Unusual presentation of more common disease/injury

Do not miss rifampicin-induced thrombocytopenic purpura

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Summary

Drug-induced immune thrombocytopenia (DITP) can be triggered by a wide range of medications. Although many cases of DITP are mild, some are characterised by life-threatening bleeding symptoms. In the treatment of tuberculosis there are special therapeutic problems related to adverse effects of drugs, compliance to treatment and microbial resistance. Thrombocytopenia is an uncommon but potentially fatal adverse effect of certain antituberculous drugs when the incriminating drug is taken by a susceptible individual. Here the authors report a case of rifampicin-induced thrombocytopenia, which although rare, needs attention.

BACKGROUND

The currently available antituberculous drugs, all have its side effects. Thrombocytopenia is an uncommon but potentially life-threatening complication of certain antituberculous drugs and is characterised by rapid destruction of platelets whenever an offending drug is taken by a susceptible person. Diagnosis of drug-induced immune thrombocytopenia may consist of identifying clinical symptoms (bruising, petechiae, bleeding), a careful evaluation of the causal relationship of the suspected causative drug, general laboratory investigation, such as total blood count and peripheral blood smear (to rule out pseudo thrombocytopenia) and platelet serology tests. The discovery of isolated thrombocytopenia in a patient taking several medications presents a challenging clinical problem. Laboratory confirmation of drug induced thrombocytopenia at time of initial presentation is often not possible because tests for drug dependent antiplatelet antibodies are not available in most clinical laboratories. The diagnosis of drug induced thrombocytopenia can be supported only by resolution of thrombocytopenia after discontinuation of suspected drug. Till date only isolated cases are reported due to rifampicin induced thrombocytopenic purpura.¹

CASE PRESENTATION

A 32-year-old female patient presented with complaints of low-grade fever, cough with expectoration, right-sided chest pain and loss of appetite for the last 2 months. She also complained of epistaxis and gum bleeding for last 5 days. A detailed clinical examination revealed palpable, non-blanching purpura on the skin of both upper and lower limbs and on the anterior abdominal wall (figure 1A,B). Subconjunctiva haemorrhage was noted in the left eye. Examination of oral cavity was normal except for bleeding gums. The patient had been taking antitubercular drugs combination of rifampicin, isoniazid, pyrazinamide and ethambutol since 10 days which was prescribed for pleural effusion.

INVESTIGATIONS

Investigations revealed haemoglobin 6.4 g (10.4 g% recorded at 1 month back), platelet count-10000/mm³

with large bizarre platelets in peripheral blood, bleeding time 11 min 08 s and coagulation time 4 min 45 s. Liver function tests and renal function test were within normal limits. Prothrombin time was 16 s (normal 10–14 s) and prothrombin concentration 60%. Viral markers for hepatitis B, C and HIV were negative. IgM dengue and antineutrophil cytoplasmic antibody were negative. Chest x-ray showed right-sided pleural effusion (figure 1C). Pleural fluid examination showed; total cell counts-580 with differential count consisted of 98% lymphocytes and 2% polymorphs, protein 4.9 g%, albumin 2.7 g% and antidiuretic hormone 235.3 u/l.

DIFFERENTIAL DIAGNOSIS

Immune thrombocytopenic purpura.

TREATMENT

We withdrew the antituberculous drugs. Promptly nasal packing was done for epistaxis and six units of platelets concentrates and two units of packed red blood cells were transfused. After 4 days of treatment, her platelet count returned to 1.5 lac/mm³ and patients improved symptomatically. Later on, after informed consent, streptomycin, ethambutol, pyrazinamide, isoniazid were started gradually without complication and her platelet counts were monitored which remained normal. Rifampicin was given after taking full precaution and informed consent from the patient. Her platelet count dropped to 16000/mm³ with appearance of purpura and epistaxis thus providing evidence of rifampicin induced thrombocytopenia. Test for rifampicin antibodies could not be done due to lack of facilities. She was again managed conservatively. All her haematological parameters were monitored regularly during her hospital stay and she was discharged on streptomycin, isoniazid, ethambutol and pyrazinamide.

OUTCOME AND FOLLOW-UP

At the end of first week his platelet count became completely normal. The patient was discharged on 10th day of admission with advice for follow-up.

Figure 1 (A) Palpable purpura over the face. (B) Palpable purpura over the legs. (C) Right-sided pleural effusion.

DISCUSSION

Rifampicin is a well tolerated and highly effective-bactericidal antituberculosis drug when administered in regular daily doses. Flulike syndrome, thrombocytopenia, acute renal failure and acute haemolytic anaemia are more common in intermittent regimens and are caused by rifampicin dependent antibodies. The appearance of these antibodies depends both on the size of the dose given and the rhythm of rifampicin administration. In a study, 16% of the patients given once weekly antituberculous treatment developed rifampicin dependent antibodies whereas only 6% developed these on twice weekly regimen.² In other study, the presence of rifampicin-dependent antibodies correlates significantly with the occurrence of adverse reactions.¹ Bassi *et al* reported rifampicin dependent antibodies in 10 out of 32 patients; these were detected 3 weeks after discontinuation of a 600 mg daily dose, although no antibodies were detected on the day after the treatment was stopped. The continuous treatment resulted in neutralisation of any antibodies formed, the complex being continuously removed without causing an allergic dose regimens allows a sufficient quantity of antibodies to be built up during antigen free interval, so that when rifampicin is re administered, an intense reaction takes place.³ However, the risk of purpura occurring with daily rifampicin cannot be completely discounted.

The drugs causing thrombocytopenia lead to either suppression of platelet production or immunologic platelet destruction. Most of the drugs induce thrombocytopenia by the latter mechanism. The platelets are damaged by complement activation following the formation of drug-antibody complex. Current laboratory tests can identify the causative agent in 10% of patients with clinical evidence of drug-induced thrombocytopenia. However,

the aetiology of drug-induced thrombocytopenia can be established by a prompt rise in the platelet count when the suspected drug is discontinued.² In the index case, the diagnosis of thrombocytopenic purpura was suspected when the platelets count was reached to normal level after 4 days of discontinuing antituberculous treatment and it got confirmed when reintroduction of rifampicin have led to sudden drop in platelets count.

The patient records showed that she had mild anaemia which is prevalent in young Indian females and which might also be due to underlying chronic disease. Severe anaemia at the time of admission might be an acute onset phenomenon. The underlying mild anaemia was exacerbated by acute haemorrhage (epistaxis and gum bleeding). Drug reaction can also lead to anaemia along with thrombocytopenia as a part of immuno-allergic destruction of both platelets and red blood. But, this patient was not icteric and serum bilirubin was normal. Packed red blood cells were transfused to patient after which her haemoglobin remained normal and did not fall even on reintroduction of rifampicin. It also suggests that anaemia was due to acute haemorrhage.

A decision of whether to discontinue medication in a patient with possible drug-induced immune thrombocytopenia (DITP) must be based on clinical considerations, as testing for drug-dependent antibodies (DDAbs) requires time and is not widely available. Although identification of a platelet-reactive DDAB is not useful in acute management, for practical reasons, antibody studies can help to implicate a specific drug as the cause of a thrombocytopenic episode and provide justification for measures taken to prevent future exposure. When necessary, pharmacologically equivalent drugs with a different chemical structure can usually be substituted safely for medications essential

to a patient's medical care. It is reasonable to give platelet transfusions to severely thrombocytopenic patients who have 'wet purpura', because of their increased risk of intracranial haemorrhage.⁴ However, the effectiveness of transfusions has not been formally studied. As most drugs are cleared within a few days, platelet levels often start to increase within 1 or 2 days after discontinuing the suspected drug. Rarely, thrombocytopenia and bleeding symptoms persist for several weeks.

It is a common practice to administer corticosteroids in DITP, but whether they are beneficial or not, is controversial.⁵ Intravenous immunoglobulins⁶ and even plasma exchange have been given for treatment of DITP with possible but not yet proven benefit.⁷ Although corticosteroid could be administered to the patient but were avoided first due to their doubtful role and second, they could also pose diagnostic difficulty by changing pathophysiology. Moreover, corticosteroids could be considered if this patient had been in shock but except for thrombocytopenia, she did not have any other indication that would necessitate us to use corticosteroid.

Learning points

- ▶ Thrombocytopenia is sometimes may be also be caused by rifampicin, has more chances to occur when high-doses are given twice-weekly.
- ▶ This complication is rare when the medication is given in small daily doses, or following a prolonged interruption of therapy.
- ▶ The diagnosis of DITP is suspected on the basis of clinical background and contemporary drug intake by patient and is best confirmed when the condition recur on reintroduction of suspected drug.
- ▶ As in most of the drug reactions, the suspected drug should be withdrawn first then other measures to be taken according to patient condition.

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Competing interests None.

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