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Methotrexate-linked Ventricular Arrhythmias

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A 36-year-old male, who 1 year previously had survived a large anterior myocardial infarction, followed by cardiac arrest, was treated a few months for psoriasis with oral methotrexate, at single weekly oral doses of up to 10 mg, when he had to be hospitalized due to anginal pain and palpitation. Repeated 24-hour electrocardiogram recordings revealed ventricular ectopy up to 580 premature beats per hour. The ventricular premature beats were almost completely abolished after a few days' discontinuation of methotrexate therapy but recurred a few hours after an attempt to restart it had been made. A coronary angiogram showed only minimal wall abnormalities. Electrophysiological testing and endomyocardial biopsy were normal. ***Key words: cytostatics; psoriasis; ventricular premature beats.***

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Methotrexate is a cytostatic folic acid analog that is widely used, not only in the treatment of certain malignancies, but also in the treatment of other diseases, including psoriasis. We present a patient history with apparent ventricular ectopic activity related to oral methotrexate administration for the treatment of psoriasis (1).

CASE REPORT

A 36-year-old male, suffering from severe erythrodermic psoriasis since 1979, was treated with orally administered methotrexate at doses of up to 15 mg per week (as a single weekly oral dose) during the years 1986–1988. In July 1988 he experienced an anterior myocardial infarction. During the recovery on ward, the patient had a cardiac arrest caused by ventricular fibrillation. No myocardial reinfarction was established, and coronary angiography showed only a minimal plaque change in the proximity of the left anterior descending coronary artery. On electrophysiological examination, ventricular tachyarrhythmias were not inducible. Empiric sotalol therapy was started with a dose of 160 mg per day.

Table I. *Hourly frequency of ventricular premature beats on 24-hour ECG recordings*
Methotrexate therapy was stopped on day 13 (upper dashed line) and restarted on day 56 (lower dashed line). Change = % change from the previous "Average (/h)" value.

Days from the first admission	Ventricular premature beats		
	Peak (/h)	Average (/h)	Change (%)
Day 6	340	76	–
Day 11	580	112	+47
Day 13	-----	-----	-----
Day 20	120	30	−73
Day 51	120	18	−40
	-----	-----	-----
Day 56	180	66	+267

Methotrexate therapy was restarted in August 1989, with oral doses of up to 10.0 mg per week. Thereafter, the patient experienced occasional palpitations and anginal chest pain, leading to hospital admission in December 1989. On arrival, ECG showed ventricular premature beats (VPBs), increasing up to long periods of bigeminy. Several drugs were tried as anti-arrhythmic medication, without any beneficial effect on ectopy. The methotrexate therapy was continued according to the schedule. On repeated 24-hour ECG recordings, multiform VPBs closely correlating with the symptoms were documented: up to 580/h (Table I). A repeated coronary angiogram did not reveal any new findings, and a right ventricular endomyocardial biopsy specimen showed normal histology.

Methotrexate medication was then discontinued, and within a week the patient became symptomless and the frequency of VPBs decreased substantially (by 73%). Five weeks after methotrexate medication had been discontinued; it was restarted at the patient's desire, but on ward under ECG surveillance. A few hours after taking a single oral dose of 2.5 mg of methotrexate, he complained of palpitations, which closely correlated to the multiform VPBs occurring with a frequency of up to 180/h (Table I). Methotrexate therapy was abandoned, and since February 1990, the patient has experienced no further cardiac symptoms.

DISCUSSION

Until recently, only one case of supraventricular extrasystoli has been reported in the context of methotrexate, administered intravenously (2). Our patient, who possibly had a "substrate" for arrhythmias due to survived infarction 17 months previously, presented a symptomatic ventricular ectopy. The observed 73% reduction of the frequency of VPBs (Table I), related to the withdrawal of methotrexate therapy exceeds the suggested 95% confidence limit to exclude the spontaneous day-to-day variability observed in ventricular ectopic activity during successive 24-hour ECG recordings (3). The 1 month reduction of VPBs from 112/h to 18/h (by 84%) does not, however, exceed the 95% confidence limit of 91% suggested for anti-arrhythmic medication for the patients with chronic heart failure (4). The 267% increase of average hourly VPBs following the single dose on attempting to restart therapy further supports our comprehension of the causal relationship between methotrexate and VPBs, although the increase does not exceed the suggested 95% confidence limit (337%) (3).

The observed ventricular ectopy did not show any tendency towards the malignant forms of ventricular arrhythmias. The insidious appearance of symptoms suggests a toxic cumulative mechanism, but the temporary recurrence of the symptoms and ectopy on attempting to restart the medication is indicative of an acute toxicity. Similarly, a dual mechanism of cardiac toxicity has also been suggested to be characteristic of the anthracycline derivatives (5). Other signs of methotrexate toxicity were, however, not found: the levels of serum creatinine and urate remained normal throughout the treatment, and the normal values of blood erythrocyte and leukocyte counts give evidence against severe bone marrow depression.

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Previously, one case of myocardial infarction possibly related to methotrexate therapy has been reported (6). In our case, the temporal relation between the infarction and methotrexate therapy was far from close. Thus, a causative role of methotrexate with respect to the myocardial infarction remains speculative.

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