Case report

Colchicine-induced leukopenia in a patient with familial Mediterranean fever: The cause and a possible approach

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ABSTRACT

A young patient with familial Mediterranean fever (FMF) developed leukopenia each time she took colchicine. However, when she discontinued the drug the white cell and the platelets counts increased but she experienced FMF attacks. Later it was found that the patient also had concomitant cytomegalovirus (CMV) infection. This complex situation posed several diagnostic and therapeutic issues concerning the real cause for the leukopenia and the possible approach to take in such conditions.

We propose that when an essential drug (such as colchicine for FMF) causes leukopenia, one should look for concurrent CMV or another viral infection. If there is no such infection, it is suggested that the mechanism leading to leukopenia be clarified. In the case of bone marrow suppression, colchicine should be continued with injections of G-CSF, whereas if the bone marrow is hypercellular it is suggested to use steroids and colchicine concomitantly.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease which primarily affects populations surrounding the Mediterranean basin (1, 2). FMF occurs predominantly in Turks, Armenians,Arabs, and Sephardic Jews. It is characterized by recurrent attacks of fever and peritonitis,pleuritis, arthritis or erysipelas-like erythema. Amyloidosis causing renal failure is one of the most severe complications of the disease.

Colchicine has been the drug of choice for FMF since 1972 (3). Usually, it controls the FMF attacks and prevents the development of amyloidosis. Colchicine acts by inhibiting leukocyte chemotaxis through a direct effect on their microtubuli. It can also reduce the expression of adhesion molecules on white blood cells and endothelial cells, thereby interfering with leukocyte transfer to the inflammatory site.

Despite the relatively long-term safety of its use, however, colchicine can cause gastric discomfort, nausea, diarrhea, azoospermia, leukopenia and thrombocytopenia (4).

In the present report we describe a young FMF patient who developed leukopenia each time she took colchicine. When she discontinued the drug the white cell and platelets counts increased, but she experienced FMF attacks. Later, it was found that the patient also had cytomegalovirus (CMV) infection concomitantly. This complex situation posed several diagnostic and therapeutic issues. We describe the case and discuss our approach to these clinical problems.

Case report

A 19-year-old girl was referred to the FMF clinic due to severe leukopenia. She was of Jewish Moroccan/Syrian origin and had been suffering from FMF since the age of 2 years. Her main FMF manifestations were: fever, recurrent arthralgia of the feet, elbows and shoulders, pleuritis and peritonitis. A clinical diagnosis of FMF was made at the age of 10 years and a recent genetic evaluation revealed that she was compound heterozygote, bearing the V726A and M694V mutations. She was treated with colchicine intermittently. However, for the past 2 years she had been treated regularly with colchicine 1.5 mg daily with a relatively good response. About 3 weeks prior to her present visit, her routine blood count disclosed leukopenia of 2,650/mm^3. Since she suspected that this could have been an adverse effect of colchicine, she stopped taking the drug immediately, after which the leukocyte count increased (Table I). She then retried colchicine and again the white cell

count decreased. Therefore, she discontinued the medication and a slow rise in the WBC count was evident. It should be emphasized that each time she discontinued the drug, the disease exacerbated and she experienced frequent acute attacks of fever and peritonitis. She came to the clinic in order to find an alternative treatment to colchicine.

Following thorough investigation, she reported that for the previous 2-3 weeks she had had a febrile disease accompanied by sinusitis, liver function disturbances and skin rash, which appeared following the administration of augmentin (amoxycilin and clavulinic acid). Due to the skin rash, this medication was also discontinued. Her physical examination was unremarkable (she was between FMF attacks) and there was no hepatosplenomegaly. Tests for antinuclear antibodies, rheumatoid factor, complement components were all negative or normal, respectively. When the patient recovered, the fever subsided and the liver function tests became normal, a re-challange with colchicine was tried. The rationale was to follow the white blood cell count and perform a bone marrow biopsy in order to clarify the mechanism of her leukopenia: peripheral destruction or direct bone marrow suppression. During this colchicine therapeutic trial the patient underwent serological tests which showed positive titers of anti-CMV IgM antibodies with no anti-CMV IgG antibodies, confirming a diagnosis of recent CMV infection. This time, despite colchicine treatment, the leukocyte count remained stable and normal.

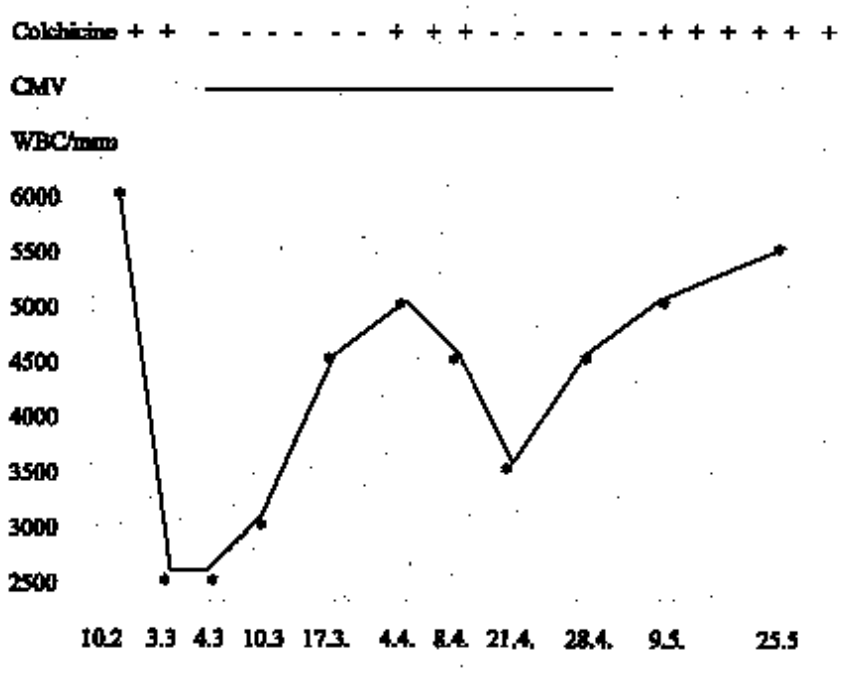

Fig. 1. Relationship between colchicine treatment,CMV duration and the WBC count in our 19-year-old patient with FMF.

Discussion

The present case raises several interesting points. First, it illustrates the serious clinical problem we may face with patients who need medication that is the best or only one effective for a disease, but causes a severe side effect. Second, it raises a question as to the real cause of the leukopenia in a patient. Was it related to the CMV infection? Was it related to the colchicine treatment? Or was it the result of the combination of both insults?

Colchicine is a medication known to have the potential of causing leukopenia. Leukopenia has been described following oral treatment with colchicine, as well as after intravenous injection of the drug (5). Therefore, FMF patients taking this medication are recommended to check their blood count at least once every 3-4 months. On the other hand, the fact that the patient described here had concomitant CMV infection may suggest that the viral infection was responsible for the leukopenia. This possibility is quite plausible, since several reports describe such a complication during CMV infection (6). Nevertheless, discontinuation of colchicine resulted in a sharp increase in the leukocyte count, despite the CMV infection, posing doubt as to this hypothesis. On the other hand, the increase in leukocytes while she was on colchicine, after she had recovered from the CMV infection, does not support the possibility that colchicine alone was responsible for this complication.

Therefore, the most conceivable explanation in the present case for the decrease in the leukocyte count seems to be related to the treatment with colchicine during a CMV infection.

This interesting observation can be added to a series of clinical situations where a drug causes a side effect only if it is administered during a concomitant viral infection. Three such examples have already been described (7,8). One is the case of ampicillin or amoxycillin which, when given to patients with infectious mononucleosis (IMN), may cause generalized skin rash which would not appear if given to patients without IMN. In Reye's syndrome, fulminant hepatitis developed following the treatment of a young patient with aspirin during a viral infection such as a "flu" caused by Influenza virus or Varicella. The third example is the development of a granulocytosis following ingestion of dipyrone. Here again, dipyrone is taken for fever and headaches which (in many cases) are caused by a viral infection, and the concomitant use of dipyrone may be deleterious. Following our experience with the present case, we wish to add the combination of colchicine and CMV infection to the list of conditions where an adverse drug reaction depends upon the concomitant presence of a viral infection.

There are several possibilities regarding the approach we should take in cases of severe FMF disease, where colchicine cannot be administered due to its serious adverse effect. Theoreti-

cally, one could suggest the use of interferon for the acute attacks (9). However, this treatment does not prevent the attacks, it must be administered parenterally, it leads to a flu-like reaction and we do not have data regarding its ability to prevent amyloidosis. Another possible solution is the use of anti-TNF antibodies (infliximab) or soluble TNF receptors (Etanercept). Preliminary results have disclosed that this treatment is beneficial in controlling acute attacks. However, it does not prevent the attacks and there are no studies regarding its effect on amyloidosis in FMF. In a single patient with TNF-receptor autoinflammatory periodic syndrome (TRAPS), etanercept did not prevent the development of amyloidosis (unpublished data).

We elected to adopt the following approach. We asked the patient to retake colchicine and to undergo a bone biopsy and marrow aspiration in order to clarify the mechanism of the leukopenia: was it the result of bone marrow suppression or was it due to peripheral destruction (in the spleen or peripheral blood vessels). We assumed that a hypercellular bone marrow with presentation of all the myelocytic and platelets precursors, would indicate that the leukopenia was due to WBC destruction in the blood vessels and/or the spleen. In contrast, a hypocellular bone marrow would indicate a direct suppression by colchicine. Our plan was to offer the patient treatment with steroids and colchicine if there was evidence of peripheral cell destruction, or colchicine and G-CSF in the case of bone marrow suppression. Fortunately, she did not require any of these, since she did not experience leukopenia after her recovery from CMV infection, despite the treatment with colchicine.

Thus, in the case of an FMF patient in whom colchicine causes a decrease in blood components, one can use the above mentioned approach in order to overcome the drug's serious side effect. Furthermore, this approach may be considered in cases where other medications are involved in causing leukopenia in diseases other than FMF.

In summary, when colchicine causes leukopenia, one should look for concurrent CMV or some other viral infection. If there is no such infection, it is suggested that the mechanism leading to leukopenia be clarified. In cases of bone marrow suppression, colchicine should be continued with injections of G-CSF, whereas if the bone marrow is hypercellular it is suggested to use steroids and colchicine concomitantly.

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