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Case Report

Hypothyroidism and Arthritis during Interferon Therapy

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Summary **The development of autoantibodies during interferon therapy is frequent, but clinical symptoms of autoimmune disease are uncommon. We report on a female patient who developed arthritis with strongly positive antinuclear factor (ANA) and autoimmune thyroiditis while being treated with alpha 2b interferon (IFN) for chronic myelocytic leukaemia (CML). The arthritis subsided promptly after discontinuation of IFN and initiation of nonsteroidal anti-inflammatory drugs.**

Key words **Alpha-interferon, Chronic Myelocytic Leukaemia, Autoimmune Thyroiditis.**

INTRODUCTION

The acute side-effects of IFN are frequent and well-known. The most frequently encountered is an influenza-like syndrome, which can be managed by paracetamol (1). The delayed effects of IFN are uncommon, more serious and some are lesser known. They can, roughly speaking, be divided into two groups: neuropsychological disorders (depression, parkinsonism,...) and autoimmune diseases, including thyroiditis (2), haemolytic anaemia (3), thrombocytopenia (4) and aplastic anaemia (5). A few cases of IFN-induced arthritis have been reported (6-12). We report on a female patient treated with IFN for CML, who developed arthritis and hypothyroidism.

CASE REPORT

A 64-year old woman was treated in 1989 with hydroxyurea and IFN (Intron A, Schering-Plough) at doses of 3 million units daily subcutaneously for classical Philadelphia-positive CML. Her thyroid hormones at this time were normal. Twelve months later, while a partial cytogenetic response was observed (three mitoses out of six were Philadelphia negative), the patient felt weakness in both shoulders accompanied by inflammatory pain in her fingers. The biological analysis carried out at this time showed a normal haemogram, hypothyroidism (TSH: 13 μU/ml, nl<3.8, free T3 and T4: normal), an absence of anti-thyroid antibodies, a negative Waaler-Rose and latex test, a positive ANA (1/640 homogeneous) with positive anti-histone. The hand X-rays showed arthrosis of the root of the thumbs; the patient was treated with physiotherapy and her condition improved. Nineteen months later, i.e., 32 months after the start of IFN therapy, the patient developed acute, symmetric and severely disabling arthritis in her hands and wrists accompanied by fever. The biological analysis carried out at this time showed progression of the haematological disorder (white cells count 17.920×10^9/L with neutrophils 66%, lymphocytes 6%, basophils 19%, Hb 98g/L; thrombocytes 897×10^9/L; caryotype: 20 mitoses, all Philadelphia-positive). L.E. cells were present with a positive ANA (1/1280, homogeneous), anti-histone antibodies, anti-double helix DNA, anti-actine (1/160) and anti-tropomyosin (1/160) and a polyclonal increase of IgG (30g/L). The latex test, Waaler-Rose reaction, anti-smooth muscles, anti-mitochondria, anti-parietal cell antibodies were all negative. The seric uric acid was normal (41 mg/L). Thyroid hormonology showed frank hypothyroidism with the presence of anti-thyroid antibodies: TSH: 9 μU/ml, free T3: 1.8 pg/ml(nl>2.5), free T4: 7 pg/ml (nl>7), anti-thyroglobulin antibodies 850 (nl<200), anti-microsome antibodies 147 (nl<100). The urine analysis was normal. The hand and wrist X-rays showed bilateral synovial swelling of

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the metacarpal-phalangeal joints, with no sign of erosion. IFN therapy was discontinued, thyroid hormone therapy was begun and the arthritis responded promptly to anti-inflammatory treatment. Since then, the patient has been treated with hydroxyurea alone. Four months later, she remained free of any autoimmune symptoms, with a regression of the ANA to 1/160 and negative anti-histone antibodies, while 12 months later anti-thyroglobulin and anti-microsome antibodies had decreased from 850 to 401 and from 147 to 37.6 respectively.

DISCUSSION

Autoantibodies appear in up to 87% of the patients treated with IFN (13). Most patients developing autoantibodies display no clinical symptoms. The clinical spectrum of IFN-associated arthritis ranges from typical SLE to seropositive or seronegative rheumatoid arthritis (RA) with patients exhibiting features of SLE/RA overlapping syndrome (6). We feel that the diagnosis of SLE best fits the clinical and serological characteristics of our patient who presented with fever, nonerosive arthritis, lymphopenia, anti-DNA antibodies and strongly positive ANA. A diagnosis of gouty arthritis can reasonably be ruled out in a patient with symmetric arthritis and normal uricaemia. Paraneoplastic arthritis has been reported in some malignant conditions but, as far as we know, has not been documented in CML.

The incidence of IFN-induced arthritis in the setting of CML treated with IFN is unknown. Some data suggest that it may be low. In a randomised prospective study by the Benelux CML study group, 83 patients were given IFN and hydroxyurea while 75 patients were treated with hydroxyurea alone (14). With a median follow-up of 13 months, IFN-induced arthritis was reported once. It cannot be excluded, however, that, as time elapses, more patients will suffer this therapy-induced complication. On the contrary, a study by Wandl et al. suggests that IFN-induced arthritis may be common: out of 46 patients who were given IFN because of CML or of essential thrombocytosis, 5 developed SLE (12). To the best of our knowledge, 19 patients with IFN-induced arthritis, including ours, have been reported (6-12). The underlying disorders were CML (9 patients), hairy cell leukaemia (3 patients), chronic active hepatitis (2 patients), large granular lymphoproliferative disorder, malignant lymphoma, melanoma, renal cancer and carcinoid tumour (one patient each). Age ranged from 19 to 71 years (median: 63 years) and both sexes were equally affected. Time from IFN therapy to the first arthritic symptoms ranged from 1 to 39 months (median 9 months) and the doses of IFN ranged from 3 MU daily to 36 MU twice a week. A diagnosis of SLE was made in 8 patients, of RA in 5 patients (including 2 seronegative RA), of RA/SLE overlapping syndrome in 3 patients; a precise rheumatologic diagnosis could not be made in 3 cases. IFN withdrawal with or without anti-inflammatory drugs, including steroids, achieved a resolution of arthritis in all but one patient. In two patients, nonsteroidal anti-inflammatory drugs made IFN continuation possible. In one patient, the articular symptoms abated when IFN was discontinued and did not recur when IFN was resumed.

The aetiopathology of IFN-induced arthritis remains poorly understood. It appears, however, that patients with pre-existing autoimmune disease or autoantibodies are at high risk of developing autoimmune symptoms, including arthritis, when given IFN (6).

As for hypothyroidism, its occurrence during IFN therapy and the decrease of anti-thyroid antibodies when IFN was discontinued point to a causal relationship with IFN therapy. Moreover, thyroid disorders have been repeatedly reported in up to 13% of patients given IFN (8).

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