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The scintigraphic diagnosis of subacute thyroiditis in hospitalized patients with acute COVID-19 infection

Raheleh Hedayati[1], Bita Reihani[2], Soroush Nematollahi[3], Saeed Kalantari[4], Donya Maleki[4], Zeynab Yassin[4]

[1]*Department of Nuclear Medicine, Rasoul Akram General Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*
[2]*Department of Nuclear Medicine, Rajaie Cardiovascular Medical and Research Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*
[3]*Department of Immunology and Infectious Diseases, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*
[4]*Antimicrobial Resistance Research Center, Institute of Immunology and Infectious Diseases, Iran University of Medical Sciences, Tehran, Iran*

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*Corresponding Author:
Dr Zeynab Yassin
Address: Department of Immunology and Infectious Diseases, Rasoul Akram Hospital, Niyayesh Street, Sattar Khan Avenue, Tehran, Iran
Email: yasin.z@iums.ac.ir

ABSTRACT

Introduction: Extrapulmonary manifestations of COVID-19 must not be neglected during the pandemic. Subacute thyroiditis is one of the possible complications people encounter during post-COVID-19 days. Thyroid scintigraphy and radioiodine uptake test help discriminate hyperthyroidism from destructive thyrotoxicosis. Finding a more precise way to diagnose subacute thyroiditis can help in the early detection and treatment of thyroid-related disorders.

Methods: In this cross-sectional study, we evaluated 69 cases of COVID-19. Patients were divided into moderate and severe groups based on their clinical conditions. A thyroid scintigraphy scan was performed on the discharge day. Imaging was done 15-20 minutes after intravenous administration of 3-5 mCi of [^{99m}Tc]TcO4$^-$. Scan findings were compared between moderate and severe groups and other participants' demographic and clinical features.

Results: In 69 patients, according to thyroid scintigraphy, 25 (36%) cases were reported as thyroiditis, and the rest were normal. There was no significant difference between the normal and subacute thyroiditis groups based on age, gender, past medical history, the severity of COVID-19, laboratory values and clinical signs and symptoms. Patients with subacute thyroiditis experienced palpitation and sore throat significantly higher than the normal group (P=0.002 and P=0.009, respectively).

Conclusion: We conclude that patients admitted due to acute COVID-19 infection experiencing palpitation and sore throat can develop subacute thyroiditis more than others. Whereas the severity of the disease and laboratory testing were not diagnostic in subacute thyroiditis, thyroid scintigraphy may help in early detection.

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INTRODUCTION

Subacute thyroiditis (SAT), also known as subacute granulomatous thyroiditis or De Quervain's thyroiditis, presents with sudden onset of neck pain and thyrotoxicosis. Although the etiology of SAT is not well understood, there have been reports of the disease incidence during viral infection outbreaks. Hence, coronaviruses, adenovirus, and some enterovirus can be a triggering factor in many cases [1, 2].

Since 2019, many countries have been dealing with the SARS-CoV-2 pandemic, a type of coronavirus that causes mild to moderate flu-like symptoms in most patients. However, they can also lead to multi-organ dysfunction, septic shock, acute respiratory distress syndrome, or kidney failure in patients with considerable risk factors [3-5]. This condition usually affects elderly patients, and their prognosis depends on lung damage severity.

Extrapulmonary complications of COVID-19 may include endocrine complications, including pituitary, pancreatic, gonadal, and thyroid disorders [6, 7]. Despite the low prevalence of autoimmune hyperthyroidism or Graves' disease, recent literature reports a substantial rate of subacute or chronic thyroiditis in COVID-19 patients. Studies show an increased prevalence of thyrotoxicosis in patients with more severe COVID-19 secondary to destructive or inflammatory thyroiditis [8-11].

SAT presents with several symptoms. The most characteristic is neck pain; however, many patients experience a painless course of the disease called 'silent thyroiditis' [1, 12-14]. Low-grade fever has been documented in many cases of SAT [13, 15]. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count rise due to the underlying inflammation [13, 14]. The level of thyroid-related factors varies in the course of the disease. Patients may experience thyrotoxicosis at first, followed by a hypothyroidism period and then may return to the euthyroid state [1].

Describing the clinical and hormonal features of thyroiditis can lead to a better diagnosis and management [16]. Scintigraphy assessment of the thyroid gland permits the determination of the Iodine-123 iodide or the [^{99m}Tc]TcO_4^- uptake and distribution, which is a precise way of diagnosing thyroid disorders such as SAT, demonstrating severely decreased radiotracer uptake throughout. Also, thyroid scintigraphy and radioiodine uptake test are helpful in distinguishing hyperthyroidism from destructive thyrotoxicosis and iodine-induced hyperthyroidism in a patient with suppressed TSH levels [17].

This can help physicians differentiate SAT from other causes of palpitation, tremor, and dyspnea, such as COVID-19 complications, and psychiatric problems, such as anxiety.

METHODS

Patients

We designed a cross-sectional study and enrolled 71 cases admitted under the diagnosis of COVID-19 to Rasoul Akram Hospital from April 21 to July 21. Patients signed an informed consent to participate in the study. Sixty-nine cases met the inclusion criteria: first, COVID-19 infection confirmed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of nasal and pharyngeal swab specimens, and second, having no prior thyroid disease. Exclusion criteria were the previous history of thyroid dysfunction, treatment with drugs that interfere with TSH levels, including levothyroxine, methimazole, iodine, and amiodarone, and death due to severe COVID-19 infection. Patients with clinical signs and symptoms of pneumonia (fever, cough, dyspnea, tachypnea) and O2 saturation > 90% were moderate. The severe COVID-19 group included moderate COVID-19 patients having at least one of the following conditions: O2 saturation < 90% in room air, central cyanosis, respiratory rate of more than 30 breaths per minute, and evidence of respiratory distress, e.g., severe dyspnea. All Patients underwent thyroid scintigraphy at the time of the discharge despite clinical symptoms. After analyzing the data, we calculated the prevalence of SAT and assessed the correlation of thyroiditis with clinical symptoms and COVID-19 severity. The current study has been approved by the Iran University of Medical Sciences ethics committee.

Instrumentation

Scintigraphy assessment of the thyroid gland was operated with a single-head gamma camera equipped with a parallel-hole high-resolution collimator with a 15 % or 20 % window centered on a 140 KeV (Tc-99m) photopeak. The collimator matrix size was 128 × 128, and zoom factor specifications were 2.

Imaging protocol

Imaging was done 15–20 minutes after intravenous administration of 3-5 mCi of [^{99m}Tc]TcO_4.

Immediately prior to imaging, patients were asked to swallow water to clear activity from the mouth and esophagus. Participants were positioned supine, with the neck comfortably extended. It was helpful to immobilize the head with gentle restraints. An anterior image of the neck is acquired for 5–10 min, whichever occurs first. The distance between the neck and the collimator was minimized. A dedicated small-field thyroid gamma camera was helpful in specific cases (e.g., patients in a wheelchair and patients with severe claustrophobia).

The outcome was compared to the patient's laboratory values and clinical characteristics.

Statistical analysis

Data were analyzed by IBM SPSS statistics version 24. Constant values were described by mean ± SD, while the frequency was reported for categorical variables. A chi-square test was performed to compare grouped variables, and two independent sample T-tests were used to assess continuous values between groups. Non-parametric tests were performed for non-normally distributed variables. The significance level was defined as $\alpha < 0.05$, and P values less than this number were interpreted as statistically significant. The outcome was compared to the patient's laboratory values and clinical characteristics.

RESULTS

Demographics and clinical features

We enrolled 69 patients in the study, 37 (53.6%) cases were males, and 32 (46.4%) were females. The mean age of the participants was 53.64 ± 12.88 years. Based on the thyroid scan, 25 (36%) cases were reported as thyroiditis, and the rest were normal. Neither age nor gender did not statistically differ between normal and thyroiditis patients. Most participants did not have a remarkable past medical history (73.9%), and after analysis, no significant difference was found between underlying disease and developing thyroiditis. Patients were sorted as moderate or severe based on the criteria mentioned above, and we found that the severity of the disease did not make a meaningful difference in the final thyroid scan findings. Table 1 shows the demographic and clinical characteristics of the patients in detail.

Table 1. Demographics and clinical features of the participants

Variable	Thyroid scan finding			P-value
	Normal	Thyroiditis	Total	
Gender, n				
Male	24	13	37	0.839
Female	20	12	32	
Age, mean ± SD (years)	52.27 ± 11.89	56.04 ± 14.40	53.64 ± 12.88	0.246
Past medical history, n (%)				
No past medical condition	33 (64.7)	18 (35.3)	51	0.962
One important underlying disease	8 (61.5)	5 (38.5)	13	
Two or more important underlying disease	3 (60)	2 (40)	5	
Thyroid Scan finding, n (%)	44 (63.7)	25 (36.3)	69	-
The severity of the disease, n (%)				
Moderate	18 (52.9)	16 (47.1)	34	0.065
Severe	26 (74.2)	9 (25.8)	35	

Laboratory values

Table 2 compares laboratory values between normal patients and cases with thyroiditis. Since we have an inflammatory process during thyroiditis, inflammatory factors such as platelet and CRP are anticipated to increase in patients with thyroiditis, as they did. However, these changes were not statistically significant. In addition to inflammatory factors, other blood components such as WBC and hemoglobin were slightly greater in the thyroiditis group, but no significant difference was found (Table 2).

Table 2. Laboratory values and their differences between normal cases and patients with thyroiditis

Variable	Thyroid scan finding		P-value
	Normal	Thyroiditis	
White blood cell (cell/μL)	7.01 ± 2.99	7.34 ± 3.74	0.924
Hemoglobin (g/dL)	13.62 ± 1.64	13.04 ± 1.65	0.348
Platelet (10^3/μL)	175.67 ± 70.02	209.94 ± 78.74	0.096
ESR* (mm/h)	39.91 ± 22.04	42.6 ± 25.22	0.636
CRP* (mg/dL)			
< 6	8	4	0.633
6-24	16	12	
> 24	20	9	

* CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate

Clinical signs and symptoms

We observed some signs and symptoms related to both COVID-19 and thyroid dysfunctions. Palpitation and sore throat were significantly increased in people who developed thyroiditis (P=0.002 and P=0.009, respectively). However, vital signs stayed the same in both groups. Table 3 shows more data on this comparison.

Table 3. Signs and symptoms of the patients

Variable	Thyroid scan finding		P-value
	Normal (n=44)	Thyroiditis (n=25)	
Palpitation, n (%)	4 (9)	10 (40)	0.002†
Sore throat, n (%)	2 (4.5)	7 (28)	0.009‡
Tremor, n (%)	3 (6.8)	4 (16)	0.210
Heart rate, bpm[1]	82.45 ± 12.19	82.40 ± 5.56	0.762
Respiratory rate, bpm[2]	19.59 ± 9.93	17.48 ± 2.61	0.273
O_2 saturation, %	88.73 ± 5.45	89.28 ± 5.48	0.513

†Pearson Chi-Square, ‡ Fisher's Exact Test
[1]beats per minute, [2] breaths per minute

DISCUSSION

Extrapulmonary invasion of COVID-19 can cause many chronic complications and must not be neglected. By designing this study, we aimed to assess the incidence of subacute thyroiditis (SAT) in COVID-19 and its relation with the patient's clinical features.

Determining the etiology of abnormal thyroid function establishes the correct diagnosis and efficient treatment of thyroid disease. Thyroid scintigraphy may easily differentiate productive from destructive thyrotoxicosis and diffuse from focal overactivity within the thyroid gland. The typical features of productive thyrotoxicosis (i.e., "true" hyperthyroidism) are as follows [18]:

- Diffuse thyroid overactivity with a homogeneous tracer distribution, reduced uptake in major salivary glands, and low background, consistent with Graves' disease.
- Unifocal or multifocal overactive areas with reduced or suppressed uptake in the remaining thyroid tissue, consistent with autonomously functioning thyroid nodule(s).
- Multiple mixed areas of focal increased and suppressed uptake, consistent with toxic multinodular goiter.

On the other hand, decreased uptake is typically observed in the early phases of destructive thyroiditis, factitious thyrotoxicosis, or exogenous iodine overload.

We found that subacute thyroiditis occurred in 25 out of 69 cases (36.23%), and none of the demographic parameters made a difference in developing it. Based on our findings, 37.5% of females developed SAT, and 35.1% of males did; however, this was not statistically significant (P=0.839). Elderlies tend to be more prone to post-viral thyroiditis, but age did not statistically differ in SAT compared to normal groups (52.27 ± 11.89 vs. 56.04 ± 14.40, P=0.246). SAT is an inflammatory process, so inflammatory factors are expected to rise during the disease. Factors such as platelet count, ESR, and CRP elevated more in patients who had SAT, but neither platelet count nor ESR and CRP significantly elevated (P=0.096, P=0.636, P=0.633; respectively) (Table 2). The relationship between SARS-COV-2 and the thyroid gland has become controversial. COVID-19 has been accused of harming the thyroid gland in multiple ways. Some hypotheses claim that SARS-COV-2 can invade the gland via upper respiratory tract infection. This invasion is assumed to occur because of ACE2 receptors on the surface of thyroid tissue which is the crucial factor in viral entrance [6, 7, 19-21]. Although there are hypotheses for the viral invasion, immunohistochemistry and PCR evaluations did not detect any SARS-COV-2 in the tissue [19-21]. In addition, histopathological alterations in different studies showed massive apoptosis, not accompanied by follicular damage, lymphocytic infiltration, and histological abnormalities [1, 22, 23]. Another way COVID-19 infection may affect the thyroid gland is by relying on immune system dysregulation. COVID-19 acts by triggering a cytokine cascade in the acute inflammatory phase, leading to tissue damage. Lania et al. [24] showed that 20.2% of the patients hospitalized due to COVID-19 had thyrotoxicosis. They also demonstrated that the levels of IL-6 were significantly higher in those patients than in normal people concluding that the cytokine storm is responsible for thyroiditis (odds ratio: 3.25, 95% confidence interval: 1.97–5.36; $P < 0.001$). Similar to the previous study, Muller et al. [25] evaluated thyrotoxicosis in patients admitted to high-intensity care units (HICU) and claimed that thyrotoxicosis is more common among patients with more severe conditions (HICU) than mild-moderate in-ward patients. We evaluated scan findings between moderate and severe groups of COVID-19 patients, and in contrast with prior studies, we found that the severity of COVID-19 did not influence the result of thyroid scintigraphy (P=0.065) (Table 1). However, it is worth mentioning that scintigraphy did not use to diagnose thyroiditis in previous studies. SAT can mimic thyrotoxicosis at the early stages, including neck pain, fever, tremor, and tachycardia. Among all the symptoms, palpitation and sore throat were significantly more frequent in patients with SAT (Table 3). Among 14 patients with palpitation, 10 cases (71%) were diagnosed with thyroiditis in thyroid scan, and only four people were normal (P=0.002). Seven out of nine cases (77%) who experienced a sore throat were confirmed SAT by thyroid scintigraphy (P=0.009). Other signs, such as tremors and vital signs, were not statistically different (Table 3). These data show that many cases which are not clinically or laboratory suspicious of SAT could develop thyroiditis. To reduce the missing rate of diagnosing SAT, we recommend using thyroid scintigraphy alongside laboratory parameters and clinical signs and symptoms.

Study Limitations

(I) Our study population was small. A bigger sample size and more measurable variables can lead to a more precise assessment. (II) The present study is a cross-sectional assessment that helps calculate a situation's prevalence without any further assertion about the cause-effect relationship. We suggest designing a cohort or case-control study with a satisfying sample size and reasonable follow-up periods to determine the causality between two events. (III) Our patients were selected from the COVID-19 ward, and none were admitted to the intensive care unit (ICU). This method of patient selection may interfere with our judgment about the relationship between COVID-19 severity and SAT. To distinguish the differences, we propose to design a study in which patients are included from both COVID-19 ICU and the COVID-19 ward. (IV) RAIU is the standard method for diagnosing acute thyroiditis but is not routinely done in our center. Besides the limitations, one of the strengths of our study was using thyroid scintigraphy to confirm thyroiditis. There is a controversial discussion about diagnosing SAT among different services. By scintigraphy of the thyroid, we can accurately confirm thyroiditis patterns in the tissue and whether laboratory findings and clinical signs are favorable.

CONCLUSION

To summarize our findings, we conclude that SAT is one of the complications during post-COVID-19 days. We found that patients with sore throats and palpitation tend to develop SAT; however, diagnosing thyroiditis needs clinical judgment and laboratory confirmation, but our study showed that thyroid scintigraphy could push our limits one step further in diagnosing thyroid disorders.

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REFERENCES

1. Naguib R. Potential relationships between COVID-19 and the thyroid gland: an update. J Int Med Res. 2022 Feb;50(2):3000605221082898.
2. Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J. 2009 Jan 12;6:5.
3. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020 Mar 26;368:m1091
4. Marazuela M, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Rev Endocr Metab Disord. 2020 Dec;21(4):495-507.
5. Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. Rev Endocr Metab Disord. 2021 Dec;22(4):803-815.
6. Lazartigues E, Qadir MMF, Mauvais-Jarvis F. Endocrine Significance of SARS-CoV-2's Reliance on ACE2. Endocrinology. 2020 Sep 1;161(9):bqaa108.
7. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020 Apr 28;9(1):45
8. Mazziotti G, Sorvillo F, Piscopo M, Morisco F, Cioffi M, Stornaiuolo G, Gaeta GB, Molinari AM, Lazarus JH, Amato G, Carella C. Innate and acquired immune system in patients developing interferon-alpha-related autoimmune thyroiditis: a prospective study. J Clin Endocrinol Metab. 2005 Jul;90(7):4138-44.
9. Farzati B, Mazziotti G, Cuomo G, Ressa M, Sorvillo F, Amato G, La Montagna G, Carella C, Valentini G. Hashimoto's thyroiditis is associated with peripheral lymphocyte activation in patients with systemic sclerosis. Clin Exp Rheumatol. 2005 Jan-Feb;23(1):43-9.
10. Kristensen B, Hegedüs L, Madsen HO, Smith TJ, Nielsen CH. Altered balance between self-reactive T helper (Th)17 cells and Th10 cells and between full-length forkhead box protein 3 (FoxP3) and FoxP3 splice variants in Hashimoto's thyroiditis. Clin Exp Immunol. 2015 Apr;180(1):58-69.
11. Trovato M, Ruggeri RM, Sciacchitano S, Vicchio TM, Picerno I, Pellicanò G, Valenti A, Visalli G. Serum interleukin-6 levels are increased in HIV-infected patients that develop autoimmune disease during long-term follow-up. Immunobiology. 2018 Mar;223(3):264-268.
12. Dalugama C. Asymptomatic thyroiditis presenting as pyrexia of unknown origin: a case report. J Med Case Rep. 2018 Feb 23;12(1):51.
13. Stasiak M, Michalak R, Stasiak B, Lewinski A. Clinical characteristics of subacute thyroiditis is different than it used to be - current state based on 15 years own material. Neuro Endocrinol Lett. 2019 Feb;39(7):489-495.
14. Stasiak M, Lewiński A. New aspects in the pathogenesis and management of subacute thyroiditis. Rev Endocr Metab Disord. 2021 Dec;22(4):1027-1039.
15. Bahçecioğlu AB, Karahan ZC, Aydoğan BI, Kalkan IA, Azap A, Erdoğan MF. Subacute thyroiditis during the COVID-19 pandemic: a prospective study. J Endocrinol Invest. 2022 Apr;45(4):865-874.

16. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. J Microbiol Immunol Infect. 2020 Jun;53(3):368-370.
17. Leow MK, Kwek DS, Ng AW, Ong KC, Kaw GJ, Lee LS. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin Endocrinol (Oxf). 2005 Aug;63(2):197-202.
18. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016 Aug 27;388(10047):906-918.
19. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, Najafian B, Deutsch G, Lacy JM, Williams T, Yarid N, Marshall DA. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. Lancet. 2020 Aug 1;396(10247):320-332.
20. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020 May;46(5):846-848.
21. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 autopsies, Oklahoma, USA. Am J Clin Pathol. 2020 May 5;153(6):725-733.
22. Caron P. Thyroid disorders and SARS-CoV-2 infection: From pathophysiological mechanism to patient management. Ann Endocrinol (Paris). 2020 Oct;81(5):507-510.
23. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, Mou HM, Wang LH, Zhang HR, Fu WJ, Luo T, Liu F, Guo QN, Chen C, Xiao HL, Guo HT, Lin S, Xiang DF, Shi Y, Pan GQ, Li QR, Huang X, Cui Y, Liu XZ, Tang W, Pan PF, Huang XQ, Ding YQ, Bian XW. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. Zhonghua Bing Li Xue Za Zhi. 2020 May 8;49(5):411-417. [Chinese]
24. Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G. Thyrotoxicosis in patients with COVID-19: the THYRCOV study. Eur J Endocrinol. 2020 Oct;183(4):381-387.
25. Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, Ferrante E, Orsi E, Resi V, Longari V, Cuzzocrea M, Bandera A, Lazzaroni E, Dolci A, Ceriotti F, Re TE, Gori A, Arosio M, Salvi M. SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol. 2020 Sep;8(9):739-741.