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CASE REPORT

A Rare Case: Rifampin-Induced Thrombocytopenia

Nadir Görülen Bir Olgu: Rifampisine Bağlı Trombositopeni

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ABSTRACT

Objective: Immune thrombocytopenia (ITP) is a hematological disorder characterized by symptoms such as oral bleeding, petechiae, ecchymosis, and nasal bleeding. Tuberculosis remains a prevalent disease in Turkey, and rifampin is an important agent used in its treatment. Although rare, drug-induced ITP cases associated with rifampin use have been reported. This case report aims to draw attention to the possibility of thrombocytopenia developing as a result of rifampin use.
Case: A 76-year-old male patient who had been receiving rifampin treatment following a diagnosis of tuberculosis presented with complaints of gum and nasal bleeding. The patient's clinical history, physical examination, and laboratory findings were evaluated. Other possible causes of thrombocytopenia, such as pseudothrombocytopenia, myelodysplastic syndrome, and infections, were ruled out. Upon admission, the patient's platelet count was found to be 3,000/mm³. Rifampin treatment was discontinued, and intravenous immunoglobulin (IVIG) and corticosteroid therapy were initiated. As a result of these treatments, a marked improvement in the patient's platelet levels was observed.
Conclusion: Although the risk of rifampin-induced ITP is low, it should still be taken into consideration. This case highlights the potential association between rifampin use and thrombocytopenia in a patient presenting with oral bleeding, nasal bleeding, petechiae, and purpura, and aims to inform clinicians of this possibility.

Keywords: Adverse drug reaction, corticosteroid, immunoglobulin (IVIG), ITP.

ÖZ

Amaç: İmmün trombositopeni ITP, ağız içi kanama, peteşi, ekimoz ve burun kanaması gibi semptomlarla seyreden bir hematolojik bozukluktur. Türkiye'de tüberküloz halen yaygın bir hastalık olup, tedavisinde rifampin önemli bir ajan olarak kullanılmaktadır. Nadir de olsa, rifampin kullanımına bağlı ilaç kaynaklı immün trombositopeni vakaları bildirilmiştir. Bu olgu sunumu, rifampin kullanımına bağlı gelişen trombositopeni olasılığına dikkat çekmeyi amaçlamaktadır.
Olgu: Tüberküloz tanısı sonrası rifampin tedavisi alan 76 yaşında erkek hasta, diş eti ve burun kanaması şikayetleriyle başvurmuştur. Hastanın klinik öyküsü, fizik muayenesi ve laboratuvar bulguları değerlendirilmiş; pseudotrombositopeni, miyelodisplastik sendrom ve enfeksiyon gibi diğer trombositopeni nedenleri dışlanmıştır. Hastanın başvurusunda trombosit sayısı 3.000/mm³ olarak saptanmıştır. Rifampin tedavisi kesilmiş ve intravenöz immünglobulin (IVIG) ile kortikosteroid tedavisi başlanmıştır. Bu tedaviler sonucunda, hastanın trombosit seviyelerinde belirgin bir iyileşme gözlenmiştir.
Sonuç: Rifampin kullanımına bağlı immün trombositopeni riski düşük olmasına rağmen, bu durum göz önünde bulundurulmalıdır. Bu olgu, ağız içi kanama, burun kanaması, peteşi ve purpura ile başvuran bir hastada, rifampin kullanımının trombositopeni ile potansiyel ilişkisini vurgulamakta ve klinisyenleri bu olasılık konusunda bilgilendirmeyi hedeflemektedir

Anahtar Kelimeler: Bağışıklık aracılı trombositopeni, ilaç yan etkisi, rifampisin tedavisinde antitüberküloz tedavi.

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INTRODUCTION

Thrombocytopenia is defined as a decrease in platelet count (PLT) below 150 x 10^9/L. In

patients with liver cirrhosis, PLT values may naturally be below this threshold due to the disease

(1). However, when PLT values drop below 100 x 10^9/L, the severity of thrombocytopenia can be associated with risks ranging from epistaxis to spontaneous intracranial hemorrhage (2). While most anti-tuberculosis drugs (ATT) are considered safe, rifampin can cause rare but potentially fatal side effects, including allergic reactions, thrombocytopenia, hemolytic anemia, renal failure, and shock (2,3).

Compared to other anti-tuberculosis drugs (isoniazid, ethambutol, rifampin, and pyrazinamide), rifampin poses a higher risk of thrombocytopenia (4). These drugs exhibit their thrombocytopenic effects either by suppressing platelet production in the bone marrow or through immune-mediated mechanisms that cause platelet destruction. The immune mechanism is considered more probable, and there are several case reports in the literature about ITP associated with rifampin (5,6). In the immune mechanism, drug-related antibodies frequently bind to the glycoprotein GPIb/IX membrane protein on platelets, causing them to be recognized and destroyed by macrophages in the reticuloendothelial system (4). Studies have found that allergic reactions and autoimmune complications occur more frequently with high-dose and intermittent administration of rifampin (5).

This article presents a case of thrombocytopenia that occurred after rifampin administration. The report underscores the importance of considering rifampin as a potential cause in patients presenting with unexplained thrombocytopenia.

Case Report:

A 76-year-old male patient presented to an external center due to gum bleeding and occasional nosebleeds persisting for 2-3 days. Initial laboratory tests at the center revealed a platelet count of 3000/mm^3, leading to his referral to our center, where he was hospitalized in the hematology department with a preliminary diagnosis of immune thrombocytopenic purpura ITP. The patient reported gum bleeding and nosebleeds that he had difficulty stopping independently over the past 2-3 days.

Upon further history-taking, it was learned that the patient had visited the pulmonology clinic

2.5 months ago with complaints of throat irritation, cough, yellowish sputum production, and a

6 kg weight loss over the past month. He had been diagnosed with seasonal allergic rhinitis and prescribed salmeterol, fluticasone propionate, levocetirizine dihydrochloride, and montelukast. Upon symptom persistence, bronchoalveolar lavage (BAL) was performed at the relevant center, leading to a tuberculosis diagnosis.

The patient was started on antituberculosis therapy (ATT) consisting of isoniazid (300 mg/day), rifampicin (600 mg/day), pyrazinamide (2000 mg/day) and ethambutol (1500 mg/day). On the 10th day of treatment, pyrazinamide and ethambutol were discontinued due to elevated transaminase levels. The patient continued treatment with isoniazid 300

mg/day and rifampicin 600 mg/day for two weeks.

Further medical history revealed that the patient was being followed up for liver cirrhosis and underwent surgery 10 months ago for a liver mass, which was diagnosed as hepatocellular carcinoma (HCC). It was noted that the patient had not received any oncological treatment for HCC since then.

Physical examination showed stable vital signs with a bronchovesicular breath sound in the right basal lung. Inspection of the abdomen revealed a surgical scar. Palpation indicated a palpable liver (10 cm) and spleen (5 cm). Percussion revealed a closed Traube's space. The patient had ecchymoses on the pretibial area, the largest measuring 3 × 4 cm, and widespread petechiae and purpura on the arms and legs. No other pathological findings were detected.

Laboratory findings included hemoglobin (HGB): 10.8 g/dl, white blood cell (WBC) count: 4890/mm³, platelet count (PLT): 2000/mm³, creatinine: 0.72 mg/dl, AST: 40 U/L, ALT: 22 U/L, and INR: 1.19. These were deemed within normal limits. A review of tests conducted one month prior showed a platelet count of 128,000/mm³.

Peripheral blood smear revealed several giant platelets (Fig.1). The patient was started on 1 mg/kg/day IV methylprednisolone and received IVIG at a dose of 1 g/kg/day for two days. Given the erythrocyte sedimentation rate of 44 mm/h and CRP of 7 mg/L, along with the absence of an infectious focus or fever, an infectious etiology was ruled out. Further evaluations for thrombocytopenia etiology included tests for antinuclear antibody, anti-dsDNA, lupus anticoagulant, and acute viral serologies (HBV, HCV, HIV, CMV, EBV), all

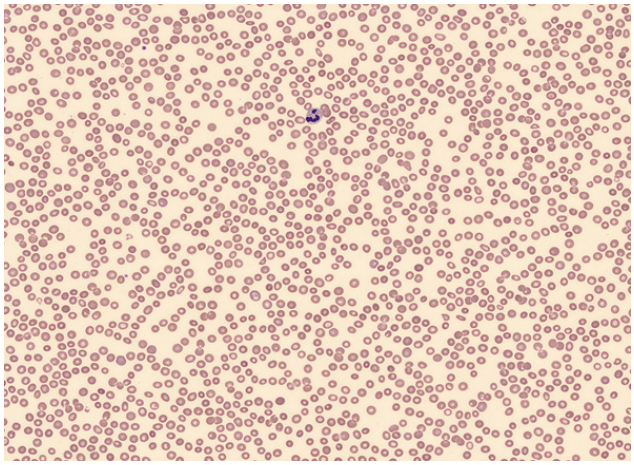

Figure 1. Giant platelets were observed in several fields; no atypical cells or schistocytes were detected.

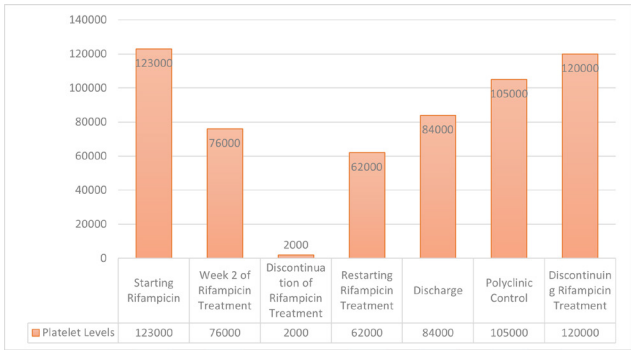

Figure 2. Platelet (PLT) levels following the discontinuation of rifampicin, initiation of treatment, and reintroduction of rifampicin.

of which were negative. Imaging studies showed no lymphadenopathy suggestive of lymphoproliferative disease.

During this time, rifampicin therapy was temporarily discontinued based on a risk-benefit assessment. On the third day of steroid therapy, the platelet count reached 30,000/mm³, and by the fourth day, it was 62,000/mm³. The patient resumed rifampicin and isoniazid therapy alongside corticosteroids. On the sixth day, the platelet count increased to 84,000/mm³, and the patient was discharged with a prescription for 80 mg/day corticosteroids, 300 mg/day rifampicin, and 600 mg/day isoniazid.

At the outpatient follow-up, two weeks into treatment, the platelet count had risen to 105,000/mm³, and the corticosteroid dose was tapered to 64 mg/day. The corticosteroid dose was subsequently reduced by 16 mg per week until a maintenance dose of 16 mg/day was reached. The antituberculosis therapy was completed after four months, and rifampicin, isoniazid, and corticosteroid treatments were discontinued. During follow-ups, platelet counts remained stable at approximately 120,000/mm³

DISCUSSION

Limited epidemiologic data exist regarding the overall incidence of drug-induced thrombocytopenia (DITP). The estimated frequency is approximately 10 cases per 1,000,000 individuals per year, although this number is likely underestimated due to underreporting and misdiagnosis (7).

In studies conducted in the literature, the relationship between hepatocellular carcinoma (HCC) secondary to liver cirrhosis and the development of idiopathic thrombocytopenic purpura ITP during clinical follow-up has been investigated. No significant correlation was found between HCC and ITP. It was observed that the ITP seen in these cases was associated with the chemotherapeutic agents used in the treatment of HCC (8).

In this case, the platelet (PLT) count of our patient, whose average PLT level was 120×10^9, showed improvement after discontinuation of the offending drug in the 4th month of treatment due to the inability to stop rifampicin during the thrombocytopenia attack as per the recommendations of the pulmonary diseases department. This observation supports the association of thrombocytopenia with rifampicin (2,4).

Standard corticosteroid regimens include 40 mg of dexamethasone intravenously once daily for four days, or 1 g of methylprednisolone intravenously once daily for three consecutive days.

IVIG is generally used at a dose of 1 g/kg, and repeated the following day if platelet counts remain below 50,000/µL (9).

Compared to the cases in the literature, an increase in liver function tests was detected during close follow-ups in our patient, who had been diagnosed with liver failure (LC-s), while on quadruple therapy. For this reason, the treatment was switched to dual therapy. One week after the initiation of dual therapy, the patient's thrombocytopenia was detected, and they were admitted to our hospital. During hospitalization, consultation with a pulmonologist was performed. The current situation was evaluated as drug-induced thrombocytopenia, and it was recommended not to discontinue rifampicin considering the risk-benefit ratio. Instead, it was decided to add steroid therapy to the ongoing rifampicin treatment.

Among differential diagnoses, pseudothrombocytopenia, myelodysplastic syndrome, and aplastic anemia were ruled out with a peripheral blood smear. The absence of schistocytes on the peripheral blood smear and normal kidney function excluded thrombotic thrombocytopenic purpura (TTP). Additionally, disseminated intravascular coagulation was ruled out as the coagulation panel and fibrinogen levels were within normal ranges.

In the literature, thrombocytopenia has also been reported in patients using rifabutin after developing rifampicin-induced thrombocytopenia (5). However, in patients

confirmed to have thrombocytopenia caused by rifampicin, treatment with rifabutin was completed alongside isoniazid, ethambutol, and pyrazinamide. Following this treatment process, the patient's platelet count was reported to be maintained between approximately 50,000 and 100,000/µL (10).

CONCLUSION

Antituberculosis drugs, generally considered safe, particularly rifampicin, can cause a sudden drop in platelet count in some individuals through immune-mediated side effects. This case highlights that rifampicin-induced thrombocytopenia, although rare, is a serious side effect requiring diagnosis and intervention when observed. (4,5)

The administration of immunosuppressive treatments such as intravenous immunoglobulin (IVIG) and high-dose prednisolone to our patient helped achieve a rapid increase in platelet count. A gradual improvement in platelet levels was observed after the initial intervention, and the patient's liver and kidney functions were closely monitored throughout the treatment.

Additionally, the gradual tapering of steroids minimized side effects, allowing the completion of antituberculosis therapy without complications.

This case underscores the necessity of regular monitoring of hematological and biochemical parameters during the treatment with rifampicin and other antituberculosis drugs. Cases of drug-induced thrombocytopenia identified early can be managed successfully through discontinuation of the drug and supportive treatment approaches. This is particularly critical in preventing potentially life-threatening bleeding complications, especially in high-risk patients. (2,4)

In conclusion, patients receiving rifampin should be closely monitored for hematologic side effects such as thrombocytopenia. Regular complete blood counts are recommended, especially during the initial weeks of therapy. In cases where thrombocytopenia develops, prompt discontinuation of the suspected drug and initiation of immunosuppressive therapy may prevent serious bleeding complications.

In conclusion, since rifampicin-induced thrombocytopenia may be mediated by immune mechanisms, it is recommended to closely monitor patients undergoing this treatment. This case demonstrates the positive impact of early diagnosis and appropriate management of the rare clinical presentation of rifampicin-induced thrombocytopenia on patient health.

Conflict of interest To the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.

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