:								
Epithelioid granulomata	+	-	+	-	+	-	+	+
Glomerular lesions	+	+	+	+	-	+	+	+
Interstitial inflammation	+	+	+	-	-	-	+	+
Nephrocalcinosis	-	+*	-	+*	+*	+*	-	-
Clinical chemistry:								
Serum Ca ⁺⁺ > 2.8 mmol/l	-	+*	-	+*	+*	+*	-	-
Serum uric acid > 416 mol/l	-	+*	-	+*	+*	+*	+	0
Urinary Ca ⁺⁺ > 5 mmol/24 hr	-	+	-	-	+	+	-	-
Creatinine clearance < 70 ml/min	+	+	-	+	+	-	+	-

* = Close correlation between nephrocalcinosis, raised serum calcium and raised serum uric acid levels in cases 2, 4, 5, and 6.

+ = Present.

- = Absent.

0 = Not done.

patient also had the most severe degree of granulomatous nephritis. No correlation could be found between epithelioid granulomata on the one hand and nephrocalcinosis and hypercalcaemia on the other.

Only one patient of the nine had all three lesions. Although four of the eight renal biopsies showed nephrocalcinosis, only two of the nine patients (cases 6 and 7) had a history, or evidence, of nephrolithiasis

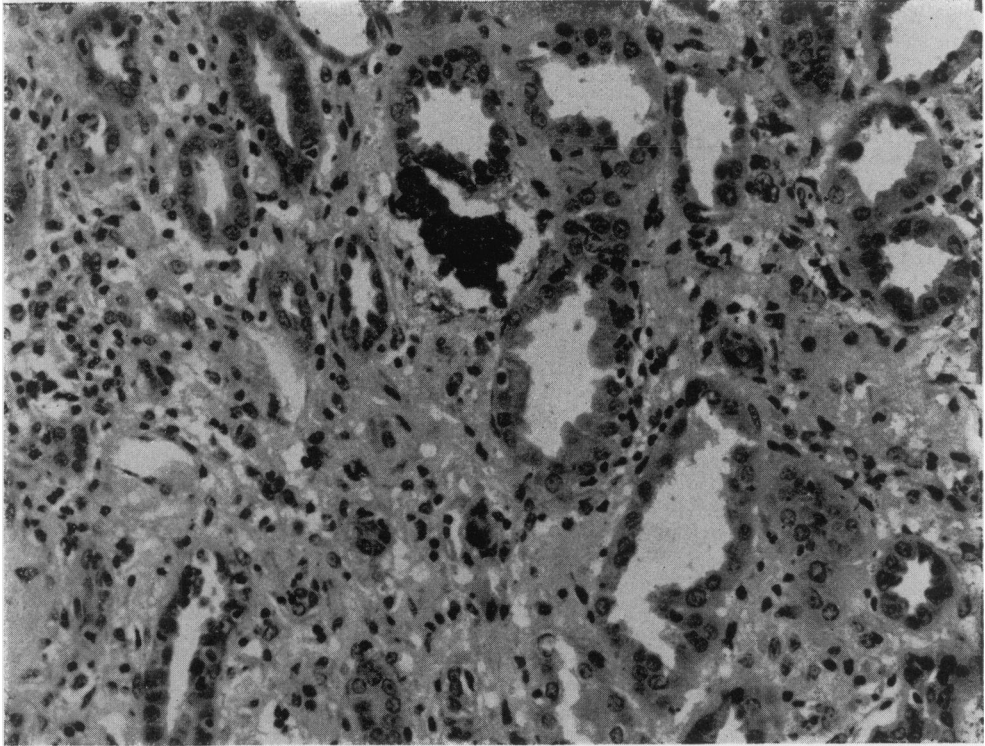


FIG. 3. Peri-tubular nephrocalcinosis, tubular atrophy, interstitial fibrosis and mild interstitial inflammation (case 4). (HE, $\times 240$.)

and none showed histological evidence of pyelonephritis. One patient died in end-stage renal failure, and although histological evidence of renal sarcoidosis was not seen at post-mortem examination, the long history (13 years) of generalized sarcoidosis with persistent hypercalcaemia, nephrocalcinosis and, latterly, severe hypertension, made it reasonable to attribute his condition primarily to sarcoidosis.

The findings in this study indicate that approximately one in ten patients with generalized sarcoidosis may have significant renal involvement and approximately 1% will proceed to end-stage renal failure. Sarcoidosis may also complicate renal disease due to other causes and so worsen the prognosis in these cases. It must be considered as being a cause of a proportion of those cases which present with end-stage renal disease of obscure aetiology.

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