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A Case of Acute Myeloid Leukemia Caused by Low Dose Methotrexate Used to Treat a Rheumatoid Arthritis Patient

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Abstract

Methotrexate is an anti-rheumatic agent used as a first-line treatment for rheumatoid arthritis. Hematological malignancies like lymphoma or acute myeloid leukemia have been reported to be secondary to treatment with Methotrexate, but are very uncommon. We report here the first Moroccan case of RA patient on low dose MTX, who developed AML. We also reviewed all similar cases.

Introduction

Methotrexate (MTX) is an anti-rheumatic agent used as a first-line treatment for rheumatoid arthritis (RA) [1-4]. Weekly single low dose of methotrexate is administrated orally or intramuscularly. Serious adverse effects can be caused by low dose MTX such as pneumonitis and bone marrow suppression. Hematological malignancies like lymphoma or acute myeloid leukemia (AML) have been reported to be secondary to MTX, but are very uncommon[1-2]. Secondary AML can occur following exposure to cytotoxic agents (therapy-related AML) or as a subsequent event in another hematologic disorder, usually myelodysplasia [3].

We report here the first Moroccan case of RA patient on low dose MTX, who developed AML. We also reviewed all similar cases.

Report of the case

We introduce a 58 years old Moroccan lady, with a history of rheumatoid arthritis treated by non steroidal anti-inflammatory drugs and 12.5mg of MTX/week for 4 years and a cumulative dose of 2400mg, who developed AML. The patient was positive for B hepatitis with initial viral charge at 204IU/ml treated by lamivudine for 4 months. She presented with a 3 weeks history of anemic, infectious and hemorrhagic conditions. Physical examination showed performance status at 2 with fever at 39 °C, pallor and gingival hypertrophy. She exhibited neither hepatomegaly nor splenomegaly and she had no palpable lymph nodes. Examination of hands revealed no typical rheumatic features, and she had no joints deformities. Complete blood count revealed hyperleukocytosis. White blood cells count was at 14,6G/L, hemoglobine at 6.8 g/dl, Mean Corpuscular Volume at 100.9fl and platelets count at 100G/L. Differential cell count showed 100% blast cells. Bone marrow examination (BME) showed hypercellular marrow with 94% of blasts AML1 blasts. Medullar cytochemistry was positive for myeloperoxydase. Immunophenotyping revealed positive myeloid markers and cytogenetic analysis failed initially. Rheumatoid factor, antinuclear antibodies and anti CCP antibody were all negative. Chest X ray was normal. Abdominal ultrasound showed parietal thickening of the caecum that can be correlated with her leukemia or inflammatory disease. Thoracoabdominopelvic CT scan revealed rectal tumoral thickening of 15mm associated to infracentimetric retroperitoneal lymph nodes. No rectal biopsy was made because of thrombocytopenia. Renal, hepatic and coagulation profiles were within normal limits. Echocardiogram findings were normal with ejection fraction at 65%. The patient was examined by rheumatologists who thought that her rheumatoid arthritis was inactive. Hepatitis B viral charge after 4 months of Lamivudine went down to less than 20IU/ml. The

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Table1: Clinical and pathologic features of acute leukemia in RA patients using MTX.

Patient Ref	12	9(1)	9(2)	9(3)	13(1)	13(2)	13(3)	13(4)	14	1	2(1)	2(2)	2(3)	15(1)	15(2)	Our case
Age	83	NA	NA	NA	71	72	52	70	60	68	73	35	52	69	83	58
Sex	F	NA	NA	NA	M	F	M	F	F	F	F	F	M	M	F	F
Year of publication	1993	1996	1996	1996	2001	2001	2001	2001	1995	2005	2009	2009	2009	2005	2005	2012
Anterior disease	RA	RA	RA	RA	RA	RA	RA	RA	RA	RA	RA	RA	Psoriasis	NA	NA	RA
Years of duration of the disease	33	0,6	11	10	16	5	2	9	23	11	15	3	0,25	2	7,75	4
MTX cumulative dose	690	NA	NA	NA	750	1200	1250	500	80	1702,5	5400	1080	90	1200	3720	2400
MTX dose (mg/week)	5	NA	NA	NA	7,5	7 , 5 - 10	7,5-10	10	5	7,5-10	7,5	7,5	7,5	12,5	10	12,5
% of medullar blasts	80	NA	NA	NA	93	72	91	98	53	9a	50	NA	80	NA	NA	94
Subtype AML Fab	NA	CMML=> M2	R T = > M2	M4	M1	M4	M0	M5	M2	M6	M D S = > M2	M D S = > M4	ALL	AML	AML	M1
Karyotype	46XX	NA	T(8,21)	NA	46XY	NA	46XY+13	46XY	T(8,21)	46XX	46XX	46XX	46XY	NA	NA	46XX
Evolution	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Palliative care	CR than relapse=> palliative care	C R = > R e l a p s e t(9,22)=> died	died	died	CR

AML: Acute Myeloid Leukemia, RA: Rheumatoid Arthritis, MTX: Methotrexate, NA: not available, CMML: Chronic Myelomonocytic Leukemia, RT: refractory anemia, FAB: French-American-British Cooperative Group classification, ALL: Acute Lymphoblastic Leukemia, CR: complete remission, MDS: Myelodysplasia.

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patient got her first chemotherapy induction with Cytarabine 100mg/m2 twice a day for 10 days (D), and Daunorubicine 50mg/m2 day1, day3 and day5. Her post first induction aplasia was marked by acquired factor VII deficiency. The deficiency was successfully treated using steroids. Day 29 BME showed therapeutic failure with 40% of granular blasts in rich bone marrow. Day 29 medullar karyotype showed normal karyotype 46, XX. The patient underwent a second induction: Cytarabine 100mg/m2 twice a day for 10 days, Daunorubicine 50mg/m2 day1, day3, day5 and Etoposide 100mg/m2 from day1 to day5. Next BME revealed complete remission. The patient got two other courses of chemotherapy for consolidation. She is actually still keeping complete remission 3 months after the last chemotherapy course.

Discussion

Since 1951, MTX administered weekly in low doses is a mainstay in the therapy of RA [1-4]. Several mechanisms have been proposed to explain the role of MTX as anti rheumatic agent: inhibition of T cell proliferation, inhibition of transmethylation reactions required for the prevention of T cell cytotoxicity, interference with glutathione metabolism leading to alterations in recruitment of monocytes and other cells to the inflamed joint and promotion of the release of the endogenous anti-inflammatory mediator adenosine [4]. Also, MTX has been shown to diminish the production of interleukin 1 and leukotriene B4, reduce the level of γδ T cells as well as double-negative cells (CD4–, CD8–), and decrease serum levels of immunoglobulins M and A as well as the rheumatoid factor [5].

The most common reported adverse effect of low dose MTX is gastrointestinal toxicity. Reported hematological side effects are ranging from 4.5% [6] to 25% [7]. These effects are often mild leukocytopenia or pancytopenia and mostly occur in elderly patients with diminished folate stores. Elevation of MCV usually precedes the occurrence of hematological toxicity [8]. MTX may be involved in causing lymphoid malignancies in patients with RA [9]. The most important risk factor for lymphoma development in patients under low dose MTX is the increased frequency of latent infection by pro-oncogenic viruses in immunosuppressive conditions. The spontaneous remission of these lymphomas after the withdrawal of MTX highlights the likely role of the drug in the evolution of these malignancies [10-11]. Acute leukemia following MTX therapy is rare [9].

A literature review identified few patients with RA who developed acute leukemia during or following low dose MTX therapy [2,9,12-15]. In 1993, the first case was reported in an 83-year-old woman. In 2009, the last case was reported in a 73 year-old woman. One case of acute lymphoblastic leukemia and 14 cases of AML have been reported. Table 1 shows the clinical details of these cases. The age of these patients ranged from 35 to 83 years old with a median age of 67.6 years old and the sex ratio F/M was two to one. All reported cases were treated by low dose MTX for RA (12 cases) or psoriasis (1case); with a weekly dose ranging from 5mg to 12.5mg/week. Cumulative dose ranges were from 80mg to 5400mg. The primary disease lasted for 0.25 year to 33 years. Our patient had RA for 4 years and was treated by 12.5 mg weekly dose of MTX with a cumulative dose of 2400mg.

Four cases had myelodysplasia transformed to AML. It reinforces the hypothesis that MTX use may be accompanied by an increased relative risk of developing MDS [5], which can be transformed into AML.

Kolte et al. thought that the occurrence of AML in patients with RA after MTX therapy represents the coincidence of these two diseases, and does not reflect a causal relationship [13]. We agree with al-Anazi et al. [2] that acute leukemia may either be a direct consequence of MTX therapy or may be related to the changes in folate metabolism induced by MTX treatment.

Conclusion

In conclusion, rheumatologists should be aware of cytopenia in RA patients taking MTX as a rare but dangerous side effect.

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