Reinfection tuberculosis: two cases in the family of a patient with drug-resistant disease

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ABSTRACT A 42-year-old housewife died of drug-resistant pulmonary tuberculosis. Two sons had earlier completed a course of treatment for drug-sensitive disease. Six months after her death both sons developed sputum-positive tuberculosis with a drug resistance pattern identical to that of their mother during her last year of life, and including resistance to drugs which neither son had received. In both cases immunocompetence to tuberculin was shown so that reinfection arose purely as a result of heavy exposure.

Recurrence of active tuberculosis is usually the result of reactivation of apparently healed disease, and the role of exogenous reinfection is thought to be small.^{1,2} We know of only two single case reports in which reinfection tuberculosis is well documented.^{3,4} We therefore wish to report a family in which two brothers developed a recurrence of pulmonary tuberculosis as a result of reinfection by their mother who had progressive, ultimately fatal, drug-resistant disease.

Case reports

CASE 1

A 16-year-old Caucasian youth was admitted to hospital in September 1971 with a nine-month history of productive cough, occasional haemoptysis, weight loss (7 kg), and vague left-sided chest pain. There were crackles in the left lower chest. A chest radiograph showed soft, bilateral, mid-zone shadowing, more pronounced on the left. Heaf test was strongly positive (15 mm of induration); he had not had BCG vaccination.

Sputum smears showed acid-fast bacilli, and cultures of several specimens yielded a growth of *Mycobacterium tuberculosis* fully sensitive to streptomycin, isoniazid, and PAS. He was given streptomycin 0.75 g daily and Pasinah D (PAS 6 g, isoniazid 150 mg) twice daily for three months as an inpatient, and was then discharged on Pasinah D twice daily.

There was progressive clinical and radiographic improvement, and sputum conversion was attained

after four months. Chemotherapy was given for 20 months, although there was some doubt as to whether he took his drugs regularly during the last six months of treatment. He was seen at intervals until May 1977, and there was no clinical or radiographic deterioration.

He presented again in May 1978 with a six-month history of cough and vague ill health. A chest radiograph showed new soft shadowing in the left upper lobe with early cavitation. Sputum was smear-positive, and cultures of several specimens were positive after two weeks, yielding a growth of *M. tuberculosis* with drug sensitivities as shown in the table. These sensitivities were confirmed by the Mycobacterial Reference Laboratory in Cardiff.

Mantoux test (1 TU) was positive (20 mm induration). Serum IgG and IgA were normal while IgM was raised at 3.10 g/l. In vitro evaluation of cellular immunity including lymphocyte transformation to PPD, T and B lymphocyte rosette formation, lymphocyte surface immunofluorescence and inhibition of leucocyte migration by BCG gave normal results.

At the time of writing he is doing well on a regimen of isoniazid, pyrazinamide, prothionamide and cycloserine.

CASE 2

A younger brother (aged 13 yr) of the first patient was seen as a contact in October 1971. A chest radiograph was normal, but Heaf test was positive (grade 4). Chemoprophylaxis with Inapasade (PAS 6 g, isoniazid 150 mg) twice daily was begun, but dosage was halved after one month because of

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Table Sputum status,* drug treatment, and drug sensitivity/resistance†

Case		1971	1972	1973	1974	1975	1976	1977	1978
1	Sputum	++	—	—	—				++
	Sensitivity	SHP							HPZEtTCy
	Resistance								SREC
	Treatment	SHP	HP	HP					
2	Sputum				+	—	—		++
	Sensitivity				SHP				HPZEtTCy
	Resistance								SREC
	Treatment	HP	HP		SHP	SH	SH		
3	Sputum				+	+	+	++	
	Sensitivity				SHP	SPR	<div style="border: 1px solid black; padding: 2px; display: inline-block;"> HPRZEtTCy ↑ ↓ ↓ SH RE C </div>		
	Resistance					HE	<div style="border: 1px solid black; padding: 2px; display: inline-block;"> SH RE C </div>		
	Treatment				SHP →HE	HE →SH	CR	ZPrCy	

* ++ = Smear and culture positive; + = Smear negative, culture positive; — = Smear and culture negative.

† S = streptomycin

R = rifampicin

Et = ethionamide

T = thiacetazone

H = isoniazid

E = ethambutol

Pr = prothionamide

Cy = cycloserine

P = PAS

Z = pyrazinamide

C = capreomycin

nausea. Treatment was continued for 12 months.

He presented again in March 1974 with new soft shadowing in the right upper lobe on chest radiograph. Several sputum cultures were positive, yielding a growth of *M. tuberculosis* fully sensitive to streptomycin, isoniazid, and PAS. He received streptomycin 0.75 g daily and Pasinah 302 (PAS 6 g, isoniazid 150 mg) twice daily for three months as an inpatient. Sputum conversion was attained in two months. He was then discharged on Pasinah 302 twice daily.

Four months after discharge there was some radiological improvement but he admitted to having stopped taking the treatment one month previously. He refused readmission. Supervised twice-weekly streptomycin 1.0 g and isoniazid 800 mg was given for 18 months until June 1976, with virtually complete radiographic clearing. He was seen at intervals until January 1978 and had no clinical or radiographic deterioration.

He had chest radiography again in July 1978 because of the new disease in his elder brother. There was new soft shadowing at the left apex. He was admitted to hospital. Sputum was smear-positive and cultures of several specimens were positive after three weeks, yielding a growth of *M. tuberculosis* with drug sensitivities as shown in the table. These sensitivities were confirmed by the Mycobacterial Reference Laboratory in Cardiff.

Tuberculin test (1 TU) was positive (40 mm induration). Serum immunoglobulins were normal. In vitro lymphocyte transformation to PPD and inhibition of leucocyte migration by BCG were also normal.

He is now doing well on a regimen of isoniazid, pyrazinamide, prothionamide, and cycloserine.

CASE 3

The mother, aged 37 yr, of these two patients was seen as a contact of the first patient in 1971. She was asymptomatic. A chest radiograph showed scattered localised calcification mainly in the right lower zone. Annual chest films to April 1974 showed no change. In September 1974 she was seen because of weight loss and nausea for one month. A chest radiograph showed new soft shadowing at the right apex, with no change in the previously noted calcification. She was admitted to hospital.

Mantoux test (10 TU) was positive, sputum culture yielded a growth of *M. tuberculosis* fully sensitive to streptomycin, isoniazid, and PAS. She was given streptomycin 0.75 g daily and Pasinah D twice daily. After one month PAS was stopped because of nausea, and ethambutol (15 mg/kg) substituted. After 46 days streptomycin was stopped, and she was discharged on isoniazid and ethambutol (Mynah 200), three tablets daily. Sputum conversion was attained six weeks after starting treatment.

She defaulted several times and was not seen until four months after discharge. At that time, however, her chest radiograph showed considerable improvement and she was culture-negative. In September 1975 she admitted to very irregular drug taking, and the radiograph showed new shadowing in the right apex and left midzone. She refused hospital admission and was started on twice-weekly supervised streptomycin 1.0 g and isoniazid 700 mg. Sputum at this time was positive on culture with drug sensitivities as shown in the table. By the time isoniazid resistance was reported she had been on the supervised streptomycin/

isoniazid regimen for 10 weeks. At this point streptomycin resistance was also assumed, and treatment was stopped.

Sputum was recultured in January 1976 (see table) when chest radiograph showed progressive disease and also early cavitation of the right upper lobe. Daily supervised capreomycin 0.75 g and rifampicin 450 mg were started. Over the next six months there was no radiological change, and sputum cultures in April and July 1976 were negative. In October 1976, however, there was radiographic deterioration with a large right apical cavity, and increased shadowing on the right. Sputum was again culture-positive, but drugs were continued until sensitivities were known. These showed resistance to capreomycin and rifampicin (see table), and treatment was stopped in April 1977. From that time she remained chronically smear-positive with these resistant organisms. The sensitivities were confirmed by the Mycobacterial Reference Laboratory in Cardiff, which also reported a mixture of isoniazid-resistant and isoniazid-sensitive organisms. The patient was eventually persuaded to enter hospital in September 1977. A regimen of pyrazinamide, prothionamide, and cycloserine was tried but had to be abandoned because of nausea and epileptiform fits. A right pneumonectomy was, therefore, performed in October 1977. One week later a bronchopleural fistula developed, which was not controlled by thoracoplasty and surgical repair. She went on to develop a discharging thoracotomy wound and bronchopneumonia in the remaining lung, and died six weeks after operation. Histology of the resected lung confirmed fibrocaceous tuberculosis. Necropsy showed only a few calcified tuberculomas and no active disease in the left lung.

Discussion

There has been contention for many years over the possible role of exogenous reinfection in the pathogenesis of tuberculosis in man. On epidemiological grounds, Stead¹ concluded that man was as difficult to reinfect as laboratory animals, that chronic or recurrent pulmonary disease was the result of reactivation of the residuum of the primary infection, and that exogenous reinfection could be discounted as a significant factor. Romeyn² however, reanalysed the data interpreted by Stead and concluded that in environments of high infectivity exogenous reinfection did play a part. He pointed out that reinfection might act either by creating new foci of infection or by reactivating old, "silent" foci, perhaps immunologically.

In the individual case, exogenous reinfection can be proved by showing that the organism responsible for the second (or later) clinical episode of disease is different from that causing the primary infection, and that this difference could not have arisen by modification of the original organism. Thus a difference may be shown either in the pattern of drug sensitivity and resistance or, more recently, in bacteriophage type.

The use of drug resistance as a marker for the tubercle bacillus was suggested by Thomas⁵ who reported several cases with organisms resistant to drugs that the patient had never received, and in some of whom the history of tuberculosis extended to prechemotherapy years, thereby suggesting exogenous reinfection. Lepeuple³ reported a case where the drug sensitivity pattern of organisms isolated from the maxillary sinus was completely different from that of the initial pulmonary disease. Contact with a case of similar sensitivity pattern showing multiple drug resistances was shown, proving exogenous reinfection. Similarly, in the case reported by Raleigh and Wichelhausen⁴ the third episode of clinical tuberculosis yielded organisms with a different drug sensitivity pattern. In this latter case organisms were also of a different phage type, and it was therefore suggested that phage typing might provide another useful marker to help establish reinfection. It has since become clear that recovery of different phage types of tubercle bacilli from the same patient, either concurrently or consecutively, is not rare, but it is by no means certain that this necessarily indicates exogenous reinfection.⁶⁻⁹ Accordingly, while phage type is certainly a stable characteristic,¹⁰ it is less reliable than drug resistance pattern in definitely distinguishing reinfection from reactivation.

In our cases we consider that the time sequence of clinical and radiological events, together with the serial drug sensitivity patterns, established reinfection beyond any reasonable doubt. The mother's bacilli, resistant to isoniazid by 1975, had reverted to a mixture of sensitive and resistant organisms during the last year of her life. The bacilli recovered from the sons in mid-1978 were fully sensitive to isoniazid. This, the only difference in drug resistance pattern between the relapses in the sons and the source of reinfection, their mother, is thought to indicate reversion to isoniazid sensitivity in the absence of the drug. The mother was chronically smear-positive during her last year of life, and both sons were shown to be immunocompetent to tuberculin. Hence reinfection in the sons arose purely as a result of heavy exposure.

These cases support the view expressed by Romeyn² that under conditions of high environmental infectivity some relapses in tuberculosis are caused by exogenous reinfection.

References

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European Conference on Sarcoidosis

A European Conference on Sarcoidosis will be held in Novi Sad, Yugoslavia, from 22 to 24 May 1980. Further details may be obtained from Professor Stevan Goldman, Institut za Plućne Bolesti i Tuberkulozu, Sremska Kamenica, 21204 Sremska Kamenica, Yugoslavia, or Dr D Geraint James, Royal Northern Hospital, Holloway Road, London N7 6LD.