□ CASE REPORT □

Thyroid Crisis following Interstitial Nephritis

Toshio Kahara¹, Miyako Yoshizawa¹, Izaya Nakaya¹, Akio Uchiyama², Atsuo Miwa²,
Yasunori Iwata¹, Muneyoshi Torita¹, Rika Usuda¹ and Hiroyuki Iida¹

Abstract

A 54-year-old man with Graves' disease had been treated with thiamazole (5 mg/day). His thyroid hormone level was increased after exodontia in February 2006. Although his prescribed dose of thiamazole was increased after exodontia on the fourth day, he developed thyroid crisis on exodontia 52nd day. Laboratory findings also showed renal dysfunction (from Cr 1.0 mg/dL in July 2005 to Cr 1.8 mg/dL on exodontia 37th day). His thyroid hormone level was normalized after subtotal thyroidectomy; however, serum Cr level was still high. He was diagnosed with interstitial nephritis as a result of renal biopsy, and he was treated with prednisolone 30 mg/day. This present case developed thyroid crisis even though the quantity of thiamazole was increased after exodontia. It seems that interstitial nephritis, as well as exodontia, is an aggravation factor of thyroid function. After a poor response to anti-thyroid drugs, it is necessary to prevent thyroid crisis by determining the aggravating factor and to then provide appropriate treatment.

Key words: interstitial nephritis, thyroid crisis, hyperthyroidism, Graves' disease

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Introduction

Thyroid crisis is defined as thyroid function that is extremely enhanced, and the clinical features are central nervous symptom dysfunction, high fever, tachycardia, heart failure, and gastrointestinal dysfunction. As the early stage of thyroid crisis only involves digestive symptoms (1), the diagnosis may be late. Although the frequency of thyroid crisis is low, the case mortality is about 20% (1) and it is important to provide appropriate treatment after diagnosis of thyroid crisis. Thyroid crisis is caused by stress such as surgery and infection, or by interruption of treatment of Graves' disease. It is necessary to treat not only thyrotoxicosis with anti-thyroid drugs but also aggravation factors such as infection.

Interstitial nephritis is a common cause of acute renal failure. The clinical features are fever, arthralgia and rash. However, these are non-specific and are present in only 10% of patients of interstitial nephritis (2). The etiology is drug-related in 71.1% of patients of interstitial nephritis, with antibiotics accounting for about a third of these cases, and

4.7% are due to tubulointerstitial nephritis and uveitis syndrome (TINU) (2). There are case reports of transient hyperthyroidism in TINU (3, 4), and interstitial nephritis may contribute to aggravation of the thyroid function.

We encountered a case of Graves' disease with interstitial nephritis who reached thyroid crisis, though the quantity of thiamazole was increased after exodontia.

Case Report

A 54-year-old man, who had been diagnosed with Graves' disease at the age of 42, had been treated with thiamazole 5 mg/day and his thyroid hormone level had been within normal range. He had taken levofloxacin for tooth root-related circumference inflammation since January 2006 and the tooth was extracted in February (day 0). Laboratory findings on the fourth day after exodontia showed thyrotoxicosis (TSH <0.006 μ IU/mL, fT3 6.7 pg/mL, fT4 2.4 ng/dL, TSAb 218%), and the thiamazole dose was increased to 7.5 mg/day. The toothache continued and he began taking clarithromycin in March. The symptom gradually disappeared. However, he experienced nausea on exodontia 36th

¹Department of Internal Medicine, Toyama Prefectural Central Hospital, Toyama and ²Department of Pathology, Toyama Prefectural Central Hospital, Toyama

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Correspondence to Dr. Toshio Kahara, kchizu1230@yahoo.co.jp; kahara@f6.dion.ne.jp

Table 1. Laboratory Data on Transfer to Our Hospital

[Urinalysis]		[Blood chemistry]		[Gas analysis (room air)]	
pH	5.5	TP	5.7 g/dL	pH	7.421
specific gravity	1.015	ALP	257 IU/L	PaCO ₂	35.1 mmHg
Protein	(+)	AST	34 IU/L	PaO ₂	104.8 mmHg
Sugar	(-)	ALT	67 IU/L	HCO ₃	21.8 mmol/L
Urobilinogen	(±)	LDH	183 IU/L	Base excess	-0.9 mmol/L
Bilirubin	(-)	TTT	1.1 KU	O ₂ saturation	97.7 %
Ketone body	(-)	ZTT	3.3 KU		
Occult blood	(+)	γ-GTP	158 IU/L	[Hormone and autoantibodies]	
		Amylase	120 IU/L	ACTH	68.9 pg/mL
[Cell blood count]		CK	53 IU/L	Cortisol	15.9 μg/dL
WBC	9,000 /μL	TC	114 mg/dL	TSH	<0.01 μIU/mL
Neutrophils	72.7 %	TG	115 mg/dL	ft3	24.2 pg/mL
Eosinophils	5 %	BUN	78 mg/dL	ft4	>6.0 ng/dL
Basophils	0.2 %	Cr	4.4 mg/dL	TgAb	3.1 U/mL
Lymphocytes	16.2 %	UA	6.2 mg/dL	TPOAb	79.1 U/mL
Monocytes	5.9 %	Cl	110 mEq/L	TRAb	2.3 IU/L
RBC	4.03x10 ⁶ /μL	Na	148 mEq/L	ANA	< x40
Hb	11.3 g/dL	K	4.4 mEq/L	SS-A/Ro Ab	(-)
Ht	35.8 %	Ca	8.1 mg/dL	SS-B/La Ab	(-)
Plt	145x10 ³ /μL	P	5.3 mg/dL	PR3-ANCA	<10 EU
		CRP	3.6 mg/dL	MPO-ANCA	<10 EU
		FPG	181 mg/dL		
		HbA1c	6.8 %		

WBC: White blood cells, RBC: Red blood cells, Hb: Hemoglobin, Ht: Hematocrit, Plt: Platelets, TP: Total protein, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, TTT: Thymol turbidity test, ZTT: Zinc sulfate turbidity test, γ-GTP: γ-glutamyl transpeptidase, CK: Creatine kinase, TC: Total cholesterol, TG: Triglyceride, BUN: Blood urea nitrogen, Cr: Creatinine, UA: Uric acid, Cl: Chloride, Na: Sodium, K: Potassium, Ca: Calcium, P: Phosphorus, CRP: C-reactive protein, FPG: Fasting plasma glucose, HbA1c: Hemoglobin A1c, ACTH: Adrenocorticotropin, TSH: Thyroid stimulating hormone, ft3: free triiodothyronine, ft4: free thyroxine, TgAb: anti-thyroglobulin antibody, TPOAb: anti-thyroid peroxidase antibody, TRAb: TSH receptor antibody, ANA: Antinuclear antibody, PR3-ANCA: Antineutrophil cytoplasmic antibody specific for proteinase 3, MPO-ANCA: Antineutrophil cytoplasmic antibody specific for myeloperoxidase.

day and was admitted to a neighboring hospital on exodontia 39th day (day 39). His body temperature was 37.5°C. Laboratory data for exodontia 37th day were as follow: WBC 10,000/μL, CRP 7.0 mg/dL, BUN 20 mg/dL, Cr 1.8 mg/dL, TSH <0.002 μIU/mL, ft3 7.3 pg/mL, ft4 3.3 ng/dL. He was treated with thiamazole 30 mg/day and piperacillin sodium 4 g/day. However, the nausea had continued, and he experienced diarrhea on exodontia 50th day. As his body weight had decreased gradually (-10 kg/2 weeks) and he had a high fever, he was transferred to our hospital on exodontia 52nd day (day 52). On physical examination, he was 174 cm in height and 68.9 kg in weight. His body temperature was 39.6°C, blood pressure was 134/81 mmHg, and pulse rate was 153 beats/minutes. He appeared markedly agitated, restless and was at the level of 1 on the Japan Coma Scale. His skin was moist and warm, but there was no rash. His eyes were exophthalmic, but there was no restriction in eyeball movement. Thyroid gland was moderately enlarged, and was firm and smooth with no tenderness. There was no rale in chest auscultation and no pre-tibial edema. There was some tremor in the fingers.

The laboratory findings are shown in Table 1. WBC was elevated, but no eosinophilia were present. CRP was also

elevated, but there were no abnormal findings on chest roentgenogram. Although there was liver dysfunction, there were no abnormal findings on abdominal CT. Tests for protein and occult blood in urine were positive, and serum Cr level was elevated (there were no abnormal findings on urinalysis in September 2005 and serum Cr level was 1.0 mg/dL in July 2005). There was no growth in blood and urine cultures. There was a finding of thyrotoxicosis, and thyroid-associated autoantibodies were positive. Ultrasonography of the neck demonstrated a diffusely enlarged thyroid, without any nodularity. His electrocardiograms showed sinus tachycardia.

The clinical course is shown in Fig. 1. Thyroid crisis was diagnosed on day 52 and he was treated with hydrocortisone sodium succinate 400 mg/day, thiamazole 45 mg/day, propranolol hydrochloride 30 mg/day and lugor (compound iodine glycerin) 10 ml/day. High fever, thyroid hormone levels, liver dysfunction and serum Cr level were improved, and his digestive symptoms disappeared, as well. Although polyuria appeared after treatment, we thought it convalescence of acute renal failure. Hydrocortisone sodium succinate infusion was stopped since exodontia 56th day; however, both his temperature and serum Cr level were elevated

Figure 1. The clinical course. MMI: thiamazole, Propranolol: propranolol hydrochloride, Lugor: compound iodine glycerin, Hydrocortisone: hydrocortisone sodium succinate, PSL: prednisolone, TSAb: TSH receptor-stimulating antibodies (reference range <180%), TRAb: TSH receptor antibodies (reference range <1.0 IU/L).

Figure 2. Thyroid postoperative histopathology (Hematoxylin and Eosin staining $\times 100$). Variable sized follicles contained colloid with the absence of follicular destruction. Large follicles lined with flattened cells showed papillary projections in some places. These results did not contradict a change in the preoperative treatment of Graves' disease.

again.

Although his thyrotoxicosis improved with administration of a large amount of steroid and iodine, subtotal thyroidec-

Figure 3. Histopathology of renal biopsy (PAS $\times 100$). The glomerulus was almost normal besides an ischemic change. There were marked lymphocytic interstitial infiltrations. There was neither granuloma formation nor vasculitic lesions. Based on the renal biopsy, interstitial nephritis was diagnosed.

tomy was performed on exodontia 72nd day (day 72) because in the present case it was not possible to prevent the onset of thyroid crisis with thiamazole. Pathological findings did not contradict Graves' disease as shown in Fig. 2. Although thyrotoxicosis was improved, fever and polyuria continued (3,000-5,000 mL/day), and serum Cr level was still high (24Cr was 28.2 mL/min.). Protein and occult blood in the urine became negative. Plasma osmolality, urinary osmolality and arginine vasopressin were 286 mOsm/kg, 204 mOsm/kg and 1.1 pg/mL, respectively. Antinuclear antibody (ANA), antineutrophil cytoplasmic antibody specific for myeloperoxidase (MPO-ANCA) and specific for proteinase 3 (PR3-ANCA) were negative, and complement levels were normal (C3 123 mg/dL, C4 34 mg/dL). Both kidneys were normal size on ultrasonography and a renal biopsy was performed on exodontia 76th day (day 76). Pathology specimens showed interstitial nephritis as shown in Fig. 3, and elevated urinary excretion of $\beta 2$ microglobulin indicated the presence of tubular damage ($\beta 2$ microglobulin 6,089.1 $\mu\text{g/L}$). There were no abnormal findings of ophthalmology such as uveitis, and angiotensin converting enzyme (ACE) level was 10.7 U/L (reference range; 8.3-21.4). He was treated with prednisolone 30 mg/day, and was discharged on April 2006 (day 84), because his temperature returned to normal. Serum Cr level with prednisolone 8 mg/day decreased to 1.4 mg/dL on March 2007, and $\beta 2$ microglobulin was 1,213.8 $\mu\text{g/L}$, and it had not returned to normal.

Discussion

Graves' disease is often accompanied with renal dysfunction such as immune complex-mediated nephritis by thyroid antigens (5, 6) and acute renal failure by rhabdomyolysis following thyroid crisis (7, 8). During propylthiouracil treat-

ment, there are cases reports of ANCA-related glomerulonephritis (9, 10) and propylthiouracil-induced tubulointerstitial nephritis (11, 12). It seems that periodic urinalysis examination is important for cases with hyperthyroidism.

Graves' disease can complicate Sjögren's syndrome with interstitial nephritis, and it is suggested that a common immunological mechanism may be involved in the development of autoimmune thyroid disease and Sjögren's syndrome (13, 14). There are case reports of transient hyperthyroidism in TINU (3, 4), and interstitial nephritis may contribute to aggravation of thyroid function.

This present case did not have dry mouth or dry eyes. There were no abnormal findings of ophthalmology such as uveitis, and it seems that this present case did not have TINU. Autoimmune antibodies such as ANA and ANCA were negative and complement levels were normal. There was no medical history of propylthiouracil treatment. The finding of a drug lymphocyte stimulation test was negative. [Stimulation index was thiamazole 124%, levofloxacin 105%, clarithromycin 169%, piperacillin sodium 103%. The results are considered to be positive if the stimulation index is greater than 181%.] Renal dysfunction was continued after these drugs withdrawn, and the possibility of drug-related interstitial nephritis seemed to be low. This present case had fever and renal dysfunction during the clinical course. It seems that interstitial nephritis was present from before the onset of thyroid crisis, although the etiology of interstitial nephritis in the present case is unknown.

The diagnostic criteria of thyroid crisis include Graves' disease and symptoms such as high fever, tachycardia, digestive symptom and neurological abnormality. However, these symptoms are non-specific, and therefore the diagnosis of thyroid crisis can be difficult. There are aggravation factors for thyroid crisis such as an operation, exodontia, injury, infections, hyperglycemia/hypoglycemia, cerebrovascular disorder, myocardial infarction and radioiodine therapy, but there are some cases where obvious aggravation factors are not known. The present case presented with digestive symptoms after exodontia, and he was admitted to neighboring hospital to prevent a thyroid crisis on day 39. Although the dose of thiamazole of this case was increased during hospitalization, thyrotoxicosis was aggravated, high fever and tachycardia appeared, and he developed thyroid crisis on day 52. Antibiotics drugs were administered before the onset of thyroid crisis, and the presence of a grave infectious disease was negative in laboratory findings in our hospital. There is no aggravation factor for thyroid crisis other than interstitial nephritis and exodontia, but it seems that interstitial nephritis, as well as exodontia, can be aggravation factors for thyroid crisis.

In conclusion, we report a case of Graves' disease that had thyroid crisis following interstitial nephritis. Although aggravation factors for thyroid crisis vary, it is important to identify these factors, especially for cases that may develop thyroid crisis in spite of increased doses of anti-thyroid drugs.

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