CASE REPORT

A Case of Primary Drug Resistant Tuberculosis

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Summary

A young man presented with primary multi-drug resistant tuberculosis. The institution of second-line regimes with insufficient efficacy due to clinical inexperience, unreliable sensitivity reports and the inavailability of second-line drugs led to the development of an organism that was resistant to ten anti-tuberculous drugs. Accurate sensitivity testing done in an overseas laboratory enabled the institution of a six-drug regimen that has resulted in clinical cure.

Key Words: Tuberculosis, Multi-drug resistance, Mycobacterial sensitivity testing, *M vaccae* immunotherapy

Introduction

Multi-drug resistant tuberculosis (MDR-TB), which is causing increasing concern in many parts of the world, is fortunately uncommon in Malaysia. MDR-TB, defined as resistance to both isoniazid (INH) and rifampicin (R) was only documented in 298 cases of tuberculosis over a five-year period. This works out to about 0.9% of all sputum positive cases diagnosed in Malaysia over that same period. However when MDR TB does occur, it causes significant morbidity and even mortality. Here we present a case of MDR-TB that is particularly useful in highlighting Malaysian MDR-TB management issues.

Case Report

A 24-year-old male was first diagnosed as having sputum positive pulmonary tuberculosis by the National Tuberculosis Centre (NTBC) in November 1992. He was started on standard TB treatment with streptomycin (SM), INH, R and pyrazinamide (PZA) and was discharged to Ipoh Chest Clinic for the rest of his treatment. He was compliant to therapy but failed to sputum convert at two months. The sputum acid-fast bacillus (AFB) culture that had been sent prior to starting treatment revealed resistance to both INH and R. He was however continued on first line maintenance therapy with SM, H and R biweekly until September 1993 when ciprofloxacin (Cipro) 250mg bd was added to his regime. He remained sputum positive and a repeat AFB culture sent in August 1993 was reported as resistant to SM and INH, but sensitive to R, ethambutol (Etb), kanamycin (K) and cycloserine (Cy). Sensitivity screening was not done for the other second line drugs. See Table I.

In January 1994 he was referred back to the NTBC where his regime was changed to enviomycin, clofazimine, Etb and R. He became sputum negative in March 1994 and remained so until June 1994 when he turned strongly sputum AFB positive again. He was reviewed at the NTBC and then put on INH, PZA, enviomycin, coflazimine and Cipro but remained sputum positive. In August 1994 he was switched to Cipro, clofazimine, R, K and Augmentin, but continued being strongly sputum positive. Sputum AFB sensitivity testing sent in January and in June 1994 documented resistance to SM, INH, R and Etb. See Table I.

The patient's condition deteriorated sharply in December 1994 and he was admitted to Ipoh Hospital with fever, hemoptysis, chest pains and dyspnoea. In January 1995 he was started on seven anti-TB medicines comprising ofloxacin, amikacin, azithromycin, INH, cycloserine and ethionamide. Irradiation-killed

Table I
AFB Sensitivity Testing Results

Date	SM	INH	R	ETB	K	CY
Nov 92	S	R	R	-	-	-
May 93	R	R	S	S	-	-
Aug 93	R	R	S	S	S	S
Jan 94	R	R	R	R	-	-
Jun 94	R	R	R	R	S	S
Oct 94	R	R	R	-	-	-
Apr 96	R	R	S	S	R	-

Key: R=resistant; S=sensitive; "-"= sensitivity testing not done
Notes:

1. *Dates refer to the date of specimen collection*
2. *Abbreviations for the drug names are the same as used in the text*

Mycobacterium vaccae was obtained from a research unit in England through a private Chest Physician in Kuala Lumpur, and 0.1ml of this vaccine was given intradermally in January 1995 and repeated in March and June 1995. The patient became sputum negative in February 1995 and his general condition improved. He was referred to a cardiothoracic surgeon for possible left upper lobe resection, but the surgeon declined.

Despite remaining on the regime started in January 1995, he relapsed in October 1995 with high sputum positivity. Another set of drugs comprising augmentin, clarythromycin, K, Cotrimoxazole, R, Etb and PZA was started. Despite this the patient remained heavily sputum positive though fairly asymptomatic. In May 1996 he left for Sabah to work with his uncle. He returned to Ipoh in November 1996 still on the regime started in October 1995, and still heavily sputum positive. Chest X-rays revealed that new cavitating lesions had developed in the right upper and mid zones.

With the help of his family doctor, a plea for assistance in sensitivity testing against second line drugs was put out on the Internet. The Mycobacterial Laboratory at the Fairfield Hospital in Melbourne, Australia was among those who responded. Sensitivity testing there revealed that his mycobacteria was resistant to INH, R, Etb, PZA, SM, K, amikacin, capreomycin, ethionamide and clarithromycin; but sensitive to rifabutin, cycloserine, clofazimine and thioacetone, with intermediate sensitivity to Cipro and ofloxacin. He was started on rifabutin, para-aminosalicylic acid, ofloxacin, augmentin, clofazimine and Cy in April 1997, and continued on these up till July 1999. His symptoms abated and serial Chest radiographs have documented resolution albeit against a background of extensive lung damage, and he became sputum negative in June 1997 and has remained so up till now (October 1999).

Discussion

This case of MDR-TB brings up numerous issues pertinent to the management of MDR-TB. This patient had no history of previous treatment for tuberculosis. Nevertheless, his first culture specimens taken prior to the commencement of treatment revealed resistance to both INH and R. He is therefore a case of primary MDR-TB probably with resistance to Etb as well, as Etb resistance was also documented prior to the commencement of Etb therapy.

Despite having primary MDR-TB, a more informed initial treatment strategy could have rapidly rendered him non-infectious and prevented the extensive lung damage that he has sustained. In September 1993 his failing regime was supplemented with the addition of Cipro alone, violating a basic tenet of MDR-TB management: *"Never add a single drug to a failing regimen"*. When MDR TB is diagnosed, a regime that includes at least 3 drugs to which the mycobacterial strain is sensitive to should be prescribed[1].

In January 1994, this patient was put on a 4 drug regimen including 2 drugs -R and Etb - to which the infecting strain was already resistant to. The decision to put this patient on this regime was no doubt based on the sensitivity testing results on specimens sent in May and August 1993. (See Table I). However isolates from the same patient collected prior to May 1993 and in January 1994 were found to be resistant to R, with the latter specimen being resistant to Etb as well. This underlines the crucial importance of accurate sensitivity data, as regimes that do not contain a minimum of 3 effective drugs prescribed at adequate doses, will only result in the creation of a strain that is resistant to an even larger number of agents.

A major problem that clinicians dealing with MDR-TB face is that, until very recently, there was only one laboratory in Malaysia that did sensitivity testing for mycobacteriae, and this laboratory was not able to provide sensitivity screening against most of the second line tuberculosis drugs. The inavailability of sensitivity data constrains the physician to put the MDR patient on 6 or more anti-TB drugs to ascertain that at least 3 effective drugs are included in the regimen. This strategy increases treatment costs and toxicity, and reduces the probability of success. The development of accurate sensitivity testing capability for a wider range of anti TB drugs would definitely increase the chances of cure in MDR-TB and reduce the probability of transmission of drug resistant TB. The setting up of a private laboratory in Klang which offers sensitivity testing for a number of second line drugs will certainly help place the treatment of MDR-TB on a more objective footing.

This patient is probably the first patient in Malaysia to receive *M vaccae* immunotherapy. The role of this in downgrading his tuberculous activity from February to September 1995 is difficult to assess as he was also started on a new set of anti TB drugs at the same time. However despite receiving both these treatment modalities, he relapsed in October 1995. It is quite clear that *M vaccae* immunotherapy did not induce any long-lasting remission of disease in this particular patient. Despite very optimistic reports[2] of *M vaccae* in the treatment of MDR-TB in Africa, the role of immunotherapy in Malaysian MDR-TB patients remains unclear.

The public health aspects of this particular case are worrying. Roullin *et al*[3] have estimated that each sputum positive case of TB will infect 5 to 10 people every year, and 10% of those infected will develop clinical disease. For the 66-month period since initial diagnosis, this patient was heavily sputum positive for 44 months! It is certainly quite possible that several individuals will develop tuberculous disease with his strain of the bacilli.

Another dilemma that the clinician faces when handling sputum positive cases of MDR-TB has been engendered by the closing of the chest wards in many of our hospitals. Ipoh Hospital, for example, no longer has a chest ward. All chest cases are admitted to the general medical wards where there are no facilities for isolation even for sputum positive MDR cases.

Conclusion

MDR-TB, though not rampant, nevertheless does exist in Malaysia, and poses a significant threat to public health especially when improperly managed. The management of MDR-TB should be carefully considered so as to avoid developing resistance to more anti TB drugs and to rapidly render the index case non-infectious. The development of accurate sensitivity testing against more TB drugs will improve the treatment of MDR-TB in Malaysia. All cases with documented resistance to any of the standard anti-TB drugs should be referred to a Chest Physician with experience in the management of MDR-TB.

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