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Painless thyroiditis incidentally diagnosed following SARS-CoV-2 infection

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SUMMARY

A euthyroid woman in her 50s with papillary thyroid cancer and primary hyperparathyroidism was referred to our hospital for surgery. Her surgery was scheduled for 4 months later but was postponed because she was diagnosed with COVID-19. Five months after the first visit, she was admitted to our hospital to undergo the planned thyroid lobectomy and parathyroidectomy. Her blood tests on admission showed thyrotoxicosis, with negative thyroid-stimulating hormone receptor and thyroid-stimulating antibody. Notably, her anti-thyroglobulin antibody and anti-thyroid peroxidase antibody, which were originally negative, became positive after SARS-CoV-2 infection. She was diagnosed with painless thyroiditis. Her general condition and vital signs were stable, and the surgery was cautiously performed. Histopathological examination of the resected thyroid revealed papillary thyroid carcinoma, and the findings were consistent with painless thyroiditis. Her postoperative course was uneventful, and her thyroid function improved 2 weeks after the operation.

BACKGROUND

Recently, there have been reports on subacute thyroiditis, Graves' disease and Hashimoto's thyroiditis following SARS-CoV-2 infection.[1 2] However, few studies have reported painless thyroiditis or postpartum thyroiditis diagnosed after SARS-CoV-2 infection.[3 4] To the best of our knowledge, no case of histologically confirmed painless thyroiditis following SARS-CoV-2 infection has been reported. Hence, we report the case of a patient with painless thyroiditis whose anti-thyroglobulin antibody (TgAb) and anti-thyroid peroxidase antibody (TPOAb) were negative before SARS-CoV-2 infection became positive after SARS-CoV-2 infection.

CASE PRESENTATION

A woman in her 50s was referred to our hospital for surgery for papillary thyroid cancer and primary hyperparathyroidism. At the first visit, her thyroid function test results were as follows: free T4, 1.35 ng/dL (normal, 0.9–1.7 ng/dL); free T3, 3.88 pg/mL (normal, 2.3–4.0 pg/mL); and thyroid-stimulating hormone (TSH), 0.785 µIU/mL (normal, 0.61–4.23 µIU/mL). TgAb was less than 28.0 IU/mL (normal, 0–40 IU/mL) and TPOAb was less than 16.0 IU/mL (normal, 0–28 IU/mL). These were all measured by electrochemiluminescence immunoassay (ECLusys; Roche Diagnostics, Tokyo, Japan). Results of other biochemical tests were as follows: serum thyroglobulin 25.9 ng/mL (normal, 0–46.05 ng/mL), serum calcium 10.8 mg/dL (normal, 8.2–10.2 mg/dL), serum phosphate 3.0 mg/dL (normal, 2.5–4.5 mg/dL) and intact parathyroid hormone (iPTH) 75 pg/mL (normal, 15–70 pg/mL). The urinary calcium/creatinine ratio calculated from spot urine was 0.017.

Thyroid ultrasonography showed a solid, hypoechoic 12 mm nodule with slightly irregular borders in the left lobe of the thyroid (figure 1). An enlarged right lower parathyroid gland was also detected (figure 2). The estimated thyroid volume was 21.2 mL, and the thyroid gland was homogeneous with normal blood flow. On fine needle aspiration biopsy, the thyroid nodule was classified as malignant (Bethesda Category VI, papillary carcinoma).

Her surgery was scheduled for 4 months later; however, 3 months later, she was diagnosed with COVID-19 by reverse-transcription PCR, and the operation was postponed. She had fever and sore throat, but her illness was mild and spontaneously resolved without treatment.

Five months after her first visit (2 months after the COVID-19 diagnosis), the patient was admitted to our hospital for surgery. The thyroid function test on admission revealed elevated free T4 of 2.54 ng/dL and free T3 of 8.96 pg/mL, with a suppressed TSH level of less than 0.005 µIU/mL. TgAb was 111.0 IU/mL and TPOAb was 34.2 IU/mL, while antibodies to the TSH receptor (TRAb) was 1.04 IU/L (normal, 0–2 IU/L) and thyroid-stimulating antibody (TSAb) was 103% (normal, 0–120%). TRAb was measured by electrochemiluminescence immunoassay (ECLIA) (ECLusys; Roche Diagnostics) and TSAb was measured using a bioassay enzyme immunoassay (Yamasa; Yamasa Shoyu, Chiba, Japan). Thyroglobulin was 62.0 ng/mL, and serum C reactive protein was less than 0.5 mg/dL (normal, 0–0.5 mg/dL). PCR test for SARS-CoV-2 on admission was negative. She had no symptoms such as neck pain, and her vital signs were stable. The anti-SARS-CoV-2 spike protein antibody was positive, with a titre of 8.77 U/mL (normal, 0–0.80 U/mL). It was measured by high throughput ECLIA (Elecsys Anti-SARS-CoV-2 S; Roche Diagnostics).

From the time of the first visit to our hospital until admission, she had no other infection aside from SARS-CoV-2 infection. She has not received any COVID-19 vaccines. Moreover, she had no prior medical history other than that of papillary thyroid cancer and primary hyperparathyroidism.

The anti-SARS-CoV-2 spike protein antibody in the remaining serum cryopreserved at the first visit was negative and the titre was <0.4 U/mL.

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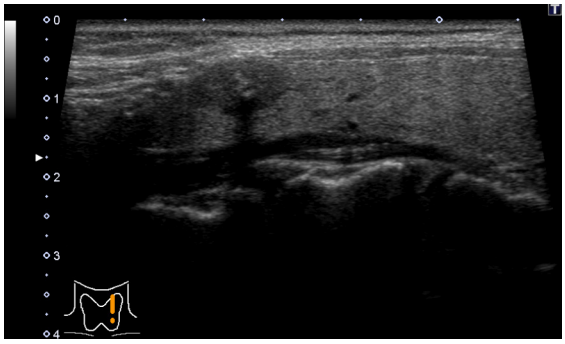

Figure 1 Thyroid ultrasonography showing a solid, hypoechoic 12 mm nodule with slightly irregular borders in the left lobe of the thyroid at the first visit.

INVESTIGATIONS

Thyroid ultrasonography showed a slightly heterogeneous, enlarged thyroid gland with an estimated thyroid volume of 26.8 mL and normal Doppler flow. The thyroid gland was slightly enlarged compared with that at the initial examination (figures 3 and 4). The nodule in the left lobe of the thyroid gland and parathyroid gland enlargement had not changed since the initial examination. Her 20 min technetium-99m thyroid scintigraphy uptake was 0.63% (normal uptake: 0.5–3.0%) (figure 5).

TREATMENT

The patient was diagnosed with painless thyroiditis. Her general condition and vital signs were stable, and the operation was cautiously performed as planned. Three days after admission, she underwent left thyroid lobectomy and parathyroidectomy.

OUTCOME AND FOLLOW-UP

The patient's postoperative course was uneventful, and blood test results on the third postoperative day were as follows: free T4 3.21 ng/dL, free T3 8.10 pg/mL, TSH 0.006 µIU/mL, serum calcium 8.9 mg/dL, serum phosphate 4.7 mg/dL and iPTH 26 pg/mL. She was discharged 4 days after surgery.

Histopathological examination confirmed the diagnosis of papillary thyroid carcinoma and parathyroid adenoma. The postoperative stage was pT1bN0M0. Thyroid tissue showed chronic inflammatory cell infiltration associated with destruction of the thyroid follicles (figure 6). The findings were consistent with painless thyroiditis.[5]

Her blood tests 2 weeks after discharge showed improved thyroid function as follows: free T4 0.93 ng/dL, free T3 3.65 pg/mL, TSH 0.011 µIU/mL, serum calcium 9.3 mg/dL, serum phosphate 3.5 mg/dL and iPTH 44 pg/mL.

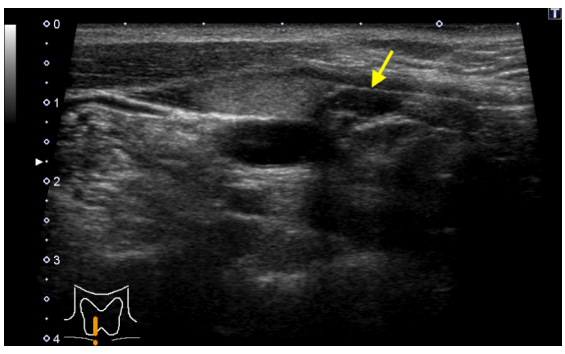

Figure 2 Enlarged right lower parathyroid gland.

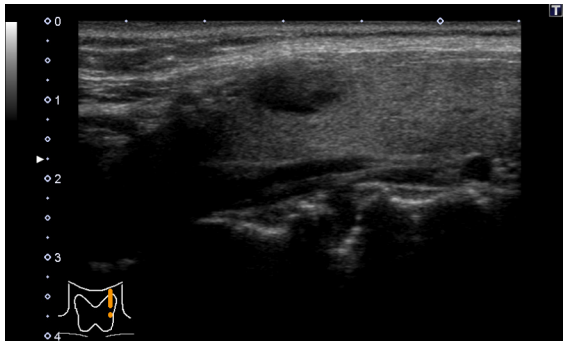

Figure 3 Ultrasound examination on admission showing a slightly enlarged thyroid gland as compared with the initial examination.

DISCUSSION

Painless thyroiditis is referred to by other names, such as silent thyroiditis, sporadic painless thyroiditis, sporadic thyroiditis, destructive thyroiditis and spontaneously resolving lymphocytic thyroiditis.[5] It is well known that a similar form of thyroiditis develops post partum, called postpartum thyroiditis. Postpartum thyroiditis is thought to be a variant of painless thyroiditis because it is frequently positive for antithyroid antibodies and shows similar histopathology and clinical manifestations.[5]

Painless thyroiditis is considered to be an immune-mediated disorder, which may be caused by immune checkpoint inhibitor drugs and various cytokines, such as interferon-alpha and interleukin-2.[5 6] The clinical course of painless thyroiditis is characterised by the destruction of the thyroid gland, resulting in excess thyroid hormones and transient thyrotoxicosis. This thyrotoxicosis improves spontaneously and is often followed by a period of hypothyroidism and full recovery.

Recently, two cases of painless thyroiditis and postpartum thyroiditis diagnosed after SARS-CoV-2 infection have been reported.[3 4] A man in his 50s admitted to the hospital for treatment of COVID-19 was incidentally found to have thyrotoxicosis in a blood test on admission. TgAb, TPOAb and TRAb were all negative. He had no symptoms suggestive of thyrotoxicosis and no neck pain. Thyroid scintigraphy showed a marked decrease in thyroid gland uptake, and he was diagnosed with painless thyroiditis. On follow-up medical examination, thyroid function normalised without any specific medication.[3] In the other case, a woman in her 20s was reported to be diagnosed with postpartum thyroiditis following SARS-CoV-2 infection. She had a history of painless thyroiditis with a background of Hashimoto's thyroiditis and was infected

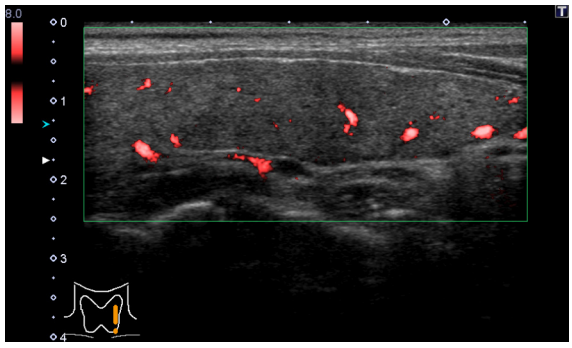

Figure 4 Thyroid ultrasonography on admission showing a slightly heterogeneous, enlarged thyroid gland with normal Doppler flow.

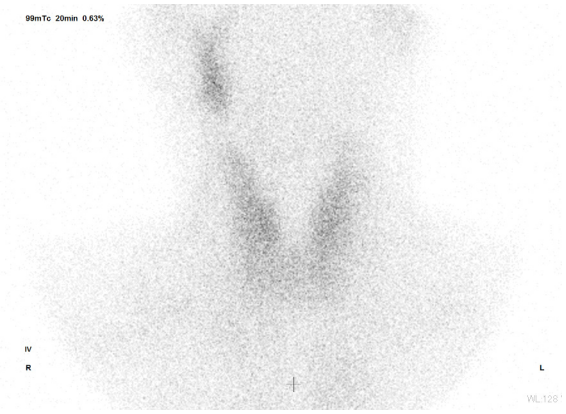

Figure 5 20 min technetium-99m thyroid scintigraphy uptake at 0.63%, which is low normal range.

with SARS-CoV-2 103 days after delivery. Thirty-three days after the SARS-CoV-2 infection, she was diagnosed with postpartum thyroiditis. Her thyroid function was as follows: free T4, 2.0 ng/dL; free T3, 5.44 pg/mL; and TSH, 0.020 µIU/mL. TgAb was positive, while TPOAb and TRAb were negative. No neck pain was found on examination. Her thyroid function normalised 2 months after SARS-CoV-2 infection without treatment.[4]

In addition to painless thyroiditis and postpartum thyroiditis, Graves' disease and Hashimoto's thyroiditis have been reported as autoimmune thyroiditis following SARS-CoV-2 infection.[2 7] SARS-CoV-2 enters the host cell through the ACE-2 receptor,[8] which is expressed in various organs, including thyroid follicular cells and lung cells.[9 10] The transmembrane serine protease 2 (TMPRSS2) is also considered to play a key role in SARS-CoV-2 cell entry,[11] and a high expression of TMPRSS2 mRNA has been reported in the thyroid tissue.[12] Additionally, SARS-CoV-2 genome and viral proteins such as spike and nucleocapsid proteins have been detected histologically in thyroid follicular cells of patients with COVID-19.[13 14] SARS-CoV-2 infection induces the release of proinflammatory cytokines, resulting in immune cell hyperactivity involving Th1/Th17 lymphocytes.[15] Interestingly, partially similar immune cell activation patterns have been reported in interferon-alpha-induced destructive thyroiditis, including painless thyroiditis.[15 16]

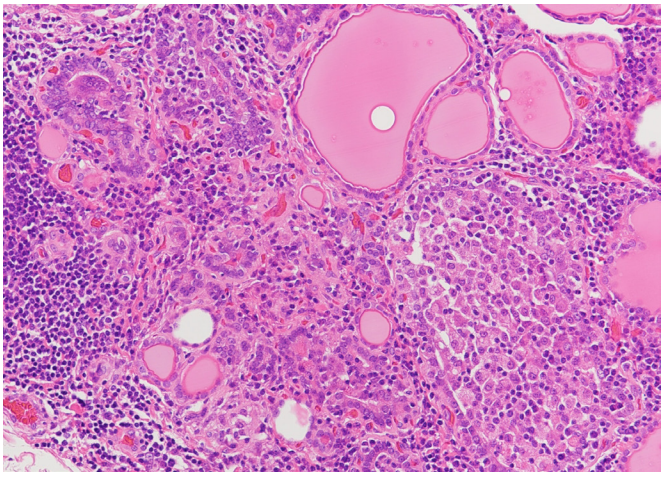

Figure 6 Thyroid tissue showing chronic inflammatory cell infiltration associated with destruction of the thyroid follicles.

PATIENT'S PERSPECTIVE

I was surprised when I was told that my thyroid hormone levels were abnormal during a blood test when I was hospitalised.
But I am thankful that the operation was successful.

Learning points

- Although the causal relationship is uncertain, autoimmune thyroiditis following SARS-CoV-2 infection has been reported.
- Painless thyroiditis may be overlooked due to its mild presentation of symptoms.
- When seeing a patient with autoimmune thyroiditis, previous instances of SARS-CoV-2 infection should be ascertained while taking medical history.

Furthermore, it has been reported that the spike protein and nucleus of SARS-CoV-2 are similar in structure to thyroid peroxidase (TPO).[17] This means that antibodies produced after SARS-CoV-2 infection may also cross-react against TPO, resulting in autoimmune thyroiditis.[2]

Cristinel *et al* reported increased TPOAb and TgAb levels in patients with autoimmune thyroid disease (AITD) and a history of chronic hepatitis C 1 month after SARS-CoV-2 infection.[18]

Notably, our case had no history of AITD, and negative TgAb and TPOAb at initial presentation became positive after SARS-CoV-2 infection. Although this does not confirm a causal relationship between SARS-CoV-2 infection and painless thyroiditis, it is postulated that SARS-CoV-2 infection may have triggered an immune response that led to painless thyroiditis.

There have been many reports of autoimmune thyroiditis following SARS-CoV-2 infection, but painless thyroiditis following SARS-CoV-2 infection is less commonly reported than Graves' disease or Hashimoto's thyroiditis. One possible speculation is that painless thyroiditis may be overlooked because of its mild symptoms. Indeed, our patient and the previously reported case[3] were asymptomatic and were diagnosed incidentally by blood tests.

Although the causal association between COVID-19 and autoimmune thyroiditis is uncertain at the current time, physicians should consider the possibility of autoimmune thyroiditis after SARS-CoV-2 infection. Therefore, a history of SARS-CoV-2 infection should be sought while taking medical history.

Even though there are several reports exploring COVID-19 and thyroid disease, their pathogeneses remain poorly understood and further research is needed.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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