A Case of Thyrotoxicosis-induced Anemia After the Onset of Painless Thyroiditis in a Patient With Pancreatic Diabetes Mellitus: Profile of Hemoglobin, Thyroid Hormones, Soluble IL-2 Receptor, LDL-C, HDL-C and Liver Function.

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Case report

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Abstract

Background: There have been several reports of secondary anemia associated with Graves' disease. There are no reports of secondary anemia resulting from thyrotoxicosis due to painless thyroiditis (silent thyroiditis). We report the case of a patient with pancreatic diabetes who developed normocytic anemia caused by thyrotoxicosis due to painless thyroiditis.

Case presentation: The patient was a 37-year-old man who visited the hospital complaining of fatigue, palpitations, and dyspnea. His hemoglobin was 110 g/l, and mean corpuscular volume was 81.5 fl. His free thyroxine (FT4) was high, at 1.004 pmol/l, the free triiodothyronine (FT3) was high, at 27.49 pmol/l, TSH was <0.01 mIU/l, and TSH receptor antibody was negative. Soluble IL-2 receptor (sIL-2R) was high, at 1,340 U/ml, low-density lipoprotein cholesterol (LDL-C) was 0.78 mmol/l, and high-density lipoprotein cholesterol (HDL-C) was 0.75 mmol/l. Propranolol was prescribed and followed up. Thyroid hormones, sIL-2R, LDL-C, and HDL-C had almost normalized by 8 weeks after onset. Anemia completely disappeared by 12 weeks after disease onset. Slight increases in liver enzyme levels and a decrease in serum albumin were observed, and recovered later than normalization of thyroid function and cholesterol levels. He developed mild hypothyroidism and was treated with L-thyroxine at 24 weeks.

Conclusions: This is the first case report of transient secondary anemia associated with thyrotoxicosis due to painless thyroiditis. Changes in sIL-2R, HDL-C, LDL-C and liver function were also observed during the clinical course of thyrotoxicosis and anemia, suggesting the autoimmune processes in thyroid gland, bone marrow and liver.

Background

Secondary anemia associated with hyperthyroidism is a relatively rare complication [1]. Many reports have shown that although anemia progresses with hyperthyroidism in Graves' disease, it is often transient, improving with treatment of Graves' disease [2, 3]. There are no reports of secondary anemia resulting from thyrotoxicosis due to subacute thyroiditis, painless thyroiditis (silent thyroiditis) [4], or other causes. Here, we report a case of transient normocytic anemia that developed after the onset of painless thyroiditis in a patient with pancreatic diabetes treated with insulin.

Case Presentation

A 37-year-old man visited our hospital due to gradually progressive fatigue, dyspnea, and palpitations of approximately 14 days duration. His pulse was 104 beats/min, and his body temperature was 36.8 °C. No increase in sweating was observed, goiter was not palpable, and no exophthalmos or ocular movement dysfunction was observed. Laboratory examination showed normocytic anemia (Hgb 110 g/l, mean corpuscular volume [MCV] 81.5 fl), and serum iron and ferritin were within the normal ranges. Reticulocytes were increased at the time of onset. The FT4 (free thyroxine) level was high, at 1.004 pmol/l, the FT3 (free triiodothyronine) level was high, at 27.49 pmol/l, and his TSH was < 0.01 mIU/l. TSH receptor antibody, anti-TPO antibody or anti-thyroglobulin antibody were negative. In other clinical tests, soluble interleukin-2 receptor (sIL-2R), measured for differentiation of hematologic malignancies, was high, at 1,340 U/ml; his low-density lipoprotein cholesterol (LDL-C) was low, at 0.78 mmol/l, and his high- density lipoprotein cholesterol (HDL-C) was low, at 0.75 mmol/l (Table 1).

Table 1
Profile of laboratory data for a diabetes patient with thyrotoxicosis due to painless thyroiditis

Variables	Standard range	Day −56	Day −28	Day 0	Day 14	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168
Red blood cells (RBC), 10^{12}/l	4.27–5.70	4.80	4.96	**3.78**	**3.77**	**3.84**	4.50	4.77	4.93	4.88	4.66
Hemoglobin (Hgb), g/l	135–176	144	146	**110**	**107**	**109**	**126**	136	142	146	140
Hematocrit (Hct), /l	0.398–0.518	0.399	0.408	**0.308**	**0.305**	**0.306**	**0.352**	**0.377**	0.392	0.396	0.408
Mean corpuscular volume (MCV), fl	81.7-101.6	83.1	82.3	81.5	80.9	79.7	78.2	79.0	79.5	82.8	83.4
White blood cells (WBC), 10^9 /l	3.5–9.8	6.4	7.4	5.3	7.2	6.5	8.8	8.6	8.8	5.8	7.4
Platelets, 10^9 /l	130–369	272	315	254	198	228	289	266	283	322	333
Reticulocytes, 10^9 /l	30–100			**108**	68						
Thyroid stimulating hormone (TSH), mIU/l	0.50-5.00			**< 0.01**	**< 0.01**	**< 0.01**	**< 0.01**		**10.1**	**15.2**	**18.5**
Free triiodothyronine (FT3), pmol/l	3.53–6.14				**27.49**	**12.61**	**9.37**		3.93	4.35	4.22
Free thyroxine (FT4), pmol/l	0.116–0.219			**1.004**	**0.914**	**0.515**	**0.331**		0.140	0.131	0.140
TSH receptor antibody (TRAb), mIU/l	< 2.0				0.4						
Anti-TPO antibody, IU/ml	< 16				9						
Ant-thyroglobulin antibody, IU/ml	< 28				11						
C-reactive protein (CRP), μg/l	< 3,000			**6,900**		**12,100**	**5,700**	**3,700**		1,200	
Fe, μmol/l	9.1–35.5			9.5		9.5					
TIBC, μmol/l	43.2–69.0			34.2		40.8					
Ferritin, μg/l	13–401			389		376	396				
Soluble IL-2 receptor (sIL-2R), U/ml	122–496			**1,340**		**1,010**	**808**		472		365
HDL-C, mmol/l	1.03–2.48	1.27	1.09	**0.75**		**0.98**	1.27	1.42	1.14	1.16	1.14
LDL-C, mmol/l	1.68–3.59	1.99	**1.63**	**0.78**		**1.45**	2.12	2.82	2.87	2.90	2.82

eGFR, estimated glomerular filtration rate. Bold data is abnormal value.

Variables	Standard range	Day − 56	Day − 28	Day 0	Day 14	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168
Triglycerides (TG), mmol/l	0.34–1.68	0.46	0.59	0.54		0.84	0.68	0.75	0.84	0.59	0.60
HbA1c (NGSP), %	4.6–6.2	6.9	7.1	7.6		6.5	6.6	6.9	7.7	7.6	7.5
AST, IU/l	13–33	19	18	21		25	30	25	22	27	23
ALT, IU/l	6–30	13	14	19		28	29	21	15	22	21
γGTP, IU/l	10–47	13	14	21		42	**57**	37	26	20	19
Albumin, g/l	40–50	41	42	**31**		**32**	**36**	**36**	**35**	41	41
eGFR, ml/min/1.73 m^2	> 60	103	97	111		115	104	90	88	79.0	80.0
Drug treatment					Propranolol 30 mg	Propranolol 30 mg					LT4 12.5 μg

eGFR, estimated glomerular filtration rate. Bold data is abnormal value.

The patient was previously diagnosed with pancreatic diabetes due to alcoholic pancreatitis at age 25 years, and thus, he was treated with a combination of insulin glargine and insulin aspart. Regular clinical examinations were performed every 28 days, and no abnormalities were found in his biochemical data or complete blood count, other than his plasma glucose and HbA1c. Propranolol (30 mg/day) was prescribed at day 14 and stopped on day 56. Thyroid ultrasonography was performed on day 28, and hypoechoic regions were observed throughout the thyroid gland (Fig. 1).

The patient's thyroid hormone levels had almost normalized by day 56, and his LDL-C and HDL-C normalized by day 56 (Fig. 2A). The anemia disappeared by day 84, and sIL-2R normalized by day 112. There were slight increases in liver enzymes at disease onset, but these increases disappeared by day 140 (Fig. 2B). However, the time to normalization was several weeks behind that of thyroid hormone, LDL-C, and HDL-C normalization. His serum albumin was low at onset but normalized by day 140. The patient's insulin regimen was not changed over the entire clinical course. He developed mild hypothyroidism on day 112 and was started on 12.5 μg of L-thyroxine replacement therapy on day 168 (Table 1).

Discussion And Conclusions

We reported a case of thyroiditis-induced thyrotoxicosis that suddenly led to normocytic anemia within 4 weeks after the patient's last visit to our hospital. The patient's TSH receptor antibody was negative, his FT3/FT4 ratio was low[5], and the destructive findings on thyroid ultrasonography indicated painless thyroiditis. This is the first report of secondary anemia associated with painless thyroiditis. Although the levels remained within the normal range, mild leukopenia and thrombocytopenia presented at disease onset, suggesting pancytopenia due to thyrotoxicosis[3]. Pancytopenia completely disappeared by 12 weeks after onset, with spontaneous remission of thyrotoxicosis.

Painless thyroiditis (silent thyroiditis) is a self-limiting inflammatory disorder of the thyroid gland characterized by an early thyrotoxicosis phase caused by the release of thyroid hormones and a late hypothyroidism phase, with complete resolution in most cases [4, 6]. The pathophysiologic mechanism of painless thyroiditis is unknown, but the possibility of immune disorder involvement has been suggested [6, 7]. Painless thyroiditis generally manifests as a lymphocyte infiltration of the thyroid follicles, causing thyroid follicular cell damage. In our case, we observed a typical course of painless thyroiditis. The secondary anemia caused by thyrotoxicosis has improved, but we would like to carefully follow up on the continuation of thyroid hormone replacement therapy.

The mechanism by which anemia develops in thyrotoxicosis is not clear. Shortened erythrocyte survival or ineffective erythropoiesis have been suggested as potential causes of anemia in thyrotoxicosis [2, 3]. Moreover, mild leukopenia and thrombocytopenia were observed in our case, which could have been due to a variety of mechanisms. The involvement of autoantibodies in leukocytes and

platelets has been reported [8]. The involvement of immune processes in the onset of painless thyroiditis could help explain the pathophysiology of pancytopenia [9]. The patient had an history of acute pancreatitis. It is interesting to assume the immune mechanisms as the pathogenesis of acute and chronic pancreatitis [10].

In addition to the clinical course of thyrotoxicosis and associated anemia, the present case provided interesting laboratory data. First, sIL-2R was high at onset but normalized by 16 weeks after onset of anemia. Elevated levels of sIL-2R have been reported in hyperthyroidism of Graves' disease [11] and thyrotoxicosis due to painless thyroiditis [12], and it is known that thyroid hormones directly enhance sIL-2R production in lymphocytes [12]. Second, LDL-C and HDL-C levels decreased due to thyrotoxicosis but then normalized. Excessive thyroid hormone levels lower serum LDL-C levels via LDL receptor [13] and PCSK9 [14] and lower HDL-C levels via increased CETP activity [15]. In addition, we previously reported that increased sIL-2R cause significant decreases levels in HDL-C and LDL-C in patients with hematologic malignancies [16]. Increased cytokines were recently reported to be associated with hypolipidemia in COVID-19 patients [17]. Presumably, increases in levels of both thyroid hormones and sIL-2R induce the decreases in HDL-C and LDL-C. In addition, slight decreases in HDL-C and LDL-C levels were observed 4 weeks before onset, which may have preceded the anemia. Third, slight increases in liver enzyme levels and a decrease in serum albumin were observed, but these changes disappeared with normalization of thyroid function. However, the time to disappearance was several weeks behind the normalization of Hgb, LDL-C, and HDL-C. The reason for this is unknown. The duration of propranolol administration and the deterioration of liver function did not match. These data suggest that autoimmune processes in the liver could be associated with the different time courses in the normalization of cholesterol and hepatic enzyme levels [9].

In conclusion, we reported the case of a diabetes patient with secondary anemia resulting from thyrotoxicosis. Thyrotoxicosis was caused by painless thyroiditis, but there have been no reports of secondary anemia induced by painless thyroiditis. Changes in sIL-2R, HDL-C, LDL-C and liver function were also observed during the clinical course of thyrotoxicosis and anemia.

List Of Abbreviations

TSH, thyroid stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; sIL-2R, soluble interleukin-2 receptor; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Declarations

Ethics approval and consent to participate

No applicable.

Consent for publication

Regarding publication of the case report, we explained that we could not reveal personal information and obtained verbal consent from the patient.

Availability of data and materials

The collection of data that supports the findings in this study is available from Okinawa Medical Hospital. Data are available from the authors upon reasonable request and with permission of Okinawa Medical Hospital.

Competing interests

The authors declare no conflict of interest.

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Author Contributions

TW has full access to all of the data from the study and takes responsibility for the integrity of the data. IK and TT were involved in study design, interpreting data, statistical analysis, creating tables and figures, and drafting the manuscript. NY and GO were involved in

interpreting data and supervised the work. All authors have contributed significantly to this work. All the authors have read the manuscript and have approved this submission.

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Figures

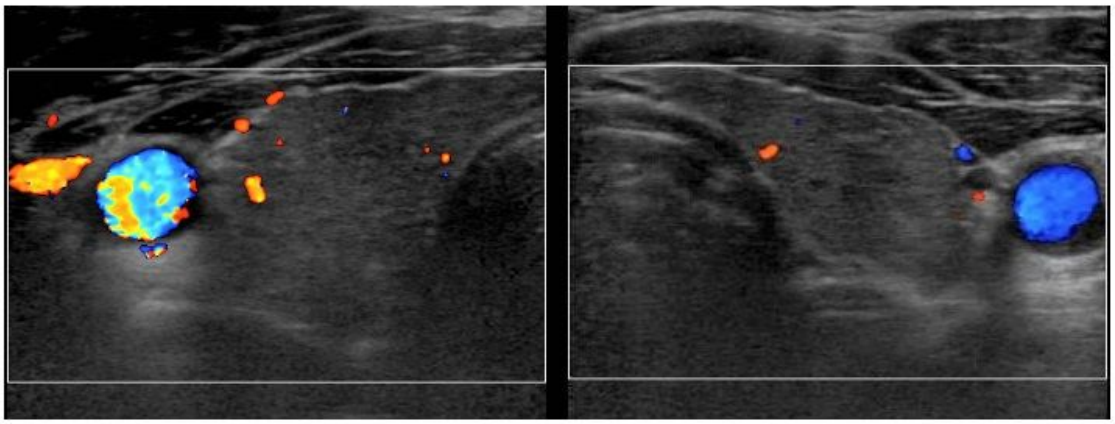

Figure 1

Thyroid ultrasonography findings. Hypoechoic regions are scattered throughout the thyroid gland. No increase in blood flow in the thyroid gland was observed.

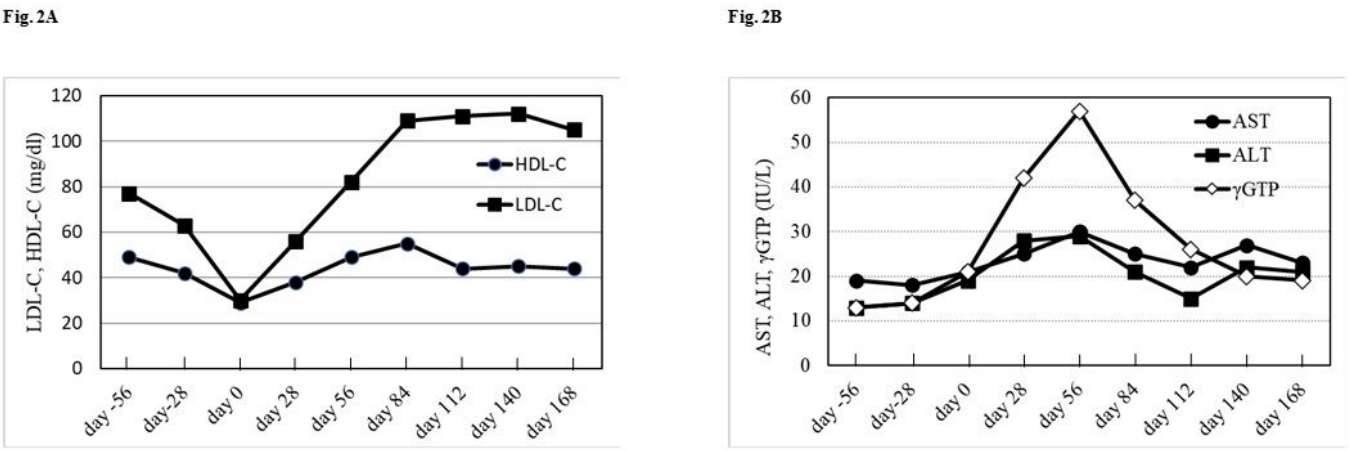

Figure 2

Profile of LDL-C and HDL-C levels and changes in liver function tests. There were slight decreases in LDL-C and HDL-C levels 28 days before onset, and levels were lowest at the time of onset. Both returned to their previous values by day 56 (Fig. 2A). Serum albumin reached its lowest level at onset but recovered by day 140. Liver enzyme levels exhibited a slight increase after the improvement of anemia and thyroid function. The liver enzyme increase continued to day 112 (Fig. 2B).