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Clinical Case of Multidrug-Resistant in King Khalid Hospital, Hail

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Abstract: ***Multidrug-resistant tuberculosis (MDR-TB) in patients with human immunodeficiency virus (HIV) infection poses multiple challenges for treatment, and has a high mortality. MDR-TB coinfection with HIV has been reported in African. In saudi , we did not come across any report of HIV and MDR-TB coinfection, though such coinfection has been reported in adults. 34 -year-old HIV-infected male requiring antiretroviral therapy (ART) developed MDR-TB and responded to second-line antituberculous therapy.***

1. Introduction

Multidrug-Resistant Tuberculosis (MDR-TB) is caused by a strain of Mycobacterium tuberculosis that is resistant to at least Isoniazid (INH) and Rifampin (RIF), the two most effective of the four first-line TB drugs**;** the other two drugs are Ethambutol (EMB) and Pyrazinamide (PZA).[1]

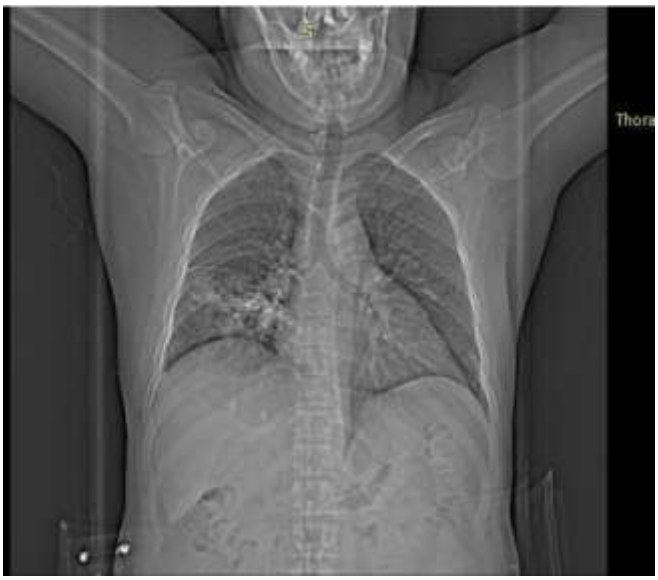
The current vaccine for tuberculosis (TB), bacillus Calmette-Guérin, has variable (mostly poor) efficacy in protecting against pulmonary TB in children and adults [2,3]. TB control is further threatened by the emergence of multidrug-resistant (MDR), extremely drug-resistant and totally drug-resistant strains of M. Tuberculosis. According to the fourth WHO report on antituberculosis drug resistance, MDR-TB has been shown to be almost twice as common in patients with HIV infection than in those without HIV. In 2010, there were an estimated 650,000 prevalent cases of MDR-TB worldwide, and at least 150,000 deaths were due to MDR-TB. In the same year, 3.4% of all newly diagnosed and 19.8% of all previously treated TB patients were estimated to have MDR-TB[4]. We present the case of a 34 year old, Non Saudi male who developed MDR-TB and responded to second-line antituberculous therapy (ATT).

2. The Case

A 34-year-old Non Saudi male presented in June 2016 with fever for 7 months and dry cough for 10 days.. He was on ATT for the past 10 months, which had been started by her treating physician for non-resolving pneumonia.

Sputum examination 5 months ago was negative for acid-fast bacilli (AFB). On examination, he was 175 cm tall and weighed 65 kg. He had oral thrush and bilateral diffuse crepitations on respiratory system examination. Other systems were normal. His haemoglobin was 10.9 g/dl and white blood cell count was 4800/cmm (64% polymorphs, 35%lymphocytes) with a platelet count of 325 000/cmm. His X-ray chest showed right-sided calcified primary complex. Her alanine aminotransferase was 29 IU/L, serum amylase 19 IU/L and CD4 count was 36 cells/cmm (1.69%). She was started on azithromycin and cotrimoxazole prophylaxis. ATT was stopped. he was also started on three-drug ART consisting of zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP).

A month later, he had fever with cough. Sputum smear examination was positive for AFB and a chest X-ray showed left lower zone consolidation. He was then started on six-drug ATT consisting of isoniazid (INH), rifampicin, ethambutol, pyrazinamide, streptomycin and cipro-floxacin. NVP was increased to 400 mg/m^2/day. Subsequently, he developed NVP-induced maculopapular rash and NVP was replaced with efavirenz. Culture of sputum after 6 weeks grew *Mycobacterium tuberculosis* resistant to streptomycin, INH, rifampicin and ethambutol. The bacteria were sensitive to pyrazinamide, kanamycin, ethionamide, para-aminosalycylic acid (PAS) and ofloxacin. Treatment under the directly observed treatment, short-course (DOTS) programme was suggested but the mother wished to continue treatment at our centre.he was started on alternate ATT consisting of kanamycin (15 mg/kg/day for 2 months), PAS (150 mg/kg/day in divided doses for 3 months), ethionamide (15 mg/kg/day for 8 months), pyrazinamide (30 mg/kg/day for 2 years) and ofloxacin (16 mg/ kg/day for 2 years).



Chest X-rays were done every 3 months.his sputum smear became negative after one month of therapy. Repeat cultures were not done since the he had stopped producing sputum. In November 2016, her weight had increased to 68 kg. However, on regular screening for adverse effects, he was found to have hypothyroidism (T3 1.3 ng/ dl, T4 60 mg/dl, TSH 7.5 mIU/ml). He was started on 25 mg of levothyroxine once a day. In December 2016, her CD4 count increased to 77 cells/cmm, in June 2007 it increased to 170 cells/ cmm and in January 2017 it increased to 304 cells/cmm. Azithromycin prophylaxis was stopped in December 2016.

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his chest X-ray done in February 2017 was normal. As his thyroid function tests remained normal, thyroxine was tapered and stopped. he was tolerating ART well. Pyrazinamide and ofloxacin were stopped at the end of 2 years.

3. Discussion

MDR TB is more difficult to treat than drug-susceptible strains of TB. The success of treatment depends upon how quickly a case of TB is identified as drug resistant and whether an effective drug therapy is available. The second-line drugs used in cases of MDR TB are often less effective and more likely to cause serious side effects such as Nephrotoxicity and or Ototoxicity. Tests to determine the resistance of a particular strain to various drugs usually take several weeks to complete. During the delay, the patient may be treated with a drug regimen that is ineffective. Once a strain's drug resistance is known, an effective drug regimen must be identified and implemented As Soon as Possible
Treatment for an MDR TB involves drug therapy over many months or years at least 18 months to 24 month..Treatment of TB and HIV coinfection is complicated by various factors including drug resistance, drug interactions and drug toxicity. He already on three-drug ART, was started on first-line ATT when He was sputum AFB-positive. Six weeks later, TB culture and drug susceptibility results showed the strain to be MDR, i.e. resistant to most of the first-line drugs including INH and rifampicin.

Conventional culture, the most common method of detecting drug resistance in developing countries, has the inherent problem of a delay in diagnosis varying from 6 weeks to 3 months. A more rapid detection of drug-resistant TB is desirable in populations with a heavy burden of MDR-TB or coinfection with HIV in order to ineffective treatment and to decrease mortality.[5,6] A history of previous treatment for TB is a useful predictive factor for MDR-TB in a cohort of HIV-infected patients with TB.[7]

One must also keep in mind that immune reconstitution in the setting of recent initiation of ART may unmask drug-resistant TB and hence timely empirical MDR-TB treatment is important in suspected cases.[8]

He HIV infection, treatment of MDR-TB is extended to 24 months[9] and an individualized treatment regimen is required. The principles of management of resistant disease include use of aggressive regimens for protracted periods, guided by drug susceptibility testing to include at least five drugs likely to be effective.[10] Fluoroquinolones play a key role in resistant TB and the later generation fluoroquinolones may be effective despite resistance to ciprofloxacin. Use of an injectable agent such as capreomycin or an aminoglycoside (e.g. kanamycin), have been shown to predict culture conversion and survival.[11]

However, resistance to more than one aminoglycoside is becoming increasingly common. The regimens may be reinforced by pyrazinamide and ethambutol despite prior exposure to these drugs, as these contribute by increasing the regimen's activity or preventing resistance to more active agents. An oral quinolone is generally continued for the duration of therapy, in combination with another agent such as ethambutol (or pyrazinamide in this case) for 18 months after smear 'conversion'..Common adverse effects of second-line ATT include gastrointestinal effects, rash, ototoxicty, peripheral neuropathy, psychiatric symptoms and jaundice. The rate of thyroid toxicity is high,[12] and may be due to ethionamide or PAS, requiring regular monitoring. Besides, serial CD4 levels, monitoring of liver function tests, lipid profile and pancreatic enzymes is essential for a child receiving ART.

A delay in laboratory diagnosis, limited choice of active drugs and increased toxicities and interactions when ATT and ART are simultaneously administered, all contribute to making the treatment of MDR-TB with HIV a challenging task. It calls for individualization of treatment.

4. Conclusion

MDR-TB remains uncommon in Hail, but its challenges are increasingly recognized. Despite delays in commencing an effective therapy; fortunately, MDR-TB is usually associated with treatment success. Adverse effects of medications are common, and treatment courses are long and complex. Specialist TB services should continue to be involved in provision of treatment, management and prevention of spreading cases of MDR-TB. (Quarantine Measurement).

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