ACUTE DRUG REACTION AND NON-COMPLIANCE TO ANTI-TUBERCULOSIS MEDICATIONS: A CASE STUDY

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SUMMARY

Introduction:

Tuberculosis (TB) is a significant re-emerging disease in Malaysia. TB treatment involves prolonged use of antibiotics, but adverse drug reaction and non-compliance to anti-tuberculosis drugs hamper the success of treatment.

Case report:

A 59 year old man with underlying diabetes and hyperlipidaemia presented with a four-day history of vomiting and diarrhoea. He was diagnosed with smear negative pulmonary TB three weeks earlier and was on TB medications. Apart from reduced air entry at both lung apices, the physical examination was normal. All blood results were normal except mild derangement of the renal profile and raised monocyte count. The patient had poor knowledge, insight and attitude towards his illness.

Conclusion:

We report a case of acute drug reaction and non-compliance to anti-TB, and the possible associated factors. Knowledge, insight and proper attitude are vital in ensuring the patient’s treatment compliance.

Key words: tuberculosis, non-compliance, knowledge, attitude

1. Medical history

1.1 Chief complaints

Mr. F was a 59 year old Malay man with underlying diabetes mellitus and hyperlipidaemia presented to the hospital with a four-day history of vomiting and one day history of diarrhoea. About three weeks prior to this, Mr. F was diagnosed with smear negative pulmonary tuberculosis and was immediately put on treatment.
1.2 History of present illness

Mr. F has been vomiting after every oral intake for the last four days prior to presentation. Each episode produced a handful of vomitus which only contained food particles. Due to his inability to tolerate orally, he complained of feeling weak. Associated symptoms included nausea, headache and loss of appetite. The patient also claimed that one day prior to admission, he experienced multiple episodes of diarrhoea. Stool was soft and not watery or bloody. There was no abdominal pain, dyspepsia or bloating. There was no history or complaints suggestive of food poisoning.

1.3 Relevant past medical history/surgical history/O&G history

Mr. F was diagnosed with smear negative pulmonary tuberculosis on 18 December, 2013. Ten days prior to the diagnosis, he had developed fever and cough. The fever was high grade and was associated with chills and rigors which worsened at night. The cough was continuous throughout the day and productive of yellowish sputum. He then visited a district health clinic and was prescribed paracetamol and antibiotics. The medications provided temporary relief. During this period, Mr. F also claimed that he had loss of appetite, experienced weight loss of almost 2 kilograms within a month and was fatigued most of the time. He denied having night sweats, haemoptysis, chest pain or shortness of breath. Mr. F was prescribed anti-TB drugs on the 19 December 2013. The medications were withheld after the patient developed rashes. They were recommenced on the 21st of December 2013. During this current admission, he was on his 16th day of the intensive phase of the TB treatment regime and claimed to be compliant to the medications.

Mr. F also suffered from diabetes mellitus diagnosed two years ago at a district health clinic where he continued his monthly follow up. He denied ever having symptoms of hypoglycaemia but admitted to having nocturia and numbness of the hands and feet. The patient also suffered from hyperlipidaemia for which he was prescribed a lipid-lowering agent. He had no surgical history.

1.4 Relevant family history

Mr. F’s father was a rubber tapper and his mother a housewife. Both of them passed away at 50 and 60 years old respectively due to unknown causes. He was married and had two sons aged 27 and 30 years. His wife passed away last year due to breast cancer at the age of 57 years. Both his sons were well and have no known medical illness.

1.5 Relevant social history/including travelling

Mr. F was a chronic smoker of 15 pack-years, but stopped smoking in December 2013 after being diagnosed with tuberculosis. He did very little travelling and has never been abroad.

1.6 Occupational history

During his younger days he worked in the palm-oil plantations but in the last few years he worked at a wood factory along with his son. There were many foreign (Indonesian) workers at the factory but no known TB cases. The workplace was an open area and well ventilated.
The use of personal protective equipment was not strictly enforced hence the workers wore them only occasionally.

1.7 Drug history

Mr. F was under directly-observed therapy short course (DOTS) TB treatment regime. The medications were Isoniazid 300mg daily, Rifampicin 600mg daily, Pyrazinamide 2000 mg daily, Pyridoxine 80 mg daily, Ethambuthol 1000 mg daily. In addition to these, he was taking Metformin 1mg twice a day and Glibenclamide tablet 5 mg twice a day for diabetes. He was also on Simvastatin 20mg daily for hyperlipidaemia. He claimed to be compliant to the medications and had no known drug or food allergies.

1.8 Relevant physical findings

Upon examination, the patient appeared comfortable, alert and conscious. His nutritional and hydration status were good. He was not pallor, jaundiced or cyanosed. His blood pressure was marginally high (130/90mmHg). All the other vital signs were normal. The capillary refilling time was less than 2 seconds. No cyanosis or clubbing was noted. The chest expansion was reduced. Tactile vocal fremitus was reduced at both right upper zones. On auscultation, vesicular breath sounds were heard with reduced intensity at the right upper zones. TB vaccination scar was noted on his left deltoid area. Abdomen was soft and non-tender with no organomegaly and the bowel sounds were normal. All other bodily systems were normal.

1.9 Clinical diagnosis

Pulmonary tuberculosis with acute drug reaction secondary to anti-TB medications.

1.10 Relevant investigation results

Liver function test showed normal levels of the liver enzymes. Full blood count investigation revealed high white cell count (10.7 x10^9/L), which were mainly monocytes (1.70 x10^9/L). No significant derangements were noted in the other differential counts. Findings were suggestive of chronic inflammation. Renal profile showed mild increase in creatinine (121umol/L) and mild decrease in urea (2.3mmol/L) and sodium (133mmol/L).

1.11 Clinical management

The patient was given supportive therapy for the vomiting and diarrhoea. The TB medications were withheld temporarily and recommenced using the same regime once his symptoms disappeared.

2. Assessment of patient environment and lifestyle (including family. From home visit finding)

2.1 Physical environment

Mr. F lived in a rural agricultural settlement in Negeri Sembilan. The patient’s house was a single storey stand-alone unit, with a living room, a dining area, kitchen, three bedrooms and three bathrooms. The house had good ventilation but had poor natural lights. Electrical lights
had to be switched on for better visibility. The house was large but unkempt. His medications were disorganized and placed in several containers.

Figure 1: Living area

Figure 2: House appeared unkempt

Figure 3: Patient’s medications

2.2 Psychological environment

The ambience of the home was calm and quiet. The patient and his younger son who lived with him provide company and comfort to each other. The son knew and understood his
father’s condition and provided help to his father when needed. They both appeared optimistic about the patient’s illness.

2.3 Behaviour and life style

After the death of his wife, Mr. F did all the housework himself, except for cooking. He bought food from the nearby stalls where he often spends time with his friends.

3. Patient belief and understanding of illness

3.1 Knowledge

The patient appeared to have poor understanding of the causes and complications of tuberculosis.

3.2 Belief

He believed that the illness began when he went to Kuala Lumpur a few months ago to attend a meeting. At that time it was raining and he started to develop fever upon returning from that meeting. He repeatedly denied having pulmonary tuberculosis because according to him he did not have any cough. He believed that he only have blood infection. At the same time, he did not believe that the illness was due to black magic and refused to take any traditional medicine.

3.3 Practice

Based on his knowledge and belief, the patient saw no need for him to be compliant to the anti-tuberculosis drugs, especially when they gave him unpleasant side effects. From observation, it was possible that the patient has not been taking his medications regularly based on the highly unorganized state of his medication sachets.

4. Impact of illness

4.1 Patient

Being diagnosed with tuberculosis had a major impact on the patient’s life. He had to stop working at the factory, be submitted to daily medications and twice weekly follow up visits at the health clinics. According to the patient the clinic visits were troublesome for him and a waste of time. He also felt guilty towards his son who had to work extra hours to make up for the lost income as he was no longer working. He seldom socialized with his friends as he felt somewhat stigmatized; and only went out when he needed to do grocery shopping. He also complained of feeling very lonely since his wife’s death.

4.2 Family

His sons have been very supportive both financially and emotionally towards the patient especially after their mother had passed away and the patient was diagnosed with TB.
5. **Assessment of patient need**

5.1 **Personnel support at home**

The patient needed support at home in terms of house chores and cooking.

5.2 **At work place**

His employer needs to be supportive of him once he returns to work after the sick leave. His workmates need to be educated about tuberculosis so as to prevent discrimination at the workplace.

5.3 **Community care**

The community needs to be educated on tuberculosis so as to avoid discrimination and stigmatization of tuberculosis patients. If there were many other tuberculosis patients in the same locality they could form a support group for better management and encouragement in their TB treatment.

6. **Assessment on communication**

6.1 **Between patient and family members**

The relationship between the patient and his family members was good mainly because they could accept his current condition. The patient had also informed his children about the TB screening process that they have to undergo but they have yet to do it. Mr. F refrained for repeatedly reminding his sons about it as he “did not want to burden his family members.” This scenario is common among the Malay community especially among the men, where there seem to be some sort of barrier in convincing and persuading family members to do certain things. The reluctance of the patient’s sons to undergo screening could also be due to several other factors such as time, knowledge, understanding and attitude.

6.2 **Between patient and health workers**

Generally, the patient had cordial relationship with the health workers. However, effective communication between them was questionable as the patient’s knowledge and understanding of his illness was still poor.

6.3 **Between health facilities**

Communication between health facilities was good. The patient was timely and appropriately referred to the hospital by the health clinic.

7. **Wellness diagnosis**

This patient has smear negative pulmonary tuberculosis with underlying diabetes mellitus and hyperlipidaemia. He developed acute drug reactions secondary to tuberculosis medications. His knowledge, insight and attitude towards his illnesses were poor and have the potential to affect his compliance to medication.
8. Wellness intervention

Wellness intervention in this patient’s case was minimal and should be improved. The most important wellness intervention is the provision of appropriate, adequate and effective education to the patient regarding his illness. The delivery of knowledge to the patient need to be done in an appropriate setting, using appropriate tools or modes of delivery such as written material, diagrams, pictures, real-life examples and video footage. The language used must be appropriate for the patient’s level of education and cultural background. Heath education must be given to the patient and family members/carers at the time of starting treatment. This should include the nature of the disease, necessity of strict adherence with the prolonged treatment, risks of defaulting treatment, side effects of medication, the risks of transmission and need for respiratory hygiene as well as cough/sneeze etiquette.

There should be a conducive avenue for the patient to ask questions. A support group consisting of TB patients and medical staff could be established to provide emotional and physical support to its members. Community awareness campaign on TB should be conducted to increase knowledge and improve the attitude of the community towards this reemerging infectious disease, improve their participation in TB screening program and to reduce stigmatization of TB patients. Other methods or approaches to improve compliance to medications should be considered, such as the use of mobile phones or home visits.

9. Discussion

In Malaysia, the incidence rate of tuberculosis in the year 2010 was 81.4 per 100,000 populations (WHO, 2010). The number of new TB cases in the country increased from 15,000 in 2005 to 19,251 in 2011(Sistem Maklumat Tubi, 2011). In 2011, the majority of patients were in the 21 - 60 years age group (69.5%) with male predominance (65%). Approximately 2.7% of TB cases in Malaysia were in the age group ≤14 years while 12.3% were those aged ≥65 years. Among all TB cases, 13.9% were foreigners (Jetan, Jamaiah, Rohela, and Nissapatorn, 2012).

The causative organism is mycobacterium tuberculosis which is spread by the inhalation of aerosolized droplet nuclei from other infected patients. Once inhaled, the organism will be lodged in the alveoli and initiate the recruitment of macrophages and lymphocytes. The macrophages undergo transformation in the epithelioid and Langhans cells, and then aggregate with the lymphocytes to form the classical tuberculosis granuloma. Numerous granuloma further aggregate to form primary lesions (also known as the ‘Ghon focus’), which are characteristically situated in the periphery of the lung. Lymphatic and hematological spread may occurs before immunity is established, seeding secondary foci in other organs including lymph nodes, serous membrane, meninges, bones, liver, kidneys and lungs.

The risk of TB infection post-exposure is further determined by a few factors such as infectiousness of the index case, nature and duration of the contact and immune status of the contact. In general, individuals with pulmonary and laryngeal TB are infectious, whereas those with extra-pulmonary TB (EPTB) are regarded as non-infectious. The infectiousness increases when the sputum smear is positive, presence of multiple pulmonary cavities in the chest radiograph, if the contact has been in close proximity or has spent a longer time together with the index case, and individuals who are immunocompromised are more susceptible to
TB disease. In our case, Mr. F was a diabetic. Diabetics have an odds ratio of 3.1 (95% CI 2.3 to 4.3) of being infected with TB (Jeon & Murray, 2008).

In pulmonary tuberculosis, the patient usually presents with productive cough, hemoptysis and chest pain, non-specific constitutional symptoms, loss of appetite, unexplained weight loss, fever, night sweat and fatigue. Adult patients presented with unexplained cough lasting more than two weeks with or without constitutional symptoms should be investigated for PTB. However, the typical symptoms may be absent in the immune-compromised such as diabetics, or elderly patients (Ministry of Health Malaysia, 2012).

Pulmonary tuberculosis is diagnosed by direct microscopy of the sputum which has been stained with the Ziehl-Neelsen stain or the rhodamine-auramine stain. A positive smear is sufficient for the presumptive diagnosis of TB but definitive diagnosis requires culture. Smear-negative sputum should also be cultured. The feature of chest x-ray in TB patients is consolidation with cavitation but any abnormality in the chest x-ray has to be considered suspicious when diagnosing TB.

Smear negative pulmonary TB case is diagnosed when are at least three sputum smear examinations negative for AFB, radiographic abnormalities consistent with active pulmonary tuberculosis, no response to a course of broad-spectrum antibiotics; and a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy; or positive culture but negative AFB sputum examinations (WHO, 2012).

Aim of TB treatment should be both cure and reduce risk of transmission. Presently, six-month regimen consisting of two months of daily Ethambutol, Isoniazid, Rifampicin and Pyrazinamide (EHRZ) followed by four months of daily Isoniazid and Rifampicin. Among the important steps to prevent the emergence of drug-resistant TB is to ensure patients adhere to their treatment. One of the strategies is to use Fixed-dose combination (FDC) drugs which incorporate two or more drugs in single tablet and offer reduction in number of pills that need to be consumed. Examples of FDC preparations registered in Malaysia are Akurit-4, Forecox, and Rimcure. Randomised controlled-trial showed that FDCs are as effective as separate-drug regimens for the treatment of TB and bioequivalent to separate-drugs formulations (Ministry of Health Malaysia, 2012).

An adverse drug reaction (ADR) is an expression that describes harm associated with the use of given medication at a normal dosage during normal use. The ADR of anti-TB drugs can be classified into two categories - ADRs which are troublesome but not serious such as nausea, tiredness, pruritus and minor rashes which can be treated symptomatically without necessarily having to interrupt treatment, as in Mr. F’s case. Most of these will resolve spontaneously even when treatment is continued. The second category comprise of ADRs which need immediate discontinuation of treatment such as severe skin reactions such as Steven-Johnson Syndrome (SJS). For anti-TB treatment, most of ADRs occur within early stage of the treatment (Kishore, Palaian, Ojha, and Shankar, 2008).

To ensure adherence and good management practice, the World Health Organization (WHO) launched the Direct Observed Therapy, Short Course (DOTS) in 1995 which combines drug treatment with political commitment, sputum smear microscopy for diagnosis and directly observed therapy (DOT). The practice of DOT in Malaysia was reported to be 97% (ranging from 93% to 100%) (Sistem Maklumat Tibi, 2011). A local study showed that patients who
were not on direct observed therapy (DOT) lived distant to the health facility, were non-intravenous drug users (IVDU) and were HIV positive had statistically significant higher odds of being non-compliant (Naing, D'Este, Isa, Salleh, Bakar and Mahmod, 2011). Therefore DOT in TB control programmes should not be of a blanket approach; instead it should be a process of negotiation and support, incorporating patients' health belief, education level, cultural background and choice, as illustrated by the case of Mr. F. A controlled trial showed a better treatment success rate in the patient-centred approach. In that trial, patient was given the choice to receive treatment at home observed by a supporter of their own choice versus daily treatment at health facilities (Egwaga et al., 2009).

Another local study showed that for non-compliant patients, reaching the treatment centre entailed greater cost and travel time; where cost of transport was the reason most frequently given for non-attendance. Non-compliant patients were more likely to have completed secondary education, working, had family members who had had the disease and were more likely to think that treatment could be stopped once they were symptom free (O'Boyle, Power, Ibrahim, and Watson, 2002). Hence, besides DOT, other proven good management practices include defaulter tracing and contact tracing using reminder letters (Liu et al. 2008) or home visits by healthcare workers (Mohan & Niazi, 2003). These have been shown to reduce the number of patients who fail to complete treatment. Success rate is also improved if a daily mobile phone call is used to remind TB patients to take medication and continue follow-up (Kunawararak, Pongpanich, Chantawong, Pokaew, & Traisathit, 2011). Reminder system using automated telephone message has been shown to reduce nonattendance at clinic appointment (Youssef et al., 2014). Instructions regarding compliance involving individuals with a prior history of TB and providing advice to patients currently under treatment (peer training) can also reduce TB treatment default.

10. Conclusion

Pulmonary tuberculosis is a re-emerging infectious disease in Malaysia. TB treatment involves prolonged regimes with multiple drugs. Adherence to treatment is vital to ensure cure of the illness and limits spread of the organism. Doctors need to have a high index of suspicion for adverse drug reaction to anti-TB medications and take appropriate actions, as ADRs may not only harm the patient but deter them from continuing treatment. Ensuring compliance among patients in the Malaysian community especially those in the rural and traditional setting need specially tailored and holistic approach. Public health personnel need to take proactive roles as well as being creative in educating and providing appropriate support for TB patients.

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References


