CASE REPORT

Empirical treatment of tuberculosis: TB or not TB?

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SUMMARY

Of the 8.6 million new cases of tuberculosis (TB) that occur globally each year, a quarter occur in India. We describe the case of a 38-year-old Indian woman who presented with symptoms of hepatitis after being treated empirically with anti-TB therapy for five months. The patient was suspected to have TB after having recurrent episodes of coughing which would improve briefly before her respiratory symptoms returned, which led to her being treated at various healthcare clinics and hospitals. We highlight the challenges the patient faced due to the lack of centralised medical records which would have prevented unnecessary investigations and treatment.

CASE PRESENTATION

A 38-year-old woman presented with jaundice, ascites and abdominal pain with an 11-month history of general malaise. Her problems began with the development of a cough which was treated by a local physician, producing some mild improvement in symptoms. However, there was a recurrence of the cough and weakness after 2 weeks and she underwent a CT scan of the thorax which was suggestive of interstitial tuberculosis (TB). Her sputum microscopy was negative for TB at this time. Anti-TB therapy was initiated on an empirical basis by a different local doctor in the community. She was treated empirically with a standard course of anti-TB therapy consisting initially of a combination of isoniazid, rifampicin, pyrazinamide and ethambutol for the first 2 months followed by a continuation phase of isoniazid, rifampicin and ethambutol for another 4 months. In the fifth month of anti-TB treatment, she developed ascites, pruritus, fever, jaundice and anorexia, making her unwell to the extent that she was unable to carry out her daily activities.

The patient lives in North Bengal and is a housewife with two daughters aged 15 and 11 years. Her husband works as a tailor and has not been able to work for the past 9 months due to the frequent travelling between their home in North Bengal and hospitals in Kolkata in the search for treatment. A community health worker took the opportunity to upload the patient's care record onto an online database accessible to all internet users to enable sharing of her clinical details to stimulate discussion among clinicians and gather a wider range of medical opinions.¹ This online medical record was also integral to understanding the patient's perspective of the situation. The patient then travelled a long distance to IQ City Hospital in Durgapur, West Bengal, once her case had received input from

a clinician based there to be assessed in person and managed appropriately.

On examination, the patient was cachectic with icteric sclera, pedal oedema, ascites, shiny nails (due to pruritus) and jaundiced skin. The patient's bloods corroborated with the clinical finding of jaundice, with a significantly increased bilirubin (6.3 mg/dL). It also indicated hepatic failure, with reduced serum albumin (1.3 g/dL) and borderline international normalised ratio (1.25). Liver function was deranged with aspartate transaminase 920 µ/L, alanine transaminase 610 µ/L and alkaline phosphatase 1823 µ/L. She was seronegative for hepatitis A, B, C and E. Results of her ascitic tap revealed a normal albumin and a total leucocyte count of 20.0 × 10⁹/L. The serum-ascites albumin gradient is 0.9. An ultrasound confirmed moderate ascites alongside bilateral pleural effusions.

The clinical picture is consistent with drug-induced liver injury from empirical anti-TB therapy. The patient was discharged following a gradual improvement of her ascites and liver function over the course of two weeks with supportive treatment. Other issues in this case that hampered diagnosis and treatment for this patient was that she was from a lower income, social status and lived in a remote location which limited her ability to access consistent healthcare.

GLOBAL HEALTH PROBLEM LIST

1. Disease burden of tuberculosis in India.
2. Lack of care continuity.
3. Empirical treatment of tuberculosis in India.

GLOBAL HEALTH PROBLEM ANALYSIS**Disease burden of tuberculosis in India**

TB is the sixth main cause of death in India.² Revised estimates of the burden of TB have been made following evidence that prior estimates between 2000 and 2015 were too low. In principle, estimating the burden of TB in any country should ideally be based on a wide-ranging monitoring system that takes in all new reported cases of TB and a system that takes in causes of all deaths. Such a system allows evaluation of TB as well as other disease incidence and mortality. However, many countries lack these systems and thus rely on TB prevalence studies as well as national mortality surveys to estimate TB burden.³ Estimates of the prevalence of TB in India has not been carried out since 1955.⁴ Another issue is of under-reporting in India which is estimated to be 41%.^{5,6} In India, this evidence has been based on a state-wide prevalence surveys, household surveys, private sales of anti-TB drugs, notification data and analysis of mortality

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data. However, TB burden estimates await results as national survey scheduled for 2017–2018.³⁷

Lack of care continuity

Our patient presented initially to her village health worker and then as her symptoms worsened, visited numerous hospitals in her area. In a country where there is little access to primary care for patients in rural areas, this form of ‘doctor shopping’ or self-referral to numerous clinics and hospitals until a treatment is found is relatively common.⁷ A 1997 WHO report indicated that 50%–80% of people with TB-like chest symptoms initially seek help from their nearest trusted healthcare provider, usually a private for-profit practitioner. Poorly qualified practitioners are common particularly in rural areas. The practitioner aims to alleviate the patient’s symptoms before the patient decides to switch providers. Thus, a diagnosis can be delayed by weeks as patients ‘shop’ around for a diagnosis and effective treatment. In many cases, treatment by private practitioners depletes funds and patients tend to then switch to government providers which means that patients with more difficult or advanced forms of TB accumulate in the government hospitals.⁸

Continuity of care is an important value particularly in primary care. Globally, it has been found that high-quality primary care correlates with improved health outcomes, and continuity of care is a crucial factor in patient-focused outcomes.^{9–10} Due to changes in the infrastructure of primary care, it has been found that patient care is shared among a wider range of allied healthcare professionals.¹¹ Thus, patients may be given conflicting advice by different members of the healthcare team.¹² A UK study found that the majority of patients valued relational continuity (an ongoing therapeutic relationship between a patient and one or more provider) particularly when being seen for psychological issues or more serious illnesses such as cancer.¹³ Another issue is that the lack of a centralised health record (as patients carry their own medical notes) can lead to confusion surrounding treatment among patients and healthcare professionals which can lead to issues around treatment compliance and repeated courses of anti-TB medication given. Patients may discontinue one or more of their prescribed drugs or share them among their family members with little to no follow-up care to supervise their treatment. All of these factors can contribute to drug resistance and lack of treatment response.

The practice of creating an online patient record would be a possible solution to improving continuity of care. It functions as a useful way for different practitioners to keep track of care provided for the patient. In this case, this online record created by a community health worker was invaluable in charting her TB treatment and the decline in her liver function. It was an open access patient record with de-identified patient documentation such as doctors’ notes, diagnostic test results and the patient’s perspective. This is a collaborative initiative headed by Dr Rakesh Biswas (currently based at Kamineni Institute of Medical Sciences) to encourage discourse among his medical colleagues regarding challenging cases that they may face, with a view for it to eventually overcome the challenge of a lack of a centralised patient record system in India.

There are several barriers to rolling this out across the state of West Bengal, and more widely, the rest of India. Access to internet would be essential to upload these records and this may be unavailable or patchy at best in rural areas. Healthcare workers would have to be trained to anonymise

patient-specific documentation and to upload the completed records to a centralised system. Having a standardised system to upload an accurate patient history and subsequent investigations would allow for the information to be accessed more easily by clinicians. Patients usually have results of their investigations such as blood test results and X-ray reports in paper form; therefore, the necessary technology will have to be available in order for photographs or scanned copies to be obtained alongside physically typing out the results (which may be prone to transcribing errors). The capacity to translate the record into English would also be required to make the record more accessible to a greater range of clinicians, rather than just those who can understand the original language—a step which is essential in a country like India, where multiple languages are spoken across and within state lines. The issue of confidentiality related to the use of an open medical record available on the internet gives rise to the potential for the development of an encrypted patient database which is only accessible by clinicians with secure passwords to guarantee patient data protection. This may only become a reality once funding and technology catches up with the challenges of a centralised patient data information system for the entire state of West Bengal, or even the entirety of India. Informed consent is currently obtained from patients from the individual who creates the initial online patient record—this is documented with a signed consent form in the patient’s language detailing the purpose of creating the aforementioned record. To build on the foundations of this workflow, healthcare workers involved in this process should be trained fully to understand the purpose of collating and presenting patient data in this manner in order to convey this accurately to patients who can then continue to provide their informed consent.

Empirical treatment of tuberculosis in India

Sputum smear microscopy is the recommended diagnostic tool for TB by the Directly Observed Treatment Short course (DOTS) strategy from WHO.¹⁴ This method is simple and inexpensive, alongside being highly specific and is available in most geographical areas, including poorer areas of developing countries. However, the sensitivity of this tool is compromised in various scenarios including when the bacterial load is <10 000 organisms/mL of sputum and when the patient presents with extrapulmonary TB, paediatric TB or if the patient is coinfecting with HIV. The observation time of slides can be reduced in scenarios where there is limited resources combined with a large volume of samples to examine, further compromising the sensitivity of this test.¹⁵ The results from this test require an extended period of time to obtain which may precipitate the loss of patients to follow-up if they are unlikely to have further encounters with healthcare professionals.¹⁶

Samples from patients with suspected TB which are found to be negative by a rapid diagnostic test should be cultured to obtain microbiological confirmation if possible; however, this is not always possible.¹⁶ The slow speed of the entire process precipitates the misdiagnosis and the loss to follow-up of patients, leading to either the undertreatment or overtreatment of TB in this population.¹⁷ If microbiological confirmation remains elusive, however, clinical suspicion of TB remains high, and patients are classified as ‘probable TB’ and are initiated on anti-TB medication.¹⁶

Nucleic acid amplification testing (NAAT) has been identified as a potential alternative to sputum smear microscopy.

However, this has proved to be a challenge as diagnostic facilities in most developing countries are unable to offer the infrastructure requirements of NAAT such as storage and continuous supply of consumable, electricity and water. Investment is also a factor as sputum smear microscopy is more cost-effective as an initial diagnostic tool compared with NAAT.¹⁵

The empirical treatment of TB is the initiation of treatment in the absence of a bacterially confirmed diagnosis. The factors which contribute to the probability of a patient having TB and/or experiencing a poor outcome are weighed up against the threshold for initiating anti-TB treatment. This threshold is subjective and may vary between clinicians. The factors which are taken into account include background TB prevalence in the geographical area, clinical presentation suggestive of TB, comorbidities such as HIV coinfection and the results of other diagnostic methods such as chest radiography if available.¹⁸ Chest radiographs have been shown to be unreliable in the diagnosis of TB with a sensitivity of 78% and a specificity of 51% and are therefore should not be used as the sole diagnostic tool.¹⁹ The high likelihood of patients being lost to follow-up and the inability to perform sputum smear microscopy or NAAT in cases where the patient is unable to produce sputum may also influence the decision to initiate empirical anti-TB treatment.¹⁸

In this case, the patient was initiated on empirical anti-TB therapy on the basis of her clinical presentation and a suspicious X-ray. Treatment was initiated despite a negative sputum microscopy result as almost 50% of all new TB cases notified annually are sputum-negative TB in low-income and middle-income countries. This is also in line with India's Revised National TB Control Programme guidelines which recommend that patients with two negative sputum smear results should be treated with broad-spectrum antibiotics for 2 weeks with a follow-up chest X-ray if symptoms persist.²⁰

The subsequent treatment resulted in the complication of drug-induced liver injury. With the exception of ethambutol, isoniazid, rifampicin and pyrazinamide are known as hepatotoxic agents. Thus, it is difficult to ascertain the incidence of hepatotoxicity due to the individual agents. However, several population-based observational studies have shown that isoniazid is the most common drug associated with hepatotoxicity with an incidence of 0.1%–0.56%. In this case, therefore, it is impossible to be certain which drug directly caused the hepatotoxicity; however, based on the evidence, it is most likely isoniazid with rifampicin and pyrazinamide playing a contributing role.²¹

Although there is no guarantee that this would not have happened if the treatment had been initiated after a definitive diagnosis of TB, a more robust risk–benefit analysis could have been undertaken if the decision of whether to stop the treatment regimen arose in this instance, balancing the risk of liver injury with the harm caused by TB.

Patient's perspective

(Prior to hospital admission, translated by a community health worker)

Right now I am just skin and bones, I have no energy. I cannot walk. My husband is a poor tailor. Our cash is very short. It has become tiresome for me to travel from North Bengal to Kolkata again and again. I want to live. I have two daughters. Please save me.

Learning points

- ▶ Robust reporting of tuberculosis (TB) cases should be the norm in order to accurately estimate TB burden in India so that appropriate targeted strategies can be put in place to tackle this issue.
- ▶ Lack of care continuity can be addressed by methods such as an informal online record with the patient's consent which can be accessed by all healthcare professionals in different settings caring for the patient.
- ▶ Gold standard diagnostic methods such as sputum smear microscopy in the case of TB should be used to avoid unnecessary initiation of anti-TB therapy.
- ▶ The side effects of anti-TB therapy should be considered when initiating therapy and the common side effects explained to patients prior to commencing the treatment course.

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