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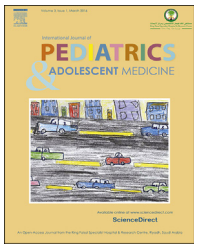

INSTRUCTIVE CASE

A child with complicated *Mycobacterium tuberculosis*

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Abstract Tuberculosis (TB) is one of the leading causes of morbidity and mortality worldwide, with ever increasing resistance to commonly used antituberculous drugs. Drug-resistant TB was recognized shortly after the introduction of an effective therapy in the late 1940s, the use of streptomycin, which was the first widely used antituberculosis drug. Patients who received this drug usually had marked and rapid clinical improvement, but treatment failures were common after the first three months of therapy. Most children are infected by household contacts who have TB, particularly parents or other caretakers. Common symptoms of pulmonary TB in children include cough (chronic, without improvement for more than three weeks), fever (higher than 38 °C for more than two weeks), and weight loss or failure to thrive. Findings on a physical exam may suggest the presence of a lower respiratory infection, whereas the clinical presentation of extra pulmonary TB depends on the site of disease. The most common forms of extra pulmonary disease in children are TB of the lymph nodes and of the central nervous system. The role of inadequate treatment and poor compliance in the emergence of resistance highlights the importance of the DOT (Direct Observation Therapy) method in improving treatment outcomes and to control the spread of resistance.

1. Introduction

TB is a disease that is caused by the bacterium *Mycobacterium tuberculosis*. The bacteria usually attack the lungs, but TB bacteria can attack any part of the body, such as the kidney, spine, or brain. If not treated properly, TB can be fatal. TB was once the leading cause of death.

2. Case presentation

A 7-year-old Saudi girl presented to the emergency department at this tertiary care hospital with a worsening course of fever, cough, weight loss, and abdominal pain over 3 weeks. She was admitted to a local hospital earlier and was suspected of having lymphoma. There was a history

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of recent contact with an aunt who was diagnosed as having pulmonary TB 6 months earlier and who was started on treatment with 4 drugs. The results of culture and susceptibility testing are not available. The child's place of residence in AL-Jouf was crowded, with many extended family members, and was poorly ventilated. Her father was 45 years old, and her mother was 35 years old. Both were healthy, but of poor socioeconomic status.

On examination, the child looked acutely ill, pale, tachypneic, and tachycardic, with a temperature of 39.6 °C, WT 11.7 < 5th centile, and HT 106 cm > 50th centile. There were multiple cautery marks over the chest wall and upper abdomen, and on chest auscultation, there was a marked decrease of air entry on the right side, with bronchial breathing and basal crepitations.

2.1. Laboratory data (Table 1)

The chest X-ray (Fig. 1) demonstrated an airspace disease involving the right lower lobe and a cystic change involving the right upper lobe with blunted cardiopulmonary angles. A CT scan of the chest (Fig. 2) demonstrated large airspace consolidation involving the right middle and lower lobes, with a large cavity in the right upper lobe, and bilateral miliary nodules that had a tree-in-bud appearance. There were multiple mediastinal necrotic lymph nodes suggestive of acute on top of chronic TB. The abdominal CT showed small hypo-dense splenic lesions.

Based on these findings, the patient was diagnosed as having pulmonary TB, iron deficiency anemia, and failure to thrive. Air borne isolation was initiated, and she was admitted to a negative air pressure room and started on INH, Rifampicin, pyrazinamide streptomycin, pyridoxine, and iron therapy. Four days after treatment, her platelet count decreased to 25 x 109/L.

Rifampicin-induced thrombocytopenia was suspected, and the drug was therefore discontinued and replaced with ethambutol. Subsequently, the platelet count rebounded to a normal level.

Table 1 Clinical investigation upon diagnosis and during treatment of DOT.

Laboratory data	On diagnosis	On DOT	Normal range
CBC and differential			
WBC, 10^9/L	19.17	5.86	4.30—11.30
RBC, 10^{12}/L	3.49	4.34	4.30—5.50
hemoglobin, g/L	67	113	110—150
Hematocrit, L/L	0.294	0.339	0.350—0.450
MCVfL	73.7	78.1	75—95
MCHCpg	22.5	26	24—30
RDW, %	19	12.9	11—15
Platelet, 10^9/L	25	231	155—435
Neutrophil absolute, 10^9/L	6.20	1.71	1.35—7.50
Lymphocyte absolute, 10^9/L	1.21	2.88	1.90—4.90
ESR, mm/h	140	9	0—15
CRP, mg/L	103	0.4	≤3 mg/L
Albumin, g/L	17	42.9	32—48
AST, U/L	373	33.5	10—45
ALT, U/L	114	24.9	10—35
Bilirubin, total, umol/L	6.3	4.9	0—21
Alkaline phosphate, u/L	269.5	246	100—300
HIV 1—2 antibody screening	Non reactive		

The Mantoux test was positive. Sputum for the AFB stain was positive, and the rapid DNA amplification test was positive for the *M. tuberculosis* complex. The culture was later reported to be positive for mycobacterium TB. The isolate was susceptible to streptomycin, isoniazid, rifampin, ethambutol, and pyrazinamide.

The general condition of the patient improved on treatment, with a normalizing respiratory rate and other vital signs, but she experienced persistent episodes of low-grade fever. Her appetite improved, with good oral intake and

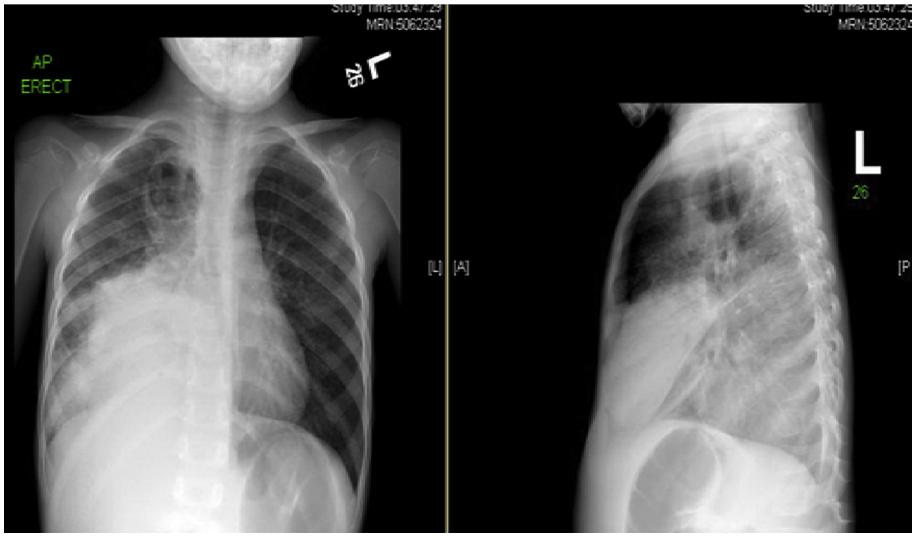

Figure 1 Airspace disease involving the right middle and lower lobe with a cystic change involving the right upper lobe.

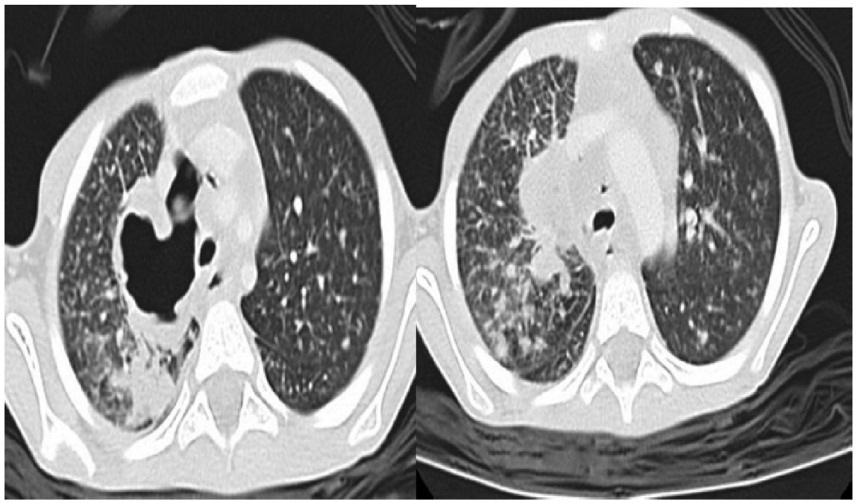

Figure 2 Improvement of the airspace disease in the right middle and lower lobe after starting treatment. Bronchial wall thickening with peribronchial infiltrates in the perihilar region.

increased weight. The baseline eye examination was normal, and follow ups were arranged. After 18 days of inpatient treatment, the patient was discharged, due in part to the insistence of the parents for an early discharge, on ethambutol, INH, Pyrazinamide, a Streptomycin IM injection once daily for 8 weeks (to be given at a local hospital), iron therapy, and pyridoxine with a follow-up OPD appointment.

On frequent repeated outpatient visits over the ensuing months, the response to treatment was suboptimal, as evidenced clinically and according to the investigation results. Poor compliance was suspected, and her antimicrobial serum levels were found to be undetectable. The local treating physician was contacted, and arrangements were made to initiate direct observation therapy (DOT); however, the family did not agree to have health care personnel in their home. This ultimately resulted in her clinical deterioration and a second admission.

At this admission, there was a history of fever with chills for one month associated with decreased oral intake and activity. The parents noticed that she developed cervical and sternal ulcers, which were progressively worsening and discharging yellow, milky material.

On examination, she was conscious, listless, unwell in appearance, pale, and dehydrated. Her vital signs were as follows: temperature: 38.4 °C, heart rate: 147 beats per minute, respiratory rate: 28 per minute, $O_{2\ \text{saturation:}}$ 100% in room air, and blood pressure: 87/48 mmHg. A chest exam showed clear vesicular breathing, with no added sounds and decreased air entry, mainly on the right side. A cardiovascular exam showed normal S1 and S2, with no murmur. The abdomen was mildly distended with no organomegaly. She had multiple ulcerative skin lesions on the right side of the neck, over the sternum, and chest as well as bilateral axillary lymph nodes, which were ulcerating and discharging milky serous material. Her hemoglobin was 5 g/dl, indicating poor nutrition and poor compliance with all medications, including iron therapy.

She was admitted with the impression of pulmonary and extra pulmonary (scrofuloderma) TB secondary to poor compliance with medical therapy in addition to social issues. The patient received packed RBCs. A review of the cultures and susceptibility results of the specimens from the sputum and lesions taken earlier showed that the organism had become first resistant to INH, then to ethionamide and

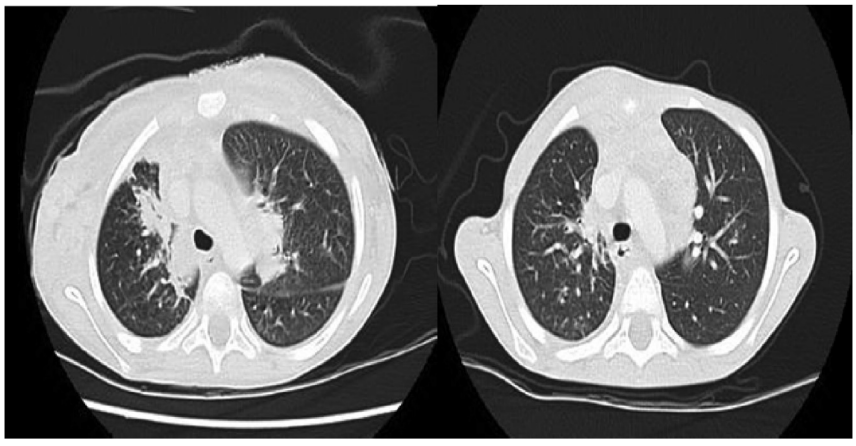

Figure 3 Improvement in the miliary nodules as well as the endobronchial tree-in-bud involvement of the right upper lobe and middle lobe after starting treatment.

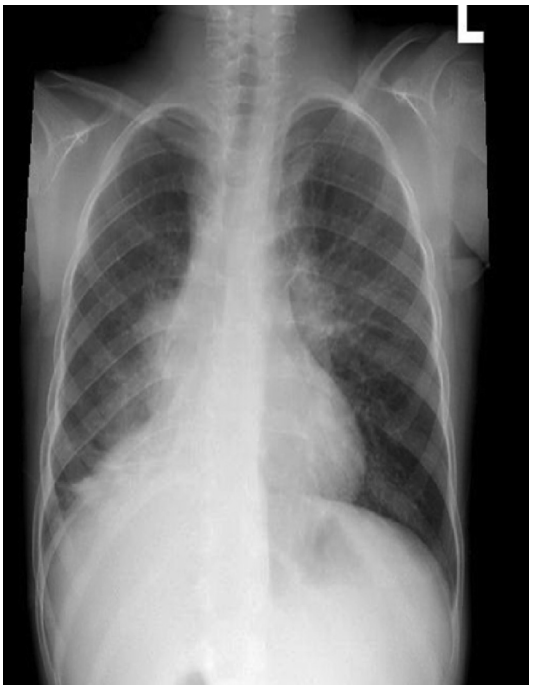

Figure 4 Chest CT: Large airspace consolidation involving the right middle and lower lobes with cavitary areas, a large cavity in the right upper lobe, bilateral miliary nodules and tree-in-bud appearance, with multiple mediastinal necrotic lymph nodes.

streptomycin. The patient was therefore started on ethambutol, pyrazinamide, cycloserine, moxifloxacin, and pyridoxine (vitamin B6) to reduce the risk of the neurotoxicity of cycloserine and iron therapy. A specimen was submitted to a specialized center abroad, and PZA was tested by broth dilution using critical concentrations and CLSI interpretive criteria. All other agents were tested by the microbroth dilution with the (minimal inhibitory concentration) MIC reported and using laboratory developed interpretive criteria. The blood culture was negative. The wound culture was positive for Streptococcus pneumonia and for MRSA, which were treated accordingly. C-reactive protein was 239. A CT chest scan with contrast (Fig. 3) showed an interval increase in the number, size, and necrosis of the previously seen enlarged cervical and axillary lymph nodes, with abscess formation in addition to patchy pneumonic consolidations of the upper, middle, and right lower lobes. A bone scan showed mild increased activity in the left clavicle, likely related to a chronic infectious process. However, according to Pediatric Surgery, there was no role for surgical intervention.

The Child Advocacy Committee (CAC) was involved because of obvious parental neglect in the form of poor compliance with medications and refusal to cooperate with local as well as this hospital's medical staff. After several sessions with the parents and in coordination with the local Ministry of Health (MOH) authorities, an arrangement was made for admission to a local hospital where the child would receive her medications as an inpatient and then be followed up later with DOT therapy along with appointments at our hospital for a total of at least 9 months.

On outpatient follow-up, the patient continued on ethambutol, pyrazinamide, cycloserine, moxifloxacin, pyridoxine, and iron therapy. She has markedly improved, with an absence of fever, weight gain, normal inflammatory markers, and clearing CXR (Fig. 4), Table 1.

3. Discussion

TB remains a significant global health problem, with nearly 9 million new cases and 1.5 million deaths estimated annually [1,2]. The estimated incidence of TB in Saudi Arabia is 14/100,000 [3]. Because of increased resistance to commonly used anti-TB drugs, management has become more complex and difficult, requiring the use of second-line drugs and, in some cases, surgical resection. Drug-resistant TB is defined as an infection caused by a strain of *M. tuberculosis* that is resistant to one of the first-line anti-TB drugs: isoniazid, rifampin, pyrazinamide, ethambutol, or streptomycin. Multidrug-resistant TB (MDR-TB) is defined as an infection caused by a strain of *M. tuberculosis* that is resistant to at least isoniazid and rifampin. Extensively drug-resistant TB (XDR-TB) is defined as an infection caused by a strain of *M. tuberculosis* that is resistant to at least isoniazid, rifampin, and fluoroquinolones, as well as either aminoglycosides (amikacin and kanamycin), capreomycin or both [4]. Totally drug-resistant TB (TDR-TB) is defined as an infection caused by a strain of *M. tuberculosis* that is resistant to all locally tested medications [5,6]. Primary drug resistance is said to occur in a patient who has never received anti-TB therapy, and secondary drug resistance refers to the development of resistance during or following chemotherapy in patients who had previously had drug-susceptible TB.

The first representative national survey conducted in Saudi Arabia showed that of 1904 patients, 79.3% had pulmonary and 20% had extra pulmonary TB, with lymph nodes being the most common site of infection (56.2%) [7]. Of the 1609 isolates from new cases of TB, 16.4% were resistant to at least one first-line drug and 1.8% were MDR. Of the 295 isolates from previously treated TB cases, 63.4% were resistant to at least one first-line drug and 15.9% were MDR. The prevalence of resistance to anti-tuberculosis agents was highest for INH followed by streptomycin and rifampicin. Regarding the geographical distribution of MDR-TB in the country, the highest prevalence was detected in the northern and southern provinces, followed by the western and central provinces, and the lowest proportion was reported in the eastern province.

The treatment of patients with INH monoresistant TB has not been evaluated rigorously in randomized trials, and therefore, approaches are generally based on expert opinion derived from retrospective or single arm studies. In general, most patients with INH monoresistance should be treated with a rifamycin (rifampin or rifabutin), pyrazinamide, and ethambutol.

The duration of therapy should be six to nine months (or four months after culture conversion) [8,9], based on trials conducted by the Hong Kong Chest Service/British Medical Research Council, which demonstrated success rates of 95—98% among 107 patients with INH-resistant disease [10]. This finding was also supported by a retrospective study of

patients with INH-monoresistant TB treated for six months, which showed comparable rates of failure or relapse among patients with drug-susceptible TB [9].

Data supporting the addition of a fluoroquinolone for the treatment of INH-monoresistant TB is inconsistent with one study of 328 patients with smear-positive TB who were randomized to receive either INH or moxifloxacin (in addition to rifampin, pyrazinamide, and ethambutol), in which culture negativity after eight weeks was comparable between the two groups (55 and 60%, respectively) [11]. On the other hand, a retrospective Danish study suggested that the inclusion of a fluoroquinolone in the treatment regimen was associated with a slightly higher success rate [12].

As per the World Health Organization (WHO) recommendation, the treatment of patients for whom drug susceptibility testing is not available but are known to reside in a region with a background level of INH resistance $>$ 7%, an acceptable approach consists of a standard initial phase (e.g., INH, rifampin, pyrazinamide, and ethambutol), followed by a continuation phase with INH and rifampin as well as the addition of ethambutol (rather than only INH and rifampin). Overall, effective therapy for INH-monoresistant TB is associated with very high bacteriologic, clinical response rates (>95%), and low relapse rates (<5%). National TB treatment guidelines strongly recommend using a patient-cantered case management approach, including directly observed therapy ("DOT"), when treating persons with active TB. DOT is especially critical for patients with drug-resistant TB, HIV-infected patients, and those on intermittent treatment regimens (i.e., 2 or 3 times weekly). DOT means that a trained health care worker or other designated individual (excluding a family member) provides the prescribed TB drugs and watches the patient swallow every dose to ensure that the medications are administered as directed. Because TB treatment entails several drugs taken regularly for several months, people from all social classes, educational backgrounds, ages, genders, and ethnicities may find it difficult to correctly adhere to the instructions. Studies show that 86—90% of patients receiving DOT complete therapy, compared to 61% for those on self-administered therapy. DOT helps patients finish TB therapy as quickly as possible, without unnecessary gaps, prevents TB from spreading to others, decreases the risk of drug-resistance resulting from erratic or incomplete treatment and decreases the chances of treatment failure and relapse [13—16].

Serious reactions to antituberculosis drugs are uncommon. Rifampicin-induced thrombocytopenia is an uncommon but potentially life-threatening complication of antituberculosis treatment [17]. Rifampicin-induced thrombocytopenia was first reported by Blajchman and co-colleagues [18] in 1970. Most of the described cases were observed with high dose intermittent therapy (1200 mg twice weekly) [19]. Only a few cases of thrombocytopenia have occurred during daily treatment or after the administration of rifampicin following an interruption of therapy [18,20]. The Tuberculosis Research Centre of Chennai reported only a single case of rifampicin-induced thrombocytopenia among more than over 8000 patients treated for tuberculosis over 30 years [21]. It has been observed that rifampicin-induced thrombocytopenia is caused by the presence of anti-rifampicin antibodies [20]. These antibodies fix a complement on the platelets in the presence of rifampicin, resulting in platelet destruction [21]. It has been found that antibodies against rifampicin are significant in number among patients who have stopped therapy; yet, rifampicin-induced thrombocytopenia is still relatively rare [18,21]. The low incidence of thrombocytopenia due to daily doses of rifampicin has been attributed to the possible development of neutralizing antibodies formed during continuous treatment or may occur because the antigen—antibody complex is continuously removed without causing an allergic reaction [22]. Thus, daily doses of rifampicin may result in immunologic tolerance, whereas intermittent dosing favors sensitization [23]. It has been recommended that rifampicin-induced thrombocytopenia be an absolute contraindication to further therapy with rifampicin [19]. However, Bhasin and co-colleagues [24] suggested that re-challenges should be performed before withdrawing rifampicin. When it is necessary to re-start rifampicin, one should check the platelets counts frequently, under supervision and with the use of steroids.

We present this case as an example of a child with complicated TB as illustrated by the initial poor clinical response to therapy caused by the emergence of resistance. On presentation, the organism cultured was sensitive to all first line agents, but because of poor compliance as documented by undetectable drug levels, the patient developed polydrug resistance. The improvement in the intake of medications and the resulting treatment success in this case was undoubtedly achieved by following the DOT method. Moreover, collaboration with the local physician and health care authorities was key in the implementation process. Confirmation of rifampicin-induced thrombocytopenia at the time of initial presentation is not often possible because tests for drug-dependent anti-platelet antibodies are not available in most laboratories. Discontinuation of the suspected drug leading to the resolution of thrombocytopenia provides strong evidence of rifampicin-induced thrombocytopenia. TB is nearly always curable if patients are treated with effective and uninterrupted antituberculous therapy. In children, parental support and an understanding of the importance of adherence to treatment as instructed is critical in bringing about cure, controlling the spread of infection, and minimizing the development of drug resistance. In the U.S.A., a Task Force composed of representatives of many federal agencies has developed a National Action Plan for addressing MDR-TB. The Task Force identified a number of objectives that must be met if MDR-TB is to be successfully combatted. These objectives fall under the categories of a) surveillance and epidemiology to determine the magnitude and nature of the problem; b) laboratory diagnostics to improve the rapidity, sensitivity, and reliability of diagnostic methods for MDR-TB; c) patient management to effectively managing patients who have MDR-TB and to prevent patients with drug-susceptible TB from developing drug-resistant disease; d) screening and preventive therapy to identify persons who are infected with or at risk of developing MDR-TB and to prevent them from developing clinically active TB; e) infection control to minimize the risk of transmission of MDR-TB to patients, workers, and others in institutional settings; f) outbreak control; g) program evaluation to ensure that TB programs are effective in managing patients

and preventing MDR-TB; h) information dissemination/ training and education; and i) research to provide new more effective tools with which to combat MDR-TB [25].

Conflict of interest

Authors declare no competing interests.

References

[1] Raviglione MC, Marais B, Floyd K, Lonnroth K, Getahun H, Migliori GB, et al. Scaling up interventions to achieve global tuberculosis control: progress and new developments. Lancet 2012;379:1902—13.

[2] World Health Organization. Global tuberculosis control report 2011. Geneva, Switzerland: World Health Organization; 2011.

[3] World Health Organization (WHO) estimates of tuberculosis incidence by country. 2013. http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1195733758290.

[4] World Health Organization (WHO). Laboratory XDR-TB definitions. Geneva: Meeting of the Global XDR TB Task Force; 2006.

[5] Velayati Ali Akbar, Masjedi Mohammad Reza, Farnia Parissa, Tabarsi Payam, Ghanavi Jalladein, ZiaZarifi Abol Hassan, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. Chest 2009;136:420.

[6] Udwadia ZF, Amale RA, Ajbani KK, Rodrigues C. Totally drug-resistant tuberculosis in India. Clin Infect Dis 2012;54:579.

[7] Sahal Al-Hajoj, Bright Varghese, Mohammed M. Shoukri, Ruba Al-Omari, Mais Al-Herbwai, Fahad AlRabiah, et al. Epidemiology of antituberculosis drug resistance in Saudi Arabia: findings of the first national survey.

[8] Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47:1.

[9] Cattamanchi Adithya, Dantes Raymund B, Metcalfe John Z, Jarlsberg Leah G, Grinsdale Jennifer, Kawamura L Masae, et al. Clinical characteristics and treatment outcomes of patients with isoniazid-monoresistant tuberculosis. Clin Infect Dis 2009;48:179.

[10] Five-year follow-up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. Hong Kong Chest Service/British Medical Research Council. Am Rev Respir Dis 1987;136:1339.

[11] Dorman Susan E, Johnson John L, Goldberg Stefan, Muzanye Grace, Padayatchi Nesri, Bozeman Lorna, et al. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. Am J Respir Crit Care Med 2009;180:273.

[12] Bang D, Andersen PH, Andersen AB, Thomsen VØ. Isoniazid-resistant tuberculosis in Denmark: mutations, transmission and treatment outcome. J Infect 2010;60:452.

[13] Treatment of tuberculosis, American Thoracic Society, CDC and Infectious Diseases Society of America. Am J Respir Crit Care Med 2003;167. on line at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm.

[14] Interactive core curriculum on tuberculosis (web-based). CDC; 2004. www.cdc.gov/tb/webcourses/corecurr/index.htm.

[15] DOT essentials: a training curriculum for TB control programs. Francis J. Curry National Tuberculosis Center; 2003.

[16] Management: directly observed therapy. New York City Department of Health; 2001.

[17] Garg R, Gupta V, Mehra S, Singh R, Prasad R. Rifampicin induced thrombocytopenia. Indian J Tuberc 2007;54:94—6.

[18] Blajchman MA, Lowry RC, Pettit JE, Stradling P. Rifampicin-induced immune thrombocytopenia. Br Med J 1970;3:24—6.

[19] Poole G, Stradling P, Worrledge S. Potentially serious side effects of high-dose twice-weekly rifampicin. Br Med J 1971;3:343—7.

[20] Mehta YS, Jijina FF, Badakere SS, Pathare AV, Mohanty D. Rifampicin induced immune thrombocytopenia. Tuberc Lung Dis 1996;77:558—62.

[21] Banu Rekha VV, Adhilakshmi AR, Jawahar MS. Rifampicin-induced acute thrombocytopenia. Lung India 2005;22:122—4.

[22] Bassi L, di Berardino L, Perna G, Silvestre LG. Antibodies against rifampicin in patients with tuberculosis after discontinuation of daily treatment (note) Am Rev Respir Dis 1976;114:1189—90.

[23] Girling DJ. Adverse effect of anti mycobacterial drugs. Drugs 1982;23:56—74.

[24] Bhasin DK, Sarode R, Puri S, Marwaha N, Singh K. Can rifampicin be restarted in patients with rifampicin- induced thrombocytopenia? Tubercle 1991;72:306—71.

[25] National action plan to combat multidrug-resistant tuberculosis. MMWR Recomm Rep 1992 Jun 19;41(RR-11):5—48.