

Severe hypothyroidism associated with the degree of edema in a patient with nephrosis

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Abstract

We report the pleural fluid values of thyroid hormones and their carrier proteins in a patient who suffered from nephrotic syndrome with renal insufficiency and transient hypothyroidism. The pleural effusion was transudate. The concentrations of thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (Alb) were approximately 30-50% of the plasma. The concentrations of total triiodothyronine (TT3), total tetraiodothyronine (TT4), free triiodothyronine (FT3), and free tetraiodothyronine (FT4) were approximately 30-50% of the plasma. Hypothyroidism was associated with the degree of edema. After improving systemic edema, proteinuria remained unchanged but the patient did not require levothyroxine. We speculate that the large amount of transudation of thyroid hormones with their carrier proteins from the blood vessels to the third space (edema and pleural effusion), thereby reducing thyroid hormones in the plasma, was associated with hypothyroidism.

Introduction

Most thyroid hormones are bound to their carrier proteins such as thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (Alb). Triiodothyronine (T3) distribution in plasma is as follows: 80% bound to TBG; 9% bound to TBPA; 11% bound to Alb, and 0.3% available as free T3 (FT3).¹ The tetraiodothyronine (T4) distribution in plasma is as follows: 68% bound to TBG; 11% bound to TBPA; 20% bound to Alb; and 0.02% available as free T4 (FT4).¹

The molecular weights of TBG (54 kDa), TBPA (54 kDa), and Alb (66 kDa) are similar.¹ In nephrosis, these proteins are passed into the urine, thereby can cause hypothyroidism because thyroid hormones are bound to their carrier proteins.^{2,3} There have been case

reports of a correlation between hypothyroidism and urinary proteins.^{4,5}

This report describes a patient with nephrosis and hypothyroidism. Notably, the amount of urinary protein remained unchanged during hospitalization. The degree of hypothyroidism was associated with the degree of edema. This is the first report of thyroid hormones and their carrier proteins in the pleural effusion of a patient with hypothyroidism. We discuss the possible relationship between hypothyroidism and edema from the viewpoint of thyroid hormone carrier proteins and their transudation from the blood vessels into the third space. This report might provide a better understanding of proper treatment for patients with hypothyroidism and edema.

Case Report

In October 2010, a 72-year-old woman was brought to the emergency department with symptoms of dyspnea, general fatigue, and systemic edema. She had a 30-year history of poorly controlled diabetes. One year before, she already exhibited diabetic nephrosis [blood urea nitrogen (BUN), 22 mg/dL; creatinine (Cre), 1.7 mg/dL; urinary protein 3+ but not quantified] and her thyroid hormones were near normal without medications; thyroid stimulating hormone (TSH), 6.48 μ U/mL (reference range, 0.35-4.94 μ U/mL); FT3, 2.08 pg/mL (reference range, 1.71-3.71 pg/mL); and FT4, 1.19 ng/dL (reference range, 0.70-1.48 ng/dL). Her height was 150 cm and her weight was 56.0 kg at admission. After several examinations, her condition was diagnosed as diabetic nephrosis [urinary protein, 9.5 g/day; blood urea nitrogen (BUN), 45 mg/dL; creatinine (Cre), 3.2 mg/dL] with pleural effusion and systemic edema. In addition, she exhibited hypothyroidism; TSH, 111.47 μ U/mL; FT3, 1.58 pg/mL; and FT4, 0.61 ng/dL (Table 1). However, no thyroid antibody was detected and thyroid echography was within normal limits.

Diuretics (Furosemide 80 mg/day) and low-dose levothyroxine (12.5 μ g/day) were initiated. However, the hypothyroidism worsened; TSH, 211.18 μ U/mL; FT3, 1.64 pg/mL; and FT4, <0.40 ng/dL (Table 1). Her dyspnea did not improve. We performed thoracentesis and evacuated the pleural effusion. We measured thyroid hormones and their carrier proteins in the pleural effusion. The pleural effusion was transudates with Light's criteria: pleural albumin / plasma albumin = 1.0 g/dL / 2.0 g/dL = 0.5 and pleural lactate dehydrogenase (LDH) / plasma LDH = 61 IU / 308 IU = 0.2. The concentrations of thyroid hormones and their carrier proteins in the pleural effusion were 30-50% of those in the plasma (Table 2).

We increased the dose of diuretics

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(Furosemide 160 mg/day) and levothyroxine (50.0 μ g/day). Then, her pleural effusion and systemic edema improved. Parallel to this improvement, her thyroid hormones also improved. Finally, she did not require levothyroxine. Her body weight fell to 43.8 kg. Notably, the amount of urinary protein remained unchanged during hospitalization (Table 1).

Discussion

In this patient, the pleural effusion included thyroid hormones and their carrier proteins, which were considered to have been transuded from the blood vessels. We hypothesize that the large amount of transudation from the blood vessels to the third space, thereby reducing thyroid hormones in the plasma, was associated with the patient's hypothyroidism, and that the hypothyroidism might have aggravated her edema. In addition, we have speculated on the explanations for the phenomena that we observed in this patient. (Question) Why did she recover to euthyroidism and no longer required levothyroxine at discharge? (Answer) Once the third space disappeared, the thyroid hormones with their carrier proteins no longer transuded from the blood vessels.

Since the patient's body weight at discharge (dry weight) was 43.8 kg, the estimated volume of blood in her body was 43.8/13=3.37 L. Her hematocrit at discharge was 25.9%; therefore, the estimated plasma volume was 3.37 \times (1-0.259) = 2.5 L. Since her body weight at admission was 56.0 kg and was 43.8 kg at discharge, 56.0-43.8 = 12.2 L of systemic edema including pleural effusion was accumulated. The amount of systemic edema (12.2 L) is approximately 5 times as much as the plasma

volume (2.5 L). The patient had a large third space at admission. If the 12.2 L of systemic edema contains 40% of thyroid hormone carrier proteins and thyroid hormones compared with those in the plasma, the systemic edema corresponds to $12.2 \times 0.40 = 4.9$ L of the plasma, approximately 2 times as much as the actual

plasma volume (2.5 L). Thus, the dose of levothyroxine may be increased in patients with edema.

Thyroid hormones and carrier protein levels in pleural fluid of patients with hyperthyroidism were recently reported,⁶ this is the first report on those in hypothyroidism.

Medical practitioners ought to pay attention to thyroid hormones in patients with edema, particularly those with nephrosis, because the loss of protein to urine can cause hypothyroidism,^{2,3,4,5} and both nephrosis and hypothyroidism can cause edema. This case report might contribute to the better understanding and treatment for patients with hypothyroidism and edema. Further studies are required to verify these results.

Table 1. The clinical course of the patient.

	Admission day 0	Severe day 18	Improve day 28	Discharge day 46
Weight (kg)	56.0	53.6	44.2	43.8
Furosemide (mg/day)	80	80	160	120
TSH (0.35-4.94 μ U/mL)	111.47	211.18	34.41	4.36
FT3 (1.71-3.71 pg/mL)	1.58	1.64	2.79	1.76
FT4 (0.70-1.48 ng/dL)	0.61	<0.40	0.92	1.02
Levothyroxine (μ g/day)	0	12.5	50	0
BUN (7-20 mg/dL)	45	35	43	57
Cre (0.4-0.9 mg/dL)	3.2	3.0	3.2	3.7
Urinary protein (0.0-0.12 g/day)	9.5	9.6	10.7	9.2

TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free tetraiodothyronine; BUN, blood urea nitrogen; Cre, creatinine.

Table 2. Thyroid hormones and their carrier proteins in the pleural effusion.

	Plasma	Pleural effusion	Reference
TBG	23.9	12.0	12.0-28.0 μ g/mL
TBPA	16.2	6.5	22.0-40.0 mg/dL
Alb	2.0	1.0	3.6-5.1 g/dL
FT3	1.64	0.6	1.71-3.71 pg/mL
TT3	57.0	< 20.0	70.0-176.0 ng/dL
FT4	< 0.40	< 0.40	0.70-1.48 ng/dL
TT4	3.2	1.2	4.8-10.5 μ g/dL

TBG, thyroxine-binding globulin; TBPA, thyroxine-binding prealbumin; Alb, albumin; FT3, free triiodothyronine; TT3, total triiodothyronine; FT4, free tetraiodothyronine; TT4, total tetraiodothyronine.

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