Drug-induced immune thrombocytopenia due to moxifloxacin

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SUMMARY

A 39-year-old woman with 1 day of oral petechiae, leg ecchymoses and epistaxis was found to have isolated thrombocytopenia. She had recently completed a 10-day course of moxifloxacin for an upper respiratory infection. On further questioning, she had developed thrombocytopenia 2 years earlier after a treatment course with moxifloxacin. After ruling out other causes, drug-induced immune thrombocytopenia due to moxifloxacin was diagnosed. Her platelets returned to normal range 15 days after finishing the medication.

BACKGROUND

To our knowledge, this is the first reported case of moxifloxacin causing isolated symptomatic thrombocytopenia. There are multiple case reports and case series of other fluoroquinolones causing drug-induced thrombocytopenia suggesting that this is a class adverse effect. Fluoroquinolones are frequently used for many types of infections. Therefore, clinicians need to be mindful of this potential adverse effect.

CASE PRESENTATION

A 39-year-old woman presented with 1 day of small bruises in her mouth, large bruises on her legs, and a bloody nose. She recently had been treated for an upper respiratory infection with a 10-day course of moxifloxacin which she finished 1 week prior to presentation. Notably, she had a history of thrombocytopenia with moxifloxacin 2 years prior.

She had a medical history significant for allergic bronchopulmonary, aspergillosis, bronchiectasis, asthma and hypothyroidism. She had no significant social or family history. Her current medications included levothyroxine, desvenlafaxine and fexofenadine.

INVESTIGATIONS

A complete blood count was normal except for a platelet count of 6000/mm³. Peripheral smear was normal except for low number of platelets. Her platelet level 1 year prior was found to be 292 000/mm³.

Prothrombin time (PT), partial thromboplastin time (PTT), International Normalized Ratio (INR), fibrinogen, antithrombin III activity and schistocyte evaluation were negative. d-Dimer was positive. Hepatitis C antibody and HIV1/HIV2 tests were negative. Serum protein electrophoresis was normal. Antinuclear antibodies panel was also negative. Rheumatoid factor was normal. Antibody levels were within normal range. Heparin-induced platelet antibody test was negative. A non-specific

platelet antibody test was positive. Ultrasound evaluation of her spleen was normal.

DIFFERENTIAL DIAGNOSIS

Evaluation of complete blood count and peripheral smear allows differentiation of thrombocytopenia into an isolated platelet problem or multiple lineage problem. Multiple lineage abnormalities may be due to aplastic anaemia, leukaemia, hypersplenism, disseminated intravascular coagulation or myelodysplastic syndromes. Isolated thrombocytopenia has several possible causes including autoimmune diseases, medications or infections. Idiopathic thrombocytopenic purpura is a diagnosis of exclusion. Viral serologies can be used to rule out common infectious aetiologies, such as hepatitis C and HIV. Autoimmune disorders can be ruled out by a thorough history and examination and measurement of autoimmune markers such as rheumatoid factor and antinuclear antibodies. Medication induced thrombocytopenia typically includes a history of a recent start of a new agent.

TREATMENT

On admission, it was confirmed that she had taken her last dose of moxifloxacin 7 days prior to presentation. Platelet transfusion began on admission, and after 7 units, her platelets increased to 11 000/mm³. They decreased back down to 6000/mm³ within 24 h, and she was started on intravenous steroids with additional platelet transfusions. Her platelet levels responded well initially but dropped to less 5000/mm³ within 12 h. On hospital day 4, she was treated with intravenous immunoglobulin, after which her platelets stabilised at 5000/mm³. Additional platelet transfusions were held at that time.

OUTCOME AND FOLLOW-UP

Over the 3 days following intravenous immunoglobulin, her platelets slowly began to increase. On the seventh hospital day, she was discharged to home with a platelet count of 28 000/mm³. Repeat platelet levels the day after discharge and 4 months later were 75 000 and 290 000/mm³, respectively.

DISCUSSION

Drug-induced thrombocytopenia is thought to occur via two mechanisms: impaired platelet production or increased platelet destruction.¹ The latter typically occurs more often than the former and is due to drug-induced immune response. While not completely understood, immune-mediated platelet destruction occurs when the drug interacts with platelets or antibodies to expedite the clearance of platelets.¹ Time course varies by

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mechanism and onset can be with first exposure, prolonged exposure, or repeat exposure. Impaired platelet production typically occurs with antineoplastic agents.

The clinical spectrum of drug-induced immune thrombocytopenia ranges from asymptomatic thrombocytopenia to symptomatic thrombocytopenia to hemolytic-uremic syndrome (HUS) or thrombotic thrombocytopenia purpura (TTP) in severe cases.¹ Typically, manifestations develop after exposure of offending medication for at least 1 week. After discontinuation of the offending agent, bleeding usually stops within 1 or 2 days, and platelets return to normal in 4–8 days. Rarely, thrombocytopenia lasts for weeks.¹

Diagnosis of drug-induced thrombocytopenia is usually a clinical diagnosis after excluding other aetiologies of thrombocytopenia. Clinical criteria (table 1) have been developed to help determine the probability that a drug caused the drug-induced immune thrombocytopenia.² Testing for antibodies that can react to platelets can aid in diagnosis but is hindered by limited availability and uncertain sensitivity.¹ Finally, a diagnostic challenge with the suspected agent can be performed but should be reserved for those who require the medication for their care.¹

Management of drug-induced thrombocytopenia usually involves discontinuing the offending medication. Platelets may be given if platelets are significantly low or if the patient has bleeding.¹ Despite common practice, the benefit of corticosteroid administration has not been established. In severe or persistent cases of thrombocytopenia, intravenous IgG and plasma exchange have been used but no proven benefit has been demonstrated.¹

To our knowledge, this is the second reported case of moxifloxacin causing drug-induced immune thrombocytopenia but the first reported case that caused isolated symptomatic thrombocytopenia.³ The other case involved moxifloxacin causing thrombotic thrombocytopenic purpura. In that case, clinical presentation consisted of symptoms of fatigue, dyspnoea on exertion, lethargy, and episodes of aphasia with laboratory findings of anaemia, thrombocytopenia, schistocytes and elevated creatine. Despite having a platelet level less than 10 000/mm³, there were no symptoms or signs of thrombocytopenia. A 5-day course of moxifloxacin was given twice in a 6-week time period and clinical manifestations began 3 days into second course. Treatment course consisted of

steroids, fresh frozen plasma, packed red blood cells and plasma-pheresis. Platelets returned to normal range within 7 days of discontinuation of moxifloxacin and treatment. In our case, thrombocytopenia was the only laboratory abnormality and symptoms were related to it.

In addition, this is the first definite causative relationship between moxifloxacin and thrombocytopenia to our knowledge.³ Our patient had two episodes of thrombocytopenia with similar symptoms. Both incidents were preceded by taking moxifloxacin, fulfilling criterion 1. Her platelets returned to normal range after discontinuing moxifloxacin and remained normal afterwards, which fulfils the second criterion. On both occasions, she had a thorough evaluation to help exclude other causes of thrombocytopenia, which fulfils criterion 3. Finally, she had recurrent thrombocytopenia after re-exposure with the moxifloxacin, fulfilling the fourth criterion. Fulfilment of all four criteria makes causative relationship between moxifloxacin and thrombocytopenia definite. The case of thrombotic thrombocytopenic purpura with moxifloxacin only fulfilled three of the clinical criteria (table 1) making it only a probable relationship.³

On additional literature review, there were several case reports and series documenting other fluoroquinolones causing drug-induced immune thrombocytopenia. Ciprofloxacin, levofloxacin, norfloxacin, tosufloxacin, alatrofloxacin, pefloxacin, temafloxacin and nalidixic acid are all fluoroquinolones that have been documented as causing thrombocytopenia.⁴ Of these, ciprofloxacin, temafloxacin and pefloxacin were associated with asymptomatic thrombocytopenia, thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome.^{4–9} Similar to this patient's case with moxifloxacin, levofloxacin, norfloxacin, tosufloxacin, alatrofloxacin and nalidixic acid were associated with isolated thrombocytopenia and one or more of the following symptoms: epistaxis, petechiae, purpura or haematoma.^{10–18}

Typically, drug-induced immune thrombocytopenia occurs after at least a week after exposure and begins to resolve within several days of medication discontinuation. Our patient presented 17 days after initial exposure, was found to have a platelet level of 6000/mm³ (which dropped after admission), and recovered to stable range 15 days after stopping medication. In comparison, cases with the fluoroquinolones that presented similarly to our case began about 12 days after initial exposure (range was 3–17 days).^{9–17} Platelets levels averaged about 13 000/mm³ on presentation (range was 1000–38 000/mm³).^{11–18} After discontinuation of the offending fluoroquinolones, it took an average of 11.5 days for platelets to return to normal (range from 4 to 43 days).^{10–18} Our patient fits within the appropriate time frames but is likely at the extremes of recovery time and degree of thrombocytopenia due to longer exposure to moxifloxacin.

Repeat exposure with a recurrent episode of thrombocytopenia makes drug-induced immune thrombocytopenia more likely. Our patient had two episodes after exposures to moxifloxacin. She did not receive that antibiotic between her two episodes, and she had a documented normal platelet level between exposures. Four cases demonstrated development or worsening of thrombocytopenia after repeat exposure to offending fluoroquinolone.^{4 7 11 18}

Since most episodes of drug-induced immune thrombocytopenia resolve after medication discontinuation, treatment is mainly supportive. Our patient received several platelet transfusions which only temporarily raised her platelet level. Due to persistently low levels, she was also treated with corticosteroids and intravenous IgG, but this therapy only briefly increased platelet levels. Only three of the reported patients in the cases we reviewed had received corticosteroids for treatment and

Table 1 Criteria used to evaluate causative relationships in drug-induced thrombocytopenic purpura

Criterion	Description
1	Therapy with the candidate drug preceded thrombocytopenia
2	Recovery from thrombocytopenia was complete and sustained after therapy with the drug was discontinued
2	The candidate drug was the only drug used before the onset of thrombocytopenia or other drugs were continued or reintroduced after discontinuation of therapy with the candidate drug with a sustained normal platelet count
3	Other causes for thrombocytopenia were excluded
4	Re-exposure to the candidate drug resulted in recurrent thrombocytopenia
Level of evidence	
I definite	Criteria 1, 2, 3 and 4 are met
II probable	Criteria 1, 2 and 3 are met
III possible	Criterion 1 met
IV unlikely	Criterion 1 not met

Source: Adapted from ref. ².

neither demonstrated significant improvement with treatment.^{3 11 16} None of the patients in case reports reviewed received intravenous IgG but one received plasma exchange.³

These cases suggest that fluoroquinolones as a class can cause drug-induced immune thrombocytopenia in certain patients. It has been hypothesised that these reactions are due to fluoroquinolones having a similar chemical structure with quinine, a chemical well known to cause antibody-mediated immune thrombocytopenia.^{3 4} However, this may not completely explain all cases of thrombocytopenia due to fluoroquinolones. If it was due to the similarity with quinine, one would expect an exposure to any fluoroquinolone should cause thrombocytopenia in a sensitive individual. In our case, the patient had been treated with ciprofloxacin and levofloxacin between episodes and developed no symptoms. There have been no documented cases of drug-induced thrombocytopenia to more than one fluoroquinolone or a combination of a fluoroquinolone and quinine.

Fluoroquinolones are commonly prescribed for various infections ranging from urinary tract infections to septic shock because of their broad bacterial coverage and good bioavailability with both oral and intravenous dosing. With their frequent use, it is likely that more cases of thrombocytopenia will occur. Physicians should consider fluoroquinolone exposure in their differential for new-onset isolated thrombocytopenia.

Learning points

- ▶ Moxifloxacin can cause drug-induced immune thrombocytopenia.
- ▶ Most of the fluoroquinolones have been shown to cause drug-induced immune thrombocytopenia.
- ▶ Diagnosis of drug-induced immune thrombocytopenia is a combination of clinical history and exclusion of other causes.

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