

Tuberculosis in maintenance haemodialysis patients. Study from an endemic area

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Summary

One hundred and fifty patients requiring maintenance haemodialysis were investigated to determine the incidence and pattern of tuberculosis. Twenty patients were found to have tuberculosis, giving an incidence of 13.3 times that of the general population. The most frequent clinical presentations of tuberculosis in these patients were pyrexia, pleural effusion and lymphadenopathy. Diagnostic difficulties were encountered in 7 patients in whom therapeutic trial with anti-tubercular drugs had to be undertaken. Two patients died from tuberculosis. Five patients received renal transplants after initial treatment of tuberculosis.

Introduction

Host resistance to infection is primarily mediated by cellular immunity which is deficient in patients with chronic renal failure (Mackness, 1971; Malaviya *et al.*, 1973). The uraemic patients have impairment of delayed hypersensitivity skin reactions and prolonged skin homograft survival (Wilson, Kirkpatrick and Talmage, 1965; Boulton-Jones *et al.*, 1973; Nakhla and Goggin, 1973; Dammin, Cough and Murray, 1957). The anergy of such patients has been attributed to either chronic renal insufficiency or to their overwhelming tubercular infection (Munt, 1971). Ogg, Toseland and Cameron (1968) were among the earlier workers to report the occurrence of tuberculosis in a patient on haemodialysis. Pradhan *et al.* (1974) reported increased frequency of tuberculosis in patients on maintenance haemodialysis (MHD) and this interested several dialysis centres to look into the problem. The clinical manifestations of tuberculosis in uraemia

may be atypical and its diagnosis may present a challenge to the clinicians. Tuberculosis is endemic in India and it was thought worthwhile to study its incidence and the pattern of the disease in patients with chronic renal failure who developed tuberculosis during the course of MHD.

Materials and methods

During the period from January 1975 to June 1980, 150 patients have been on MHD at the Dialysis Unit of the All India Institute of Medical Sciences Hospital, New Delhi. The chronic dialysis programme at this Unit is predominantly transplant-orientated. Twenty out of these 150 patients were found to have developed tuberculosis during the course of MHD. There were 15 males and 5 females, their age ranged from 20 to 54 years. The basic renal disease in these patients was as follows: chronic glomerulonephritis (CGN), 15 cases; chronic pyelonephritis (CPN), one case; renal calculi with secondary CPN, 2 cases; gout with CPN, one case; diabetic glomerulosclerosis, one case. The specific investigations included radiological studies; cultures of sputum, urine, pleural fluid, ascitic fluid and cerebrospinal fluid for acid-fast bacillus (AFB); biopsies of lymph node, pleura, liver and bone. Specimens from abdominal laparotomy were available in one case and post-mortem specimens were available in another. Whenever the clinical picture was suggestive of tuberculosis but a definitive diagnosis could not be substantiated by investigation, a therapeutic trial with antitubercular drugs was undertaken and a presumptive diagnosis made in those patients showing a good therapeutic response.

Results

The main clinical features and results of special investigations are given in Table 1. The duration of renal failure as judged from past medical records and development of uraemic symptoms varied from 2 to 30 months. It is likely that the renal failure was of longer duration in some of the cases. The duration of MHD before the recognition of tuberculosis varied from one week to 9 months in 18 patients. Tuberculosis was detected at the time of onset of haemodialysis in the remaining 2 patients. Two patients had a past history of tuberculosis, one (no. 9) had had pulmonary tuberculosis 15 years before and the other (no. 20) had had cervical lymphadenopathy and tuberculoma of the brain one year before the onset of chronic renal failure.

The clinical features of all cases are summarized in Table 2.

Cultures

Cultures for AFB were obtained from sputum, pleural fluid, ascitic fluid, urine and CSF whenever indicated. There were 4 cases with pulmonary involvement; sputum, however, was available only in 3. The sputum was positive for AFB in one patient (no. 15) and negative in the remaining 2 (nos 2 and 9). The pleural fluid was positive for AFB culture in only 2 of the 10 cases. Ascitic fluid cultures in the ascites cases were repeatedly negative in both. One of the cases with ascites (no. 6) showed tubercles on the peritoneum, liver and spleen. Cultures of urine, CSF, and bone abscess were done in one case each, and the first 2 were negative.

Histology

The peripheral lymph nodes were available for biopsy in 6 patients and showed evidence of tuberculosis in all cases. The pleural biopsy was compatible with tubercular granuloma in 2 of the 5 cases where it was done. Liver biopsy was done for evidence of tuberculosis in 2 cases with hepatomegaly and ascites; it was negative in both. Post-mortem examination of case no. 1, who had shown tubercular cervical lymphadenopathy in life, revealed histological evidence of tuberculosis of tracheobronchial and hilar lymph nodes.

Diagnosis

The diagnosis of tuberculosis was considered definite if there was positive culture for *Mycobacterium tuberculosis* or a classical histological picture of tubercular granuloma on histology specimens. Thirteen of 20 patients fulfilled such criteria for 'definite diagnosis'. In the remaining 7 cases the diagnosis of tuberculosis was considered 'probable'. There was unequivocal clinical improvement after a therapeutic trial with antituber-

cular drugs despite the absence of bacteriological or histological proof in these 7 cases. Table 3 shows the diagnostic yield of tuberculosis by various methods. Five patients subsequently underwent renal transplantation after initial treatment with antitubercular drugs for periods varying from 3 to 5.5 months. One patient died one week after renal transplantation because of acute rejection, and tuberculosis of the tracheo-bronchial and hilar lymph nodes was found at post-mortem.

Antitubercular therapy

All patients received a combination of 2 anti-tubercular drugs, isoniazid 200 mg/day and rifampicin 10 mg/kg body weight per day. Ethambutol was used in addition in some of the cases where tubercular disease was more widespread and more acute. Its dose had to be modified because of renal failure, the usual dose employed was 7.5 mg/kg body weight per day. The antitubercular drugs were given in a single dose in the evening. On days of dialysis, the drugs were given at the end of dialysis. The patients awaiting renal transplantation were given a minimum of 3 months of antitubercular treatment before surgery, some had to be treated for longer periods to achieve control of active disease. The antitubercular treatment was continued for a minimum period of 2 years.

Mortality

Twelve out of 20 patients died during the period of observation. Death was due to tuberculosis in only 2 cases. Six patients died from the consequences of renal failure or hypertension; in 4 of these, dialysis treatment was irregular and inadequate owing to financial limitations. One patient died from extensive gastrointestinal bleeding, one from fulminant chest infection and deaths of 2 transplant recipients were due to rejection. Another 3 transplant recipients in this series are doing well and follow-up after surgery in these 3 cases has been 27 months, 15 months and 3 months to date (March 1981). Five patients are doing well on MHD.

Discussion

Tuberculosis is a serious health problem in India. The incidence of tuberculosis in children and adults in India has been reported to be about 1% (National Tuberculosis Institute, 1974) and 1.31% in a recent survey in Delhi (Goyal, Mathur and Pamra, 1978). Tuberculosis was found in 13.3% of the present MHD patients. It is obvious that patients with chronic renal failure on MHD run a very high risk of developing tuberculosis with an incidence varying from 6 to 16 times that of the general population as has been reported from many countries (Papadimitriou, Memmos and Metaxas, 1979; Amedia

TABLE 1. Tuberculosis (TB) in maintenance haemodialysis patients (MHD)—salient clinical observations and results of investigations

Age, sex (years, M or F)	Diagnosis	Before onset of TB		Diagnosis of TB				Special remarks and outcome	
		Duration of CRF (months)	Duration of MHD (months)	Clinical	Radiology	Culture	Histology		Therapeutic response
1*	CGN	11	1	Fever L	neg.	O	L pos.	pos.	Renal transplant after 5 months of treatment for TB. Died—1 week post-transplant. TB-L at post-mortem
2**	CGN	4	1	Fever/PUO, cough	Chest—middle lobe infiltrate	neg. sputum	O	pos.	Died—CRF
3**	CGN	3	0.25	Fever/PUO	Chest— hilar-L	O	O	pos.	Died—TB
4**	Diabetic, nephropathy	2	At onset	Pleural effusion	Pleural effusion	neg. pleural fluid	Pleura neg.	pos.	Died—CRF
5*	CGN	27	3	Pleural effusion	Pleural effusion	neg. pleural fluid	O	pos.	Died—gastrointestinal bleeding
6*	CGN	12	9	Fever, pleural effusion, ascites, hepatomegaly, anorexia	Pleural effusion	neg. pleural ascitic fluids urine	Mesentery spleen liver pos.	pos.	Renal transplant after 5.5 months of treat- ment for TB. Died— graft rejection 5 months post-transplant
7*	CGN	8	4	L	neg.	O	L pos.	pos.	Died—CRF, hyper- tension
8*	CGN	30	5	Pleural effusion	Pleural effusion	pos. pleural fluid	O	pos.	Died—CRF
9	Renal stones CPN	4	1.5	Fever, pleural effusion	Chest—old TB, pleural effusion	neg. pleural fluid, neg. sputum	Pleura pos.	pos.	Died—fulminant chest infection
10*	CGN	24	At onset	Fever, weakness, pleural effusion L	Pleural effusion	LN pos.	LN pos.	pos.	Died—TB
11**	CGN	24	1	Fever, anorexia, ascites, hepatomegaly	neg.	neg. ascitic fluid	Liver neg.	pos.	Renal transplant after 5 months of treatment of TB, doing well

12*	45F	Gout CPN	6	1	Fever L	neg.	O	LN pos.	Doing well on MHD for 2 years
13*	48M	Renal stones CPN	9	4-5	Fever, bony swelling	Skeletal changes	pos. bone abscess	O	Died—CRF
14*	40F	CGN	3	0-75	Fever L	neg.	O	LN pos.	Renal transplant after 3 months of treatment for TB, doing well
15*	30M	CGN	3	1-5	Fever, pleural effusion	Chest suggestive of TB	pos. sputum	Pleura neg.	Doing well on MHD
16*	38M	CGN	12	3-5	Fever, pleural effusion	Pleural effusion	neg. pleural fluid	Pleura pos.	Died—CRF, hyper- tension
17*	42M	CGN	6	1	Fever L	neg.	O	LN pos.	Renal transplant 5 months after treatment for TB, doing well
18**	32F	CPN	20	2	Pleural effusion	Pleural effusion	neg. pleural fluid	O	pos. Doing well on MHD
19**	37M	CGN	6	At onset	Fever, pleural effusion	Pleural effusion	neg. pleural fluid	Pleura neg.	Doing well on MHD
20**	24M	CGN	2	1	Fever-PUO, weight loss	neg.	O	O	pos. Doing well on MHD

PUO = pyrexia of unknown origin; L = lymphadenopathy; CPN = chronic pyelonephritis; CGN = chronic glomerulonephritis; * diagnosis definite; ** diagnosis probable; O = not done; neg. = negative; pos. = positive; CRF = chronic renal failure.

TABLE 2. Tuberculosis (TB) in maintenance haemodialysis patients—clinical features

Clinical features (no. of cases)	Details of clinical features	Other associated clinical features	Special remarks
Fever (15)	Fever irregular Occasionally very high	Pleural effusion (6) Lymphadenopathy (4) Pulmonary abnormalities (2)	PUO (3), therapeutic trial pos. in all 3
Pleural effusion (10)	Exudative effusion Unilateral (9) Bilateral (1)	Fever (6) Lymphadenopathy* (1) Military TB* (1)	Pleural fluid cultures pos. (2) Pleural biopsy pos. (2) Sputum culture pos. (1) Tubercles on mesentery (1) Lymph-node biopsy pos. (1) Therapeutic trial pos. (3)
Lymphadenopathy (6)	Cervical (5) Axillary (1)	Fever (4) Pleural effusion (1)	Lymph node biopsy pos. (6)
Pulmonary abnormalities (4)	Typical (2) Atypical (2)	PUO (2 initially) Pleural effusion (1)	Sputum culture pos. (1) Therapeutic trial pos. (2) Reactivation of old TB (1)
Ascites and hepatomegaly (2)	Exudative ascites	Miliary tuberculosis (1) Tubercles on mesentery on pre-transplant laparotomy	Therapeutic trial pos. (1)
Other features (4)	Marked anorexia (2) Abnormal weight loss (1) Bony swelling (1)	Both patients with anorexia had hepatomegaly and ascites	Bone abscess culture pos. (1)

*Biopsy/culture positive for tuberculosis; **Pleural biopsy could be done in 5 cases only; PUO = pyrexia of unknown origin; neg. = negative; pos. = positive.

TABLE 3. Tuberculosis in maintenance haemodialysis patients. Basis for diagnosis of tuberculosis

Method	Diagnostic yield with number of cases
Histology	Lymph node* (6) Pleura (2) Mesentery (1)
Bacteriology (culture positive)	Pleural fluid (2) Lymph node* (1) Bone abscess (1) Sputum (1)
Therapeutic trial	Response to antitubercular drugs (7)

*In one case lymph node had evidence of tuberculosis both on culture and histology.

and Oettinger, 1977; Druke *et al.*, 1978; Lundin *et al.*, 1979; Sasaki *et al.*, 1979). The variable incidence of tuberculosis in different countries and communities can be ascribed to difference in environmental factors, availability of diagnostic and treatment facilities, acceptability of available facilities by the population and efficiency of treatment programmes and policies. Tuberculosis was evident in 11 among the 20 cases in this series either at the onset of dialysis treatment (3 cases) or within the first month of dialysis treatment (8 cases). Considering the high incidence of tuberculosis in the general population in India, it seems likely that environmental factors must have contributed to the high incidence of tuberculosis in the present MHD patients in addition to the role played by the uraemic state.

The existence of tuberculosis in chronic renal failure may not always be easy to diagnose. The unusual presentations and atypical features continue to baffle the clinicians. Proudfoot *et al.* (1969) have drawn attention to the cryptic form of miliary tuberculosis in adults. This type of tuberculosis does not present the usual clinical and radiological features of miliary tuberculosis and is missed in life quite frequently. Tuberculosis has undergone a considerable change in its clinical presentation over the last 25 years from a comparatively acute and extensive disease among the young to more chronic and less extensive disease among the elderly (Nagpal 1978).

The pattern of tuberculosis seen by the present authors was somewhat different from that reported in the literature. The most important clinical

presentations of disease in the present series were fever, pleural effusion and lymphadenopathy. Hepatomegaly which was an important finding in the series of Lundin *et al.* (1979) and bone tuberculosis which was frequently found by Papadimitriou *et al.* (1979) seen infrequently by the present authors. Pulmonary abnormalities were found in only 4 cases in this study. The incidence of miliary tuberculosis was low in contrast to that of Sasaki *et al.* (1979). Two of the present patients had a past history of tuberculosis and it is likely that reactivation of the disease occurred in these after the onset of chronic renal failure.

Pyrexia in patients with chronic renal failure may sometimes pose a diagnostic challenge. The investigations for various recognized forms of infections may prove to be negative. Pyrexia of unknown origin (PUO), however, can be a major form of presentation in the cryptic form of tuberculosis (Proudfoot *et al.*, 1969): 3 cases in that study presented as PUO; Amedia and Oettinger (1977) and Druke *et al.* (1978) found PUO to be an important presentation of tuberculosis.

Pleural effusion in uraemics may arise as a result of circulatory congestion, uraemic pleuritis or nephrotic syndrome. Tubercular pleural effusion can, however, usually be distinguished from such pleural effusion by gross, microscopic, culture and chemical examination of pleural fluid. The clinical manifestations of tuberculosis in other organs and sites may be found in some cases. Pleural fluid AFB smear and culture was found to be positive in 30–70% and 10–70% of cases (Gryzbowski, 1968). Pleural biopsy may confirm the diagnosis in some of the patients as happened in 2 of the present cases.

Ascites was seen in 2 of the present cases but can occur in patients with renal failure without underlying infection (Cinque and Letteri, 1973). The protein content of ascitic fluid in such cases is usually less than 3 g/dl. The ascitic fluid is usually acellular or hypocellular and the cell count is rarely above $0.02 \times 10^9/l$. Most patients with idiopathic ascites have a past history of peritoneal dialysis which may have produced chronic peritonitis.

There is no diagnostic problem in uraemic patients with superficial lymphadenopathy. Histopathological proof of tuberculosis is easily obtained in such patients as was the case in 6 patients in this study.

Tuberculosis was the cause of death in only 10% of cases in this study, although overall mortality was high for other reasons. Average mortality due to tuberculosis in MHD patients has been reported to be 11% (Papadimitriou *et al.*, 1979).

The tuberculin skin test is negative in the majority of uraemics with tubercular infection; it was positive in only 5 of 15 patients in the present study. These

observations are similar to those of Druke *et al.* (1978) and Amedia and Oettinger (1977).

There have been differences of opinion regarding the use of antitubercular drugs, their dose and the duration of treatment in the management of tuberculosis in patients with renal failure. A combination of rifampicin and isoniazid is considered safe. Rifampicin is largely excreted in the bile and modification of its dose is not needed in renal failure. The risk of isoniazid therapy is well recognized, it is subject to acetylation in the liver and for slow acetylators a reduction of dose is necessary (Bowersox, 1973). It is good practice to restrict the dose of isoniazid to 200 mg/day in patients with tuberculosis and end-stage renal disease. Ethambutol is excreted *via* the kidneys 80% unchanged. With renal failure its dose should be reduced to 5 mg/kg/day (Maher, 1978). Opinion is divided regarding optimum duration of antitubercular treatment; the chemotherapy, however, must be given for a period of at least 2 years.

Tuberculosis must be considered in clinical settings and geographic areas where there is a high incidence of tuberculosis. If the usual means of evaluation have been exhausted without revealing an aetiology for clinical features which could be tuberculosis in patients of chronic renal failure and the therapy with common antibiotics has failed, a trial of antitubercular chemotherapy is justified. Lundin *et al.* (1979) observed that the diagnosis and treatment of extrapulmonary tuberculosis may be delayed because of difficulty in obtaining positive cultures. This led to death of 2 of their patients in a group of 8 on maintenance haemodialysis having tuberculosis.

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