Exacerbation of Hypothyroidism Following Tumor Necrosis Factor-α Infusion

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A 46-year-old woman with chronic thyroiditis who had been receiving thyroid hormone treatment for 10 yr developed severe hypothyroidism (FT₄ 0.37 ng/dl, FT₃ 1.38 pg/ml, TSH 151.00 μU/ml) following tumor necrosis factor-α (TNF) infusion for the treatment of a complicated cutaneous T-cell lymphoma. Indirect immunofluorescence staining of thyroid follicular cells showed aberrant expression of HLA class II antigens. The mechanisms underlying the exacerbation of the hypothyroidism may be an augmentation of immunological processes in the thyroid and a direct action of TNF on the synthesis and secretion of thyroid hormone.

Key words: autoimmune thyroiditis, cytokines

Introduction

The influence of various cytokines on endocrine functions has been increasingly reported, providing interesting findings on their actions, in vitro and in vivo (1-8). One such cytokine, tumor necrosis factor-α (TNF), is responsible for producing changes in the hypothalamic-pituitary-thyroid axis by directly acting on each level (9). This substance is an important modulator of the immunologic reactions produced by interferon-γ (IFN-γ) of HLA class II molecules in human thyroid follicular cells (10). Clinical studies for the treatment of neoplastic disease with this agent are currently underway (11). Here, we report a patient with chronic thyroiditis who had received long-term thyroid hormone replacement and developed severe hypothyroidism while receiving TNF for the treatment of a complicated cutaneous T-cell lymphoma (CTCL).

Case Report

The patient, a 46-year-old Japanese woman, had a history of hypothyroidism and had received thyroid hormone replacement therapy for the past 10 yr. She was in generally well until 1983 when she noted multiple, small, elevated red eruptions on her face and trunk. The rash gradually became worse, despite applications of a steroid ointment. In March 1989, microscopic examination of a skin biopsy specimen revealed CTCL. On April 20, the patient was admitted to the Department of Dermatology of our hospital for the treatment with TNF. Physical examination revealed a diffuse goiter with a firm consistency and a granular surface. She exhibited no exophthalmos or pretibial edema. The patient had received 60 mg of desiccated thyroid powder for at least the past three months. Thyroid function tests on admission showed a decreased level of free thyroxine (FT₄; 0.49 ng/dl, normal range: 0.7 to 2.1 ng/dl), a normal level of free triiodo-thyronine (FT₃; 3.56 pg/ml, normal range: 2.25 to 5.36 pg/ml) and a slightly elevated level of TSH (8.69 μU/ml, normal range: 0.27 to 6.00 μU/ml). Thyroxine-binding globulin was 40.4 μg/ml (normal range: 12 to 30 μg/ml) and thyroglobulin was 26.3 ng/ml (normal range: <30 ng/ml). Tests for both antithyroglobulin antibody (TGHA; ×20²) and antimicrosomal antibody (MCHA; ×40²) were positive, but a test for anti-thyrotropin-receptor antibody (TBII) was negative. Results of hepatic and renal function tests were within normal limits. Because the clinical and laboratory data on admission indicated mild hypothyroidism, on April 26 the dose of thyroid hormone was changed from 60 mg of desiccated thyroid powder to 50 μg of l-thyroxine (l-T₄) for the purpose of increasing the dose.

For the treatment of CTCL, from April 24 to 26 the patient received infusions of TNF, 5,000 IU per day, and from April 27 to June 12 the dose of TNF was increased...
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Fig. 1. Serum free triiodothyronine (FT3; o--o), free thyroxine (FT4; •--•) and thyrotropin (TSH; □--□) concentrations, and serum titers of antithyroglobulin (TGHA) and antimicrosomal (MCHA) antibodies in relation to the treatment with tumor necrosis factor-α (TNF-α). Des. thyroid: desiccated thyroid powder, l-T4: l-thyroxine.

To 10,000 IU/day. There was some regression of the skin lesions; however, by May 8 thyroid function tests showed an FT4 level of 0.51 ng/dl, FT3 1.44 pg/ml, and TSH 56.03 μU/ml. The patient showed symptoms of severe hypothyroidism, including general malaise and easy fatigability. On May 22, thyroid functions showed the following: FT4 0.49 ng/dl, FT3 1.55 pg/ml and TSH 133.00 μU/ml. On June 12 the values were: FT4 0.37 ng/dl, FT3 1.38 pg/ml and TSH 151.00 μU/ml (Fig. 1). A needle biopsy of the thyroid was performed on June 9. Histological examination by light microscopy revealed diffuse thyroiditis with marked infiltration of mononuclear cells. Indirect immunofluorescence (IFL) staining of thyroid follicular cells was performed using mouse monoclonal antibodies against human Ia1 antigen for HLA-DR and against human Leu 10 antigen for HLA-DQ. Aberrant expression of HLA class II molecules was revealed (Fig. 2). However, the serum level of IFN-γ as measured by ELISA on May 25 was within the normal range (0.07 U/ml, normal range: 0 to 2.8 U/ml). Although the titers of TGHA and MCHA each increased slightly during the course of the TNF infusion (TGHA from ×202 to ×402; MCHA from ×402 to 802), the TBII remained negative throughout the patient’s course.

The infusion of TNF was discontinued and the patient was discharged on June 12. Thyroid function tests on June 28 showed a trend towards improvement: FT4 0.51 ng/dl, FT3 1.81 pg/ml and TSH 29.88 μU/ml. Since the patient complained of persistent malaise and easy fatigability, the dose of l-T4 was increased to 100 μg/day. TNF was then reinstated at a dose of 10,000 IU infused twice weekly from July 1 to October 7, and once weekly from October 8 to February 17, 1990. During these intermittent TNF infusions, the patient’s thyroid function improved with the following values recorded on July 19: FT4 0.74 ng/dl, FT3 2.17 pg/ml and TSH 29.88 μU/ml. Values were normal on August 16 (FT4 1.16 ng/dl, FT3 2.57 pg/ml, TSH 2.78 μU/ml) even though the dose of thyroid hormone was the same. However, from September 1989, the patient gradually developed sub-

Fig. 2. HLA DQ staining of thyroid follicular cells by indirect immunofluorescence (IFL) using mouse monoclonal antibody against human Leu 10 antigen. (×400)
clinical hypothyroidism despite administration of the same daily dose of L-T4. Finally, on January 6, L-T4 was increased to 150 μg/day. The patient is currently maintained in the euthyroid state on this dosage (Fig. 1) and is doing well.

Discussion

TNF, a product of activated macrophages (12), is cytotoxic to selected tumor cell lines in vitro (13) and demonstrates in vivo activity against a variety of murine tumors (14). Clinical trials of TNF as an antineoplastic agent in CTCL and other conditions are currently in progress. Recent evidence shows that this cytokine is also associated with such diverse biological effects as the acute phase response to inflammatory stimuli (15, 16), augmentation of specific immune functions (17, 18), angiogenesis (19) and metabolic disorders (20, 21).

This 46-year-old patient with chronic thyroiditis received TNF for complicated CTCL with some regression of the skin manifestations. After starting TNF, she rapidly became severely hypothyroid. To our knowledge, this is the first report showing an influence of TNF clinically on thyroid function. Several mechanisms may be considered to exacerbate hypothyroidism.

First, TNF may act directly on the thyroid gland to inhibit the synthesis and secretion of thyroid hormone. Pang et al (9) found, by administration of synthetic human TNF to male Sprague-Dawley rats, that TNF acts on the hypothalamic-pituitary-thyroid axis at multiple levels. As for the thyroid gland, 125I-uptake and release of T₄ and T₃ in response to bovine TSH were reduced with increasing daily doses of TNF. Although the mechanism of action of TNF were not indicated in that study, they showed by using FRTL-5 cell lines that TNF affects thyroid cell function by binding to the TNF receptor (22). On the other hand, it was found that the TNF treatment significantly reduced the serum levels of TSH and TRH. TNF is known to be responsible for changes in hypothalamic and pituitary function (9). The present patient had exacerbated primary hypothyroidism, but not low T₃ or low T₄ syndrome, during the daily administration of TNF, as indicated by the decrease in FT₄ and FT₃ with elevated levels of TSH. Because she had preexisting chronic thyroiditis, the administration of TNF may have exhibited a different effect on the thyroid gland, the pituitary and the hypothalamus. Perhaps the diseased thyroid is more sensitive to the effects of TNF than the pituitary or the hypothalamus with the consequence of becoming progressively hypothyroid as shown.

Secondly, the augmentation of aberrant HLA class II expression on thyroid follicular cells may have exacerbated the underlying autoimmune process in this patient with chronic thyroiditis. Marked levels of HLA-DR and DQ antigen expressions on thyrocytes in the IFL study performed during TNF treatment were observed. However, the aberrant expression of HLA class II may not be due to TNF infusion but rather may be a feature of the autoimmune thyroiditis. Although this possibility cannot be ruled out, we believe that TNF may play a role in the expression of HLA class II since it has been reported that the administration of TNF in combination with IFN-γ enhances the expression of HLA class II molecules on normal human thyroid cells in vitro (11). In this regard, the present finding that serum levels of IFN-γ were normal in this patient was disappointing; however, serum levels do not always reflect the local tissue concentrations near the thyrocytes. Furthermore, the fact that the patient had autoimmune thyroiditis led us to consider that infiltrating mononuclear cells may produce IFN-γ. Therefore, it is possible that TNF plays an important role in HLA class II expression and on the subsequent immunological process of presenting thyroid-specific antigens to specific auto-reactive T lymphocytes (23).

Thirdly, it is shown that TNF additively or synergistically with IFN-γ activates thyrocytes by modulating the expression of intercellular adhesion molecule 1 (ICAM-1) (24). Since the cellular interaction between thyrocytes and T-lymphocytes can be stimulated by ICAM-1, the immune reaction may be augmented and cause the exacerbation of the hypothyroidism.

Needless to say, TNF is not a specific cytokine to cause hypothyroidism. Numerous reports have stated that other cytokines such as interleukin-1, interleukin-6 and IFN-γ including TNF modulate the thyroid function by inhibiting iodine incorporation or stimulating autoantigen-specific T cells and facilitating T cell activation (25, 26). Recently, Atkins et al (27) have reported that treatment with interleukin-2 (IL-2) and lymphokine-activated killer cells (LAK cells) may cause hypothyroidism in patients with advanced neoplasms, possibly by exacerbating their preexisting autoimmune thyroiditis. They believe that the most likely cause of the hypothyroidism is an autoimmune mechanism since IL-2 and LAK-cell therapy may activate or exacerbate other autoimmune phenomena as indicated by the appearance of vitiligo and the exacerbation of cutaneous vasculitis during their administration. Similar to the cases they reported, the present patient had autoimmune thyroiditis but no other autoimmune disease. Thus, we did not find an association between thyroid function and other autoimmune phenomena. We agree with the hypothesis that a preexisting autoimmune thyroiditis may be necessary to induce hypothyroidism.

Long-term treatment with TNF in this patient demonstrated an interesting effect on thyroid function. The daily infusion of TNF led to a severely hypothyroid state although the initial replacement doses of L-T4 may not have been adequate. However, the progressive hypothyroidism led us to consider that it could not be ascribed solely to the smaller replacement doses. On the other hand, thyroid function was normalized by increasing the
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dose of l-T4 despite the continuance of twice weekly infusions of TNF. The patient then gradually developed subclinical hypothyroidism while receiving the same regimen of TNF and l-T4. The explanation for this phenomenon is not clear. It seems likely that immunologic modulations of the thyroid gland by TNF may occur, in that, a direct action of TNF on the thyrocytes could not explain these events.

In conclusion, the infusion of TNF in a patient with autoimmune thyroiditis led to the exacerbation of hypothyroidism. Microscopic examination of her thyroid tissue revealed diffuse thyroiditis and the infiltration of mononuclear cells while indirect IFL staining showed the aberrant expression of HLA class II antigens on the thyrocytes. The mechanism underlying the hypothyroidism may be an augmentation of immunological processes in the thyroid and a direct action of TNF on the synthesis and secretion of thyroid hormone. Accordingly, TNF should be administered with caution in patients with hypothyroidism and other autoimmune endocrine diseases.

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References


