CASE REPORTS

A case of rheumatoid arthritis complicated by a chronic myeloid leukemia associated with pyoderma gangrenosum

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Abstract Rheumatoid arthritis may be associated with an increased risk of hematological malignancy. Increased lympho-proliferative malignancy in rheumatoid arthritis is often described; however an increased risk of leukemia is not a common finding. A few cases of rheumatoid arthritis have been documented associated with chronic myeloid leukemia in the literature. We report a new case.

Case presentation: A 36-year-old Moroccan female diagnosed as rheumatoid arthritis eight years ago, was on remission under Methotrexate and prednisone. This therapy was stopped one year before her admission at our hospital because of thrombopenia and anemia. She had polyarthritis flare. The physical examination found splenomegaly, hepatomegaly, and skin lesions at the trunk and limbs. Peripheral blood findings, peripheral smear and bone marrow aspiration diagnosed myeloid leukemia in a blastic accelerated phase with negative Philadelphia chromosome. The skin lesions were diagnosed as pyoderma gangrenosum (skin biopsy). She received oral prednisone and chemotherapy (Cytarabine and 6-Mercaptopurine). She had a complete response on the skin lesions, partial regression of splenomegaly, and improvement of her hematologic disorders. Unfortunately the patient died from septic shock after two weeks of post-chemotherapy pancytopenia.

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Conclusion: We report an unusual case of rheumatoid arthritis complicated by chronic myeloid leukemia associated with pyoderma gangrenosum. It is unclear whether the development of chronic myeloid leukemia in the patient with rheumatoid arthritis occurs by chance alone, is due to the underlying disease, or is facilitated by drugs. Whatever the cause is, it should be kept in mind that chronic myeloid leukemia may develop in the course of rheumatoid arthritis.

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1. Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that may be associated with an increased risk of hematological malignancy (most often lympho-proliferative disorders), perhaps as a result of RA itself or its treatments [1,2]. We describe through this article an unusual case of a patient with longstanding RA requiring Disease-Modifying Antirheumatic Drugs (DMARDs) (Methotrexate), who developed a myeloproliferative malignancy (chronic myeloid leukemia) associated with pyoderma gangrenosum (PG).

2. Case report

A 36-year-old Moroccan female diagnosed as a sero-positive RA (fulfilling the criteria of the American College of Rheumatology 1987 [3]) 8 years ago, was on remission under the combination of Methotrexate (15 mg weekly) and prednisone 10 mg per day. This therapy was stopped one year before her admission to our hospital because of thrombopenia and anemia. She had polyarthritis flare. Disease activity was assessed by DAS 28 [4] which was at 7,07 (tenderness joints count = 28, swollen joints count = 0, ESR = 87 mm, global score = 70%). Her rheumatoid factor was positive at 52 U/ml (0–14 UI/ml), anti-citrulline peptide antibodies were positive at 185 UI/ml (<5 UI/ml), antinuclear antibodies and extractable nuclear antigen were negative, ESR was 87 mm (first hour), and C-reactive protein was 32 mg/l.

The physical examination found splenomegaly, hepatomegaly and bullous and vesiculo-pustular skin lesions at the trunk and limbs (Figs. 1 and 2).

We thought about drug toxicity, but peripheral blood findings were: anemia with hemoglobin at 9,3 g/dl and thrombopenia with platelets at 53000/mm³. The WBCs were high at $50 \times 10^3$/mm³ (neutrophils: 28990/mm³, monocytes: 14020/mm³). Peripheral smear revealed 9% blasts, 7% promyelocytes, 17% myelocytes, 8% metamyelocytes, 25% neutrophils, 1% eosinophils, 8% lymphocytes, and 6% monocytes. Bone marrow aspiration diagnosed myeloid leukemia in a blastic accelerated phase with negative Philadelphia chromosome.

The skin lesions were diagnosed as pyoderma gangrenosum (PG) when the patient underwent skin biopsy.

We consider that she had an unusual secondary hematological malignancy (CML) with skin assessment (PG). So she received oral prednisone (1 mg/kg/day) for two weeks, and at the same time, she started chemotherapy combining a low dose of Cytarabine (100 mg/m²/day) and 6-Mercaptopurine (1,5 mg/kg/day).

The results were first a complete response to the skin lesions, partial regression of splenomegaly, and improvement of her hematologic disorders (WBC = 9800/mm³) after one week of treatment. Unfortunately the patient died from septic shock after two weeks of post-chemotherapy pancytopenia.
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(WBC = 580/mm³, hemoglobin = 6 g/dl, platelets = 25000/mm³).

3. Discussion

Increased hematological malignancies are well recognized in patients with RA, but there is disagreement about which subtypes occur with a consistent description of lymphoproliferative malignancies. Persistent lymphocytes activation, with dysregulation of B cell proliferation in RA, can induce malignant transformation, in case of a chronic disease, or advanced age, or immunosuppressive drugs using or both [1,5–7]. More recent reviews have discussed the role of high inflammatory disease activity, Epstein-Barr virus infection. Methotrexate (MTX) treatment may be a risk factor for lymphoma in patients with RA. A study of the distribution of lymphoma subtypes in patients with RA who had received MTX found an increased incidence of diffuse large B cell lymphoma: 67% [1,8,9].

However an increased risk of leukemia in patients with RA is not a common finding. Chronic myelogenous leukemia (CML) is a disease characterized by an overproduction of cells of the granulocytic series, especially the neutrophilic series and occasionally the monocytic series, leading to marked splenomegaly and very high white blood cell counts. There is no consensus on the risk of this hematological disease in RA. A few cases of RA have been documented associated with CML in the literature, in which a variety of interactions have been described between these 2 diseases [2,9–11]. There are some reports regarding the relationship between the low dose of MTX (<20 mg weekly) and the development of leukemia in RA. The possibility of the side effect of MTX as a cause of CML can be evoked, because of long-term use. We experienced a case of CML (36-year-old woman) associated with sero-positive RA who was treated with low dose of MTX (15 mg weekly for 6 years), and steroid drugs. She was diagnosed CML after 7 years of therapy. Dubin Kerr et al. reported a similar case in a patient with sero-positive RA who developed CML after short-term low-dose use of MTX [2,9,10]. Miyachi et al. reported the case of an 80-year-old man who developed CML after a 5-year history of RA [2,11]. Soner Senel et al. reported the fourth patient in English literature who was diagnosed with CML after RA treated with MTX. Some studies suggest that MTX increases this risk of hematologic proliferative malignancies [1,2,5,7,12], whereas others do not [2,13]. Although MTX treatment may be a risk factor for CML in patients with RA, there is evidence that RA itself may be associated with increased hematological malignancy. An explanation may be that a persistent immune stimulation in RA, disease chronicity, and high inflammatory disease activity participate in the development of CML. It is unclear whether the development of CML in patient with RA occurs randomly, or because of the underlying disease, or is facilitated by drugs. Whatever the cause is, it should be kept in mind that CML may be developed in the course of RA. Our patient presented sero-positive RA since 2004, was treated with MTX for 6 years and has developed a CML after 7 years of treatment. But it remains difficult to determine whether the development of CML is caused by the disease itself or facilitated by immunosuppressive treatment.

This case report is consistent with the observation of CML in a patient with sero-positive RA associated with pyoderma gangrenosum (PG). PG is a rare neutrophilic dermatosis that can be associated with other medical illnesses (50% of affected patients) like systemic lupus erythematosus (37%), inflammatory bowel disease (15%), and hematological disease especially myelogenous leukemia [14,15]. Uniquely interesting is that our patient presented an atypical PG. Characteristic feature of this atypical PG is that it begins as bulla and it is superficial. Patients with this type of PG develop painful rapidly enlarging bullous lesion which becomes superficially erosive and then ulcerative [14,16,17]. High dose of corticosteroids (1 mg/kg/day) is usually the first line therapy until lesion is healed, but most cases are resistant to steroids. The presence of these lesions is an indicator that the patient with leukemia has a poor prognosis [14,18]. The pathogenesis and the link between PG and leukemia are poorly understood. Leukocyte colony stimulating or other bone marrow factors, as well as chemotheraphy might play a role in the development of the symptoms.

In conclusion, rheumatoid arthritis may be associated with an increased risk of hematological malignancy. Increased lymphoproliferative malignancy in rheumatoid arthritis is often described; however an increased risk of leukemia is not a common finding. DMARDS in RA should be chosen reasonably. Methotrexate, yes, but for how long? Should we stop it? These are questions that rheumatologists should ask to have responses in a large cohort of patients with a long follow-up.

Conflict of interests

The authors declare that they have no conflict of interests.

References


