Multidrug-resistant tuberculosis

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ABSTRACT

The prevalence of multidrug resistant Mycobacterium tuberculosis is rising worldwide and carries a high fatality rate. We report here two cases of multidrug resistant Mycobacterium tuberculosis infections, which were successfully treated in our hospital. The problems of antimicrobial therapy of this infection are briefly highlighted and the attention of physicians is drawn to the ominous implications for community health.

Keywords: Multidrug resistant mycobacterium tuberculosis, treatment, control.


The recent increase in the incidence of Mycobacterium tuberculosis (MTB) has been reported worldwide, but most commonly in developing countries, where the fatality rate has been highest.1-3 However, there has been a concurrent increase in the prevalence of MTB resistant to multiple first-line antituberculosis agents. Multidrug resistant (MDR) MTB have been defined as strains resistant to isoniazid and rifampicin, with or without resistance to other drugs.4 MDR have been reported in most countries, especially among patients with human immunodeficiency virus (HIV) infections and acquired immunodeficiency syndrome (AIDS).5

Drug resistant MTB may arise from pitfalls in the management. These include monotherapy, poor patient's compliance, failure to supervise treatment and to identify non-compliance and treatment failures, in addition to primary resistance.6 Other risk factors are the history of previous antituberculosis therapy, history of contact with a known case, history of hospitalisation, institutionalisation or incarceration at a facility with a known MDR TB outbreak, and recent immigrants from Asia, Africa, and Central and South America to developed countries.7 The extent of MDR TB worldwide is not known and has been difficult to estimate.8 An ongoing initiative by the World Health Organization is in progress to produce a realistic assessment of resistance of Mycobacterium tuberculosis in many developing countries.6 The prevalence of MDR TB in the Kingdom is largely unknown, except for a few studies from some Institutions reported in the literature. There are some risk factors which may contribute to the development of MDR TB in the Kingdom such as: availability of antituberculosis drugs over the counter without prescription; and the use of some antituberculosis drugs for the treatment of some conditions such as brucellosis and leprosy.9 In addition, the presence of large numbers of immigrant workers in the Kingdom, from countries where TB is highly endemic.10 However their contribution to the prevalence of MDR TB is largely unknown, but can be assumed.

Of great concern has been the recent reports of the transmission of MDR not only to household contacts but also to HIV-negative health care workers and institutional personnel.11,12,13 Consequently, our ability to control the present level of the disease and the occurrence of future cases will be compromised. However, in clinical practice the problem encountered by the chest physician is to decide upon a regimen for an individual patient prior to the

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Table 1 - Prevalence of MDR in previous studies in Saudi Arabia.

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>% of all resistant</th>
<th>% of INH resistant</th>
<th>% of RIF resistant</th>
<th>% of MDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schiott et al, 1985* (Gizan area)</td>
<td>108</td>
<td>43.7</td>
<td>40.8</td>
<td>20.4</td>
<td>19.4</td>
</tr>
<tr>
<td>Al-Orainy et al, 1989 (Riyadh area)</td>
<td>432</td>
<td>21.3</td>
<td>19.4</td>
<td>9.7</td>
<td>8.8</td>
</tr>
<tr>
<td>Jarallah et al, 1992 (Taif area)</td>
<td>678</td>
<td>22.6</td>
<td>6.5</td>
<td>15</td>
<td>3.8</td>
</tr>
<tr>
<td>Ellis et al, 1996 (Riyadh area)</td>
<td>289</td>
<td>8.7</td>
<td>7.2</td>
<td>3.1</td>
<td>2.8</td>
</tr>
</tbody>
</table>

*In this study, 103 isolates of MTB from 108 subjects were studied and the given resistant percentage are referred to the total number of isolates.

INH = Isoniazide
RIF = Rifampicin
MDR = Multi drug resistant
MTB = Mycobacterium tuberculosis

The availability of susceptibility results or treatment records of patients suspected of acquiring primary MDR MTB infection. Several approaches have been proposed for the treatment of patients with MDR depending on the pattern of drug resistance, but no single regimen has been universally acceptable for all cases. Moreover, regimens for the treatment of MDR TB infections usually involve agents known to be toxic or difficult to tolerate.

We report here two cases of MDR MTB diagnosed and treated in our hospital and both of whom made remarkable recovery in a relatively short time.

Case reports

**Patient 1.** This is a 42-year-old female patient who was diagnosed as active pulmonary tuberculosis on several occasions over the last 10 years and was treated on each occasion with anti-tuberculosis medication in different hospitals, but was notoriously non-compliant with her medication. She stopped her last course of anti-tuberculosis medication two months before presenting herself at the King Khalid National Guard Hospital in Jeddah. She gave a history of fever, night sweating, haemoptysis, and shortness of breath for the preceding 3 months.

On physical examination, she was pale and jaundiced, with decreased air entry on the right side, with fine crepitations. Cardiovascular examinations was within normal limits. There was no coughing or lymphadenopathy. Her liver was palpable with a liver span of 18cm.

**Investigations.** Urea and electrolyte estimations were normal. Liver function tests showed AST-168, Alkaline phosphatase 148, ALT 173, but normal bilirubin, and albumin. Hepatitis screen showed negative hepatitis B surface antigen and hepatitis B surface antibody, but hepatitis C virus antibody was equivocal and Hepatitis C Polymerase Chain Reaction (PCR) was positive. The patient's chest X-ray showed multiple ring shadows on the right mid- and lower zones suggestive of bronchiectasis (Figure 1). Sputum smears for acid-fast bacilli were negative on three consecutive samples. A Mycobacterium species was isolated on the 25th April 1997, from one out of the three samples and was sent to Biosciencia Laboratory in Germany for identification and sensitivity testing. Meanwhile, Mycobacterium tuberculosis DNA was detected by PCR in the culture of the isolate performed in our laboratory.

The patient was started on 1st line anti-tuberculosis therapy on 4th May 1997, which consisted of isoniazid, rifampicin, pyrazinamide and ethambutol at standard dosages based on the weight of the patient. Direct observation therapy was not performed since patient lives in the south where medical facilities are limited.

Identification and sensitivity report was back in June 1997, which confirmed the PCR result of Mycobacterium tuberculosis, resistant to all first-line anti-tuberculosis agents except pyrazinamide. Based on the sensitivity report, the patient was switched to second line anti-tuberculosis agents on June 22nd, 1997, which consisted of ciprofloxacin 500mg bid, clarithromycin 250mg bid, and pyrazinamide 2.0g daily.

The second set of three consecutive sputum samples was collected and sent for Ziehl-Neelsen (ZN) stain and culture on 18th, 19th and 20th, May 1997. All were negative for acid-fast bacilli by the ZN stain. However, culture was positive for...

Figure 1 - Case 1. Chest X-ray showing multiple ring shadows on the right mid and lower zones suggestive of bronchiectasis.

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Mycobacterium species in one of the samples. MTB DNA was not detected this time by PCR in the culture of the isolate in our Laboratory. Identification of the Mycobacterium species was available by August 1997 which revealed Mycobacterium simiae, an organism rarely pathogenic in human lung. Sputum samples were re-examined on 20th and 21st, September. All were negative by ZN staining and routine culture on LJ medium.

Clinically, the patient responded remarkably to treatment, when reviewed in September 1997, i.e., her cough almost disappeared, no more sputum or haemoptysis, her appetite improved, and she gained 7 kilograms in weight compared with the beginning of the treatment in our hospital with the first-line anti-tuberculosis agents. Her liver enzymes improved initially and she generally felt and looked well. At the time of writing, she has had 8 weeks of first line agents and 5 months of second line anti-tuberculosis agents. She is being on anti-tuberculosis therapy and follow up at our out patient clinic.

Patient 2. This is a 29-year-old lady who presented with 2 months history of chronic productive cough, associated with yellow sputum and occasional dyspnoea. There was no history of fever, but considerable night sweats and weight loss.

Investigations. Routine investigations showed that her full blood count, liver function tests, urea and electrolytes were all within normal limits. ESR was 72. Her chest X-ray showed opacities in the middle lobe and possibly in the lingula. High resolution CT scan showed right middle lobe bronchiectasis confined mostly to the medial segment with only a few scattered thick walled bronchi in the apico-posterior segment of the lower upper lobe and apical segment of the right lower lobe (Figure 2).

Three consecutive sputum samples examined by ZN stain were negative for acid fast bacilli. Sputum culture performed on 13th May 1996 was positive for Mycobacterium species after 4 weeks incubation. The isolate was sent to Bioscienza Laboratory in Germany for identification and sensitivity testing. Meanwhile, on 15th July 1996, the patient was started on first-line anti-tuberculosis therapy, i.e., isoniazid 300mg OD, rifampicin 600mg OD, ethambutol 900mg OD, pyrazinamide 500mg TDS. However, by October 1996, Microbiological report from Germany was received which confirmed the identity of the isolate as Mycobacterium tuberculosis, resistant to all first line agents except ethambutol.

The patient was reviewed again at our Outpatient Clinic on October 13th, 1996. Her symptoms were unchanged and was observed to lose weight from 57.5 kilogram in April 1996 down to 54.3 kilogram.

With the given sensitivity of the Mycobacterium tuberculosis, the first line anti-TB agents were stopped (except for ethambutol 900mg OD) and the
patient was started on ciprofloxacin 750gm Q 12 hours, clarithromycin 500mg BID, cyclosporin 250mg Q12 hours. However, due to unavailability of the cyclosporin, it was substituted by augmentin 375mg Q 8 hours.

The patient improved remarkably when reviewed on 8th December 1996, and had no more sweating, the weight had increased to 60 kg, and her productive cough had disappeared. Her ESR had fallen to 26. Repeated sputum smear examination carried out one week after starting second line therapy on 20th October 1996 was negative for acid-fast bacilli on three consecutive days. Cultures of two of the samples were negative for Mycobacteria. However, the third sample was positive on culture for Mycobacterium species. Two months later the isolate was reported to be Mycobacterium avium intracellulare. Three Sputum samples collected in September 1997 for examination were all negative by ZN for acid-fast bacilli and culture.

Altogether she has had 12 weeks of treatment with first line agents and 13 months on second line agents.

**Discussion.** In the last two decades the shift of tuberculosis management to outpatient care has encouraged reduced compliance and erratic drug ingestion leading to rising rates of treatment failure, relapse and acquired drug resistance. The Directly Observed Treatment Short Course Chemotherapy (DOTS) program ensures adherence to medication and hence reduces the frequency of primary drug resistant, acquired drug resistant, and relapse. It requires that a health-care provider will observe the patient while he ingests anti-MTB drugs, and it can be conducted with regimens given once a day, twice a week, or three times a week. DOTS strategy depends on the implementation of a policy package with 5 component: (1) Government commitment; (2) Case detection by microscopy through predominantly passive case finding in existing primary health care services; (3) DOTS: a standardised short course chemotherapy regime administered under close control, given free of charge, for new and re-treatment cases with smear positive; (4) Regular drug supply of all essential anti-tuberculosis drugs; (5) Establishment and maintenance of monitoring mechanisms of case detection and treatment outcomes, based on recording individual patient information in district registers and a system of quarterly reporting.

In all countries that have adopted the DOTS strategy, under programme conditions the cure rates (and the success rates) of TB smear positive cases are already over 80%. From recent reports on MDR, the most important indicator of the presence of MDR is the history of treatment for tuberculosis. Inadequate therapy was reported to be the most common means by which MDR are acquired and patients who have previously undergone therapy should be presumed to have MDR until proved otherwise. In addition, patients with cavitary lesions have a high frequency of resistance, presumably because they harbour greater numbers of Mycobacteria.

Our first case was a non-compliant patient with a 10 years history of active pulmonary tuberculosis who had received several courses of anti-tuberculosis therapy prior to presenting at our hospital with fever, night sweats and weight loss with chronic cough. She was proved by culture to have MDR pulmonary tuberculosis with cavitary lesions on radiography. This notwithstanding, she responded well to first line of anti-tuberculosis therapy for six weeks, followed by four months of treatment with second-line agents. The isolation of M. simiae was regarded as a colonisation of an existing MTB lesion.

The second case was started on first line anti-tuberculosis therapy based on a clinical diagnosis and radiological evidence of bronchiectasis, supported by positive ZN sputum smear. The diagnosis MDR pulmonary tuberculosis was confirmed by culture. Sputum culture became negative after 3 months of therapy with first-line agents, even though the isolate was an MDR MTB. However, subsequent therapy was carried out with second-line agents with remarkable improvement in the patient's condition. The isolation of Mycobacterium avium intracellulare was regarded as a colonisation, since the patient was not immunocompromised and does not fulfil the American Thoracic Society of diagnostic Criteria for Non-Tuberculosis Mycobacteria infection.

Thus, in both cases the sputa become negative with first line agents despite MDR isolate; this raises the possibility that drugs to which the organism is individually resistant may yet be effective when used in combination with other agents. This clinical observation may be due to the synergistic effect of drug combinations. However, this needs to be confirmed in vitro by the demonstration of synergism in the laboratory by testing susceptibility with two and three drug combinations. One may conclude that although in vitro sensitivity may show MDR-MTB, it is important to observe clinical and microbiological response before embarking on discontinuing any drug.

The prevalence of MDR in the Kingdom is largely unknown, except for a few studies confined to the large centres. However, it varies from 2.8% to 19.4% as illustrated in Table 1. This great variability in MDR frequency may reflect differences in patient populations studied and in Microbiology practices. Most of these studies were mainly epidemiological, with very little reference to treatment and control of MDR TB. In many hospitals drug susceptibility testing facility of MTB is not available and where there is, the results are not usually available for 2 to 4
months. Consequently, in our community even though the prevalence of MDR MTB is low, it is prudent to administer the 4-drug regimen of rifampicin, isoniazid, ethambutol and pyrazinamide to all new patients with MTB and particularly to those patients who have a previous history of MTB infection and/or treatment, while awaiting the results of microbiological tests, in order to ensure that mutants that are resistant to a single drug do not emerge.\textsuperscript{4,9}

It has been suggested that a tuberculosis retreatment regimen should always include at least four but possibly as many as six or seven drugs, since the four-drug regimen has been reported inadequate in some instances.\textsuperscript{2} The number of drugs will vary according to the extent of the disease, potency of the available agents and the in vitro susceptibility results.\textsuperscript{1,2,18} Regimens of multiple drug, which generally, are poorly tolerated and more toxic than traditional regimens must be administered for 18 to 36 months.\textsuperscript{1,2,18} Some reports suggest that even the best available treatment is often unsuccessful, with only about 65% success rate.\textsuperscript{10} If chemotherapy is not successful, the potential benefits of resectional surgery will need to be considered.

The control of MDR MTB pulmonary infection in any community poses a serious problem, in view of its high mortality, low therapeutic response and ominous implications for the community health.

References

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