CASE REPORT

Individualised second line anti-tuberculous therapy for an extensively resistant pulmonary tuberculosis (XDR PTB) in East Malaysia

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SUMMARY

Clinical experience with extensively Drug Resistant tuberculosis (XDR-TB) has not been reported in Malaysia before. We describe the clinical characteristics, risk factors, progress and therapeutic regimen for a healthcare worker with XDR-TB, who had failed therapy for multidrug resistant TB (MDR TB) in our institution. This case illustrates the risk of TB among healthcare workers in high TB-burden settings, the importance of obtaining upfront culture and susceptibility results in all new TB cases, the problem of acquired drug resistance developing during MDR-TB treatment, the challenges associated with XDR-TB treatment regimens, the value of surgical resection in refractory cases, and the major quality of life impact this disease can have on young, economically productive individuals.

CASE REPORT

A 31 year-old healthcare worker presented to our institution in January 2010 with anorexia, weight loss and productive cough for 4 months. She had a complicated history: pulmonary tuberculosis (PTB) had been diagnosed in 2004, treated with 2EHRZ/4RH regimen for 6 months. Tuberculous lymphadenitis was diagnosed in 2005 based on histological biopsy, for which she completed the WHO (World Health Organization) retreatment regimen for 8 months. Reactivation of smear-positive PTB occurred in 2007, for which she was prescribed 2EHRZ/4RH again for 6 months. Adherence was thought to be adequate on each occasion. *Mycobacterium tuberculosis* (MTB) culture/susceptibility results were unavailable from these episodes.

A sputum sample in January 2010 yielded acid fast bacilli (AFB) on microscopy, and *Mycobacterium tuberculosis* (MTB) on culture, resistant to Isoniazid, Rifampicin and Streptomycin and susceptible to Ethambutol. She was therefore diagnosed with smear-positive multidrug resistant tuberculosis (MDR-PTB). She commenced MDR-TB therapy in January 2010 with a combination of intramuscular Amikacin and oral Ofloxacin, Ethambutol, Pyrazinamide, Ethionamide and Cycloserine. She responded well with conversion to sputum smear-negative after 4 months of therapy but subsequently became smear and culture positive at 6 months of therapy, again with resistance to Isoniazid, Rifampicin and Streptomycin and susceptibility to Ethambutol. She was continued on the same regimen. Sputum smear and culture conversion were achieved after 10 months of therapy.

By 18 months, adjunctive surgical treatment was felt to be warranted, and was able to be offered at another tertiary institution, as she remained underweight and symptomatic, and computerized tomography (CT) thorax showed bilateral upper lobe cystic bronchiectasis with a left upper lobe cavity. A left upper lobectomy was performed which was complicated by bleeding; requiring repeat thoracotomy for vessel ligation. She recovered well post-operatively. Histopathology confirmed caseating tuberculous pneumonitis.

The patient continued anti-TB therapy until April 2012 where she defaulted from medications for 2 weeks because of neuropsychiatric side effects, potentially attributable to Ethionamide or Cycloserine. She was admitted to hospital to restart the regimen, ensure adherence and manage side effects. She continued to suffer intolerable neuropsychiatric side effects including depression, visual hallucinations, insomnia and dizziness, requiring Ethionamide to be withheld. Relapse occurred, as sputum cultures were again positive for MTB in October and November 2012 (33 months after commencing MDR-TB treatment), indicating treatment failure. Her symptoms improved minimally with only occasional purulent cough and increasing body weight 4 kg from start of therapy. Her chest radiograph features were similar with bronchiectatic changes and evidence of left upper lobe collapse post lobectomy.

The patient's symptoms again worsened in January 2013, with further loss of weight, decreasing effort tolerance and increasing amount of sputum purulence. Her sputum microscopy was persistently AFB positive. Sputum MTB culture with drug susceptibility testing (using liquid medium) showed resistance to Isoniazid, Rifampicin, Streptomycin, Fluoroquinolones, Capreomycin, Amikacin and Kanamycin with susceptiblity to Ethambutol/ Viomycin. A confirmatory second sample sent to a reference laboratory in Singapore

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showed discordance with the Capreomycin result but concordance with the other findings, and provided results for additional second line agents. These included: resistance to Kanamycin, Streptomycin, Isoniazid, Rifampicin, Ofloxacin and susceptibility to Ethambutol, Ethionamide, Capreomycin, Clofazimine and Para Amino Salicylic Acid (PAS).

She was diagnosed as having Extensively Resistant Pulmonary Tuberculosis (XDR-TB) in February 2013, 9 years after her initial presentation with TB and 3 years after commencing MDR-TB treatment (see Table). Her medication was withheld while the few options for a tailored regimen based on susceptibility results were discussed. Options included Capreomycin, Gatifloxacin, high-dose Isoniazid and compassionate access to Bedaquiline. In view of the difficulty of obtaining these drugs due to technical and cost issues, a new individualized regimen was commenced in June 2013 guided by WHO guidelines, comprising: intensive induction with intravenous Amoxicillin/Clavulinic Acid 1.2 g bd for 1 month then orally at the same dose, with oral Moxifloxacin 400 mg daily, Clofazimine 150 mg daily, Linezolid 300 mg twice daily, Ethambutol 600 mg daily, high dose Isoniazid 550 mg (equivalent to 20mg/kg) daily and Pyridoxine 10 mg daily.

Other important management elements comprised: hospital admission for the first month, strict Directly Observed Therapy (DOTS), regular screening for side effects, self-isolation at home after the initial first month of therapy, psychological and financial support by family and healthcare workers involved, monthly medical review, monthly sputum AFB microscopy / culture, 1-3 monthly blood screening especially for the possibility of liver impairment and cholestasis (due to Augmentin, Moxifloxacin and Isoniazid) and bone marrow suppression (Linezolid).

At the time of this report, the patient has received the XDR-TB treatment regimen for 1 year and is tolerating it well. Symptoms such as cough with purulent sputum and intermittent fever have reduced significantly. Her current body weight has increased from 29.5 kg to 33.5 kg. Chest radiographic features are static. Sputum AFB smears converted to negative after the 4th month of therapy. Sputum specimens at months 3 and 6 were contaminated, but at month 10, were found to be culture negative for MTB. The intention is to continue treatment for 18-20 months after conversion to culture negativity, or to obtain access to additional agents if treatment failure occurs.

DISCUSSION

XDR-TB is a form of MDR-TB with additional resistance to quinolones and one of the second-line injectable agents (Amikacin, Kanamycin or Capreomycin). It is an emerging phenomenon described in at least 45 countries since 2006.[1] We provide the first clinical description of this disease in Malaysian literature. The genome of a single XDR-TB isolate has been published from University of Malaya, Kuala Lumpur, but the details and outcome of that case were not reported.[2]

Sabah contains approximately 10% of Malaysia's total population, but a disproportionally high burden of the country's TB cases, estimated at 20-30%.[3] Our data from the Sabah outpatient setting demonstrate that drug resistance is uncommon.[4] Concerningly, the notification rate of TB among Sabah health care workers has been estimated to be almost double that of the general Sabah population (280.4/100,000 versus 153.9/100,000).[5] This case illustrates how devastating TB can be for healthcare workers. Our patient, a healthcare worker first acquired TB at the age of 21; whether this was definitely attributable to workplace exposure is unclear. She was unable to continue in employment for most of the period of MDR/XDR-TB treatment, due to physical incapacity, potential infection control in a clinical setting and the demands of the treatment regimen itself.

There were no available susceptibility data from the initial three TB presentations in 2004-2007; therefore we cannot know whether primary infection with a resistant strain (e.g. isoniazid-resistant) occurred, with evolution to MDR-TB then XDR-TB, or whether all resistance mutations were acquired de novo. Without typing data, it is possible that the 2010 presentation was due to reinfection with a new strain, given her increased risk as a healthcare worker; however, the low rate of community MDR-TB transmission[4] and the complicated pre-treatment history make relapse more likely. New Malaysian guidelines recommend upfront culture/susceptibility be performed in all new TB diagnoses.[3] Additionally, extended second line susceptibility testing at the outset of MDR-TB diagnosis in this case would have been valuable. However, access to culture and susceptibility testing is limited in Sabah currently.

In addition to her at-risk occupation, many risk factors for XDR-TB acquisition are evident in this unfortunate case: prior TB treatment, including with an inappropriate first-line regimen in 2007 for the third episode of TB; the absence of initial susceptibility results; adherence problems at some stages in treatment due to drug side effects, and continuation of a failing regimen because of lack of other second line agents in 2010 and in the second half of 2012. Furthermore, the large disease extent with high organism burden would have provided high opportunities for resistance mutations to develop.[1,3]

The current average rate of MDR-TB cure is estimated at only 48% globally.[1] Principles of management as per WHO guidelines are to treat with at least 4 agents to which the isolate is susceptibility, choosing drugs from Groups 1-5 (see Table II) in hierarchical order, for a minimum of 18 months after culture conversion.[1] The individualised XDR-TB drug regimen was constructed according to these guidelines, including the recommendation that individualised regimens not be based solely on susceptibility results. Lack of standardised methods, uncertainty about appropriate laboratory breakpoints, and lack of correlation between breakpoints for reported susceptibility and phenotypic susceptibility, are problems facing laboratory testing for many second-line agents. We opted for ethambutol as the Group 1 agent, as susceptibility results for pyrizinamide were unavailable (susceptibility tests for this first-line drug are also unreliable and were therefore not offered by either

Table I: Chronological history since diagnosis of multi-drug resistant Tuberculosis (TB)

Parameters/Date	2010	2011	2012	2013
Sputum AFB	1+ (Jan) Negative (March) 3+ (June/July) 1+ (Aug/Sept) Neg (Oct)	Neg (Jan/Apr)	2+ (April) 3+ (May) Neg (June/July/Aug) 3+ (Oct-Dec)	3+ (Jan/Jun) Neg (Aug/Oct)
Sputum Culture DST Results (R-resistant) (S-Susceptible)	R to INH/Rif/St S- E (January & June)	Neg (April/June)	Positive for MTB (April/May) **R- Rif, St** **S- INH, E** Full DST(Nov)- **R- INH/Rif/St** **S- E**	Positive for MTB (March/April) **R- INH/Rif/E/St** Positive for MTB (June) **R- INH/Rif/St** **S- E**
Sputum Culture DST Results	DST 2nd line not done	DST 2nd line not done	DST 2ND line (Nov) **R- Ofx/Am/C/K** **S- Viomycin**	**R- Ofx/Ami/C/K) (March/Apr)** **R- Ofx/K** **S-Eth/C/PAS/Clofazimine(June)**
ATT regime	Am/E/PZA/Ofx Eth (Added Cyc in July and withheld E)	Amikacin (3x/week)	Amikacin (3x/week) (April)-restarted similar regime	Augmentin/Moxifloxacin/ Clofazimine/Linezolid/E/INH (June)
Symptoms Body weight		Left upper lobectomy(July)	Relapse of cough and purulence	Increase body weight(4 kg) after new therapy and less cough/purulence
Side effects	Withhold Eth (neuropsychiatric side effects) - rechallenge gradually	Ami changed to 3x per week (painful daily injection)	Ethionamide withheld due to neuropsychiatric side effects(Nov)	Hyperpigmentation due to clofazimine. Request not to be put on Ethio (*unable to obtain Bedaquiline/Capreomycin/ Gatifloxacin)
Blood parameter/ Radiograph	HIV Screening neg Urine pregnancy test negative	Hemoglobin 10.4 (normochromic normocytic anemia) Albumin 27, Normal renal and liver profile test	HRCT Thorax (March) - bilateral tubular/cystic bronchiectasis both lungs, mucus plugging both lungs. Thick walled cavity with irregular soft tissue mass in left upper lung.	Hemoglobin 10.0 (anemia) Albumin 41 ESR 38 Normal renal/liver profile Thyroid function- euthyroid Urine analysis and pregnancy test- negative and normal

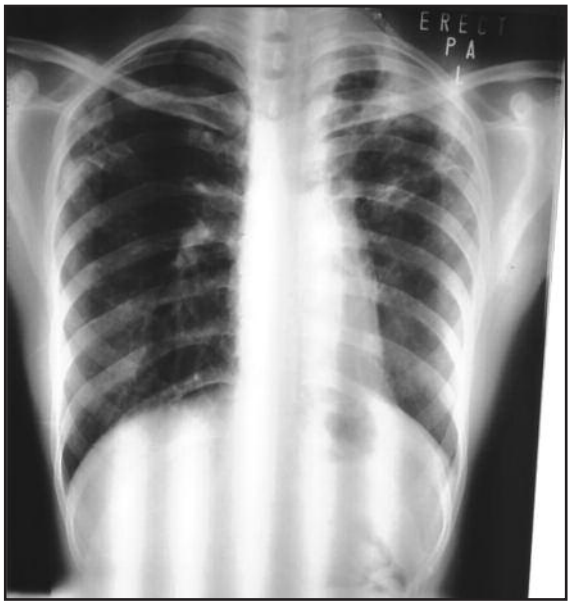
AFB- Acid fast bacilli, MTC- Mycobacterium tuberculosis, DST- Drug susceptibility testing, INH- Isoniazid, Rif- Rifampicin, E- Ethambutol, St- Streptomycin, PZA- Pyrazinamide, Ofx- Ofloxacin, Eth- Ethionamide, Cyc- Cycloserine, Ami- Amikacin, K- Kanamycin, C- Capreomycin, PAS- Para Amino salicylic Acid HIV- Human immunodeficiency virus, HRCT- High resolution contrast tomography ESR- Erythrocyte sedimentation rate

laboratory). Capreomycin(the only potential sensitive injectable agent in her case) was not given chiefly because it was unavailable, but also because one laboratory reported resistance, and the patient was reluctant to receive further parenteral treatment. We used moxifloxacin to replace ofloxacin, since later-generation quinolones are more effective, and may retain efficacy in the setting of laboratory-reported resistance. Regarding Group 4 agents, PAS was unobtainable and the estimated delay despite efforts to access it hindered its use. Prior exposure to and major adverse effects from ethionamide and cycloserine ruled these agents out, as well as prothionamide, to which cross-resistance may have developed. Linezolid was included as the most promising and widely-used of the Group 5 agents, with excellent lung penetration. However it necessitates vigilance in monitoring for myelosuppression and peripheral / optic neuropathy. Clofazamine appeared to be an important predictor of success in the MDR-TB short-course regimen published from Bangladesh, and was included in this case for that reason. The unorthodox nature of this regimen (as it includes no injectable agents, lack of Group 4 drugs and the use of four agents from Group 5) may seem risky but under the unfortunate circumstances in this case it was judged to be the best available regimen in view of the XDR PTB culture pattern and the unfavourable side effect profile of other agents in the previous MDR TB therapy.

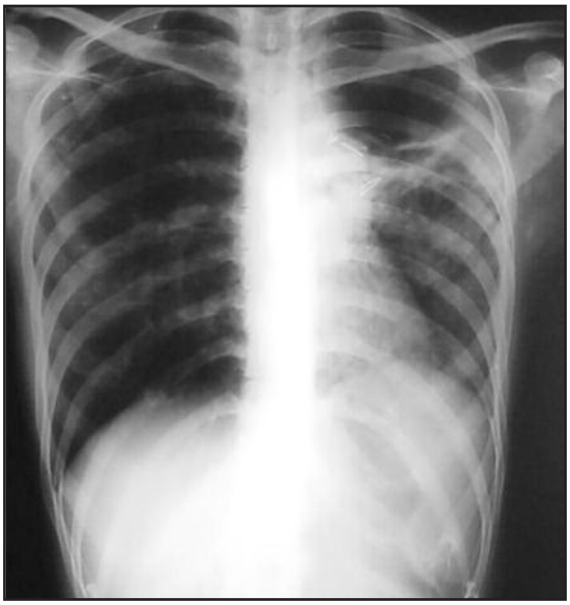
Surgical management was not without risk, complicated by major post-operative bleeding, but we believe it has been an important contributor to a good outcome in this case. The patient's current progress is cause for optimism; she is tolerating this regimen well and has high adherence, has converted to smear and culture negativity, and is improving symptomatically. Multidisciplinary management (medical, surgical, supportive) has proven effective thus far in this very difficult case, which has had major quality of life impacts for this young patient. It is of major importance that people experienced in managing TB, with case conferencing and a

Table II: Groups of drugs to treat MDR-TB [1]. Patient's XDR-TB regimen shown in bold

Group	Drugs
Group 1: First-line oral drugs	**Ethambutol** Pyrazinamide
Group 2: Injectable drugs	Kanamycin Amikacin Capreomycin Viomycin
Group 3: Fluoroquinolones	Levofloxacin **Moxifloxacin** Gatifloxacin
Group 4: Oral bacteriostatic second-line drugs	Ethionamide Prothionamide Cycloserine Terizidone Para-Aminosalicylic Acid
Group 5: Drugs of unclear efficacy (Not recommended for routine use in MDR-TB patients)	**Clofazimine** **Amoxicillin/clavulanate** Clarithromycin Azithromycin **Linezolid** Thioacetazone Imipenem **High-dose Isoniazid**



Chest Radiography 1: Pretreatment Chest radiograph taken in 2010 prior to MDR and XDR therapy.



Chest Radiography 2: Taken in 2013 showing post lobectomy effect, with stump ligation and pin, with residual infiltrates of remaining left lung and diaphragm tenting.

multi-disciplinary approach, manage patients with complex drug-resistant TB in a tertiary centre.

Learning points from this case include appreciation of the TB risk among healthcare workers in high TB-burden settings; the importance of obtaining upfront culture and susceptibility results in all new TB cases; the problem of acquired drug resistance developing during MDR-TB treatment; the challenges associated with MDR/XDR-TB treatment regimens, including difficulty accessing drugs and severe side effects; the value of surgical resection in refractory cases and the major quality of life impact this disease can have on young individuals.

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