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(CASE REPORT)

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Description of a patient with Graves' disease post COVID-19 with negative serology

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Abstract

We are presenting a 62-year-old African-American female who was admitted to our Emergency Department (ED) with septic shock due to pneumonia and diverticulitis. After improvement of the admitting conditions, we found out that the patient developed 1-month post-COVID-19 pneumonia Graves' disease. The diagnosis was challenging because the patient was negative for thyroid-stimulating immunoglobulin (TSI) and thyroid receptor antibodies (TRAb). The clinical picture was highly suggestive of GD. The patient complained of increased sweating, palpitation, lower extremities weakness, and lack of sleep before the septic shock and after the COVID-19 infection. We palpated a trill and we heard a bruit on her thyroid gland which was a specific finding for the hypervascular gland as in GD. Our physical findings were confirmed by the laboratory findings of thyrotoxicosis with increased free thyroxin levels (Ft4) and very low thyroid stimulating hormone (TSH). The Doppler flow ultrasound of the thyroid confirmed bilateral hypervascular thyroid gland suggestive of hyperthyroidism without nodules. The patient did not have any thyroid disease or complaints before her COVID-19 infection. This is as far as we know the first described patient post-COVID-19 induced GD without TSI and TRAb.

Keywords: Graves' Disease; Covid-19 infection; Thyroid stimulating immunoglobulin; Thyroid receptor antibodies; Thyroid Doppler ultrasound; Free thyroxin hormone; Thyroid stimulating hormone; Total triiodothyronine hormone.

1. Introduction

Since the outbreak of the SARS-CoV-2 pandemic, there have been many reports of autoimmune diseases triggered by or related to COVID-19. These diseases include but are not limited to such diseases as Guillain–Barre's syndrome, autoimmune hemolytic anemia, autoimmune thrombotic thrombocytopenic purpura, or autoimmune thrombocytopenic purpura. Regarding thyroid disease, there have been three case reports of subacute thyroiditis or silent thyroiditis as well as Hashimoto thyroiditis leading to primary hypothyroidism post-COVID-19 infection [1,2,3,4,5]. Also, there were reports of autoimmune Graves disease which was associated with thyroid-stimulating antibodies [5,6,7,8]. There are in recent years more reports implicating the COVID-19 virus in thyroid dysfunction, including thyrotoxicosis due to both thyroiditis and Graves' disease (GD) [8,9,10,11]. GD is a form of autoimmune hyperthyroidism that is mediated by autoantibody stimulation of the thyrotropin receptor called Thyroid Stimulating Immunoglobulin (TSI). TSI is positive in 95-99% of patients with Graves' disease (GD). It stimulates the thyroid gland to secrete increased quantities of thyroid hormones and causes hyperthyroidism. It occurs in genetically predisposed individuals exposed to environmental stressors. These stressors might include viruses or bacteria as well as a disruption in iodine homeostasis, exposure to certain medications, radiation, and physiologic stress. Recent case reports have implicated COVID-19 as a cause of both new-onset – and relapse of dormant – Graves' disease in genetically predisposed patients [4,8]. One possible mechanism through which the COVID-19 virus might trigger Graves' disease is through molecular mimicry with activation of the autoimmune pathways [4]. The autopsy studies did not show COVID-19 particles in the thyroid gland. This suggests an immune-mediated mechanism that leads either to the destruction of the

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thyroid gland and clinical picture of subacute/silent or Hashimoto thyroiditis with or without permanent primary hypothyroidism, or the production of TSI and hyperfunction of the thyroid gland and clinical picture of Graves's disease [4]. In our case report, we describe for the first time as far as we know a patient with Graves' disease post Covid-19 infection with negative TSI.

2. Case presentation

A 63-year-old African-American female who had COVID-19 pneumonia a month ago came into the Emergency room with Complaints of feeling feverish, having chills, nausea, vomiting, abdominal pain, and mild shortness of breath for 3-days. She was found to have septic shock due to community-acquired pneumonia and sigmoid diverticulitis. The patient had a past medical history of hypertension, ileostomy due to small bowel resection, thrombocytopenia due to immune thrombocytopenic purpura, and hyperlipidemia.

On physical exam, she was found to have vital signs of temperature 40 degrees C, heart rate 140 beats per minute, blood pressure 78/44mmHg, respiratory rate 22, SpO_2 91%. She was short of breath when speaking in full sentences. Her thyroid was non-tender, enlarged, and without palpable nodularity. We felt trill and heart bruit on her thyroid gland. She had decreased breath sounds in the bases of her lungs with rales, had tachycardia, and abdominal pain without guarding. Her ileostomy was patent. She had a peripherally inserted central catheter (PICC) which looked fine and was receiving at-home total parenteral nutrition (TPN). The patient's white count was elevated at 12,000/microliter. When the blood cultures grew Klebsiella pneumonia, the PICC line was discontinued, and the patient was hydrated by placing a peripheral line. We believe the blood cultures were positive due to her diverticulitis and or pneumonia. The PICC line was not infected. CT of the chest and CT angiogram with iodinated contrast ruled out pulmonary embolism and confirmed bilateral lower lobe pneumonia and the CT abdomen showed sigmoid diverticulitis. The patient was treated successfully with an intravenous infusion of normal saline, norepinephrine, albumin, and antibiotics. The patient had prerenal acute kidney injury which resolved with intravenous fluids.

Table 1 Change in Thyroid function test over time

Laboratory thyroid function tests	**Reference range**	**# Weeks from COVID-19**		
		4	7	12
TSH (mIU/L)	0.35–4.70	0.01	0.01	1
Free T4 (ng/dL)	0.8–1.46	2.68	1.2	1.34
Total T3 (ng/dL)	70–195	70	77	73
TRAb (IU/L)	0–1.75	0	0	0
TSI (IU/L)	0–1.3	0	0	0
TPO Ab (IU/mL)	0.0–9.0	0	0	0

TSH = thyroid-stimulating hormone; TRAB = thyrotropin receptor antibody; TSI = thyroid-stimulating immunoglobulin; TPO Ab = thyroid peroxidase antibody. Abnormal values are in bold.

EKG of the patient showed sinus tachycardia with rapid ventricular rate (rate 142 bpm). Thyroid ultrasound and color flow Doppler showed bilateral heterogeneous thyroid gland and isthmus with increased vascular flow consistent with hyperthyroidism without asymmetry, nodules, or focal lesions. The patient could not undergo a thyroid uptake and scan because of the use of iodinated contrast in the Emergency Department (ED). COVID-19 nasal swab PCR was negative on this admission, but positive a month ago with Covid-19 pneumonia.

The patient had no prior history of thyroid disease, other endocrinopathy, autoimmune disease, arrhythmia, coronary artery disease, or cardiomyopathy. Her COVID-19 infection had occurred one month before her presentation to the ED; at that time, she had symptoms of cough, exertional dyspnea, and sinus congestion – which resolved entirely. The patient complained that after the COVID-19 pneumonia resolved and before the current presentation to the ED she felt increased sweating, palpitations, inability to sleep, and weakness in her lower extremities.

We checked the patient's TSH which was very low at 0.01 mU/L reference range (0.4-4.0 mU/L), Free Thyroxine levels (FT4) levels which were elevated at 2.68 ng/dl with the reference range (0.8-1.46 ng/dl) and normal total triiodothyronine (T3) level of 71 ng/dl with the reference range (70—195 ng/dl). Surprisingly the patient's Thyroid stimulating immunoglobulin was 0(0%) with a reference range of less than 1.3 IU/L (130%) and the thyroid peroxidase

antibodies (TPO) and thyroglobulin antibodies were also not present. A thyrotropin receptor antibody (TRAb) was also sent at this time and resulted in normal at 0 IU/L (Nl 0.00–1.75IU/L). With a very low TSH, increased Ft4, and signs of hyperthyroidism, the patient was treated with methimazole.

She followed up with an endocrinologist in the hospital and there was a normalization in 10- days of her FT4 - 1.4 ng/dl. In subsequent visits to her primary care physician, weeks 4,7 and 12 FT4 stayed normal and her TSI, TRAb, TPO, and thyroglobulin antibodies never became positive, while TSH normalized while the Methimazole was decreased from 10 mg to 2.5 mg a day.

3. Discussion

Thyrotropin receptor antibodies (TRAbs) are of three types [12,13]. TSH receptor stimulating antibody (TSAb), TSH receptor blocking antibody (TBAb), and neutralizing antibody. Among the three sub-types, the clinically significant ones are the TSAb which stimulates the TSH receptor causing Graves' disease, and the TBAb which blocks the TSH receptor causing hypothyroidism. There are two methods to check the TRAb; the TSI assay which measures the stimulating antibody and the TBII (thyrotropin binding inhibiting immunoglobulin) assay which measures the stimulating, blocking, and neutralizing antibodies. In our case, TSI and TRAbs were both negative. The big dilemma we had in our case was are we dealing with silent thyroiditis post-COVID-19 infection in the thyrotoxic phase or Graves' disease. Subacute thyroiditis frequently described after COVID-19 infection in the literature was not in our differential diagnosis, because of a lack of tenderness on the thyroid gland [4,5]. In subacute thyroiditis also the TSI antibodies and TRAb have been described as being positive rarely, but the clinical and ultrasonographic picture is completely different than in patients with GD[13,14]. Our patient complained before her presentation in ED and after her COVID-19 infection of palpitation, sweating, inability to sleep, and significant lower extremities weakness. After we saw her in ED we palpated a trill and heard a bruit on her thyroid gland suggestive of Graves' disease. Also, the thyroid ultrasound with flow Doppler did not show a hypoechoic thyroid gland with decreased blood flow but a bilateral heterogeneous thyroid gland and isthmus with increased vascular flow consistent with hyperthyroidism without asymmetry, nodules, or focal lesions. The intriguing feature of our presentation was the lack of positive TSI and TSAb which can happen in 1-5% of patients with Graves' and is seen more commonly in children [15] but has never been described in patients post-COVID-19 infection-induced GD in the literature. In conclusion, GD cannot be ruled out in patients with a clinical presentation compatible with hyperthyroidism and negative TRAb. It is important to be aware of this potential presentation to initiate treatment with antithyroid agents as soon as possible if the clinical and the Doppler flow ultrasound picture of the thyroid are compatible with GD.

4. Conclusion

We described the patient with clinical, laboratory, and flow Doppler ultrasound pictures suggestive of GD post-COVID-19 infection. The patient had negative autoimmune markers of the disease. Her TSI and TRAb were negative and never became positive in her follow-up visits. It is important to remember that 1-5% of patients with GD do not express the TSI. If the suspicion of GD is high the treatment with antithyroid medications should not be delayed. As far as we know this is the first description of TSI-negative GD post-COVID-19 infection in the literature.

Compliance with ethical standards

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Disclosure of conflict of interest

None to be disclosed for all of the authors: Dr. Andre Manov, Dr. Yasra Badi, Dr. Andrew Wang, and Dr. Rakahn Haddadin

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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