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Case Report

Thrombocytopenia due to the use of rifampicin in brucellosis

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Abstract. Thrombocytopenia may develop after drug therapy and is a life-threatening condition. Thrombocytopenia may also occur after high-dose use of rifampicin which is an antibiotic. Here, we report five cases of thrombocytopenia developing after the use of rifampicin for the treatment of brucellosis. Four cases had experienced diffuse petechiae and ecchymosis with severe thrombocytopenia. The other patient had a complicated thrombocytopenia with intracerebral hemorrhage. As a result, the usage of rifampicin in the treatment of brucellosis could lead to systemic or central complications.

Key words: Brucellosis, rifampicin, thrombocytopenia

1. Introduction

Drug-related thrombocytopenia is a condition that is rather widely encountered and has serious clinical consequences. Many medications can lead to the formation of antibodies against thrombocytes, which are responsible for removal of thrombocytes from the circulation (1). This situation results in sudden decrease of the number of thrombocytes when the drug is taken. The differentiation of drug-related thrombocytopenia from idiopathic thrombocytopenic purpura and identification of the causative drug is of vital importance.

Drug-related thrombocytopenia is diagnosed by excluding the other causes and to observe the discontinuation of thrombocytopenia following cessation of the medications which are thought to be the cause (2).

Rifampicin is an antibiotic used in several diseases and has a potential of producing immune thrombocytopenia. Thrombocytopenia is generally related to high dose and twice a week use. It has been demonstrated that rifampicin-dependent antiplatelet antibodies are responsible for the development of this complication (3-6).

Rifampicin-induced thrombocytopenia cases are generally in the form of rare case reports (7, 8). Here, we report five thrombocytopenic cases due to rifampicin. All cases were admitted to the hospital due to severe thrombocytopenia and bleeding after rifampicin treatment which had begun for brucellosis.

2. Cases

2. 1. Case

A 35 year-old woman, who had been admitted to health clinic because of fever, sweating, arthralgia and weakness, was diagnosed as having brucellosis. The laboratory test results were as follows: hemoglobin (Hgb) 11.2 gr/dL, white blood cell (WBC) count $5.7x10^9$/L, platelet (PLT) count $198x10^9$/L and the brucellosis standard agglutination test (SAT) value was 1/640 positive. Rifampicin 600 mg/day and doxycycline 200 mg/day were started as the treatment for her brucellosis. The patient was referred to our hospital due to the appearance of rashes on the extremities and tongue on the 7th day of treatment. On the physical examination, widespread petechiae and ecchymosis were observed on the whole body. The spleen was palpable 2 cm under the costal arch. The laboratory tests revealed as follows: Hgb 10.6 gr/dL, WBC count $6.4x10^9$/L, PLT count $3x10^9$/L and brucellosis SAT 1/640 positive. In the history, we learned that the patient had received

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brucellosis treatment two years ago, but had to stop because of the rashes on the body. Because the thrombocytopenia was thought to be related wto the use of rifampicin, this drug was stopped. The treatment was continued by doxycycline and ciprofloxacin. No additional treatment was given for the thrombocytopenia. On the third day, the number of thrombocytes started to increase about $70x10^3$/L. The patient was discharged from the hospital after the number of thrombocytes reached to a normal range in the second week.

2. 2. Case

An 18 year-old woman was admitted to the emergency room due to unconsciousness, inability to speak and weakness on the right side. The patient had been diagnosed as having brucellosis a week ago in another health clinic and had been given doxycycline 200 mg/day and rifampicin 600 mg/day. The first laboratory results in that clinic was found to be as follows; Hgb 11.8 gr/dL, WBC count $3.7x10^9$/L, PLT count $218x10^9$/L, and the brucellosis SAT 1/1280 positive. After the first week of treatment, rashes in the arms and the upper part of the trunk had been seen. In physical examination, there were widespread body petechiae and ecchymosis. The patient was somnolent, the losses of strength in the right upper extremity was 1/5 and in the right lower extremity, it was 3/5. There was neck stiffness and the finding of a mild meningeal irritation. In the laboratory evaluation, the Hgb was 13 gr/dL, WBC count was $9.2x10^9$/L, PLT count was $3x10^9$/L. On cranial tomography, it was seen that there was a 7.5x5 cm area of intracranial hemorrhage in the left parietal lobe (Figure 1). A few hours after the hospitalization, the level of consciousness turned into stupor and the patient experienced an epileptic convulsion. For this reason, a control cranial CT was performed. It was seen that the hemorrhagic area had widened. As the number of thrombocytes had been normal at the time of diagnosis, the possible cause of thrombocytopenia was thought to be rifampicin and therefore it was ceased. In the history, it was learnt that there had been no use of rifampicin before. It was given 1 gr methylprednisolone per day for three days and 1 gr intravenous immunoglobulin per kilogram weight for two days, in addition to thrombocyte transfusion. After this treatment, the number of thrombocytes started to increase on the second day. It reached to the normal level on the ninth day. Despite all efforts, the patient died on the 18th day because of intracranial hemorrhage.

2. 3. Case

A patient, who had been admitted to a hospital because of weakness, fatigue, fever and lumbar pain 8 days ago, was diagnosed as having brucellosis after the evaluations of laboratory tests (Hgb: 10 gr/dL, WBC count: $3.4x10^9$/L, PLT count: $221x10^9$/L and brucellosis SAT 1/640 positive). Rifampicin 600 mg/day and doxycycline 200 mg/day had been given as the treatment. On the fifth day of the treatment, small rashes were observed on the arms. The patient was referred to us on the seventh day because of spreading of the rashes on the body. The patient's physical examination was normal except for the widespread skin petechiae and ecchymosis. Laboratory evaluation revealed that: Hgb 11 gr/dL, WBC count $4.1x10^9$ /L, and PLT count $5x10^9$/L. Because the thrombocyte number had been normal during the diagnosis, the possible reason was thought to be rifampicin and hence, the rifampicin was stopped. The treatment was continued with doxycycline and ciprofloxacin because the brucellosis SAT was 1/640 positive.

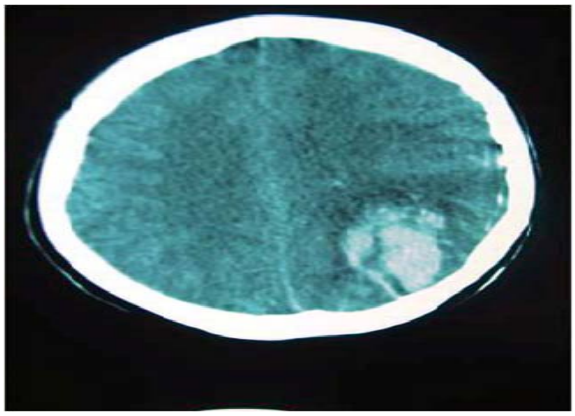

Fig. 1. Intracranial haemorrhage in the left parietal lobe with dimensions of 7.5x5 cm.

The clinical condition of thrombocytopenia was followed without any additional medication. The number of thrombocytes began to increase on the third day. The number of thrombocytes reached the normal level on the tenth day.

2. 4. Case

A 35 year-old female patient had been diagnosed as having brucellosis at a healthcare center. In the laboratory evaluation, the Hgb was 12.9 gr/dL, WBC count was $5.2x10^9$/L, PLT count was $320x10^9$/L, and the brucellosis SAT was 1/320 positive. Rifampicin 600 mg/day and doxycycline 200 mg/day was prescribed for the patient. At the first week of treatment, rashes and ecchymosis were seen on the body. The patient was referred to us by her physician with the suspicion of vasculitis. The laboratory evaluation revealed that: Hgb level 12 gr/dL, WBC count $6.9x10^9$/L, PLT count $4x10^9$/L, and brucellosis SAT 1/320 positive. On the physical examination, there were widespread petechiae and ecchymosis in the body and oral mucosa. The spleen was 1.5

cm palpable under the costal arch. It was learnt from the history that the patient had received intermittent brucellosis treatment for three years, because the patient had used the treatment irregularly. The reason of thrombocytopenia was thought to be rifampicin. The treatment was continued by doxycycline and ciprofloxacin. The patient was given high-dose methylprednisolone (HDMP) (1 gr methylprednisolone per day) for three days and 1 gr intravenous immunoglobulin per kilogram weight for two days, because of the nasal bleeding. At the fourth day, steroid treatment was continued with oral 1mg/kg methylprednisolone for a week (9-11). The number of thrombocytes began to increase on the third day. The number of thrombocytes reached to the normal level on the tenth day. The increase in the thrombocyte count was both related to the usage of methyl prednisolone and cessation of rifampicine.

2. 5. Case

A 28 year-old woman, who had been admitted to the hospital because of fever, arthralgia and weakness, was diagnosed as brucellosis. In the laboratory evaluation, Hgb: 11.7 gr/dL, WBC count: $3.9x10^9$/L, PLT count: $184x10^9$/L and the brucellosis SAT value: 1/640 positive have been found. Rifampicin 600 mg/day and doxycyclin 200 mg/day have been started as a treatment. The patient was referred to us due to rashes on the extremities on the 10^{th} day of treatment. On the physical examination, widespread petechiae and ecchymoses were observed. In the laboratory evaluation, Hgb was 10 gr/dL, WBC count was $5.2x10^9$/L, and PLT count was $22x10^9$/L. The rifampicin treatment was stopped. The treatment was continued by doxycycline and ceftriaxone. Any additional treatment was not given for the thrombocytopenia. On the fifth day, the level of thrombocytes had started to increase. His clinical symptoms were disappeared and laboratory findings improved (thrombocyte count: $187x10^3$/L) at the second week.

3. Discussion

Drug-related thrombocytopenia may be seen due to several differently structured medications. The clinical condition is characterized by thrombocytopenia, petechiae, purpura and sometimes intracranial hemorrhage. Drug-induced thrombocytopenia that highlighted one of the first drugs is quinine (12). This effect was thought to be related to the consequent antibody production against thrombocyte membrane glycoproteins (13). Antibody-bound thrombocytes were quickly removed from the circulation by the reticuloendothelial system. Later, it was reported that other drugs could result in antiplatelet antibody production that could lead to thrombocytopenia. These drugs were sulfonamides, rifampicin and ranitidine (14-16).

The side effects of rifampicin are abdominal and cutaneous symptoms, flue-like symptoms, increased liver function tests and thrombocytopenia. These side effects are generally seen in patients who receive intermittent treatment rather than daily use. It was reported that continuous rifampicin treatment had resulted in immunological tolerance. On the other hand, intermittent treatment had resulted in sensitization and led to gross reaction after retreatment with rifampicin. Antibody-coated thrombocytes are removed from circulation and antibodies are developed against to platelet Gp IIb/IIIa and Gp I-V-IX antigenes (17, 18). Pool et al. reported in three cases that there is an important correlation between the side effects of rifampicin and rifampicin-related antibodies in patients who had received rifampicin given twice a week (19). However, thrombocytopenia due to daily use of rifampicin has also been reported (8). Our first case received treatment with the rifampicin-doxycycline combination. On the seventh day of second rifampicin treatment for the same disease, widespread body ecchymoses were seen. The fourth case had received irregular rifampicin treatment several times. The other three patients had no history of previous use of rifampicin.

Specific criteria have been postulated for assessing the likelihood for development of immune thrombocytopenia related to medication (20,21). These criteria are; suspicious drug use before the thrombocytopenia, exclusion of other etiologies for thrombocytopenia, and relapsing of the disease with re-use of the drug. However, the best evidence is the sudden increase in the number of thrombocytes after cessation of the drug.

In our cases, thrombocytopenia may be thought to be related to brucellosis. Thrombocytopenia was reported in 1-26% of the cases with brucellosis. It is rarely related to hemorrhage (22-24). But thrombocyte counts of our patients were normal when diagnosed brucellosis in the healthcare centers where the brucellosis treatment had been planned and thrombocyte count decreased after treatment. Furthermore, increase in the number of thrombocytes after cessation of rifampicin is indicative of drug-related thrombocytopenia. In rifampicin-induced thrombocytopenia, the number of thrombocytes in most cases had started to increase 7-10 days following the cessation of the drug. In our study, all the patients had reached the normal thrombocyte number in the second week without treatment. In some patients, the number of

thrombocytes would decrease to a level that severe bleedings could occur. In the treatment of these patients, steroid, platelet transfusion, intravenous immunoglobulin and plasmapheresis may be needed. We used high dose steroid and intravenous immunoglobulin in two of our patients who had intracerebral hemorrhage and nasal bleeding. The other three cases did not receive any treatment because there was no severe bleeding. Only rifampicin was stopped and followed closely. The number of thrombocytes of these two cases began to increase on the third day. The number of thrombocytes reached the normal level in the second week.

In conclusion, all of the reported cases of rifampicin-induced thrombocytopenia had been receiving tuberculosis treatment, which was an intermittent treatment. The reason for reporting these cases was to mention that the used dose and the way of application for brucellosis treatment in the high brucellosis incidence areas could result in this complication due to rifampicin. We believe that informing the patients about the complications and signs of this complication would result in early referral to the physician before the appearance of serious complications.

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