Case Report / *Olgu Sunumu*

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Multidrug-Resistant Tuberculosis in the Child Presenting with ITP-like Clinic

İTP Kliniğinde Başvuran Çok İlaca Dirençli Tüberküloz Olgusu

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Abstract

Multidrug-resistant tuberculosis (MDR-TB) is resistance to both isoniazid and rifampicin. In treatment, five sensitive drugs should be given, one parenteral and one quinolone. Five cases with family contact are presented. A girl presented with bleeding from the mouth and nose and petechiae on the feet. There were hypercarbia, anemia, severe thrombocytopenia, increased CRP and D-dimer. Myeloid leukocyte and megakaryocytic series were increased and erythrocyte series were decreased in bone marrow. Chest X-ray was consistent with necrotizing pneumonia. In the foreground, immune thrombocytopenic purpura (ITP) was accepted as the diagnosis. She did not benefit from intravenous immunoglobulin (IVIG) treatment. ITP was excluded because there was no platelet destruction after platelet replacement. When history was deepened, it was learned that the mother had MDR-TB a year ago. Her calories were increased. The mother's other three children and niece living in the same house were also screened. All of the children were girls, and their ages, symptoms, findings, treatment and side effects are given in the table. Audiometric follow-up, visual examinations, electrocardiography, blood sugar level, liver, kidney, and thyroid functions were monitored regularly. Linezolid-induced neutropenia was observed in two patients and the linezolid dose was reduced by 30%. After this change, neutropenia resolved in one patient, and treatment including linezolid was continued. Since there was no improvement in the other patient, linezolid was discontinued and para-amino salicylic acid treatment was started, and then neutropenia

Öz

Çok ilaca dirençli tüberküloz (ÇİD-TB), hem izoniazid hem de rifampisin direncidir. Tedavide biri parenteral, biri kinolon olmak üzere beş duyarlı ilaç verilmelidir. Aile teması olan beş olgu sunulmuştur. Bir kız çocuğu ağız ve burun kanaması ve ayaklarında peteşi şikayeti ile başvurdu. Hiperkarbi, anemi, şiddetli trombositopeni, artmış CRP ve D-dimer vardı. Kemik iliğinde miyeloid lökosit ve megakaryositik seriler artmış, eritrosit serileri azalmıştır. Akciğer grafisi nekrotizan pnömoni ile uyumluydu. Ön planda tanı olarak immün trombositopenik purpura (İTP) kabul edildi. İntravenöz immünglobülin (İVİG) tedavisinden fayda görmedi. Trombosit replasmanından sonra trombosit yıkımı olmadığı için İTP dışlandı. Hikaye derinleşince annenin bir yıl önce ÇİD-TB olduğu öğrenildi. Kalorisi artırıldı. Annenin aynı evde yaşayan diğer üç çocuğu ve yeğeni de tarandı. Çocukların tamamı kız olup yaşları, belirtileri, bulguları, tedavileri ve yan etkileri tabloda verilmiştir. Odyometrik takip, görsel muayeneler, elektrokardiyografi, kan şekeri düzeyi, karaciğer, böbrek ve tiroid fonksiyonları düzenli olarak izlendi. İki hastada linezolide bağlı nötropeni görüldü ve linezolid dozu %30 azaltıldı. Bu değişiklikten sonra bir hastada nötropeni düzeldi ve linezolid içeren tedaviye devam edildi. Diğer hastada düzelme olmaması üzerine linezolid kesilerek para-amino salisilik asit tedavisi başlandı ve ardından nötropenisi düzeldi. Pediyatrik hastalarda ÇİD-TB tedavisi sabır ve özveri gerektiren bir süreçtir. Çocuklarda ikinci basamak ilaçların kullanımı, yaşamı tehdit eden ÇİD-TB'yi tedavi

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resolved. Management of MDR-TB in pediatric patients is a process that requires patience and dedication. The use of second-line drugs in children is necessary to treat life-threatening MDR-TB, but careful monitoring is required to recognize dose- and duration-dependent drug adverse events quickly.

etmek için gereklidir ancak doza ve süreye bağlı ilaç yan etkilerini hızlı bir şekilde tanımak için dikkatli izleme gereklidir.

Anahtar Kelimeler: ÇİD-TB, çocuklar, İTP

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is the resistance of the tuberculosis bacillus to both isoniazid and rifampicin (1). It is estimated that approximately 25.000-32.000 children develop MDR-TB or rifampicin-resistant tuberculosis each year (2). Mortality in children with MDR-TB is reported to be approximately 22% (3). Treatment of MDR-TB should include at least five drugs, one parenteral and one quinolone, which are known to be susceptible and have not been used previously (1). Standard treatment requires an injection regimen of up to approximately 6 months in adults and 18 months of treatment continuity after the culture becomes negative; an individualized shorter injection regimen is applied in children (4). In this article, we present an MDR-TB case with ITP-like clinic secondary to tuberculosis and her four family contacts.

Case Report

In June 2021, a 15-year-old girl was presented with the complaint of bleeding from the mouth and nose. She had a one-month history of cough, weight loss, and night sweats. Hypercarbia, anemia, severe thrombocytopenia, hypoalbuminemia, elevated CRP and D-dimer were found. There were no atypical cells and platelets in blood smear.

On physical examination, there was no fever. She was cachectic. She had decreased breath sounds in the right lung and bilateral crackles. She had no tachypnea. She had petechiae on her feet. Chest X-ray and chest tomography were consistent with necrotizing pneumonia and pleural effusion. Interferon-gamma release assay could not be done due to socioeconomics reasons (Figure 1).

Transamine therapy was not started due to hematuria. Teicoplanin and ceftriaxone treatments were started. Bone marrow aspiration was performed: Myeloid leukocytes and megakaryocyte counts were increased, and erythrocyte counts were decreased. Flow cytometry was normal. The diagnosis of immune thrombocytopenic purpura (ITP) was accepted, and the patient was treated with steroid and intravenous immunoglobulin. She did not benefit from intravenous immunoglobulin and steroid treatment. Platelet count was still 9.000/µL. Platelet count was 51.000/µL after platelet replacement. ITP was excluded because there was no platelet destruction again, and steroid treatment was discontinued. Platelet count was 72.000/µL on the second day of treatment for pneumonitis and first day of the treatment for tuberculosis. On the second day of treatment, platelet count was 137.000/µL. On day four, platelet count was 186.000/µL. On day six, platelet count was 206.000. On day 13, platelet count was 290.000/µL.

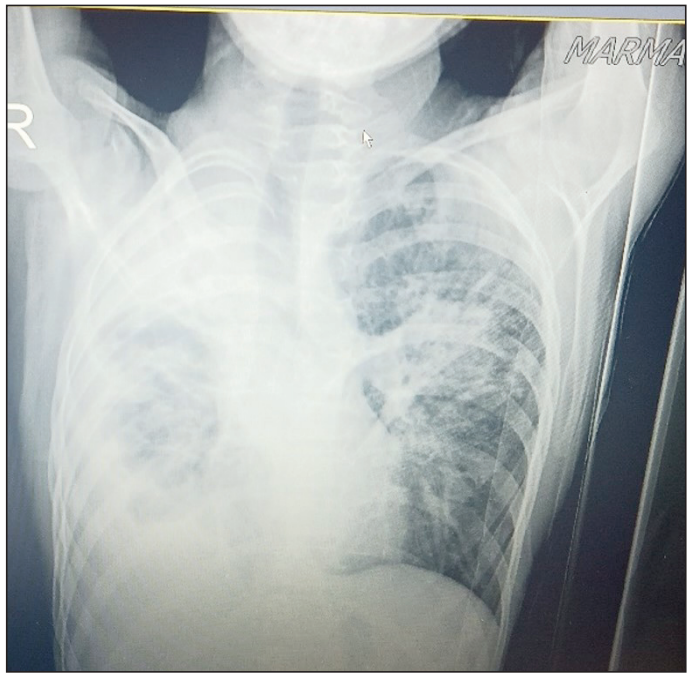

Figure 1. Chest X-ray at first admission. The patient's thorax CT in 2021 was taken in another hospital. There is no thorax CT in the archive system of Marmara University Pendik Training and Research Hospital and Süreyyapaşa State Hospital, but thorax CT is written this way in the epicrisis. The patient could not be found on E-Nabiz system because he was Syrian.

When patient history was deepened, it was learned that the mother had tuberculosis a year ago, and she had MDR-TB (Table 1). Acid-resistant bacteria were observed in the third sputum culture of our patient, and *Mycobacterium tuberculosis complex* grew. Her diet was adjusted, calories were increased. Her isoniazid and rifampicin resistance were not detected with sputum culture. In her mother's drug susceptibility test, there was resistance to isoniazid and rifampicin. After 15-17 days of treatment, the patient still had crepitation and mycobacterial growth in sputum culture and bronchoalveolar lavage, so she was accepted as MDR-TB, for her mother had MDR-TB. The mother's other three children and her niece living in the same house were also screened. All of the children were girls, and their ages were 15, 13, 12, 6, and 1.5 years. Symptoms, findings, treatment, and side effects are given in (Table 2). Index case was 27 kg (<3th percentile), and case 2 was 38.6 kg (5th percentile), and 136 cm (25-50th percentile); case 3 was 35 kg (3-10th percentile) and 153 cm (10-25th percentile); case 4 was 18.3 kg (10-25th percentile), and 117 cm (75-90th percentile); and

Table 1. Mother's sputum culture antibiogram

Date	Laboratory name	Material type	Tuberculosis Control Dispensary Lab No.	Culture Drug Sensitivity Test lab sequence No.	Compaction	Culture	H	R	E	S
9.3.20	Region Lab	Sputum	369	1652/1	1+	Growth	R	R	H	H
H: Sensitive, R: Resistant.										

Table 2. Symptoms and signs of the cases

Case	1 (index case)	2	3	4	5
Age	15	13	12	6	18 months
Symptoms	Coughing, bleeding from mouth and nose	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic
Thorax CT	Pleural effusion measuring 5 cm in the right hemithorax, partially consolidating density increase in the upper lobe of the left lung consistent with pneumonia and accompanying millimetric nodular densities.	9 mm lymph node in the right hilar region, focal air trapping in the left lung lower lobe superior, 1 cm diameter density and millimetric centriacinar nodules that may belong to nodule or consolidation in this area, 4 mm diameter nodule at the level of the right major fissure.	Pulmonary nodule smaller than 4 mm in the apical segment of the upper lobe of the right lung.	Nodule showing calcification in the right paratracheal and right hilar region, the largest of which is 8 x 7 mm. An 8 x 7 mm nodule with popcorn calcification was detected in the upper lobe of the right lung.	Lymphadenopathy and lymph nodes are seen in the mediastinum and right hilar region, the largest of which is located in the subcarinal region, with a short diameter of 10 mm.
ESR (mm/h)	119	32	30	8	5
PPD (mm)	Anergic	18	15	15	Anergic
Fasting gastric juice	*Mycobacterium tuberculosis* complex grew. ARB(+)	No growth ARB (-)	No growth ARB (-)	No growth ARB (-)	No growth ARB (-)
Anti-tuberculosis treatment given	Levofloxacin, ethionamide (discontinued), ethambutol, cycloserine, linezolid, para amino salicylic acid	Moxifloxacin, pyrazinamide, cycloserine, linezolid, amikacin	Amikacin, moxifloxacin, pyrazinamide, cycloserine, linezolid	Moxifloxacin, pyrazinamide, cycloserine, linezolid (discontinued), para amino salicylic acid, amikacin	Moxifloxacin, pyrazinamide, cycloserine, linezolid, amikacin
Treatment related side effects	Allergy	Neutropenia	Not seen	Neutropenia, hyperuricemia	Not seen

case 5 was 10 kg (50th percentile), and 80 cm (90th percentile). Their platelet counts were normal. They had no BCG vaccinations. The interesting thing about the case is that she came with ITP clinic and active tuberculosis disease was detected in all her siblings at the same time.

In Case 1, amikacin was discontinued on day 20 due to hearing loss. She received pyrazinamide for 66 days, isoniazide, rifampicin, etambutol for 24 days, PAS, protionamide, cycloserin, moxifloxacin for 8 months and then PAS, cycloserin, etambutol, linezolid, levofloxacin for 10 months because of protionamide hepatotoxicity.

MDR tuberculosis treatment was recommended due to a history of contact with a resistant tuberculosis case, malnutrition, sedimentation and PPD test positivity, and radiological findings. Based on the resistance mechanism in the mother, it was decided that MDR tuberculosis treatment was appropriate for case 2.

There was right hilar lymphadenitis (less than 1 cm), non-specific nodule in the apical segment (incidentally), and there were no features in the lung parenchyma in the first Thorax CT of case 3. Case 3's sedimentation and PPD was positive, and she had no symptoms. There was contact with MDR tuberculosis case. It was decided to follow-up the patient without

treatment and prophylaxis with contrast-enhanced low-dose thorax CT every three months in the first year and every six months in the second year. It was thought that giving prophylaxis could trigger resistance. Her diet was regulated, calories increased. However, there was progress in thorax CT, 11 x 7 mm lymph node in the right hilar region. In the follow-up, the right upper lobe apical nodule regressed, and pulmonary nodules smaller than 4 mm were detected in the right middle and lower lobes, and there was no regression at sedimentation four months later. It was decided that MDR tuberculosis treatment was appropriate for case 3.

MDR tuberculosis treatment was recommended due to a history of contact with a resistant tuberculosis case, and radiological findings. Based on the resistance mechanism in the mother, it was decided that MDR tuberculosis treatment was appropriate for case 4.

MDR tuberculosis treatment was recommended due to a history of contact with a resistant tuberculosis case, sedimentation positivity, and radiological findings. Based on the resistance mechanism in the aunt, it was decided that MDR tuberculosis treatment was appropriate for case 5.

Audiometric follow-up, visual examinations, electrocardiography (ECG), blood sugar level, liver, kidney, and thyroid functions were monitored regularly. The index case received a total of 23 months of treatment, six of which were as inpatients. Linezolid-induced neutropenia was observed in two patients and the linezolid dose was reduced by 30%. Neutropenia developed on day 39 in both patients. Following this change, neutropenia resolved in case 2, and treatment with linezolid was continued. As there was no improvement in case 4, linezolid was discontinued and treatment with para-amino salicylic was initiated, with subsequent resolution of neutropenia. Hyperuricemia was controlled with allopurinol treatment.

Discussion

Immune thrombocytopenia (ITP) is a generally autoimmune disease that can result in fatal bleeding. Also, infectious and non-infectious conditions can trigger ITP. Tuberculosis-associated ITP is rarely presented in the literature. Weber et al. have described a 22-year-old case who was diagnosed with ITP due to tuberculous lymphadenitis and presented with symptoms of hypermenorrhea and petechiae. In this case, recovery of thrombocytopenia was only possible with tuberculosis treatment, and it was stated that this period took two days in some cases and three months in others (5). In our case, a rapid improvement was observed within three days. If platelet destruction does not continue after platelet replacement, especially in endemic areas, tuberculosis should be considered as a cause of thrombocytopenia for early diagnosis and treatment against the risks of bleeding, transfusion and immunosuppression (5). It was understood that ITP developed secondary to tuberculosis. This case demonstrates how tuberculosis can actually progress silently.

Conclusion

Diagnosis and treatment may be delayed because of the non-specificity of TB symptoms in children, the difficulty of microbiological tests, and the low sensitivity of diagnostic tests. In children known to have contact with an adult who has MDR-TB, MDR-TB should be considered, even if isoniazid and rifampicin resistance are not detected with culture. Treatment of MDR-TB should include at least five drugs, one parenteral and one quinolone, administered under surveillance in hospital. Close monitoring for side effects is required. Hearing loss, vestibular and renal toxicity, gastrointestinal disorders, hepatotoxicity, neurotoxicity, endocrine effects, hypoglycemia, hypokalemia, hypothyroidism, myelosuppression, peripheral neuropathy, optic neuropathy, headache, dizziness, tremor, drowsiness, nervousness, sleep problems, nightmares, convulsions, psychosis, depression, suicide attempt, tinnitus, restlessness, syncope, skin reactions, and QT prolongation may be observed (1,2).

Management of MDR-TB in pediatric patients is a process that requires patience and dedication. The use of second-line drugs approved according to WHO guidelines in children is necessary to treat life-threatening MDR TB, but careful monitoring is required to quickly recognize dose -and duration- dependent drug adverse events.

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