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CASE REPORT

HYPOTHYROID MYOPATHY AS A COMPLICATION OF INTERFERON ALPHA THERAPY FOR CHRONIC HEPATITIS C VIRUS INFECTION

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SUMMARY

Interferon alpha (IFN-α) therapy is associated with a number of immunological side-effects, including autoimmune diseases and a 10% prevalence of thyroiditis. Hepatitis C virus (HCV) infection itself predisposes to autoimmune phenomena including hypothyroidism and myositis. The development of clinical hypothyroidism in the presence of positive thyroid antibodies in patients infected with HCV and treated with IFN-α suggests a possible association between the viral disease and the therapy. HCV infection may predispose to autoimmune thyroid disease and IFN-α therapy may secondarily lead to the development of thyroid dysfunctions. We report the single case of a female patient who developed a severe proximal myopathy in conjunction with primary hypothyroidism (Hoffmann's syndrome) secondarily to IFN-α therapy for HCV infection. This case highlights the need for careful clinical and biological monitoring for potential side-effects in such patients.

KEY WORDS: Thyroid autoimmunity, Hypothyroidism, Myopathy, INF-α.

INTERFERONS are cytokines produced by lymphocytes and macrophages whose antiviral, antitumoral and immunomodulatory properties are increasingly exploited for therapeutic purposes. Interferon alpha (IFN-α) has been accepted as therapy for malignancies such as AIDS-related Kaposi sarcoma and T-cell leukaemia and, more recently, as treatment for chronic hepatitis B virus (HBV) and HCV infections. In chronic HCV infections, transaminase activity returns to the normal range in 40–50% of IFN-α-treated patients, but reactivation was found in 50% of primary responders during the first 3 months of treatment [1].

A number of side-effects are associated with IFN-α therapy. They range from a benign influenza-like syndrome to autoimmune hypothyroidism, and there have been case reports of rheumatoid arthritis and systemic lupus erythematosus secondary to the treatment [2, 3].

We report the case of a woman with chronic HCV infection who was treated with INF-α and in whom developed a symptomatic proximal myopathy secondary to autoimmune hypothyroidism.

CASE HISTORY

In November 1995, a 33-yr-old housewife developed right upper quadrant abdominal pain associated with liver function test abnormalities [aspartate aminotransferase (SGOT) 69 IU/l, alanine aminotransferase (SGPT) 123 IU/l, normal: <41]. Ten years previously, she suffered from jaundice which was attributed to HCV infection, although there was no serological proof for this. Further investigations included virological tests which confirmed the diagnosis of active HCV infection (positive HCV RNA in serum and anti-HCV antibody) and a liver biopsy which revealed chronic aggressive hepatitis with moderate lobular destruction and periportal lymphoid follicles. Autoantibody screen [antinuclear antibodies (ANA), anti-mitochondrial, anti-parietal cell] was negative. Thyroid function tests performed before the onset of INF-α therapy showed thyroid-stimulating hormone (TSH) of 1.76 mU/l (normal range 0.20–3.50). Treatment with INF-α at 3×10^6 units three times weekly s.c. was started. At the onset of treatment, she suffered mild side-effects in the form of nausea, headache and transient arthralgias of the wrists and ankles, with improvement of liver function tests.

INF-α therapy was stopped in April 1996, 6 months after onset of the treatment, because of joint pains and swelling associated with morning stiffness. The pains were partially relieved with non-steroidal anti-inflammatory drugs. No improvements were observed during the following weeks and the patient was referred for a rheumatological opinion.

On physical examination, her height was 157.5 cm and weight 63.7 kg (body mass index 25.7 kg/m^2); blood pressure was 110/75 mmHg. All her peripheral joints [with the exception of the ankles and metacarpophalangeal (MCP) joints] were tender to palpation with mild limitation of range of movement, but there was no synovial effusion. There was soft-tissue swelling around both ankle joints and all MCP joints. The skin was diffusely indurated, without signs of sclerodermatous changes. The s.c. tissues and muscles were indurated and tender over both forearms and lower legs. Muscle strength was diminished in the proximal and distal muscle groups of the upper limbs, but well preserved in the lower limbs. Tendon reflexes were slightly prolonged.

Laboratory tests showed a normal white blood cell count and erythrocyte sedimentation rate. The C-reactive protein was <6 mg/l (normal: <10), and renal function tests were normal. Liver function tests revealed a high SGOT of 96 [normal range (NR) 9–32 IU/l] and a normal SGPT. Serum muscle enzymes revealed an increased level of creatine phosphokinase (CPK) of 2398 IU/l (NR 25–140), increased aldolase of 11.5 (normal: <7.8). Immunological investigations showed the absence of ANA and anti-DNA antibodies, normal C3 and C4 levels, and the presence of antiperoxidase antibodies (TPO-Ab) of 340 kU/l (normal: <100). Rheumatoid factor was not measured. Thyroid function tests showed a high TSH level of >75 mU/l (NR 0.2–5) and a lowered total T4 level of 1.3 pmol/l (NR 10–24).

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Magnetic resonance imaging (MRI) of both forearms showed a thickness of peri- and intramuscular fascia with local contrast enhancement compatible with fasciitis (Fig. 1). Because of a suspicion of possible scleroderma, a skin biopsy of the distal forearm was performed which showed slight non-specific inflammation of the dermis without fibrosis. Immunofluorescence examination was negative.

A diagnosis of myxoedema and hypothyroid myopathy secondary to INF-α therapy was made and the patient started on oral L-thyroxine 0.15 mg daily. Two months after starting treatment, there was complete resolution of periarticular soft-tissue swelling and joint pains. Laboratory tests at 3 months showed a normalization of CPK level at 199 U/l and normalization of total serum T4 level at 24.2 pmol/l and TSH level at 0.78 mU/l. A follow-up at 6 months was completely normal. HCV RNA remained negative, 6 months after the interruption of INF-α therapy.

DISCUSSION

Our patient developed a severe hypothyroid myopathy in association with INF-α therapy, which clinically fits the description of Hoffmann's syndrome, an unusual complication of myxoedema [4]. Although musculoskeletal symptoms are common in hypothyroid patients, affecting as many as 50%, in Hoffmann's syndrome there is myopathy with pseudohypertrophy of distal muscle groups, due to increased amounts of connective tissue and mucopolysaccharide deposits in muscles. In our patient, there was a marked elevation of CPK and aldolase, indicating muscle involvement. An MRI scan was performed due to an initial suspicion of fasciitis, which revealed gadolinium enhancement of the perimysial and intermuscular fascia, compatible with fasciitis. To our knowledge, this is the first report of MRI findings in this syndrome, and suggests that both muscular and perimuscular involvement contribute to the clinical manifestations. We were unable to find any other report of a similar complication relating to IFN-α treatment.

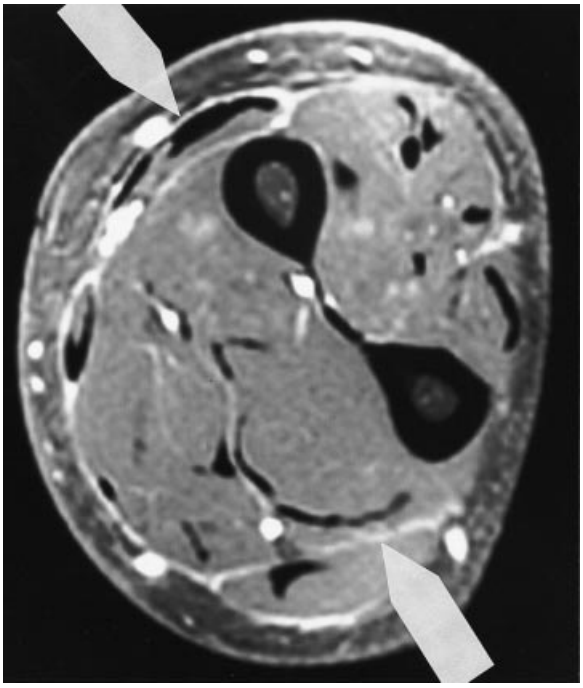

FIG. 1.—MRI of forearm with gadolinium injection: a T1 image showing contrast enhancement of perimysial and intermuscular fascia (arrows).

Thyroid dysfunctions are commonly reported with IFN-α treatment. In HCV-infected patients, one study reported an increasing prevalence of antithyroid antibodies on IFN-α, rising from 10.7% before therapy to 45.3% at 12 months. After cessation of therapy, the prevalence of antithyroid antibodies declined, to reach 22.7% 6 months afterwards [5]. The pathogenetic mechanism is thought to be due to IFN-induced thyroid autoimmunity. Recombinant INF-α stimulates the production of proteins with antiviral and immunomodulatory effects. They may influence humoral mechanisms of immunity by stimulating the production of antibodies mediated through T-helper cell activation and, possibly, through T-suppressive cell inhibition. Effects on cellular immune mechanisms include natural killer cell activation, increased membrane expression of MHC antigens and enhanced antibody-dependent lymphocyte cytotoxicity [1].

Two theories have been proposed to explain the occurrence of immunological disorders with INF-α treatment. Firstly, a direct toxicity of INF-α on particular organs and, secondly, a possible exacerbation of a silent pre-existing autoimmune disease by the INF-α.

Another possible pathogenetic mechanism is autoimmunity induced by HCV infection itself. Apart from the well-known association between chronic HCV infection and mixed essential cryoglobulinaemia, HCV infection has also been reported in association with rheumatoid arthritis [2], Sjögren's syndrome [6, 7] and inflammatory myositis [3]. HCV infection *per se* may also increase the risk of developing thyroid autoimmunity. Preziati *et al.* [8] reported that of 78 HCV-infected patients who received IFN-α, 35.9% had increased anti-peroxidase antibodies and 16.7% increased levels of anti-thyroglobulin antibodies before treatment started. Of 35 patients who remained on treatment at 12 months, 11 had developed thyroid disorders: seven had primary hypothyroidism, one had transient hypothyroidism and three hyperthyroidism. Among these 11 patients, eight had elevated basal anti-TPO and/or anti-thyroglobulin (TG) antibody levels that increased during therapy. We assayed for the presence of these antibodies retrospectively in our patient, and she was found to have elevated levels of both anti-TPO and anti-TG antibodies before starting therapy (1405 and 123 KU/l, respectively, normal: <100 kU/l). We therefore postulate that HCV infection by itself predisposes to thyroid autoimmunity, which in our patient was silent before treatment started, but which became symptomatic during her therapy. No studies to date allow us to say whether this form of 'exacerbated autoimmunity' is limited to thyroid diseases, or whether it extends to include other autoimmune states related to HCV infection, as detailed earlier.

In light of the increased predisposition to autoimmunity in HCV-infected patients, treatments which increase this risk, such as IFN-α, need especially careful monitoring in order to avoid side-effects, as illustrated in the case of our patient. Pre-treatment measurements of autoantibodies are indicated, and monitoring of changes in anti-thyroid antibody levels should also be performed at the end of treatment, to avoid iatrogenic autoimmunity.

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