

## Thyrotoxicosis secondary to thyroiditis following SARS-CoV-2 infection

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Subacute thyroiditis is a granulomatous inflammatory disorder often triggered by a preceding viral infection. Patients typically present with complaints of anterior neck pain associated with a tender enlarged thyroid gland. The coronaviruses have never before been implicated in the aetiology of subacute thyroiditis. It is postulated that the pathogenesis related to thyroid disease in Coronavirus disease 2019 (COVID-19) is multifactorial. Contributory factors include effects of the virus-related cytokine storm and direct action of the virus on SARS-CoV-2 receptors in the thyroid. This article further reviews the association between thyroiditis and COVID-19. The clinical characteristics, diagnostic workup and management of a patient who presented with subacute thyroiditis following COVID-19 are discussed. Furthermore, complications are entertained and suggestions for the management of thyroiditis following COVID-19 are provided.

**Keywords:** Coronavirus disease-2019 (Covid-19), de Quervain's, SARS-CoV-2, sub-acute, viral thyroiditis

### Introduction

De Quervain's thyroiditis or subacute granulomatous thyroiditis is a rare inflammatory condition triggered by a viral infection that occurred 2–6 weeks earlier.<sup>1,2</sup> Many viruses have been implicated in the development of thyroiditis, but prior to the current pandemic coronavirus infection has never been associated with clinical subacute thyroiditis.<sup>3</sup> Single-cell RNA profiling of the angiotensin converting enzyme 2 receptor (SARS-CoV-2 receptor), has proposed multiple tissue cells as the potential targets of SARS-CoV-2.<sup>4</sup> Subsequent analysis across 36 tissues revealed a rank list of candidate cells potentially vulnerable to SARS-CoV-2. The top targets are lung cells and macrophages, cardiomyocytes, adrenal gland stromal cells and lastly stromal cells in testis, ovary and thyroid.<sup>5</sup> Thyroiditis following COVID-19 may be under-recognized and the complications overlooked if thyrotoxicosis is not considered.

### Case presentation

A 53-year-old woman presented to the Endocrinology Department complaining of anterior neck pain and palpitations. Five weeks prior to this presentation she was diagnosed with SARS-CoV-2 after she complained of mild upper respiratory tract infection (URTI) symptoms (postnasal drip, cough and fever). The URTI symptoms resolved completely 10 days after onset. In the second week of isolation for COVID-19, she developed anterior neck pain, which radiated to her right ear with concomitant low-grade fever. After completion of the 14-day isolation period, she consulted a general practitioner and was prescribed antibiotics. The symptoms persisted for another week and she experienced new onset palpitations. On reconsultation, four weeks after the COVID-19 diagnosis, thyroid function testing revealed thyrotoxicosis (Table 1). A beta blocker (bisoprolol) and prednisone were prescribed. The patient consulted our division querying the utility of prednisone, which was self-deferred up to now.

Physical examination revealed a heart rate of 84 bpm, but she had self-administered the beta blocker prior to the consultation.

Furthermore, she was noted to be afebrile with warm peripheries and a very fine tremor. There were no features of URTI. Pathognomonic features of Graves' disease were absent. The thyroid gland was minimally enlarged and slightly tender to touch. The rest of the physical examination was unremarkable. The clinical impression was in keeping with de Quervain's thyroiditis or subacute thyroiditis with mild thyrotoxicosis.

### Investigations

Biochemistry confirmed thyrotoxicosis: free thyroxine (FT4) and free triiodothyronine (FT3) were both elevated and the thyrotropin (TSH) level was lower than the detectable limit. Thyroid antibodies (antithyroglobulin, and antithyroperoxidase [TPOAb]) including TSH receptor antibodies were negative. The white cell count was within normal range; however, the C-reactive protein (CRP) was elevated (Table 1).

Thyroid scintigraphy (Figure 1) demonstrated no radiotracer uptake, in keeping with thyroiditis. Thyroid ultrasound (Figure 2a and b) revealed bilateral patchy hypoechoic areas with normal vascularity. Sub-centimetre colloid cysts and small reactive lymph nodes were also noted, in keeping with the clinical diagnosis.

### Treatment

Pharmacological management was initiated with prednisone 25 mg daily, etoricoxib 90 mg daily and propranolol 10 mg 6 hourly, as needed. Aspirin (75 mg daily) was also given. Six weeks after the COVID-19 diagnosis and 4 weeks after presenting with thyrotoxic symptoms, the patient was asymptomatic. The FT4 concentration had improved to just above the upper limit of normal (Table 1). The FT3 and CRP had now normalised.

### Discussion

The differential diagnoses for painful thyroiditis include subacute post-viral thyroiditis or de Quervain's thyroiditis, acute suppurative thyroiditis and painful Hashimoto's thyroiditis. Acute suppurative thyroiditis is a medical emergency that may lead

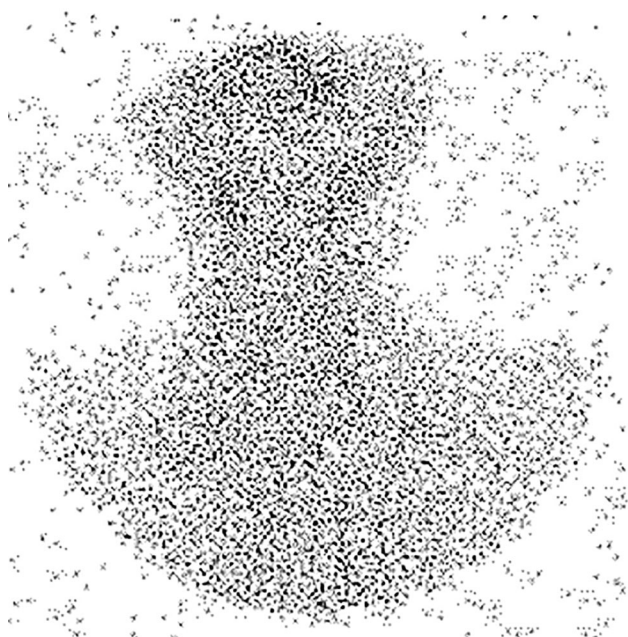
**Table 1:** Serial symptoms, biochemistry and intervention following COVID-19 symptom onset

Symptoms	COVID-19 diagnosis						Normal range
	Day 0 URTI symptoms present COVID-19+	10 days Resolution of URTI symptoms	2 weeks Anterior neck pain starts GP consultation	4 weeks Anterior neck pain and palpitations Re-consultation	5 weeks Anterior neck pain and palpitations improving Steroids initiated	6 weeks Anterior neck pain and palpitations resolved	
<b>Management</b>							
FT4 (pmol/l)				49.1	36.5	27.6	12–22.0
FT3 (pmol/l)				Not done		5.3	3.1–6.8
TSH (mIU/l)				< 0.01	< 0.01		0.27–4.20
CRP (mg/l)				68.4	13	2	< 10
ESR (mm/hr)				Not done	30	Not done	0–10

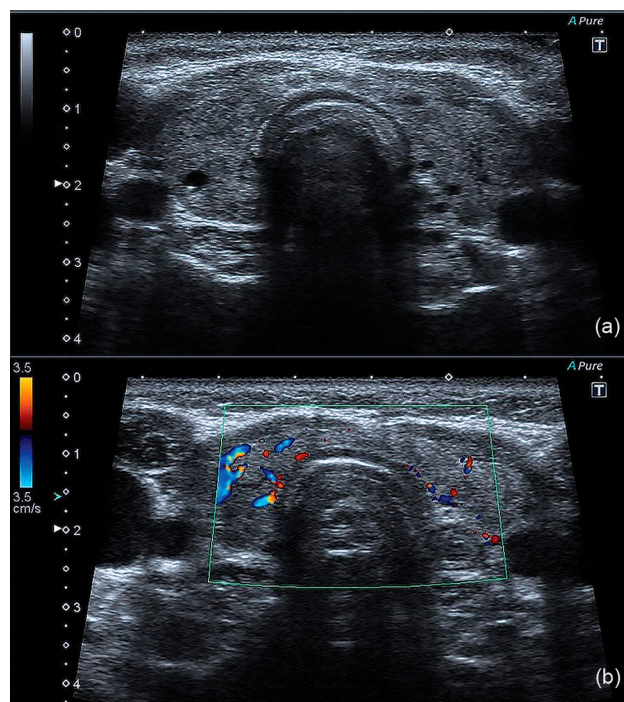
to airway compromise. It usually follows a procedural intervention (e.g. fine needle aspiration), does not cause thyrotoxicosis per se, and appears as an abscess on ultrasound.<sup>6</sup> Hashimoto’s thyroiditis is usually painless, mostly affects women and infrequently presents with thyrotoxicosis. A rare variant of painful Hashimoto’s has been described but, contrary to our patient, painful Hashimoto’s typically features an elevated serum level of thyroid antibodies (antithyroperoxidase or antithyroglobulin).<sup>7</sup> Thyrotoxicosis in subacute thyroiditis is the result of the destruction of thyroid follicles and the release of thyroid hormones, as opposed to increased production of FT3 and FT4 as seen in Graves’ disease. The destruction of thyroid follicles is represented by the absence of uptake on the thyroid scintigram in our patient.

Thyroid scintigraphy is an important imaging modality in the evaluation of thyrotoxic patients and allows for the differentiation of hyperthyroidism from other causes of thyrotoxicosis. In cases of Graves’ disease, or nodular thyroid disease with autonomous function, various patterns of increased uptake are seen. In the early thyrotoxic phase of subacute thyroiditis,

decreased or absent uptake is observed.<sup>8</sup> It can be confirmed semi-quantitatively by calculating the percentage of thyroid uptake. Differential diagnoses to consider with decreased or absent thyroid uptake in the context of thyrotoxicosis include other types of thyroiditis (subacute thyroiditis, amiodarone-induced thyroiditis, acute thyroiditis), iatrogenic or factitious thyrotoxicosis (due to exogenous thyroxine) and ectopic hyperfunctioning thyroid tissue.<sup>9</sup> The role of thyroid ultrasound in diffusely enlarged thyroid glands is to exclude pathology undetectable on clinical examination and, in the case of a painful gland, the exclusion of suppurative thyroiditis. It also enables fine-needle aspiration if malignancy is suspected. The characteristics in subacute thyroiditis include patchy poorly circumscribed hypoechoic areas with decreased vascularity on doppler.<sup>10</sup> Lee categorises these changes into nodular, non-nodular and mixed subtypes that can be focal or multifocal, unilateral or bilateral.<sup>11</sup> These findings can overlap with malignancy and other forms of thyroiditis, therefore clinical



**Figure 1:** The Tc-99 m thyroid scintigram showed no uptake in the expected position of the thyroid, whereas the salivary gland uptake had normal uptake. This was done four weeks after COVID-19 diagnosis.



**Figure 2:** Thyroid ultrasound. IC = internal carotid, T = trachea, NT = normal thyroid. Figure 2a depicts bilateral colloid cysts in a heterogeneous thyroid gland, and hypoechoic nodular areas, specifically in the left lobe (see arrow). In 2b, vascularity is shown, which is not increased.

correlation is of utmost importance. Most changes normalise after one year, but nodular change might persist.<sup>10</sup>

Subacute thyroiditis of viral origin is usually self-limited, and pain and fever resolve spontaneously after a period of 8–16 weeks.<sup>12</sup> Normalisation of FT4 and FT3 levels parallels the resolution of the pain. Treatment is supportive and intended to reduce inflammation and symptoms.<sup>12</sup> The clinical course can, however, vary, and whilst transient hypothyroidism is the norm, some patients develop permanent hypothyroidism irrespective of medical intervention.<sup>13</sup> Little is known about the clinical course and outcomes of subacute thyroiditis following COVID-19. Brancatella *et al.* described typical clinical features in a case series, with resolution at six weeks and thyroid functions either normalised or subclinical hypothyroidism present.<sup>14</sup>

The prevalence of thyroiditis following COVID-19 infection is still to be elucidated as more knowledge is gained. A single-centre study retrospectively assessed thyroid function tests performed in 287 patients hospitalised for COVID-19, based on the hypothesis that the cytokine storm associated with COVID-19 may influence the thyroid function tests and/or that SARS-CoV-2 may directly act on thyroid cells. One in five patients (20.2%) were found to have thyrotoxicosis and it was significantly associated with higher pro-inflammatory marker (interleukin-6) levels (odds ratio: 3.25, 95% confidence interval 1.97–5.36;  $p < 0.001$ ), supporting an indirect immune-modulated pathogenesis.<sup>15</sup> The high prevalence of thyrotoxicosis in this study also suggests a possible causal relationship between COVID-19 and abnormal thyroid function.

Hyperthyroidism is associated with a hypercoagulable state through various mechanisms including alteration in synthesis and action of coagulation factors, effects on platelet maturation and function, an alteration in blood viscosity and effect on endothelial function.<sup>15–17</sup> Furthermore, in addition to the effect of the circulating thyroid hormones, there may be immunological abnormalities contributing to the hypercoagulable state.<sup>16</sup> Though many questions remain, COVID-19 has also been associated with a systemic coagulopathy and an acquired thrombophilia, with platelets uniquely produced by extramedullary megakaryocytes. Pathologists have recognised macro- and microvascular platelet-fibrin microthrombi in post-mortem studies.<sup>18</sup> In hospitalised COVID-19 patients, prophylactic doses of low molecular weight heparin (LMWH) are commonly advocated, pending the outcome of ongoing trials on higher doses, antiplatelet agents and other anticoagulants such as rivaroxaban.<sup>19,20</sup> A clear temporal association for thromboembolic disease following systemic glucocorticoid use has also been demonstrated.<sup>21</sup> These factors formed the basis of aspirin in addition to glucocorticoids in our patient.

The full extent of post-COVID-19 related inflammatory manifestations still need to be described. Whether systemic manifestations, including thyroiditis, can be classified under the umbrella of a multisystemic inflammatory syndrome is still to be elucidated. As knowledge is gained regarding COVID-19 and thyroid disease, a causal relationship should be contemplated and guidance for optimal treatment and future care provided.

### Key learning points

1. Thyroid involvement following SARS-CoV-2 infection is increasingly being reported.

2. Clinicians need to be aware of the association of COVID-19 related thyroid disease and maintain a high index of suspicion in the right clinical context.
3. Management should focus on both the acute and long-term complications of subacute thyroiditis, namely hypercoagulability and variable hypothyroidism.
4. Surveillance of patients with COVID-19 related thyroiditis should be prioritised to inform future care.

### Declaration of originality

This paper has not been published or submitted for publication elsewhere.

### Declaration of authorship

All authors have contributed significantly and in keeping with the latest guidelines of the International Committee of Medical Journal Editors. All authors are in agreement with the content of the manuscript and accept full responsibility for the content of the manuscript.

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