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Journal of Clinical and Translational Endocrinology: Case Reports 22 (2021) 100094

Contents lists available at ScienceDirect

Journal of Clinical and Translational Endocrinology: Case Reports

journal homepage: www.elsevier.com/locate/jctecasereports.com

Manifestations of thyroid disease post COVID-19 illness: Report of Hashimoto thyroiditis, Graves' disease, and subacute thyroiditis

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ARTICLE INFO

Keywords:
COVID-19
Thyroid disease
Subacute thyroiditis
Hashimoto thyroiditis
Grave's disease

ABSTRACT

Objective: We present three cases of thyroid dysfunction such as Hashimoto thyroiditis, Graves' disease and subacute thyroiditis which developed few weeks after resolution of acute phase of COVID -19 infection in patients with no prior thyroid disease.
Methods: We discuss clinical presentation, diagnostic evaluation and subsequent management and follow-up in three patients.
Results: All three patients tested positive for COVID-19 infection prior to diagnosis. Patient 1. A 38-year-old female developed hypothyroidism 6 weeks after COVID-19 infection, confirmed by TSH 136 mIU/L (range 0.34–5.6), free T4 level 0.2 ng/dL (range 0.93–1.7). Patient 2. A 33-year-old female developed Graves' disease 8 weeks after COVID-19 infection, with a TSH <0.01 mIU/L (range 0.4–4.5), Free T4 2.1 ng/dl (range 0.8–1.8), total T3 216 ng/dl (range 76–181), elevated TSI 309 (normal <140). A 24-h thyroid uptake was calculated at 47.1% (normal values between 8% and 35). Patient responded favorably to methimazole 10 mg in few weeks. Patient 3. A 41-year old healthy female developed thyroiditis at 6 weeks after COVID-19 infection, with a TSH 0.01 mIU/L and free T4 1.9 ng/dL accompanied by low 24-h thyroid uptake, calculated at 0.09%. Three weeks later, she developed hypothyroidism, with a TSH 67.04 mIU/L and free T4 0.4 ng/dl.
Conclusion: The temporal relationship between COVID-19 infection in the patients described here raises the question of possible effects of COVID-19 on the immune system and the thyroid gland.

1. Introduction

Little is yet known about the full-spectrum of effects of COVID-19 in relationship with autoimmune endocrine diseases, but endocrine involvement has been increasingly reported [1–3]. Since its outbreak in December 2019, several associations have been described between COVID-19 virus and inflammatory diseases like subacute thyroiditis, Guillain-Barre syndrome, and pediatric multisystem inflammatory syndrome, as well as emerging reports of autoimmune thyroid disease.

In this report, we describe two patients who developed autoimmune thyroid disease, specifically a case of Hashimoto thyroiditis with severe hypothyroidism and a case of Graves' disease, along with a third patient who presented with subacute thyroiditis few weeks after resolution of acute phase of COVID-19 infection.

2. Case reports

2.1. Patient 1: Hashimoto thyroiditis and hypothyroidism

A 38-year-old female healthcare worker developed throat pain, a low-grade fever, a dry cough, and shortness of breath upon exertion with an impaired sense of smell and taste, diarrhea, myalgias, fatigue, and lack of appetite. She was confirmed positive for COVID-19 via RT-PCR on May 4, 2020. Her symptoms resolved over the course of the month with supportive care at home. On June 15, the patient experienced anterior neck discomfort and noticed thyroid enlargement along with extreme fatigue, dry skin, hair loss, and worsening depression. Labs were significant for TSH 136 mIU/L (range 0.34–5.6), free T4 level 0.2 ng/dL (range 0.93–1.7), anti-thyroid peroxidase antibody >900 IU/mL (normal less than 9) and anti-thyroglobulin antibodies >1000 IU/ml (normal less than 1). Thyroid ultrasound indicated thyromegaly with a heterogenous and hypoechoic sonographic appearance. A fine needle aspiration biopsy targeting a diffusely heterogeneous and hypoechoic

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https://doi.org/10.1016/j.jecr.2021.100094
Received 2 April 2021; Received in revised form 29 July 2021; Accepted 20 August 2021
Available online 26 August 2021

part of the left upper pole indicated the presence of a small number of follicular cells along with mixed inflammatory cells, including groups of histiocytes with epithelioid morphology suggestive of granulomatous inflammation, without clear lymphocytic infiltration (Table 1). Patient reported improvement in fatigue and depression over the course of four weeks along with resolution of pressure like symptoms in the anterior neck area after starting thyroid hormone replacement.

Table 1
Summary of the 3 patients demographics, time between COVID infection and onset of symptoms, clinical presentation, laboratory results before and after COVID infection, and thyroid imaging.

	Patient 1	Patient 2	Patient 3
Age	38 years old	33 years old	41 years old
Gender	Female	Female	Female
Clinical features	Anterior neck discomfort, thyroid enlargement, fatigue, dry skin, hair loss, depression	Palpitations, shortness of breath, fatigue	Persistent palpitations, insomnia
Time between COVID-19 infection and onset of symptoms	6 weeks	7 weeks	6 weeks
TSH before COVID	3.10 mIU/ (0.34–5.6) 10 months *before COVID*	0.83 mIU/L (0.4–4.5) 6 months *before COVID*	NA
TSH after COVID	136 mIU/L (0.34–5.6)	<0.01 mIU/L (0.4–4.5)	0.01 mIU/L (0.4–4.5)
fT4 before COVID	1.13 ng/dL (0.93–1.7)	NA	NA
fT4 after COVID	0.2 ng/dL (0.93–1.7)	2.1 ng/dl (0.8–1.8)	1.9 ng/dL (0.8–1.8)
Thyroglobulin	NA	8.8 ng/ml (2.8–40.9)	2.4 ng/mL (2.8–40.9)
Thyroglobulin Antibodies (TGAb)	>1000 IU/ml (normal less than or equal to 1)	14 IU/mL (normal less than or equal to 1)	3 IU/mL (normal less than or equal to 1)
Thyroid Peroxidase Antibodies (TPO)	>900 IU/mL (normal less than 9)	NA	69 IU/mL (normal less than 9)
Thyrotropin Receptor Antibody (TRAb)	NA	<1 IU/L (normal less than or equal to 2)	1 IU/L (normal less than or equal to 2)
Thyroid Stimulating Immunoglobulin (TSI)	NA	309 (normal less than 140%)	89% (normal less than 140%)
Thyroid Ultrasound	Thyromegaly with a heterogenous and hypoechoic sonographic appearance	Mild thyromegaly with heterogeneous and diffusely hypervascular sonographic appearance	NA
Thyroid Uptake Scan	NA	47.1% (normal between 8 and 35)	0.09% (normal between 8 and 35)
Fine Needle Aspiration	Small number of follicular cells with mixed inflammatory cells, including groups of histiocytes with epithelioid morphology suggestive of granulomatous inflammation, without clear lymphocytic infiltration	NA	NA

2.2. Patient 2: Graves' disease

A 33-year-old female healthcare worker developed cough, chills, fever and shortness of breath, along with loss of taste and smell, diarrhea, fatigue, headache, sinus pain, and dry cough and confirmed positive for Covid-19 via RT-PCR on April 28, 2020. She reported symptomatic improvement in her symptoms in one week. By end of June, she developed palpitations and shortness of breath accompanied by worsening fatigue. Propranolol was started for treatment of palpitations. Further evaluation on July 21, 2020 indicated TSH <0.01 mIU/L (range 0.4–4.5), Free T4 2.1 ng/dl (range 0.8–1.8), total T3 216 ng/dl (range 76–181), elevated TSI 309 (normal <140%), thyroglobulin normal 8.8 ng/ml (range 2.8–40.9), CRP and ESR normal. A thyroid ultrasound on July 27, 2020 indicated mild thyromegaly with heterogeneous and diffusely hypervascular sonographic appearance. A 24-h thyroid uptake was calculated at 47.1% (normal values between 8% and 35). Patient started methimazole 10 mg with clinical improvement (Table 1). She was able to discontinue propranolol and she reported symptom relief with resolution of palpitations in two weeks.

2.3. Patient 3: subacute thyroiditis

A 41-year-old female teacher in a local public school developed headache, fatigue, loss of appetite and mild degree fever and she was diagnosed with COVID-19 on September 15th. She recovered at home, with symptomatic treatment. Approximately 6 weeks later she developed persistent palpitations and insomnia. She did not endorse pressure like symptoms over the anterior neck area, no fever or irradiation pain over the anterior neck. Laboratory evaluation was remarkable for TSH 0.01 mIU/L, free T4 1.9 ng/dL and positive thyroid peroxidase antibodies 69 IU/mL (normal less than 9). A nuclear medicine thyroid uptake and scan indicated an abnormal 24-h thyroid radioiodine uptake, calculated at 0.09%, consistent with a diagnostic of thyroiditis (Table 1). Three weeks later, she developed hypothyroidism, with a TSH 67.04 mIU/L and free T4 0.4 ng/dl and started on thyroid hormone supplementation with levothyroxine 112 mcg daily.

3. Discussion

The association between COVID-19 and various autoimmune diseases affecting the thyroid and other systems in the body is still the subject of ongoing investigation. Initial reports have described the relationship between COVID-19 and subacute thyroiditis resulting in transient hyperthyroidism [4–9], but emerging new case reports mention new onset Hashimoto thyroiditis [10] and Graves' disease [11–13]. The temporal relationship between COVID-19 infection in the patients described here raises the question of possible effects of COVID-19 on the immune system and the thyroid gland [14].

Hashimoto thyroiditis is the most common thyroid disorder in the United States. Both cell-mediated and humoral autoimmunity are involved. T-lymphocytes invade the thyroid gland, giving the appearance of lymphocytic thyroiditis under the microscope. Additionally, detectable antithyroid antibodies such as anti-thyroid peroxidase (*anti*-TPO and anti-thyroglobulin antibodies (*anti*-Tg) are present in the serum of most patients. Both antibodies were markedly elevated in our first patient. One case report indicated a mild case of Hashimoto thyroiditis and subclinical hypothyroidism in a 45-year-old Chinese man [10], in contrast with our case of profound hypothyroidism secondary to Hashimoto's thyroiditis post-COVID-19 infection.

Graves' disease hallmark, at the opposite spectrum of autoimmune thyroid disease, is the presence of thyroid stimulating immunoglobulins (TSI) with unsuppressed thyroid hormone release and classical presentation of hyperthyroidism. Most reported case series of hyperthyroidism

during active COVID-19 infection suggested that a destructive viral thyroiditis contributed to clinical presentation of subacute thyroiditis, with prompt symptomatic improvement with steroids (prednisone) and resolution of biochemical abnormalities (TSH normalization) [4–9,14]. A large case series confirmed, in few patients, a typical pattern of reduced thyroid gland vascularity on thyroid ultrasound along with lack of iodine uptake on nuclear medicine thyroid uptake and scan [4]. Our report of new onset Graves' disease soon after resolution of COVID-19 infection in a healthcare worker with significant exposure to COVID-19 during the peak of the coronavirus pandemic in April joins few other case reports published so far [11,15].

Data on thyroid involvement by COVID-19 is scarce. Going back to the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003, data showed lower free T3 and T4 levels in patients with SARS compared to controls [10,16–18]. An autopsy study in COVID-19 patients showed destruction of the follicular and parafollicular cells of the thyroid [19]. For our patient who developed profound hypothyroidism, the histologic appearance of the thyroid tissue sampled from most representative inflammatory aspect of the thyroid gland sheds a new light on the mechanism of autoimmune hypothyroidism post COVID-19. The pathology report did not indicate a typical lymphocytic infiltration as seen in classical Hashimoto thyroiditis. The presence of mixed inflammatory cells and histiocytes along with granulomatous inflammation along with scattered follicular cells suggest a pattern of destructive follicular thyroiditis. Reports from thyroid autopsies in patients who demised from COVID-19 infection did not indicate the presence of viral particles in the thyroid gland, suggestive of an indirect, immune mediated mechanism associated with destructive changes and cellular apoptosis [20]. Several viruses have been implicated in the development of thyroid autoimmune diseases [14,20] and those include Epstein-Barr Virus (EBV), hepatitis C, HTLV-1, and parvovirus B19. Given the novelty of COVID-19, it is unclear whether this virus is also involved in the development of autoimmune thyroid disease. COVID-19 has been implicated in various autoimmune diseases, but the incidence has been rare. Among those diseases are Guillain-Barre Syndrome (GBS), idiopathic thrombocytopenic purpura (ITP), and autoimmune hemolytic anemia. One possible mechanism through which the virus might trigger certain auto-immune disorders is through molecular mimicry with activation of immune pathways which remain to be defined by future studies.

4. Conclusion

The association between COVID-19 and various autoimmune diseases affecting the thyroid and other systems in the body is still the subject of on-going investigation. We present three essential workers who developed autoimmune thyroid disease such as profound hypothyroidism and Graves' disease at 6 weeks and 8 weeks after COVID-19 infection, respectively. Our report suggests that the temporal relationship between COVID-19 infection and the autoimmune thyroid disease manifestations in the patients described here raises the question of combined effects of COVID-19 on the immune system and the thyroid gland.

Consent

The three patients consented to the submission of the case report to the journal.

Patient Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-chief of this journal on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Dworakowska D, Grossman AB. Thyroid disease in the time of COVID-19. Endocrine 2020:1–4. https://doi.org/10.1007/s12020-020-02364-8.
[2] Bellastella G, Maiorino MI, Esposito K. Endocrine complications of COVID-19: what happens to the thyroid and adrenal glands? J Endocrinol Invest 2020:1–2. https://doi.org/10.1007/s40618-020-01311-8.
[3] Pal R, Banerjee M. COVID-19 and the endocrine system: exploring the unexplored. J Endocrinol Invest 2020:1–5. https://doi.org/10.1007/s40618-020-01276-8.
[4] Is subacute thyroiditis an underestimated manifestation of SARS-CoV-2 infection? Insights from a case series - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/32780854/ (accessed March 30, 2021).
[5] Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: a retrospective study. Thyroid 2021;31:8–11. https://doi.org/10.1089/thy.2020.0363.
[6] Campos-Barrera E, Alvarez-Cisneros T, Davalos-Fuentes M. Subacute thyroiditis associated with COVID-19. Case Rep Endocrinol 2020;2020:8891539. https://doi.org/10.1155/2020/8891539.
[7] 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;183:381–7. https://doi.org/10.1530/EJE-20-0335.
[8] Mehmood MA, Bapna M, Arshad M. A Case of Post-COVID-19 Subacute Thyroiditis. Cureus n.d.;12. https://doi.org/10.7759/cureus.12301.
[9] Ruggeri RM, Campennì A, Siracusa M, Frazzetto G, Gullo D. Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic. Hormones (Basel) 2020:1–3. https://doi.org/10.1007/s42000-020-00230-w.
[10] Tee LY, Harjanto S, Rosario BH. COVID-19 complicated by Hashimoto's thyroiditis. Singap Med J 2020. https://doi.org/10.11622/smedj.2020106.
[11] Mateu-Salat M, Urgell E, Chico A. SARS-COV-2 as a trigger for autoimmune disease: report of two cases of Graves' disease after COVID-19. J Endocrinol Invest 2020;43:1527–8. https://doi.org/10.1007/s40618-020-01366-7.
[12] Jiménez-Blanco S, Pla-Peris B, Marazuela M. COVID-19: a cause of recurrent Graves' hyperthyroidism? J Endocrinol Invest 2021;44:387–8. https://doi.org/10.1007/s40618-020-01440-0.
[13] Speer G, Somogyi P. Thyroid complications of SARS and coronavirus disease 2019 (COVID-19). Endocr J 2021:129–36.
[14] Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY, et al. Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with COVID-19. J Clin Endocrinol Metab 2021;106:e926–35. https://doi.org/10.1210/clinem/dgaa813.
[15] Pastor S, Molina Á, De Celis E. Thyrotoxic Crisis and COVID-19 Infection: An Extraordinary Case and Literature Review. Cureus n.d.;12. https://doi.org/10.7759/cureus.11305.
[16] Caron P. Thyroid disorders and SARS-CoV-2 infection: from pathophysiological mechanism to patient management. Ann Endocrinol 2020;81:507–10. https://doi.org/10.1016/j.ando.2020.09.001.
[17] Endocrine changes in SARS-CoV-2 patients and lessons from SARS-CoV - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/32527756/ (accessed March 30, 2021).
[18] Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. Rev Endocr Metab Disord 2020:1–13. https://doi.org/10.1007/s11154-020-09615-z.
[19] Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. Zhonghua Bing Li Xue Za Zhi 2020;49:411–7. https://doi.org/10.3760/cma.j.cn112151-20200312-00193.
[20] Viruses and thyroiditis: an update - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/19138419/ (accessed March 30, 2021).