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CASE REPORT

Trombocytopenia related to colchicine: report of two cases

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Abstract
Familial Mediterranean fever (FMF) is the most frequent autoinflammatory disease which can be well controlled with lifelong use of colchicine. Daily colchicine use has been shown to reduce the frequency, severity, and duration of attacks. Colchicine also has been found to be effective in decreasing the prevalence of amyloidosis. Therapeutic oral dose of colchicine (0.5-2.0 mg/ day) may cause cramping, abdominal pain, hyperperistalsis, diarrhea and vomiting. Besides, colchicine may rarely cause bone marrow failure, agranulocytosis and/ or thrombocytopenia as well. Here in we report two pediatric cases of FMF who developed trombocytopenia after colchicine medication and call attention to colchicine related trombocytopenia.

Keywords: Familial Mediterranean Fever; Colchicine; Trombocytopenia.

INTRODUCTION

Colchicine, derivated from lily, is a drug which is used for the treatment of various rheumatological diseases such as familial Mediterranean fever (FMF), Behcet Disease and gouty arthritis. FMF is the most frequent autoinflammatory disease which can be well controlled with lifelong use of colchicine (1) The disease is frequently observed, especially in the Mediterranean region among Sephardic Jews, Armenians, Turks, and Arabs (2) .Daily colchicine use has been shown to reduce the frequency, severity, and duration of attacks (1) Colchicine also has been found to be effective in decreasing the prevalence of amyloidosis (1). Therapeutic oral dose of colchicine (0.5- 2.0 mg/ day) may cause cramping, abdominal pain, hyperperistalsis, diarrhea and vomiting (3, 4) Besides, colchicine may rarely cause bone marrow failure, agranulocytosis and thrombocytopenia as well (4). In contrast, it is reported that colchicine treatment in addition to steroids and intravenous immune globuline has promising results in patients with Evans Syndrome (5,6). Here in we report two patients with FMF who developed thrombocytopenia after colchicine use and attract attention to this side affect.

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CASE REPORT

Case 1

An eleven year old girl with FMF who has been on colchicine treatment for nine years was consulted to hematology because of thrombocytopenia. She had attacks of fever with unknown origin when she was two years old. Since it was a consanguineous marriage and some elder relatives had a diagnosis of FMF, genetic analysis was done which revealed a homozygous mutation of M694V 95, she was diagnosed FMF. She received 1 mg/ day colchicine. Her thrombocyte levels was normal in the early visits. Past medical history revealed nothing but FMF. Physical examination was normal. Her hemoglobin level was 12.4 gr/ dl, leucocyte 4300/ mm^3, absolute neutrophil count 2000/ mm^3, thrombocyte 29000/ mm^3 and MPV 8.9 fl. Peripheral blood smear examination showed predominantly single and rare dual sets of platelets, there was no other abnormality in other series. Ferritin, folate and vitamin B 12 levels were within normal limits, coombs test was negative. Considering the complications of severe thrombocytopenia, colchicine treatment of the patient is ceased. One week after the cessation of the theraphy, her thrombocyte count raised up to 120000/ mm^3 and reached up to 190000/ mm^3 at the end of one month.

The improvement in thrombocyte levels after cessation of colchicine was considered to be related to the drug, and bone marrow aspiration was not performed. After readministration of colchicine treatment, no reduction in thrombocyte count was determined during a period of 6 months. Patient is still under clinical follow-up.

Case 2

Sixteen year old girl who is under colchicine treatment for 2 months with a diagnosis of FMF is consulted to department of hematology with a platelet count of 90000/ mm^3. She had recurrent attacks of fever and abdominal pain lasting for 3 days. Except for these attacks, the patient's medical history and familial history was uneventful. Genetic analysis showed a compound heterozygous mutation of E148Q/ M694V, so she was diagnosed FMF. She received colchicine at a dose of 1 mg/ day. It is reported that the patients' platelet count was also below 150000/ mm^3 (110000- 130000/ mm^3) before colchicine treatment, but after administration of the drug platelet count further decreased. There was no pathological finding in the physical investigation. In laboratory examination her hemoglobin level was 13 gr/ dl, white cell count 6700/ mm^3, absolute neutrophil count 4000/ mm^3, platelet count 90000/ mm^3 and mean platelet volume 14.6 fl. Giant platelets and clusters of multiple platelets was observed in peripheral blood smear investigation. Ferritin, folate and vitamin B 12 levels were within normal limits. In order to rule out other etiological factors of thrombocytopenia; Coombs test, C3 and C4 levels, viral markers, salmonella and brucella serology were studied and found out to be negative. CD41 and CD42 expression on the platelets were normal in flow cytometry. Her mother and father's platelet values were within normal limits. Colchicine treatment was ceased for 2 months. 2 months after drug discontinuation platelet values raised up to 120000 / mm^3. Bone marrow aspiration was not necessarily performed. Considering the benefits of the patient, colchicine was restarted. After reuse of the drug, her platelet counts were higher than 100000/ mm^3 and she is still under follow-up.

DISCUSSION

FMF is a common disease in Turkey. Colchicine is very effective in preventing FMF attacks and amyloidosis (1,4). It is an anti-mitotic drug that blocks mitotic cells in metaphase. The primary mechanism of action is tubulin disruption. The other mechanisms on immune system include inhibition of neutrophil chemotaxis, adhesion and mobilization. Colchicine also has anti-fibrotic activities and various effects on endothelial function (7).

A starting dose of ≤0.5 mg/day for children < 5 years of age, 0.5-1.0 mg/day for children 5-10 years of age, 1-1.5 mg/day in children>10 years of age is recommended. FMF treatment should be intensified to the tolerated maximum dose (2.0 mg/day) in AA amyloidosis (8).

Bone marrow alterations (hemolytic or aplastic anemia, pancytopenia, neutropenia, and thrombocytopenia) have beeen reported in cases of acute intoxication, but rarely observed in the usual doses given orally (9). In our patients, colchicine doses were in the therapeutic range but thrombocytopenia developed. Course suggests that thrombocytopenia is due to non-immune marrow damage, a finding consistent with previous reports(10, 11).

Colchicine is a substrate for intestinal and hepatic cytochrome P4503A4(CYP3A4), and also a substrate for P-glycoprotein1(P- gp) reflux transporter. Certain drugs increase the potential for colchicine toxicity via modulation of P-gp and CYP3A4 activity (7). Life-threatening and fatal drug interactions have been reported in patients treated with colchicine with concomitant P-gp inhibitors (e.g., cyclosporine) and strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole and ketoconazole) and daily grapefruit consumers. In the majority of cases, the doses of colchicine were within the therapeutic range (7,12).

But the patients described here were not on any medication other than colchicine. The literature mostly provides thrombocytopenia in toxic doses of colchicine. Although pancytopenia is seen mostly with administration of toxic doses of colchicine (>0.5mg/ kg), pediatric patients may present clinical manifestations of intoxication under toxic doses and should be closely monitored in terms of hematological side effects (13).

In conclusion, patients on colchicine treatment should be monitored for hematological side effects, even if they are on therapeutic doses.

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