

Managing a Case of Extensively Drug-Resistant (XDR) Pulmonary Tuberculosis in Singapore

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Abstract

Introduction: Extensively drug-resistant tuberculosis (XDR-TB) is an emerging global health risk. We present the first case report of XDR-TB in Singapore. **Clinical Picture:** A 41-year-old Indonesian lady with previously treated pulmonary tuberculosis presented with chronic cough. Her sputum was strongly acid-fast bacilli positive and grew *Mycobacterium tuberculosis complex* resistant to first and second-line TB medications. **Treatment:** She received 5 months of intensive multidrug treatment without sputum smear conversion. She then underwent resection of the diseased lung. The total cost incurred amounted to over S\$100,000. **Outcome:** She achieved sputum smear/culture conversion post-surgery, but will require further medical therapy for at least 18 months. **Conclusion:** XDR-TB is poorly responsive to therapy and extremely expensive to manage. Its prevention by strict compliance to therapy is paramount.

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Introduction

Extensively drug-resistant tuberculosis (XDR-TB) is defined as TB which is resistant not only to the 2 best first-line anti-TB medications, rifampicin and isoniazid (known as multidrug-resistant or MDR-TB), but also to at least 1 of 3 injectable second-line agents (amikacin, kanamycin or capreomycin) and to any fluoroquinolone.^{1,2} XDR-TB is extremely difficult to treat, requiring the prolonged use of costly, but less effective and more toxic second and third-line medications. XDR-TB has already been reported in 58 countries and has emerged as a global health threat.³ We report our experience with the first XDR-TB case treated in Singapore since this condition was first defined by the World Health Organization (WHO) in 2006.

Case Report

A 41-year-old Chinese lady from Indonesia arrived in Singapore in January 2010 to seek medical treatment. She presented to the emergency department of a public hospital with chronic cough associated with intermittent fever. She was referred to the hospital's Respiratory Physician who promptly referred her as an outpatient to the Singapore TB

Control Unit (TBCU). She gave a history of pulmonary TB which was diagnosed and treated in Indonesia with 9 months of self-administered therapy in 2003; and an episode of relapse in 2004 for which she received 2 months of medications before defaulting treatment. There was no past history of diabetes mellitus or other chronic medical condition, and she was a life-long non-smoker. She developed worsening cough in 2009, at which time her sputum culture and drug susceptibility testing (DST) in Indonesia grew *Mycobacterium tuberculosis complex* (MTC) resistant to the 4 first-line anti-TB drugs, i.e. streptomycin, isoniazid, rifampicin and ethambutol. She gave a history of having received treatment with kanamycin for 3 months in 2009 (it was unclear if this was given in conjunction with other oral therapies); and with self-administered rifampicin, isoniazid, pyrazinamide and ofloxacin in the 3 months prior to seeking medical consultation in Singapore.

At presentation to our clinic, her sputum was acid-fast bacilli (AFB) smear 4+. Hain Genotype resistance testing detected *Mycobacterium tuberculosis* with mutations in the *rpoB* and *katG* genes, indicating resistance to rifampicin and isoniazid respectively. Her chest X-ray revealed extensive,

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dense opacification in the left upper and mid zones, with cavitation. In addition, there were also scattered opacities in the right upper and mid zones (Fig. 1a). She was HIV negative.

She was hospitalised under air-borne isolation in a negative pressure room. Treatment with an injectable second-line agent (kanamycin), oral second-line drugs [(levofloxacin, cycloserine, ethionamide and para-aminosalicylic acid (PAS)], and oral third-line agents (augmentin and clofazimine) was commenced while awaiting our local DST results. Arrangements were made to procure a supply of capreomycin (which was not available in Singapore) to strengthen her treatment regimen. DST (Nonradiometric MGIT 960 Automated system)⁴ subsequently showed MTC resistant to all first-line drugs (rifampicin, isoniazid, streptomycin, ethambutol and pyrazinamide) as well as to kanamycin, ofloxacin and clofazimine, thus fulfilling the definition of XDR-TB. Her MTC isolate was susceptible to levofloxacin, ethionamide, PAS and capreomycin. Clofazimine and kanamycin were discontinued, and capreomycin added to her remaining therapy.

Despite a treatment regimen of 6 drugs (which included the 4 drugs to which her isolate demonstrated in-vitro susceptibility) administered under inpatient directly-observed therapy (DOT), her sputum smears remained AFB positive (1+ to 2+) at 4 months of treatment. Her sputum cultures at 4 months demonstrated MTC growth at 15 days. The drug sensitivity pattern of MTC isolated at 4th and 5th months of TB treatment was unchanged. Her clinical course was complicated by drug-related side effects and toxicity. She developed a drug hypersensitivity reaction characterised by a fever and raised eosinophil counts requiring prednisolone cover to allow treatment continuation. She also developed

hypothyroidism (a known adverse effect of ethionamide and PAS) with clinical signs of a large goitre, which was treated with L-thyroxine replacement. Furthermore, she expressed suicidal ideation and low mood, which was attributed to reactive depression secondary to her illness, her prolonged isolation and cycloserine.

At 5 months of treatment, her sputum AFB smears finally decreased to “scanty”; sputum culture at this time-point however still demonstrated MTC growth at 15 days (Fig. 2). Radiological improvement was noted (Fig. 1b).

In view of her high initial bacterial load and persistent bacterial excretion despite 5 months of intensive multi-drug treatment, surgery was considered in order to further decrease bacillary burden and to accord her the best chance of a successful treatment outcome. CT thorax revealed disease mainly affecting her left upper lobe (Fig. 3). She underwent a left upper lobe lobectomy and left lower lobe wedge resection. Intra-operatively, the disease affected the entire left upper lobe and extended to a small portion of the apex of left lower lobe.

Postoperatively, she developed delirium secondary to sepsis of which the source was undetermined. However, her condition improved with intravenous antibiotics and antipsychotics. Three consecutive sputum AFB smears and cultures were negative, at 9, 10 and 11 days post-surgery. After the demonstration of three consecutive negative sputum TB cultures, she was allowed out of air-borne isolation, and to return home to Indonesia for continuation of treatment.

Discussion

This case report highlights the immense challenges faced

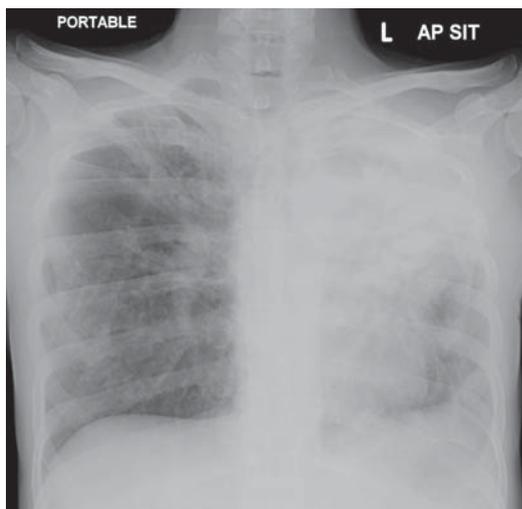
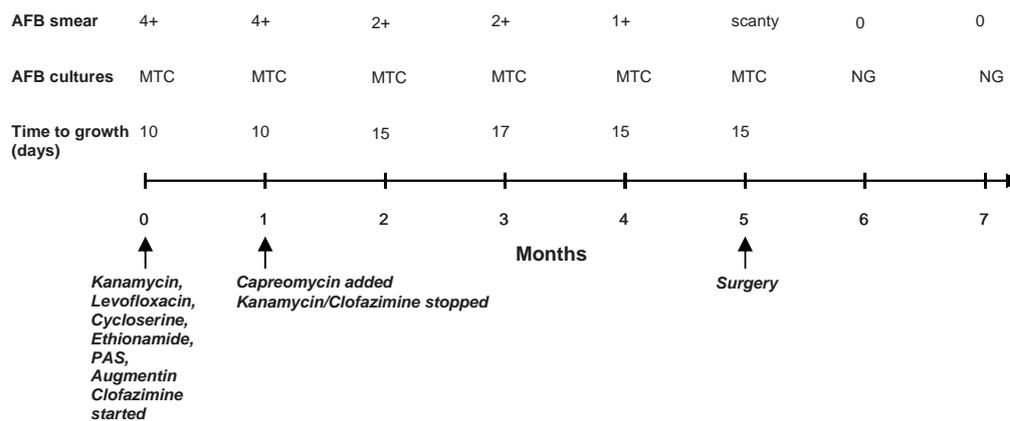


Fig. 1. Plain Chest X ray films (a) (left) on admission, (b) (right) after 5 months.



MTC: *Mycobacterium tuberculosis* complex isolated; NG: No growth
 Fig. 2. Summary of inpatient treatment.

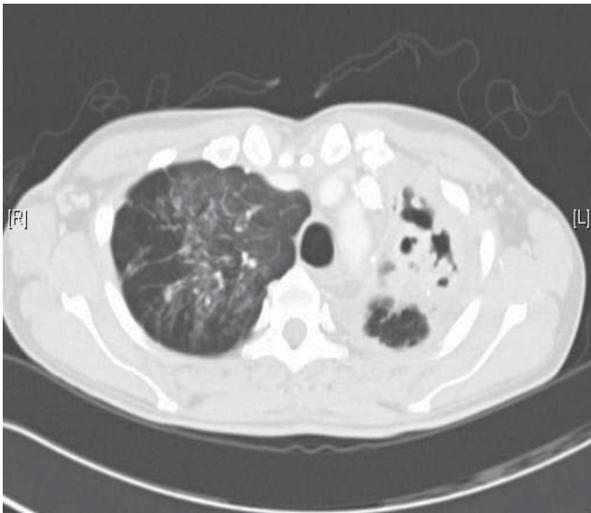


Fig. 3. CT thorax: Destroyed left upper lobe with cavitation.

by the patient, healthcare providers and healthcare system in the management of XDR-TB. At the time of writing, the medical bill for this patient had already exceeded S\$100,000: this was mainly due to the cost of hospitalisation, and the second-line anti-TB drugs.

Management of XDR-TB requires at least 4 to 5 drugs to which the MTC isolate is sensitive or likely to be sensitive. The optimum duration of treatment is not known, but expert recommendation is for treatment to be continued for at least 18 months after culture conversion, including 12 months of an injectable agent.⁵ Most patients would need to be treated for at least 2 years.

The prolonged use of less effective second- and third-line drugs in treating XDR-TB carries increased toxicity risks, some of which can be potentially severe, leading to poor compliance. Precautions can be taken to minimise

this but often, the offending drug cannot be discontinued permanently without compromising therapy. Until new drugs to combat TB become available, responsible use of TB medications in the community remains of prime importance.

The role of surgery in drug-resistant tuberculosis with pulmonary involvement remains controversial. Whilst it has been reported that patients undergoing surgery have improved outcomes,⁶ others have been less optimistic.⁷ However, surgical treatment should be considered for multi or extensively drug resistant tuberculosis particularly when medical treatment is expected to fail and the disease is localised.⁸

It is important for surgery to be timed at the nadir of bacillary load, i.e. at 3 to 5 months of drug treatment. The primary reason is to minimise the risk of stump breakdown with resulting bronchial fistula formation. Additionally, the safety of the operating theatre staff needs to be considered.

XDR-TB emerged as the consequence of poorly functioning public health systems in which use of inadequate treatment regimens, lack of laboratory capacity, interruptions to drug supply and lack of treatment supervision/poor patient adherence have led to the development and amplification of drug resistance.⁹ Our patient originated from Indonesia where MDR TB has been reported in 446 cases among 2608 TB patients in whom DST was performed between 2007 and 2010.¹⁰ Reported treatment outcomes for XDR-TB have been poor, and mortality rates high.¹¹ The global spread of XDR-TB has, worryingly, undermined TB control efforts worldwide, and threatens to divert attention and resources from the management of drug-sensitive TB. It poses a tremendous burden on already underfunded TB programmes in the midst of the current global economic crisis.

Directly Observed Therapy (DOT), i.e. supervision of the patient taking each dose of TB medications, is key to the prevention of the emergence of drug resistance, and

to achieving successful treatment outcome. DOT as the standard of care for TB patients has been a pillar of the Singapore TB Elimination Programme (STEP) for the last 13 years. We believe that DOT, together with real-time treatment surveillance of all TB cases in the country have been vital in maintaining the current low rate of 0.3% MDR TB in the local Singapore population.¹²⁻¹⁴ The best management of MDR- and XDR-TB is its prevention.

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