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(1) Title page

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A pregnant woman with an autonomously functioning thyroid nodule: A case report

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(2) Abstract

Abstract

Background

The epidemiology and natural history of autonomously functioning thyroid nodules (AFTNs) have not been elucidated. Here we report the pregnant Japanese woman with an AFTN.

Case presentation

The patient was a 31-year-old woman who was hospitalized due to the placenta previa associated with threatened abortion at the 16 weeks of her third pregnancy. At her second pregnancy, she was euthyroid but had a single, 2.3 cm nodule on her right thyroid lobe. Her thyroid hormone level was trended increased with her pregnancy progression, and the thyrotoxic state was remained after delivery. Before her third pregnancy, her hyper-vascular nodule enlarged to 3.4 cm at regular monitoring. When she visited our hospital, she was at 16 weeks of pregnancy and had thyrotoxicosis with negative TSH-receptor antibody. She delivered a baby weighing 2,615 grams without hypothyroidism at 39 weeks of pregnancy by natural delivery. After delivery, a ^{99m}Tc scintigram showed a hot spot in her right thyroid lobe. She was diagnosed with AFTN and treated with methimazole while nursing.

Conclusions

This case showed that hCG stimulation during pregnancy caused thyroid nodule enlargement and enhanced thyroid hormone production. The pregnancy could be the pathological stimulus and provides chance to diagnosis for AFTNs.

Key words

54 autonomously functioning thyroid nodule, epidemiology, pregnancy, hyperthyroidism

55

(3) Main text

Background

An autonomously functioning thyroid nodule (AFTN) is a common cause of hyperthyroidism, especially in iodine-deficient areas [1]. Epidemiologically, half of all causes of hyperthyroidism in regions with iodine deficiency are AFTNs [1]. In such iodine-deficient area, somatic mutations of the thyrotropin (TSH)-receptor gene and the gene encoding the α subunit of stimulatory GTP-binding protein (Gsα) have shown to be the main causes of a functional goiter [2,3].

In Japan, an iodine-rich region, more than half of the AFTN patients display somatic mutations of the TSH-receptor gene or Gsα gene as that of similar to iodine-deficient region [4]. However, in Japan the incidence of AFTN is a very rare and accounts for approximately 0.15-0.3% of all hyperthyroidism patients in Japan[5]. According to an epidemiological survey from Denmark, the average ages at diagnosis of multinodular toxic goiter and solitary toxic adenoma were 75.2 and 65.5 years, respectively [6]. When limited to younger patients in this cohort, hyperthyroidism caused by an AFTN was quite rare under the age of 40 years. For these reasons, the natural history and disease onset of young AFTN patients are not well established.

Case presentation

The patient was a 31-year-old Japanese woman who was pregnant with her third child. She had no specific past medical history other than bronchial asthma. When she was 27 years old in her second pregnancy, she had a single nodule, 2.3 cm in size, in her right thyroid lobe. She visited the previous hospital, and confirmed the levels of her

thyroid hormones (free-triiodothyronine (FT3) 3.1 pg/mL, free-thyroxine (FT4) 0.9 ng/dL, and TSH 1.25 μU/mL) were within normal ranges. Her thyroid hormone levels were elevated toward the end of pregnancy-delivery. After her second delivery, however, thyrotoxic state was remained but mild without requirement for antithyroid drug. When she was 29 years old, she was also experienced a thyrotoxic state with a negative TSH-receptor antibody (TRAb), and she was diagnosed with painless thyroiditis.

She has been continuous monitored her thyroid function and thyroid ultrasonography. One month before her third expected pregnancy, her hyper-vascular nodule enlarged to 3.4 cm. Her clinical course is shown in Figure 1. At the 16 weeks of her third pregnancy, she came to our hospital for treatment for placenta previa and threatened abortion. She had suffered from general fatigue, and her skin was moist. She was referred to our department for further evaluation of her right anterior neck swelling and thyrotoxicosis. Her temperature was 36.0 °C, heart rate was 98 beats/min, and blood pressure was 117/86 mmHg. Table 1 shows the results of the laboratory examinations at her first visit. Endocrinological examinations showed increased levels of FT3 (5.8 pg/mL) and FT4 (1.6 ng/dL). TRAb and TSH-stimulating antibody (TASb) were both negative. Human chorionic gonadotropin (hCG) at 16 weeks of pregnancy was 31,100 mIU/mL. Neck ultrasonography showed a 3.4-cm, hypoechoic, heterogeneous nodule with defined margins and a regular shape (Fig. 2). Color Doppler scanning showed nodular hypervascularity. The normal thyroid area was not enlarged and was relatively hypo-vascular compared to the thyroid nodule. Fine needle aspiration showed normal follicular epithelial cells without nuclear atypia. In the differential diagnosis of her thyrotoxicosis, gestational transient thyrotoxicosis (GTT), subacute thyroiditis and AFTN were included. However, thyroid scintigraphy was not performed because of her pregnancy. She was

104 treated with potassium iodide, and her thyroxine levels were maintained in the upper limit
105 of the normal range. She delivered a baby weighing 2,615 grams without hypothyroidism
106 at 39 weeks of pregnancy by natural delivery. The newborn's APGAR score was 6 and 8
107 points. After delivery, her hyper-vascular nodule enlarged to 4.3 cm, and a ^{99m}Tc
108 scintigram showed a hot spot in her right thyroid lobe (Fig. 3). She was diagnosed with
109 an AFTN and treated with methimazole while she was nursing.
110
111 ***Discussion and Conclusions***
112 A summary of this case; she was euthyroid with single 2.3-cm nodule in her
113 second pregnancy. Her thyroid hormone levels were elevated toward the end of
114 pregnancy-delivery and thyrotoxic state was remained after delivery. Her thyroid nodule
115 had become 3.4 cm before the third pregnancy. During the third pregnancy, the nodule
116 size and the level of thyroid hormones were increased. After delivery, her hyper-vascular
117 nodule was further enlarged to 4.3 cm with hot spot accumulation by ^{99m}Tc scintigram.
118 This course suggests that tumor growth was associated with elevated thyroid hormone.
119 According to the guidelines of the American Thyroid Association for the
120 management of thyroid disease during pregnancy, AFTN is quite rare under the age of 40
121 years even in iodine-deficient areas [7]. Therefore, the present case is valuable for
122 considering the natural history and disease onset of AFTN.
123 In the pregnancy, GTT is the most common cause of hyperthyroidism. The
124 incidence rates of GTT in all pregnancies have shown to be 0.3-11% [8-10]. Recent
125 studies in Japan demonstrated that GTT incidence was 2.6-5.5% [11,12]. Graves' disease
126 occurs in less than 0.5% of pregnancies. The serum hCG level was not useful for
127 differentiating between Graves' disease and GTT [13]. AFTN is a much rare cause of

thyrotoxicosis in pregnancy when compared to these two diseases, and natural history of AFTN in pregnancy is absolutely unknown. Even though rare, AFTN should be kept in mind when thyroid hormone levels remains higher after the second trimester.

An observational study of AFTN patients showed that nodule size was an important factor related to elevation of thyroid hormone levels [14]. In nodules less than 2.5 cm, only 1.9% were toxic thyroid nodule (TTN), whereas in nodules larger than 2.5 cm, 42.6% were TTN. Other AFTN patient series reported that most toxic AFTNs were 3 cm or larger [15,16]. Furthermore, an observational study in the USA demonstrated the development of toxicity was observed in patients whose thyroid nodule enlarged [14]. In the present case, before her second pregnancy, her thyroid nodule was 2.3 cm in diameter, and she was euthyroid. However, during her third pregnancy, her goiter expanded to 3.4 cm in diameter associated with thyrotoxicosis status. This clinical course suggests that nodule enlargement induced by hCG in pregnancy is involved in her thyrotoxic state after pregnancy.

The structure of hCG is similar to that of luteinizing hormone, follicle stimulating hormone, and TSH. These hormones have an α subunit and a hormone-specific β subunit [17]. The amino acid sequence of hCG has 85% homology with the β subunit of TSH, and hCG stimulates thyroid hormone production. Because the level of hCG is the highest in the first trimester, GTT develops in the first trimester and improves with hCG reduction in the second trimester. hCG stimulates thyroid cell proliferation via the TSH receptor [18,19]. In the present case, thyrotoxicosis was overt after the patient's second pregnancy with thyroid nodule enlargement. This suggests that hCG stimulation in pregnancy plays pathological roles of an AFTN in such cases.

In conclusion, a case of AFTN diagnosed after pregnancy was presented. Nodule

enlargement induced by hCG stimulation could be important triggers of thyrotoxicosis with an AFTN. This case suggests that pregnancy is one of the important factors elucidating the natural history of AFTNs.

Abbreviations

AFTN, autonomously functioning thyroid nodule; TRAb, TSH receptor antibody; TSAb, thyroid stimulating antibody; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; GTT, gestational transient thyrotoxicosis; TTN, toxic thyroid nodule; hCG, human chorionic gonadotropin

(4) Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Written informed consent for publication of their clinical details and clinical images were obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable

Authors' contribution: MN was responsible for patient care. MN performed the data collection. MN wrote the initial draft of the manuscript. MY and TS contributed to critically reviewed the manuscript. KK assisted in the preparation of the manuscript. All authors approved the final version.

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Availability of data and materials: The datasets used during the current report available from the corresponding author on reasonable request.

(5) References

1. Laurberg P, Pedersen KM, Vestergaard H, et al. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs. high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland [Comparative Study]. J Intern Med. 1991 May;229(5):415-20.
2. Parma J, Duprez L, Van Sande J, et al. Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas [Research Support, Non-U.S. Gov't]. Nature. 1993 Oct 14;365(6447):649-51.
3. Lyons J, Landis CA, Harsh G, et al. Two G protein oncogenes in human endocrine tumors [Research Support, Non-U.S. Gov't]. Science. 1990 Aug 10;249(4969):655-9.
4. Nishihara E, Amino N, Maekawa K, et al. Prevalence of TSH receptor and Gsalpha mutations in 45 autonomously functioning thyroid nodules in Japan [Research Support, Non-U.S. Gov't]. Endocr J. 2009;56(6):791-8.
5. Ito K, Mimura T. [Autonomously functioning thyroid nodule and its diagnostic problems]. Nihon Rinsho. 1983 Jun;41(6):1197-202.
6. Carle A, Pedersen IB, Knudsen N, et al. Epidemiology of subtypes of hyperthyroidism in Denmark: a population-based study [Comparative Study

Research Support, Non-U.S. Gov't]. Eur J Endocrinol. 2011 May;164(5):801-9.
7. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum [Research Support, Non-U.S. Gov't]. Thyroid. 2017 Mar;27(3):315-389.
8. Tanaka S, Yamada H, Kato EH, et al. Gestational transient hyperthyroxinaemia (GTH): screening for thyroid function in 23,163 pregnant women using dried blood spots. Clin Endocrinol (Oxf). 1998 Sep;49(3):325-9.
9. Glinoer D, de Nayer P, Bourdoux P, et al. Regulation of maternal thyroid during pregnancy [Research Support, Non-U.S. Gov't]. J Clin Endocrinol Metab. 1990 Aug;71(2):276-87.
10. Yeo CP, Khoo DH, Eng PH, et al. Prevalence of gestational thyrotoxicosis in Asian women evaluated in the 8th to 14th weeks of pregnancy: correlations with total and free beta human chorionic gonadotrophin [Research Support, Non-U.S. Gov't]. Clin Endocrinol (Oxf). 2001 Sep;55(3):391-8.
11. Kinomoto-Kondo S, Umehara N, Sato S, et al. The effects of gestational transient thyrotoxicosis on the perinatal outcomes: a case-control study. Arch Gynecol Obstet.

2017 Jan;295(1):87-93.
12. Orito Y, Oku H, Kubota S, et al. Thyroid function in early pregnancy in Japanese healthy women: relation to urinary iodine excretion, emesis, and fetal and child development. J Clin Endocrinol Metab. 2009 May;94(5):1683-8.
13. Yoshihara A, Noh JY, Mukasa K, et al. Serum human chorionic gonadotropin levels and thyroid hormone levels in gestational transient thyrotoxicosis: Is the serum hCG level useful for differentiating between active Graves' disease and GTT? [Comparative Study]. Endocr J. 2015;62(6):557-60.
14. Hamburger JI. Evolution of toxicity in solitary nontoxic autonomously functioning thyroid nodules. J Clin Endocrinol Metab. 1980 Jun;50(6):1089-93.
15. Blum M, Shenkman L, Hollander CS. The autonomous nodule of the thyroid: correlation of patient age, nodule size and functional status. Am J Med Sci. 1975 Jan-Feb;269(1):43-50.
16. Molnar GD, Wilber RD, Lee RE, et al. On the Hyperfunctioning Solitary Thyroid Nodule. Mayo Clin Proc. 1965 Sep;40:665-84.
17. Jameson JL, Hollenberg AN. Regulation of chorionic gonadotropin gene expression [Research Support, Non-U.S. Gov'tResearch Support, U.S. Gov't, P.H.S.Review]. Endocr Rev. 1993 Apr;14(2):203-21.
18. Yoshikawa N, Nishikawa M, Horimoto M, et al. Human chorionic gonadotropin promotes thyroid growth via thyrotropin receptors in FRTL-5 cells. Endocrinol Jpn. 1990 Oct;37(5):639-48.
19. Kraiem Z, Sadeh O, Blithe DL, et al. Human chorionic gonadotropin stimulates thyroid hormone secretion, iodide uptake, organification, and adenosine 3',5'-monophosphate formation in cultured human thyrocytes [Comparative Study Research Support, Non-U.S. Gov't]. J Clin Endocrinol Metab. 1994 Aug;79(2):595-9.

(7) Table

		unit	Normal range
WBC	7450	/μL	(3300-8600)
neutro	76.3	%	(40-75)
RBC	384 $\times 10^4$	/μL	(386-492 $\times 10^4$)
Hg	10.2	g/dL	(11.6-14.8)
Plt	20.7 $\times 10^4$	/μL	(15.8-34.8)
Alb	3.4	g/dL	(4.1-5.1)
T-Bil	0.4	mg/dL	(0.4-1.5)
AST	13	U/L	(13-30)
ALT	11	U/L	(7-23)
γ-GTP	3	U/L	(9-32)
LDH	201	U/L	(124-222)
BUN	9.2	mg/dL	(8.0-20.0)
Cr	0.43	mg/dL	(0.46-0.79)
CRP	0.13	mg/dL	(<0.14)
Na	141	mEq/L	(138-145)
K	3.7	mEq/L	(3.6-4.8)
Cl	107	mEq/L	(101-108)
FPG	87	mg/dL	(73-109)
HbA1c	4.7	%	(4.9-6.0)
FT3	5.8	pg/mL	(2.1-3.8)
FT4	1.6	ng/dL	(0.8-1.5)
TSH	<0.01	μU/mL	(0.5-3.00)
TRAb	<0.9	IU/L	(<2.0)
TSAb	105	%	(≦120)
TPOAb	115	IU/mL	(<3.0)
TgAb	309	IU/mL	(<5.0)
Tg	3.3	ng/mL	(≦33.7)
hCG	31,100	mIU/mL	(≦2.7)

WBC, white blood cell; RBC, red blood cell; Hg, hemoglobin; Cr, creatinine; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TSH, thyroid-stimulating hormone; TRAb, TSH receptor antibody; TSAb, thyroid stimulating antibody; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; hCG, human chorionic gonadotropin.

(8) Figure legends

Figure 1

Summary of the clinical course of thyroid hormone levels and nodule size from the patient's second pregnancy to her first visit. FT3, free-triiodothyronine; FT4, free-thyroxine; TSH, thyroid stimulating hormone.

Figure 2

Ultrasonography on the first visit shows a hypoechoic lesion tumor (△) with defined margins and a regular shape, appearing hypervascular and heterogeneous. Tumor size is 3.4 cm.

Figure 3

99m-Tc scintigraphy after pregnancy. The intake rate of the hot spot is 6.52% (normal

thyroid 0.2-3.0%)

Fig. 1

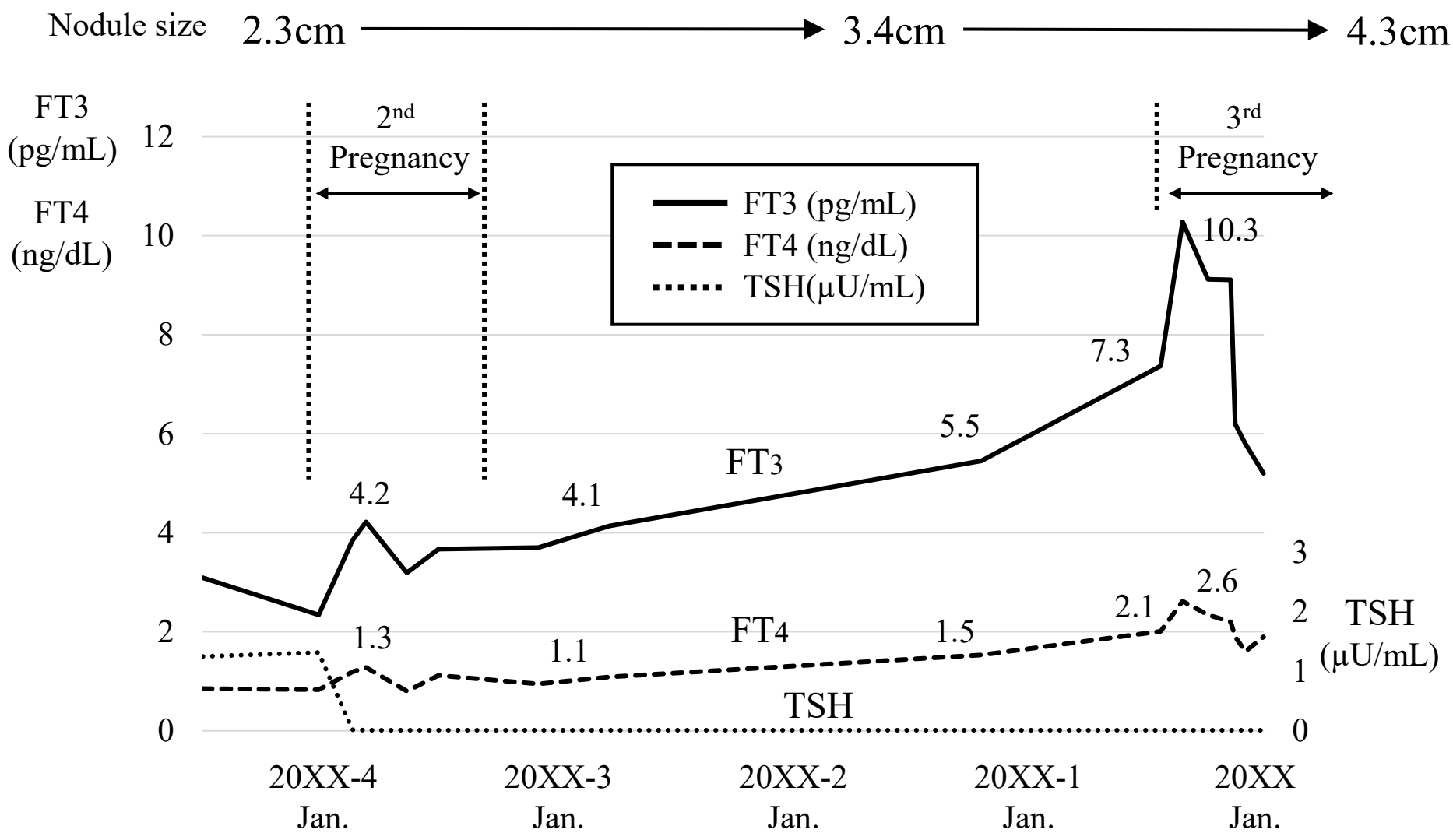
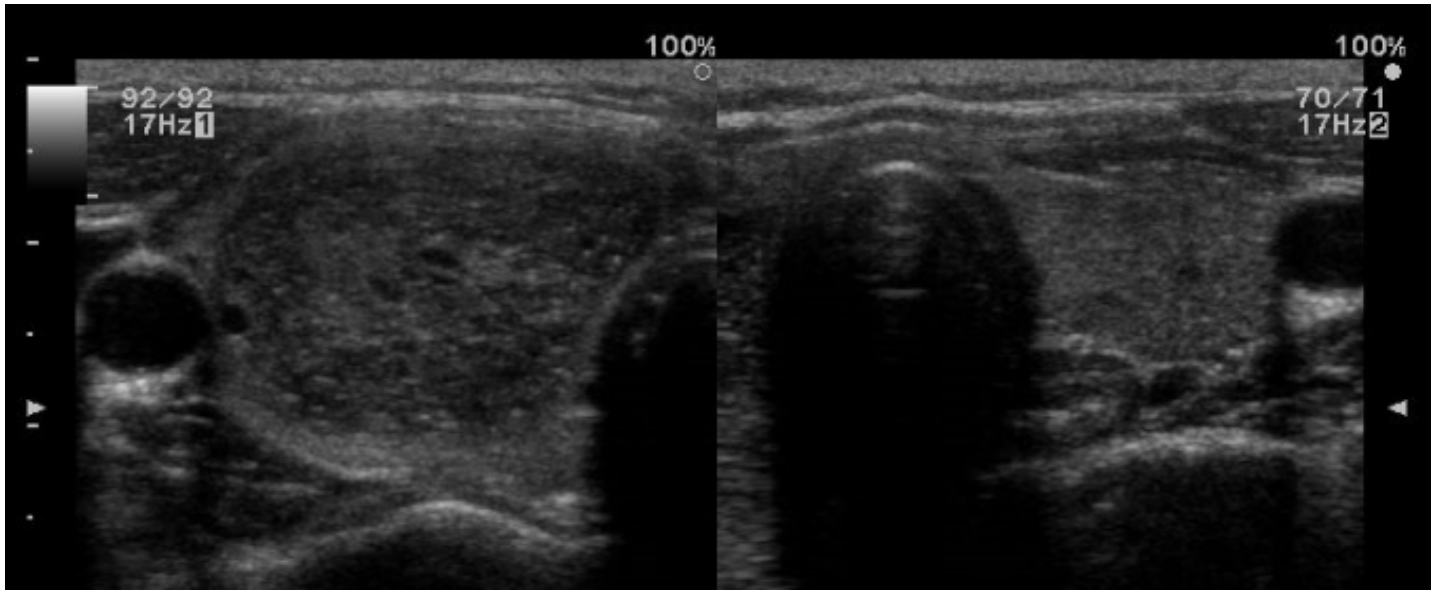
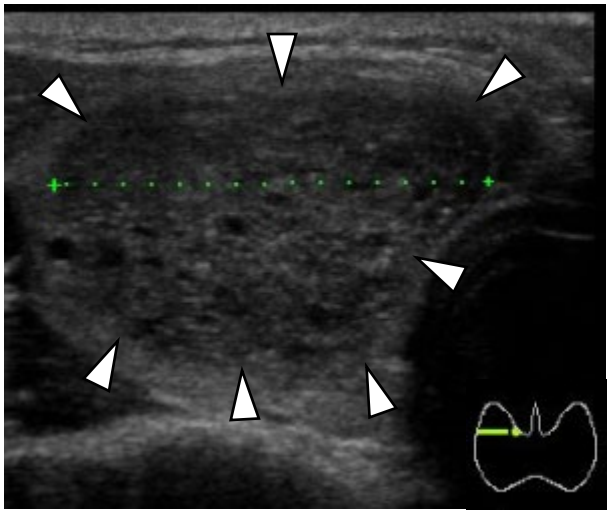
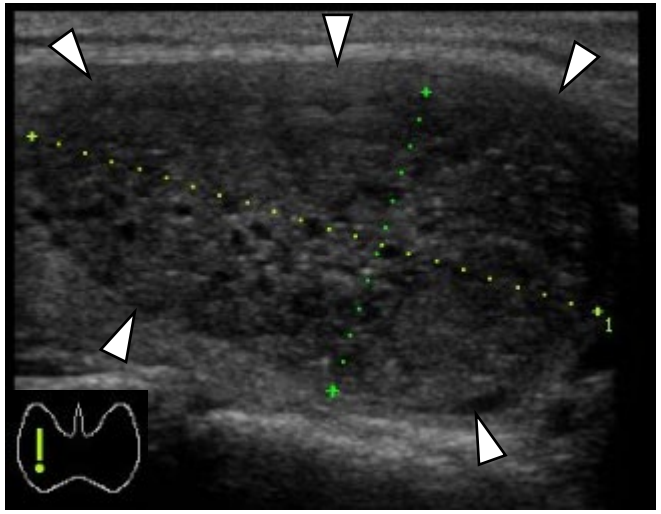

Nodule size
2.3cm
3.4cm
4.3cm
FT3 (pg/mL)
FT4 (ng/dL)
2nd Pregnancy
3rd Pregnancy
FT3 (pg/mL)
FT4 (ng/dL)
TSH(μU/mL)
12
10
8
6
4
2
0
4.2
4.1
5.5
7.3
10.3
FT3
1.3
1.1
1.5
2.1
2.6
FT4
TSH
3
2
1
0
TSH (μU/mL)
20XX-4 Jan.
20XX-3 Jan.
20XX-2 Jan.
20XX-1 Jan.
20XX Jan.

Fig. 2







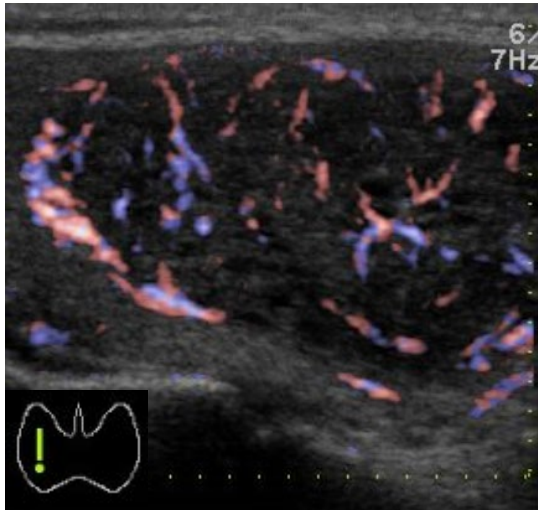
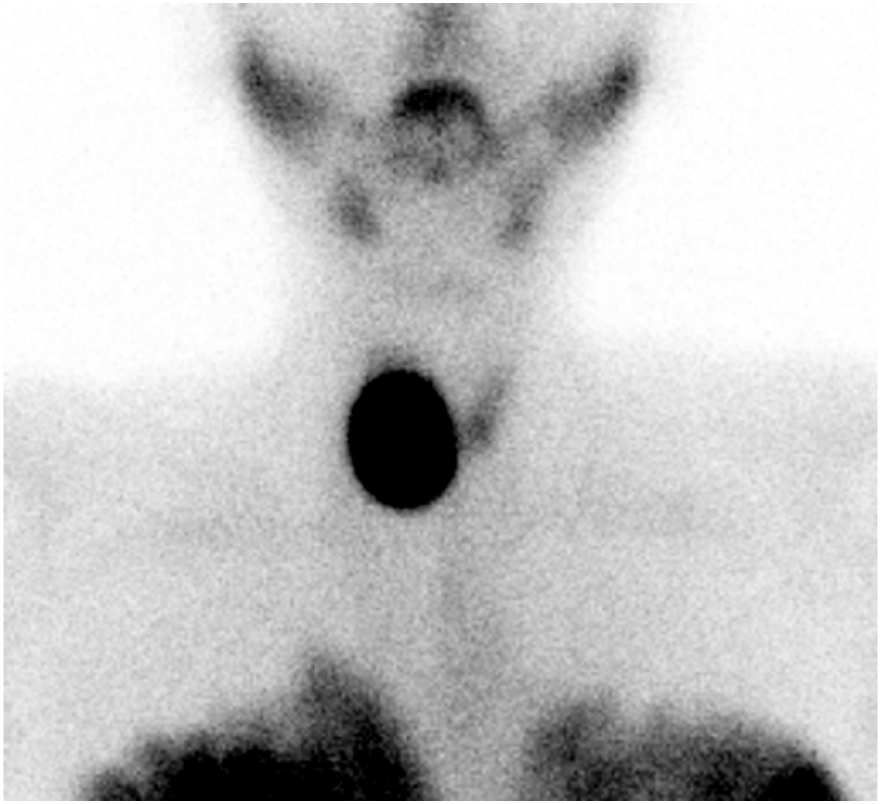


Fig. 3



Intake rate 6.52%