

Methotrexate Induced Accelerated Nodulosis

V Agarwal, Amita Aggarwal, R Misra

Abstract

Methotrexate induced accelerated nodulosis (MIAN) is a rare but unique side effect of methotrexate therapy. There is paucity of data from our country about this entity. We analyzed 14 cases of MIAN and studied its association with gender, rheumatoid factor positivity and dose and duration of methotrexate. Fourteen patients (8 females), 12 with rheumatoid arthritis (8 seropositive), one each with juvenile idiopathic (JIA) and psoriatic arthritis (PsA) were detected to have MIAN during study period. All the patients presented with acute onset of multiple nodules. Radial border of fingers was the most commonly involved site. Disease was inactive in all but two patients at the time of appearance of MIAN. There was no association of MIAN with gender, rheumatoid factor positivity, disease duration, cumulative dose and duration of methotrexate therapy. Two patients each were treated with colchicine, D-penicillamine or hydroxy-chloroquine for 3-6 months without any response. We conclude that MIAN is a benign side effect of methotrexate treatment. ©

INTRODUCTION

Methotrexate, the most common disease modifying drug used in patients with rheumatoid arthritis (RA), has been associated with a rare, but unique side effect i.e. methotrexate induced accelerated nodulosis (MIAN). The prevalence rate of MIAN varies between 8-11 % in different series.^{1,2} Typically, it presents as acute onset, multiple, small, painless or painful nodules over fingers and pulp spaces. Unusually, however, involvement of helix of ear, sole of feet, penis, meninges, scalp, chest, heart, surgical incisions and lungs has also been reported.² MIAN is associated with HLA DR B1 *0401 in Caucasians.^{2,3} A total of 58 cases of MIAN have been reported in the English language literature till the year 2001.⁴ Only one case of MIAN has been reported from India so far.⁵ The reason for paucity of reports on MIAN from our country could be related to lack of awareness, low incidence or under-reporting. We looked for the presence of MIAN in patients receiving methotrexate for various rheumatological conditions at our centre.

MATERIAL AND METHODS

From January 1997 to December 2000 about 700 patients receiving methotrexate for various rheumatological conditions at the out-patient clinic of department of Clinical Immunology at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow were screened for MIAN.

The association of MIAN with gender, rheumatoid factor seropositivity, disease activity, extra articular manifestations, dose and duration of methotrexate therapy, and its response to hydroxychloroquine, D-penicillamine and colchicine were analyzed. The disease activity was assessed by the physician based on tender joint count, swollen joint count, duration of early morning stiffness, ESR and patients were categorized as having active or inactive disease.

RESULTS

Fourteen patients (8 females), 12 with rheumatoid arthritis (RA), one each with juvenile idiopathic (JIA) and psoriatic arthritis (PsA) were detected to have MIAN (Table 1). The mean age, disease duration, cumulative dose of methotrexate and duration of methotrexate treatment were 44.7 years (range 6.5 -58 years), 83.57 months (range 12-204 months), 691.2 mg (range 60-2400) and 23.07 months (range 4-60 months) respectively. Of the twelve patients with RA eight were seropositive, none had extra-articular manifestations. None of the patients had pulmonary nodules on chest radiographs. In all the cases, multiple nodules erupted acutely with size varying from 0.3 to 2 cm. Nodules were painless in all but four cases. The various sites of involvement by MIAN were; radial border of fingers (n=11; Fig.), elbow (n=5), metatarsophalangeal joints (n=4), dorsum of hands (n= 3), dorsum of feet (n=2), and one each on palms and soles, tendoachilles and shin.

Twelve patients had inactive disease at the time of appearance of MIAN. Two patients each were treated with, colchicine, D-penicillamine and hydroxychloroquine in addition to methotrexate for 3-6 months but did not have any

Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.
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Table I

Pt.	Age	Sex	Diagnosis	MIAN	Duration of MTX (months)	Cumulative dose of MTX (mg)	RF	Drugs for MIAN (12 months)	Outcome	Arthritis	Past h/o nodules
1	46	M	RA	Painless	12	480	+	None	Spontaneous recovery	Active	No
2	48	F	RA	Painful	30	900	—	HCQ	No response	Inactive	Yes, One previous episode
3	58	M	RA	Painful	24	1030	+	Colchicine	No response	Inactive	No
4	55	F	RA	Painful	11	330	+	Colchicine	Partial response	Inactive	No
5	36	F	RA	Painful	60	2400	+	HCQ	Partial response	Inactive	Yes, Two episode, self limiting
6	42	F	RA	Painless	30	1200	—	None	Spontaneous recovery	Inactive	No
7	43	F	RA	Painless	5	150	+	None	Spontaneous recovery	Inactive	No
8	32	F	RA	Painless	5	150	+	None	Spontaneous recovery	Inactive	No
9	44	F	RA	Painless	24	960	+	None	Spontaneous recovery	Inactive	No
10	41	M	RA	Painless	36	1440	—	D-Pen	Persisting	Inactive	Yes, One episode, self limiting
11	6.5	M	JIA	Painless	16	160	—	None	Persisting	Inactive	No
12	40	M	PsA	Painless	6	240	—	None	Recovered, MTX stop	Active	No
13	51	M	RA	Painless	4	60	—	D-Pen	Persisting	Inactive	No
14	41	F	RA	Painless	60	360	+	None	Spontaneous recovery	Inactive	No

JIA: Juvenile idiopathic arthritis; PsA: psoriatic arthritis



Fig. 1 : Photograph of hand showing small nodule on the border of the fingers in a patient with MIAN

regression of nodules. Four patients, however, had spontaneous disappearance of nodules on continuation of same dose of methotrexate, whereas in two patients nodules

disappeared on reducing the dose of methotrexate by 2.5 mg per week. Rest of the patients continued to have persistent nodulosis. Three patients had episodic nodulosis with resolution.

Histopathology done of nodule from left index finger in patient number five showed central zone of necrosis encircled by palisading macrophages and multinucleated giant cells, features consistent with rheumatoid nodule. HLA typing available for patient number 1 and 9 did not reveal presence HLA DR 04.

DISCUSSION

Our study reveals that MIAN is not uncommon in India. Rheumatoid nodule and MIAN may be difficult to differentiate, but acute onset of multiple nodules, atypical site of involvement especially over the fingers, seronegative status, quiescent arthritis and absence of extra-articular manifestations, suggest MIAN whereas rheumatoid nodules are classically detected in patients with severe active disease with extra-articular manifestations. Our findings are in agreement with the literature.^{1,2}

Lack of efficacy of hydroxychloroquine, D- penicillamine and colchicine in our study is in contrast to earlier reports.^{3,5,6} We used these agents for a short period, which may not be adequate as reported earlier.³ There is no consensus regarding the various therapeutic options; discontinuation of

methotrexate, addition of additional antirheumatic drugs while continuing methotrexate or observation alone while continuing the methotrexate. Ahmed et al have reported protective efficacy of hydroxychloroquine in patients of RA with HLA DR B1*0401 allele. Based on the postulated mechanism of formation of MIAN, role of adenosine A1 receptor blockers seems interesting.

Four of the patients had spontaneous recovery of MIAN despite continuation of methotrexate. These patients are unlikely to have rheumatoid nodules as they all had acute onset, atypical sites of involvement, inactive arthritis (both clinically and serologically) and absence of extra-articular manifestations. In addition, two of these patients were seronegative for rheumatoid factor. The reasons for the spontaneous resolution of MIAN despite continuation of methotrexate need further study.

How do these nodules develop? One of the mechanisms of action of methotrexate is through increase in adenosine levels. Adenosine binds to both adenosine 1 receptors to produce anti-inflammatory effect. Whereas binding to adenosine 2 receptor on monocytes has been shown to multinucleated giant cell formation and spindle shaped transformation of monocytes, cells similar to that seen in nodule formation.⁸ Histopathology of these nodules is identical to rheumatoid nodules showing central zone of necrosis surrounded by palisading monocytes and multinucleated giant cells.⁹

MIAN is not unique to RA and has been reported in other conditions like JIA,¹⁰ dermatomyositis² and psoriatic arthritis¹¹ as was seen in two of our patients.

The inactive disease status at the time of appearance of MIAN in most of our patients and the benign nature of these nodules suggests against the discontinuation of methotrexate in all the patients of MIAN. However, the potential for fatality,² should caution both the physicians and the patients to have a close monitoring.

None of the two patients whose HLA typing was available with us had HLA DR B*0401. However, HLA typing of more patients is needed to discern the true genetic susceptibility towards MIAN in Indian patients.

Ours is the first study of MIAN from India and we feel that it is not uncommon and presents in a similar manner as in

Caucasians. Like in Caucasians, it has no association with rheumatoid factor positivity, past history of nodules, disease activity and cumulative dose and duration of methotrexate therapy. Response to drugs like hydroxy-chloroquine, D-Penicillamine or colchicine needs further study in Indian patients.

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Announcement

The Department of Immunology, Sanjay Gandhi Post-graduate Institute of Medical Sciences, Lucknow will be conducting the '**Vth National Autoantibody Workshop**' from **September 13-18, 2004**. In addition one day '**Postgraduate clinics in Rheumatology**' will be held on **September 12**.

For information please contact : **Dr. Amita Aggarwal**, Department of Immunology, SGPGIMS, Lucknow 226 014. Fax : 0522-2668017; E_mail : amita@sgpgi.ac.in