Lactate Dehydrogenase (LDH)-Linked Immunoglobulin in a Patient with Graves' Disease Treated with Methimazole

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A 26-year-old woman who received methimazole treatment for Graves' disease is discussed. Two months following treatment, her serum GOT level rose to 45 K.U, her GPT to 60 K.U, and her lactate dehydrogenase (LDH) to 645 W.U; a hepatic disorder was then suspected. Later, the serum GOT and GPT concentrations decreased to a normal range, but her serum LDH continued to maintain a high level. An LDH isoenzyme analysis showed an abnormally broad band between LDH 3 and 5, and electroimmunosyneresis revealed that IgG(*k*) was bound to the LDH. The IgG that was linked to the LDH is suspected to have been the result of her underlying autoimmunity, the methimazole treatment, and the development of her hepatic disorder. Thus, this IgG was thought to be the autoantibody to LDH.
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Key words: enzyme-linked immunoglobulin, autoantibody

Introduction

Several reports discuss the formation of lactate dehydrogenase (LDH, EC 1.1.1.27) and immunoglobulin complex (LDH-Ig) which produces unusual electrophoretic patterns of the LDH isoenzyme (1–7). However, whether this is the result of a specific antigen-antibody reaction, or simply a nonspecific protein-immunoglobulin complex is not clear. Herein we describe a woman with Graves' disease whose LDH was bound to IgG of the kappa class during her treatment with methimazole (MMI). This IgG was thought to be the autoantibody to LDH.

Case Report

A 26-year-old woman visited our hospital because of a goiter. For several years, her family had noted a swelling of the anterior neck but she sought no treatment. A year and a half before her visit, however, she began to experience episodes of heavy sweating, edema of the lower legs, and a hand tremor, and one year before her visit she developed amenorrhea. During a medical examination at her company in May 1989, the enlargement of

her thyroid was brought to her attention, and this caused her to come to our hospital on May 25, 1989 for further examination.

The results of her physical examination showed a moderately nourished woman with moist skin, 52 kg in weight and 154 cm tall. Also noted were tachycardia, hand tremor, general enlargement of the thyroid gland, exophthalmos of the left eye, a functional systolic heart murmur, and edema of the lower legs.

The laboratory findings on her first visit revealed a low level of serum total cholesterol (113 mg/dl) and iron-deficient anemia (RBC 537×10^4 , Hb 7.8 g/dl, MCHC 25.7%, Fe 34 μ g/dl, TIBC 499 μ g/dl). The results of her urinalysis, chest X-ray, and electrocardiogram were normal. Also her liver (GOT 16 KU, GPT 15 KU, LDH 289 W.U) and kidney functions were within the normal range. Her thyroid function test, however, showed typical features of Graves' disease; the serum levels of her thyroid hormones were high (FT₄ 7.5 ng/dl, T₃ 494 ng/dl), the serum TSH level was suppressed ($<0.1 \mu$ U/ml), and the TSH receptor antibody was positive.

She thus was given MMI at an initial dose of 30 mg per day, starting from May 25, 1989 (Fig. 1). The T₄ and T₃ serum concentrations, and the titer of the TSH receptor

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Fig. 1. Changes of free T_4 (FT $_4$), free T_3 (FT $_3$) and TRAb during the course of treatment. MMI: methimazole, PRO: propranolol, TRAb: TSH receptor antibody, upper panel $\bullet$ — $\bullet$ FT $_4$, $\times$ — $\times$ FT $_3$, Δ — Δ TRAb; lower panel $\bullet$ — $\bullet$ GOT, $\times$ — $\times$ GPT, $\bullet$ — $\bullet$ LDH

antibody then gradually decreased. In contrast, at the end of July 1989, her serum levels of GOT, GPT, and LDH increased, and a hepatic disorder was suspected. Three months later, the serum GOT and GPT levels were normalized, but the LDH continued to maintain a high level. On October 26, 1989, an electrophoretic isoenzyme analysis of the LDH showed an abnormally broad band between LDH 3 and LDH 5 rather than five normal bands (Fig. 2). This unusual pattern may have been caused by the formation of LDH-Ig. Electro-immunosyneresis (8) revealed an LDH-linked IgG(*k*) from findings that showed a retardation of mobility by anti-IgG and anti-*k* (Fig. 3).

A retrospective isoenzyme analysis showed that an abnormal LDH pattern had already appeared at the end of July 1989, and that it had lasted until January 1990

Fig. 2. a) Electrophoretic patterns of LDH isoenzyme in sera from the patient and a normal man. b) Densitometric tracing of LDH isoenzyme pattern in serum from the patient. NS, normal serum; PS, the patient's serum obtained on October 26, 1989.

(Fig. 4). At the end of March 1990, her LDH serum level decreased to the normal range, and an isozyme analysis showed a normal pattern.

Discussion

In the present patient with Graves' disease Ig was bound to LDH that had developed during treatment with MMI. It has been reported that the incidence of LDH-Ig in healthy individuals is about 0.1%, and that the LDH-linked Ig is primarily IgA. On the other hand, the incidence of LDH-Ig in patients is about 0.3%. Further, it has been reported that if the Ig of the type IgG is present in a patient under 50, the occurrence of an LDH-linked Ig is frequently associated with an autoimmune disease (7). The present patient was suffering from Graves' disease, i.e., an autoimmune disease. Therefore, it is possible to speculate that the LDH-linked IgG developed because of her autoimmune abnormalities.

There are two reports which discuss enzyme-linked Ig (E-Ig) in patients with Graves' disease (9, 10). Nakashima et al (9) reported a 28-year-old woman with an amylase-linked IgG, and Nagai et al (10) reported a 48-year-old woman with an LDH-IgG. In both these women with Graves' disease, E-Ig was found to have appeared during

Fig. 3. Electroimmunodiffusion. NS; normal serum, PS: the patient's serum obtained on October 26, 1989.

Fig. 4. Time course of the densitometric tracings of LDH isoenzyme patterns in sera from the patient.

treatment with MMI. Since the E-Ig decreased when the MMI was stopped or when propylthiouracil was substituted for the MMI, this suggests that MMI might be related to the E-Ig that developed in these women. Moreover, the occurrence of insulin autoantibodies during MMI treatment is well known (11). In the present patient, the LDH-IgG disappeared spontaneously during the use of MMI. However, it can not be denied that the MMI treatment may have been the cause of the formation of the LDH-IgG.

A further speculation is that in this patient the LDH-IgG was detected following a liver disorder, so that the denatured LDH might have acquired an antigenicity, and the antigenic LDH may have triggered the formation of the LDH-linked Ig.

These factors suggest that the abnormal immunoresponse of this patient, her treatment with MMI, and the development of a liver disorder might all be associated with the development of an LDH-linked IgG. Given these factors and the fact that the LDH-linked Ig was monoclonal, this IgG was thought to be the autoantibody to LDH.

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