



THYROTOXICOSIS MISDIAGNOSED AS LONG COVID BY TELEMEDICINE – A CAUTIONARY TALE

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ABSTRACT

Introduction: Individuals who have had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may develop post-coronavirus disease conditions, also known as long COVID. The symptoms of long COVID are nonspecific, and there are similarities between the symptoms of long COVID and those of Graves' disease (GD). Therefore, it is important to rule out GD in patients suspected of having long COVID. Telemedicine is widely used to avoid the risk of SARS-CoV-2 infection. However, owing to the lack of in-person examinations, diagnostic errors can occur.

Case description: A 27-year-old Japanese woman presented complaining of persistent fatigue, dyspnea, and low-grade fever, and after in-person examination was finally diagnosed with GD. She had been diagnosed with SARS-CoV-2 infection four months earlier and her symptoms had resolved within 5 days but then recurred. Subsequently, she had 3 telemedicine visits and had been diagnosed with long COVID.

Discussion: With telemedicine there may be delayed diagnosis of GD in patients with a recent history of SARS-CoV-2 infection. Some symptoms and abnormalities cannot be confirmed in telemedicine visits performed using a simple mobile phone. Therefore it is important to know which findings obtained in telemedicine visits with a simple mobile phone are suggestive of GD. Low-grade fever and tachycardia are often observed in patients with GD, but rarely occur in patients with long COVID.

Conclusion: Tachycardia and persistent low-grade fever after SARS-CoV-2 infection, which can be confirmed by telemedicine, can be clues for the diagnosis of GD. Therefore, in-person examination should be added if these symptoms are confirmed by telemedicine.

KEYWORDS

Long COVID, Graves' disease, Telemedicine, Delayed diagnosis

LEARNING POINTS

- The symptoms of Graves' disease (GD) and long COVID may overlap.
- With telemedicine there may be delayed diagnosis of GD, in patients with recent history of severe acute respiratory syndrome mediated by coronavirus 2 (SARS-CoV-2) infections.
- In telemedicine visits, tachycardia and persistent low-grade fever could be clues for the diagnosis of GD after SARS-CoV-2 infections on telemedicine.



INTRODUCTION

More than 3 years after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic began, the long-term sequelae of SARS-CoV-2 infection are cause for concern. Some patients may still have persistent pulmonary and other symptoms after acute SARS-CoV-2 infections, and this condition is called long COVID. The World Health Organization defined long COVID as the continuation or development of symptoms 3 months after the initial SARS-CoV-2 infection, with symptoms lasting for at least 2 months with no other explanation^[1]. The prevalence of this condition is approximately 12.7% in patients 90 to 150 days after acute infection with SARS-CoV-2^[2]. As the symptoms observed in patients with this condition are nonspecific, a differential diagnosis is needed for the diagnosis of long COVID.

Graves' disease (GD) is an autoimmune disease that is characterized by stimulation of the thyroid gland by thyroid-stimulating hormone (TSH) receptor antibodies (TRAbs) and is the most common cause of thyrotoxicosis. It is found in 0.02 to 0.32 % of the Japanese population. The main symptoms of this disease are fatigue, malaise, palpitations and dyspnea, which partially overlap with symptoms of long COVID^[3]. Therefore, it is important to rule out GD, when diagnosing patients suspected of having long COVID.

Telemedicine is a service that is rapidly evolving to provide increased access to high-quality, efficient, and cost-effective healthcare and could reduce the risk of infection to medical staff. However, availability bias is always present in telemedicine and the inability to perform an in-person physical examination can lead to diagnostic errors. Here, we report a delayed diagnosis of GD, in a patient who had been diagnosed with long COVID via telemedicine visits.

CASE DESCRIPTION

A 27-years-old Japanese woman presented to our hospital complaining of persistent fatigue, dyspnea, and low-grade fever. Her medical history was unremarkable except for

SARS-CoV-2 infection approximately 4 months earlier. Her symptoms of SARS-CoV-2 infection had included fatigue, sore throat, and low-grade fever, which had improved within 5 days. However, she developed recurrent episodes of fatigue, dyspnea, and low-grade fever approximately 3 weeks after the onset of SARS-CoV-2 infection. She had then been to our hospital for 3 telemedicine visits and had been diagnosed with long COVID. In our hospital, a simple mobile phone is used in telemedicine visits for the doctor to communicate with the patient who is in a room with a nurse. Patients in poor physical conditions are interviewed by input into the device, and then their vital signs are measured by a nurse with appropriate infection control precautions. Based on this information, the patient is then seen by a physician using the mobile phone. Telemedicine with high-definition cameras is not available in our hospital. In some cases, the medical examination is completed via a simple mobile phone and the patient receives a prescription. In other cases, in-person examination and further testing is added after testing for SARS-CoV-2. The patient's symptoms, vital signs, and diagnosis at her 5 visits are listed in *Table 1*.

When the patient presented to our hospital 117 days after the onset of SARS-CoV-2 infection an in-person examination was performed once SARS-CoV-2 infection was ruled out by polymerase chain reaction testing. Her blood pressure was 121/78 mmHg, her pulse rate was 133 bpm, her body temperature was 37.4 °C, and her saturation of percutaneous oxygen was 99%. Her body weight and body mass index were 49.4 kg and 21.1 kg/m², respectively, and an unintentional weight loss was noted (4 kg in approximately 4 months). In-person physical examinations revealed mild goiter, tremors, and perspiration. The laboratory findings are shown in *Table 2*. It was noted that the patient had thyrotoxicosis: TSH < 0.01 mIU/l, free triiodothyronine >20.0 pg/ml, free thyroxine 3.94 ng/dl, but there was no elevation of the white blood cell count and C-reactive protein level. TRAb, anti-thyroglobulin antibody, and anti-thyroid peroxidase antibody were, 5.9

	At the diagnosis of SARS-CoV-2 infection (Day 0)	First telemedicine visit (Day 30)	Second telemedicine visit (Day 62)	Third telemedicine visit (Day 99)	At the diagnosis of GD (Day 117)
Symptoms	fatigue, sore throat, low-grade fever	fatigue, dyspnea, low-grade fever	fatigue, dyspnea, low-grade fever	fatigue, dyspnea, low-grade fever	fatigue, dyspnea, low-grade fever
Blood pressure (mmHg)	126/60	116/80	114/76	106/66	121/78
Heart rate (bpm)	88	120	108	114	133
Body temperature (°C)	37.8	37.7	37.6	37.1	37.4
SpO ₂ (%)	98	98	97	99	99
Diagnosis	SARS-CoV-2 infection	Long COVID	Long COVID	Long COVID	GD

Abbreviations. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, COVID: coronavirus disease, GD: Graves' disease

| *Table 1. Symptoms, vital signs, and diagnosis at the 5th visit.*

	Result	Normal range
White blood cell count (/μl)	6700	3000-9100
Red blood cell count (×10 ⁴ /μl)	457	376-500
Haemoglobin (g/dl)	14.9	11.3-15.2
Platelets (×10 ⁴ /μl)	22.5	13-36.9
Blood urea nitrogen (mg/dl)	8	8-22
Creatinine (mg/dl)	0.32	0.5-0.8
Aspartate transaminase (U/l)	46	13-33
Alanine transaminase (U/l)	76	6-28
γ-Glutamyl trans peptidase (U/l)	75	10-47
Sodium (mEq/l)	139	135-149
Potassium (mEq/l)	4.1	3.5-4.9
Chlorine (mEq/l)	105	96-108
C-reactive protein (mg/dl)	0.3	0-0.3
Thyroid-stimulating hormone (μIU/ml)	<0.01	0.34-3.88
Free triiodothyronine (pg/ml)	>20	2.13-4.07
Free thyroxine (ng/dl)	3.94	0.95-1.74
Thyroglobulin (ng/dl)	0.215	0-33.7
Thyroid-stimulating hormone receptor antibody (IU/l)	5.9	0-2
Anti-thyroid peroxidase antibody (IU/ml)	358.6	0-16
Anti-thyroglobulin antibody (IU/ml)	1960	0-28

Table 2. Laboratory findings at the 5th visit.

IU/l (0-2 IU/l), 1960 IU/ml (0-28 IU/ml), and 358.6 IU/ml (0-16 IU/ml), respectively. Thyroid ultrasound showed bilateral lobe enlargement and increased blood flow. Thyroid uptake of ^{99m}Tc-pertechnetate was 13.6% (0.5-4%). The patient was diagnosed with GD based on the Japan Thyroid Association diagnostic criteria. Oral thiamazole 15 mg per day was administered, and the thyroid hormone levels were normalized. With the normalization of thyroid hormone levels, her fatigue, low-grade fever, and shortness of breath improved. The dose of thiamazole was decreased gradually. After 1 year of treatment with thiamazole, the dose was decreased to 5 mg every 2 days and no relapse of GD was observed.

DISCUSSION

GD and long COVID have many similarities. Fatigue (82.1%), general malaise (77.6%), palpitations (71.6%), and dyspnea (70.1%) are common symptoms in patients with thyrotoxicosis^[3], whereas fatigue (53%), dyspnea (43%), and chest pain (22%) are common in patients with long COVID^[4].

Moreover, it has been reported that GD may be more likely to develop after SARS-CoV-2 infection^[5]. Indeed, after SARS-CoV-2 infection, levels of many cytokines, including interleukin-6, increase^[6]. Moreover, gene expression of TSH receptor (TSHR) messenger ribonucleic acid (mRNA) was upregulated in the leukocytes of patients with SARS-CoV-2 compared to healthy controls^[7].

On in-person physical examinations, goiter, skin perspiration, and tremors can be easily identified in patients with GD. However, we cannot confirm these symptoms and abnormalities via telemedicine. Therefore, we should know which of the findings obtained in telemedicine visits suggest a high likelihood of GD. Low-grade fever occurs in approximately 30% of patients with thyrotoxicosis, but rarely in those with long COVID^[3,4]. Tachycardia is usually not observed in patients with long COVID, but observed in appropriately 50% of patients with primary hyperthyroidism^[8]. These two vital signs could be confirmed via telemedicine. Thus, in-person examination should be added, if these vital signs are confirmed via telemedicine. Although in-person examination is the most effective way to evaluate a patient with GD, telemedicine with high-definition cameras, not just a simple mobile phone, can be very useful, to confirm some physical findings of GD. Therefore, physicians should add in-person examination or telemedicine with high-definition cameras, if these two abnormal vital signs are observed in patients who have recently had SARS-CoV 2 infection.

Delayed diagnosis in patients with GD may increase the risk of thyroid storm, which is associated with a mortality rate of approximately 10.7%^[9]. Moreover, approximately 45% of cases of thyroid storms developed within 1 year after the initial diagnosis of GD or before the diagnosis of GD^[9]. These findings mean that avoiding diagnostic delays in patients with GD is important to prevent the transition to a thyroid storm.

CONCLUSION

Tachycardia and persistent low-grade fever after SARS-CoV-2 infection, which can be confirmed by telemedicine, can be clues for the diagnosis of GD.

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