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Caso Clínico

# An Exuberant Manifestation of Subacute Thyroiditis SARS-CoV-2-Related

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A B S T R A C T

A variety of clinical manifestations attributable to SARS-CoV-2 has been described, including subacute thyroiditis (SAT). Here we describe an atypical case of SAT SARS-CoV-2-related.
A 34-year-old previously healthy woman presented to the emergency room complaining of intense cervical pain, non-responsive to ibuprofen, 12 days after being diagnosed with infection with SARS-CoV-2. Clinical, laboratory, and imaging features were compatible with SAT. She was discharged with prednisolone 40 mg/day. After reducing prednisolone, cervical pain recurred, and she experienced intense thyrotoxicosis symptoms and fever. Due to persistent high fever and absence of improvements with treatment, the patient was hospitalized. Imaging did not show abscesses. Clinical improvement was seen when prednisolone was increased to 60 mg/day. Ten weeks after the initial symptoms, she was asymptomatic, with normal free T3 and T4.
SAT is a possible complication of SARS-CoV-2 infection. Clinicians should be alerted to this diagnosis and to potentially refractoriness to standard treatment, and more exuberant and long-lasting forms of SAT, even in the presence of mild forms of COVID-19.

## Uma Manifestação Exuberante de Tiroidite Subaguda Associada a Infeção por SARS-CoV-2

R E S U M O

Têm sido descritas inúmeras manifestações clínicas atribuídas ao SARS-CoV-2, incluindo tiroidite subaguda (TSA). Descrevemos um caso atípico de TSA associada à infeção por SARS-CoV-2.
Mulher de 34 anos, previamente saudável, recorreu ao serviço de urgência por dor cervical intensa, não responsiva a ibuprofeno, 12 dias após infeção por SARS-CoV-2. Quadro clínico, analítico e imagiológico compatível com TSA. Alta medicada com prednisolona 40 mg/dia. Após redução da dose, teve agravamento das queixas álgicas, febre e sintomatologia acentuada de tireotoxicose. Por ausência de melhoria com tratamento sintomático e persistência da febre, decidido internamento. Sem evidência de abcesso nos exames de imagem. Melhoria após aumento da prednisolona para 60 mg/dia. Dez semanas após os sintomas iniciais, a doente ficou assintomática, com frações livres dentro dos valores de referência.
A TSA é uma possível complicação da infeção por SARS-CoV-2. Os clínicos devem estar alerta para este diagnóstico e para a possibilidade de refratariedade ao tratamento convencional e de manifestações mais exuberantes e prolongadas de TSA, mesmo em casos de sintomas ligeiros de COVID-19.

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## Introduction

The highly contagious disease called coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has rapidly spread around the world, and it is associated with important morbimortality.[1,2] Although most patients with COVID-19 have respiratory tract symptoms, a wide range of clinical manifestations attributable to this infection have been described, such as neurological,[3] gastrointestinal4, and endocrinological[5] complications. One of the endocrine organs commonly affected is the thyroid gland, leading to various disorders, including subacute thyroiditis (SAT).[5,6]

SAT is a self-limited inflammatory thyroid disease, and it is a relatively infrequent cause of thyrotoxicosis.[7,8] Evidence supports a viral or postviral origin for this disease, being often preceded by an upper respiratory tract infection. Many viruses have been reported as potentially causative agents, such as influenza, adenovirus, or coxsackie.[9,10]

We describe a case of COVID-19-related SAT associated with exuberant manifestations, with high fever, persistent intense cervical pain, and the need for high doses of prednisolone for a prolonged period.

## Case Report

On 8th December 2020, a 34-year-old caucasian woman, with no relevant past medical history, developed ageusia, anosmia, myalgia, and subfebrile temperature (37.5-37.8ºC). On 11st December, a real-time reverse transcription-polymerase chain reaction of a nasopharyngeal swab was performed confirming infection by SARS-CoV-2. No specific treatment was necessary, and the patient was expected to recover completely. Nonetheless, five days after the diagnosis of COVID-19 and eight days after the initial onset of symptoms, the patient reported severe permanent pain in the anterior cervical region, with irradiation to the retroauricular region, predominantly on the right side. She self-medicated with ibuprofen (600 mg thrice daily), with a slight improvement of the pain. After an initial improvement, five days later, she started experiencing severe cervical pain and *de novo* subfebrile temperature (~37.5ºC) refractive to ibuprofen. Due to that, two days later, after seven days taking the non-steroidal anti-inflammatory drug and 12 days after the diagnosis of COVID-19, she presented to the emergency department (ED). She had also lost 4 kg unintentionally during that week. She denied any upper respiratory symptoms. Physical examination was unremarkable except for an enlarged and markedly painful thyroid gland at palpation.

Laboratory tests were requested (Fig. 1) showing a low TSH [0.127 uUI/mL; reference range (RR) 0.55–4.78], high free triiodothyronine (FT3) (6.05 pg/mL; RR 2.3-4.2), high free thyroxine (FT4) (2.26ng/dL; RR 0.89-1.76), high C-reactive protein (CRP) (206 mg/L; RR <5.0), an elevated white blood cell count ($12.7\times10^3$/uL; RR 4.0-11.0) with high neutrophil percentage (81%), and elevated platelet count ($450x10^3$/uL; RR 150-400). These results were suggestive of SAT with overt destructive thyrotoxicosis. Erythrocyte sedimentation rate (ESR) was not evaluated. Chest X-ray did not have relevant alterations. Cervical ultrasonography showed a diffusely enlarged thyroid gland, with heterogeneous parenchyma – findings compatible with thyroiditis; no enlarged lymph nodes were detected (Fig. 2).

There was no history of thyroid disease, history of exposure to iodinated contrast or radioactive iodine therapy, recent surgeries or trauma, recent pregnancy or the possibility of being pregnant, nor any pharmacological treatment except for the ibuprofen. There was no known family history of thyroid or autoimmune diseases. All findings were consistent with the diagnosis of SAT, apparently caused by COVID-19. The patient was discharged with prednisolone 40 mg daily as the starting dose, and with referral to Endocrinology for further evaluation. The glucocorticoid tapering scheme instituted was 40 mg daily in the first week, 20 mg daily in the second week, and 10 mg until the consultation. Within a few days of corticosteroid treatment, pain markedly improved, and temperature normalized.

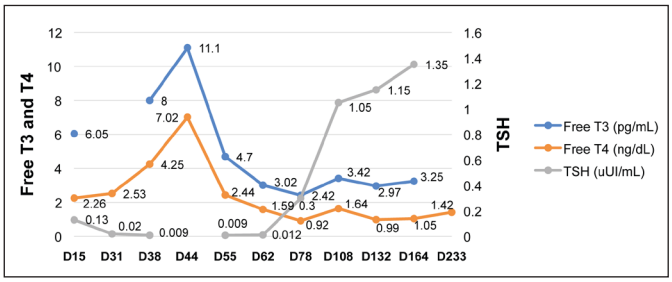


*Figure 1.* Evolution of thyroid function tests during the follow-up
D – days after the onset of symptoms of infection by SARS-CoV-2.

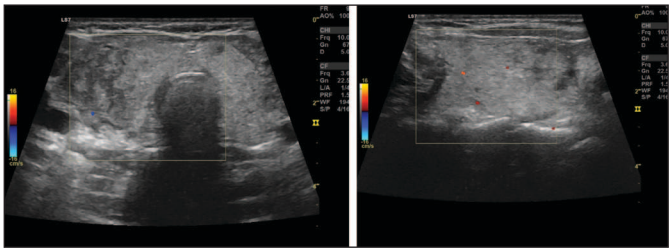

*Figure 2.* Cervical ultrasonography performed at the emergency department. Diffusely enlarged thyroid gland, with heterogeneous parenchyma and overall decreased vascularization at color Doppler.

She was evaluated at the Endocrinology outpatient clinic for the first time two weeks after ED discharge and 28 days after the diagnosis of COVID-19. Clinically, she reported palpitations, anxiety, and hand tremor. Cervical pain and subfebrile temperature had resolved. Physical examination revealed mild bilateral hand tremor and a visible diffuse goiter with tenderness to palpation (more on the right side, with an apparent palpable nodule). The thyroid was firm, mobile with swallowing, with no bruits, and some cervical lymph nodes, enlarged and tender, were detected on palpation. Thyroid function tests were repeated: TSH 0.016 uUI/mL and FT4 2.53 ng/dL. Because of the symptoms she reported, propranolol 20 mg twice daily was prescribed. She had initiated the 10 mg daily of prednisolone on that day, so it was decided to maintain that dose and reevaluate the patient within a week. However, three days after the first evaluation in the outpatient clinic, the patient contacted the department due to recurrence of the cervical anterior pain with irradiation to the retroauricular and occipital areas, fever (38º-39ºC), and *de novo* odynophagia. The dose of prednisolone was augmented to 20 mg daily and the propranolol was maintained. There was no improvement and three days later (and 34 days after the diagnosis of COVID-19), she went again to the ED. She was discharged with etoricoxib 60 mg daily and paracetamol 1000 mg thrice daily. Four days later, she was reevaluated at the Endocrinology clinic. She maintained all the symptoms, namely, cervical and occipital pain, fever, odynophagia, and sporadic palpitations. Meningeal signs were excluded and laboratory tests showed suppressed TSH levels, high FT4 (4.25 ng/dL), FT3 (8.0 pg/dL) and total triiodothyronine (TT3) (2.45 ng/mL;

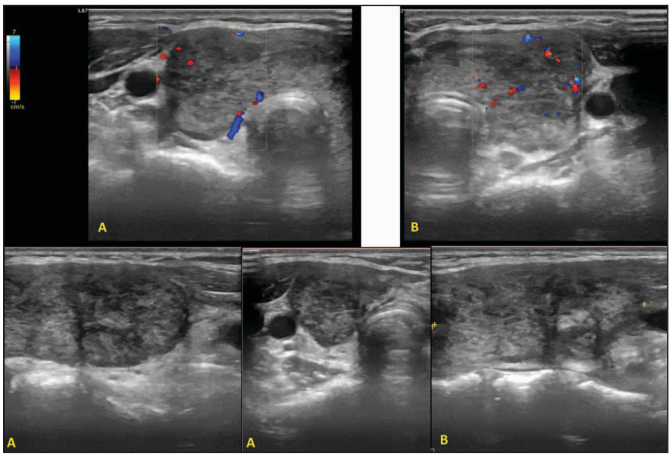


*Figure 3.* Cervical ultrasonography performed two weeks after the emergency department discharge.
Diffusely enlarged, heterogeneous, and hypoechogenic thyroid gland (volume 22.25cm3) with normal vascularization at color Doppler and multiple pseudonodular areas. A – Right lobe. B – Left lobe.

RR 0.6-1.81); negative anti-thyroglobulin antibodies, anti-peroxidase antibodies, and anti-TSH receptor antibodies levels. Inflammatory markers were elevated [ESR 83 mm/h (RR 1-20); CRP 204.30 mg/L]. Prednisolone and propranolol were augmented to 40 mg daily and 40 mg twice daily, respectively. Two days later, the cervical ultrasonography was repeated (Fig. 3) and showed a diffusely enlarged, heterogeneous, and hypoechogenic thyroid gland (volume 22.25 $cm^3$) with normal vascularization at color Doppler and multiple pseudonodular areas. The patient reported sustained fever (~39ºC). She was hospitalized the next day, 41 days after the diagnosis of COVID-19 and 36 days after the initial symptoms of SAT appeared. The hospitalization was due to the persistent high fever and intense cervical pain, leading to the suspicion of acute suppurative thyroiditis. Prednisolone 60mg daily and propranolol 40 mg twice daily were prescribed. Cervical and thoracic computed tomography angiography was performed to exclude potential complications such as an abscess. Apart from an enlarged thyroid extending to the superior mediastinum and small jugular-carotid lymph nodes, no other relevant alterations were detected. FT3 (11.1 pg/dL), TT3 (3.76 ng/mL), FT4 (7.02 ng/dL) and thyroglobulin levels (1297 ng/mL; RR 0.73-84) were markedly increased. CRP was 155.2 mg/L, with leukocytosis ($14.9x10^3$/uL) and thrombocytosis ($613x10^3$/uL). Amino-terminal pro-brain natriuretic peptide levels were mildly elevated (359.0 pg/mL; RR <125). Thromboplastin time, activated partial thromboplastin time, phospocalcium metabolism profile, and hepatic and renal function were normal. Blood cultures were negative. An electrocardiogram showed sinus rhythm with a heart rate of 90 beats per minute. During the hospital stay, the patient remained apyretic. She was discharged after four days with prednisolone 60 mg daily and propranolol 40 mg twice daily, and the cervical pain resolved.

The patient was reevaluated one week later. She clinically improved, with no recurrence of pain or fever and with a weight regain of 2 kg, although she still reported palpitations and anxiety. FT3 and FT4 had also decreased, being close to the upper limit of normal. Prednisolone was reduced to 40 mg per day. One week after that, 59 days after the diagnosis of COVID-19 and 54 days after the diagnosis of SAT, FT3 and FT4 normalized and the patient reported only sporadic palpitations and cervical tenderness. Two weeks after, the patient was asymptomatic, with normal FT3 and FT4 levels, and with normal CRP and no leukocytosis or thrombocytosis. Prednisolone was reduced to 30 mg per day, with a slow tapering scheme following that. Glucocorticoid therapy was suspended approximately nine months after the SAT diagnosis.

At the last follow-up, 12 months after the diagnosis of SAT, the patient remained asymptomatic, and thyroid function tests were in the normal range (TSH 1.954 uUI/mL, FT4 1.30 ng/dL).

## Discussion

Different mechanisms for thyroid involvement due to SARS-CoV-2 infection can be involved, such as direct virus damage to the organ, systemic inflammation due to cytokines and chemokines, and/or autoimmune reactions.[11,12] Additionally, another important plausible mechanism is that SARS-CoV-2 targets angiotensin-converting enzyme 2 (ACE2), using it as a functional receptor to enter the cells. ACE2 is expressed in various tissues, including thyroid follicular cells, possibly making them susceptible to SARS-CoV-2 entry.[13,14] However, there is still limited available evidence to indicate the pathophysiological pathway of thyroid injury caused by SARS-CoV-2.[6]

We report a case of an atypical SAT, apparently triggered by a SARS-CoV-2 infection. Our case, in addition to others, strongly supports that SARS-CoV-2 should be considered an etiologic agent for the onset of SAT.[5,6] However, although COVID-19 most common manifestations were mild as in the other reported cases,[5,6,15] in our case, the patient presented with an atypical form of SAT, with intense cervical pain, high fever, refractoriness to standard therapy schemes, needing higher doses of corticosteroids, and with a longer duration of the thyrotoxicosis (54 days). We have established the diagnosis of SAT having into consideration the values of thyroid function parameters available and its evolution, the recent upper respiratory viral infection, the characteristics of the cervical pain, the subfebrile/febrile temperature, the progressively worsening of the inflammatory parameters, the initial quick response to glucocorticoid therapy within a few days, and the lack of hypervascularity on color Doppler. Nevertheless, we acknowledge that thyroid scintigraphy would be a relevant exam to perform to help differentiate etiologies of thyrotoxicosis and further establish our diagnosis of SAT. This exam was not considered initially as its execution in our institution would not be promptly.

We acknowledge that the initial glucocorticoid tapering approach used was not conventional, and that this strategy might raise concerns. Generally, the clinical course of SAT is mild and self-limited and treatment with nonsteroidal anti-inflammatory agents (NSAIDs) and β-adrenergic-blocking drugs is recommended.[16] Antithyroid drugs do not have a role in the treatment of SAT. Use of corticosteroids is limited to patients who do not respond to NSAIDs over several days of use or present with moderate to severe pain and/or symptoms of thyrotoxicosis, as was the case for our patient.[16] The standard recommendations by the American Thyroid Association (ATA) for corticosteroid therapy in SAT are prednisone 40 mg per day for 1-2 weeks followed by a gradual tapering scheme over 2-4 weeks or longer, depending on the clinical response.[16]

Nevertheless, we believe the approach instituted does not justify the more exuberant and atypical clinical course of our SAT case. Firstly, our patient had self-medicated with a high dose of NSAID for seven days, the first-line therapy recommended by the ATA for SAT, but the symptoms persisted and gradually worsened with severe cervical discomfort and fever. Secondly, prednisolone 40 mg per day was initiated but higher doses were needed (maxi-

mum daily dosage: 60 mg). Most of the previous reports of SAT associated with COVID-19 used initial lower doses of prednisolone (most commonly 25 mg daily, n=12 out of 27 reported cases) without needing higher doses. The remaining patients n=2 were treated with a lower dose of prednisolone (16 and 20 mg), n=2 were treated with aspirin, and n=3 were treated exclusively with NSAID. Only five patients were initially treated with higher doses of prednisolone (n=2 prednisolone 40 mg/day, n=1 prednisolone 30 mg/day, n=1 dexamethasone 4 mg every 8 hours for 5 days, n=1 methylprednisolone 40 mg/day for 3 days).[6,15] In addition to this, based on the available published data, it appears that, once recognized, SAT associated with COVID-19 does not requires a different treatment approach when compared with non-COVID-19 cases.[17] So, lastly, the basis for the recommend titration scheme by ATA was not established by prospective studies. In a prospective study performed by Sharma *et al*.[18] it was shown that 20 mg of prednisolone per day tapered over four weeks is an adequate treatment of SAT, with symptoms resolving in two weeks in 94% of the patients, with a low recurrence rate (7.3%). Their cohort after two weeks was initiated with 10 mg of prednisolone, like our patient. Additionally, previous research had already demonstrated that prednisolone 15 mg per day with a tapering scheme of 5 mg every two weeks is a safe and effective mean to quickly reduce the pain in SAT, being that specific study referred in the ATA.[16,19] Recently, a systematic review and meta-analysis was published with the objective to identify the lowest effective initial dose of prednisolone for the treatment of subacute granulomatous thyroiditis.[20] They concluded that 15 to 20 mg per day of prednisolone was the most effective dose with the lowest recurrence rate in the treatment of SAT. Additionally, iIt is well-established that glucocorticoids are beneficial for relieving SAT symptoms more quickly and for reducing the recurrence rate, and, in more serious manifestations of COVID-19, this type of treatment improves the outcomes, namely the mortality rate.[21] Taking this into account, we hypothesize that small doses of glucocorticoids might be a more appropriate treatment option than NSAIDs for SAT caused by SARS-CoV-2. In conclusion, it seems that our patient was initiated with a higher dose than she theoretically needed according with the current literature. Nevertheless, we recognized, as abovementioned, that the reduction from 40 to 10 mg in two weeks was not ideal, and we cannot exclude it might partially have contributed to a progression of the symptoms, as it is known that symptoms can recur as the dose of corticosteroid is reduced.[22] Still, in this case, exuberant, long-lasting and *de novo* clinical symptoms emerged; it was not exclusively a recurrence of previous reported symptoms.

On the contrary, we believe that the second tapering approach was excessively long. This was due to several factors. Firstly, in January 2021, the available evidence on this subject was scarce, with few published case reports and no consolidated knowledge or recommendations in terms of the treatment approach of this entity. Secondly, the SAT in our patient had an atypical presentation, with a longer duration of thyrotoxicosis, more exuberant symptoms, refractiveness to the standard first-line treatment and the need for higher doses of prednisolone. Thirdly, the initial tapering approach possibly was too quick for this specific case, as previously discussed, and we did not know at the time the influence of that initial titration in the natural evolution of the disease, so we decided to not repeat a short treatment period, which might have been an overzealous approach. Fourthly, the patient was under a high dose of prednisolone for Lastly, after the need for hospital admission, the patient was fearful the symptoms would recur with the reduction of the dosage, the inflammatory parameters were elevated for several weeks after discharge, and she experienced residual cervical discomfort with the first new titrating of dose, contributing to our decision for a more conservative tapering scheme and a longer clinical surveillance in our department. Additionally, we would like to add that in the last six months the patient was with a low dosage of corticosteroid (hydrocortisone 5 mg daily for two months and in alternate days for four months) and the patient asked for the reschedule of one of the consultations, delaying the suspension of the therapy by three months.

The atypical form of SAT that occurred in our case could be potentially justified by various factors, namely, the specific SARS-CoV-2 variant she presented and her vaccinal status. As our patient was diagnosed with COVID-19 in December 2020, the information available then regarding SARS-CoV-2 variants was scarce, and the variant she contracted is unknown. Additionally, at that time, the patient was not eligible to receive the vaccine for COVID-19. According to The National Health Institute Doutor Ricardo Jorge, in December 2020, the most common variant in Portugal was variant 20A.EU1 (S:A222V) - responsible for 67% of the cases - followed by 20A.EU2 variant (8.7%) and various other less frequent variants.[23] Nonetheless, there are no published studies specifically comparing SAT's incidence and severity between variants of SARS-CoV-2. We hypothesize that there might exist differences in terms of susceptibility to SAT and its presentation, as there is evidence in model animals showing that different SARS-CoV-2 variants associate with varying clinical manifestations of COVID-19, due to differences in pathogenicity, immune activation, and organ tropism.[24] In humans, however, these findings and comparisons were performed in more recent variants such as Omicron and Delta.[25-27] Regarding vaccinal status, there is no evidence comparing the risk or severity of SAT SARS-CoV-2-related between immunized and non-immunized patients. However, there is a new entity – SAT following the vaccine for COVID-19. It is known that SAT after immunization is typically less symptomatic than SAT for other causes and is associated with good long-term outcomes. Previous infection with SARS-CoV-2 as not been associated with an increased nor a decrease in the risk to develop this disease after vaccination.[17] Therefore, we can only speculate that if the patient was immunized, she might have had a less exuberant form of SAT.

In an article reviewing the early and late endocrine complications of COVID-19, thyroid gland dysfunction was evaluated and eight studies reporting SAT associated with COVID-19 were included (n=23).[5] Notably, like our patient, all the patients in this study had non-severe COVID-19 infection symptoms, with only mild fever and upper respiratory tract symptoms and none needed to be admitted to intensive care units. The symptoms of SAT were typical and included fever, anterior cervical pain, fatigue, tremors, sweating, and palpitations, while the time between COVID-19 diagnosis and typical SAT symptoms ranged between 5 and 42 days. Many of these patients presented with typical SAT ultrasonographic features.[5,28] Most of the patients were treated with corticosteroids (prednisolone 25 mg/day), and the symptoms improved within a few days; thyroid function normalized after 1 to 2 months. There was no report of recurrence of symptoms or a more severe form of SAT than expected.

As time goes on, mounting evidence emerges describing new clinical manifestations are being attributable to COVID-19 disease. To this date, and to the best of our knowledge, SAT SARS-CoV-2-related is apparently a rare complication of COVID-19 disease, as in a recent review article from 2022, only 81 cases were reported worldwide.[17] Consequently, there is still contradicting evidence re-

lated to this new entity. The abovementioned review article states that differences among other forms of SAT still need to be established since the available statistical evidence is scarce.[17] However, it seems that, in most of the cases, the clinical manifestations are indeed similar to SAT associated with other viral infections, and it does not require a distinct treatment approach.[17]

We believe that our case, by the severity, long duration of the symptoms, and need of high doses of glucocorticoids, should raise the hypothesis that atypical manifestations of SAT might arise in patients with mild or asymptomatic forms of COVID-19, and we should be more alert to alterations in thyroid function even in milder presentations of SARS-CoV-2 infection. In fact, this could be a specific marker of this virus. This hypothesis was previously proposed by Brancatella *et al*,[29] but other authors state that not all the available data supports this statement.[17] This same article refers that less severe manifestations of SAT are seen in patients with mild infection, as opposed to our case.

In conclusion, although it is a rare entity, our case highlights the importance of considering SARS-CoV-2 infection as a potential trigger for SAT. Clinicians should be alerted to this diagnosis; and should be aware that more severe, refractory to the standard treatment, and long-lasting manifestations of SAT may occur, even in the presence of mild forms of COVID-19.

## Contributorship Statement / Declaração de Contribuição:

S Campos Lopes: conceptualization, data collection, writing original draft, and final approval.
J Marques Sá, V Fernandes, C Machado: data collection, review, and final approval.
AM Monteiro: conceptualization, supervision, review, and final approval.

## Responsabilidades Éticas

**Conflitos de Interesse:** Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
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## References / Referências

1. Wang Z, Deng H, Ou C, Liang J, Wang Y, Jiang M, Li S. Clinical symptoms, comorbidities and complications in severe and non-severe patients with COVID-19: A systematic review and meta-analysis without cases duplication. Medicine. 2020;99:e23327. doi: 10.1097/MD.0000000000023327.
2. Lusczek ER, Ingraham NE, Karam BS, Proper J, Siegel L, Helgeson ES, et al. Characterizing COVID-19 clinical phenotypes and associated comorbidities and complication profiles. PLoS One. 2021;16:e0248956. doi: 10.1371/journal.pone.0248956.
3. Sharifian-Dorche M, Huot P, Osherov M, Wen D, Saveriano A, Giacomini PS, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. J Neurol Sci. 2020;417:117085. doi: 10.1016/j.jns.2020.117085.
4. Galanopoulos M, Gkeros F, Doukatas A, Karianakis G, Pontas C, Tsoukalas N, et al. COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. World J Gastroenterol. 2020;26:4579-88. doi: 10.3748/wjg.v26.i31.4579.
5. Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, et al. Early and late endocrine complications of COVID-19. Endocr Connect. 2021;10:R229-39.
6. Chen W, Tian Y, Li Z, Zhu J, Wei T, Lei J. Potential Interaction Between SARS-CoV-2 and Thyroid: A Review. Endocrinology. 2021;162:bqab004. doi: 10.1210/endocr/bqab004.
7. Nishihara E, Ohye H, Amino N, Takata K, Arishima T, Kudo T, et al. Clinical characteristics of 852 patients with subacute thyroiditis before treatment. Intern Med. 2008;47:725-9.
8. Benbassat CA, Olchovsky D, Tsvetov G, Shimon I. Subacute thyroiditis: clinical characteristics and treatment outcome in fifty-six consecutive patients diagnosed between 1999 and 2005. J Endocrinol Invest. 2007;30:631-5.
9. Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J. 2009;6:5.
10. Latrofa F, Ricci D, Montanelli L, Altea MA, Pucci A, Pinchera A, Vitti P. Thyroglobulin autoantibodies of patients with subacute thyroiditis are restricted to a major B cell epitope. J Endocrinol Invest. 2012;35:712-4.
11. Parolin M, Parisotto M, Zanchetta F, Sartorato P, De Menis E. Coronaviruses and endocrine system: a systematic review on evidence and shadows. Endocr Metab Immune Disord Drug Targets. 2021;21:1242-51. doi: 10.2174/1871530320666200905123332.
12. Marazuela M, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Rev Endocr Metab Disord. 2020;21:495-507. Erratum in: Rev Endocr Metab Disord. 2021;22:145. doi: 10.1007/s11154-020-09569-2.
13. Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. Eur J Clin Microbiol Infect Dis. 2021;40:905-19. doi: 10.1007/s10096-020-04138-6.
14. Rotondi M, Coperchini F, Ricci G, Denegri M, Croce L, Ngnitejeu ST,et al. Detection of SARS-CoV-2 receptor ACE-2 mRNA in thyroid cells: a clue for COVID-19-related subacute thyroiditis. J Endocrinol Invest. 2021;44:1085-90. doi: 10.1007/s40618-020-01436-w.
15. Trimboli P, Cappelli C, Croce L, Scappaticcio L, Chiovato L, Rotondi M. COVID-19-associated subacute thyroiditis: evidence-based data from a systematic review. Front Endocrinol. 2021;12:707726. doi: 10.3389/fendo.2021.707726.
16. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL,et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26:1343-421.
17. Popescu M, Ghemigian A, Vasile CM, Costache A, Carsote M, Ghenea AE. The new entity of subacute thyroiditis amid the COVID-19 pandemic: from infection to vaccine. Diagnostics. 2022;12:960. doi: 10.3390/diagnostics12040960.
18. Koirala KP, Sharma V. Treatment of acute painful thyroiditis with low dose prednisolone: a study on patients from Western Nepal. J Clin Diagn Res. 2015;9:MC01-3.
19. Kubota S, Nishihara E, Kudo T, Ito M, Amino N, Miyauchi A. Initial treatment with 15 mg of prednisolone daily is sufficient for most patients with subacute thyroiditis in Japan. Thyroid. 2013;23:269-72.
20. Soltani A, Nourani F, Roudsari SB, Jouybari L, Fathi M, Haghighat S,et al. Identifying the lowest effective initial dose of prednisolone for the treatment of subacute granulomatous thyroiditis: a systematic review and meta-analysis. Curr Rev Clin Exp Pharmacol. 2022;17:135-43. doi: 10.2174/2772432816666211012092112.

21. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693-704.
22. Fatourechi V, Aniszewski JP, Fatourechi GZ, Atkinson EJ, Jacobsen SJ.Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. J Clin Endocrinol Metab.2003;88: 2100–5. doi: 10.1210/jc.2002-021799.
23. Instituto Nacional de Saúde Dr. Ricardo Jorge. Diversidade genética do novo coronavírus SARS-CoV-2 (COVID-19) em Portugal [accessed May 5th 2022] Available at: https://insaflu.insa.pt/covid19/relatorios/INSA_SARS_CoV_2_DIVERSIDADE_GENETICA_relatorio_situacao_2020-12-28.pdf
24. Stolp B, Stern M, Ambiel I, Hofmann K, Morath K, Gallucci L, et al. SARS-CoV-2 variants of concern display enhanced intrinsic pathogenic properties and expanded organ tropism in mouse models. Cell Rep. 2022;38:110387. doi: 10.1016/j.celrep.2022.110387.
25. Abdullah F, Myers J, Basu D, Tintinger G, Ueckermann V, Mathebula M, et al. Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in tshwane, south africa. Int J Infect Dis. 2022;116:38-42. doi: 10.1016/j.ijid.2021.12.357.
26. Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared With Previous Waves. JAMA. 2022;327:583-4. doi: 10.1001/jama.2021.24868.
27. Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. Lancet. 2022;399:1618-24. doi: 10.1016/S0140-6736(22)00327-0.
28. Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, et al. SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol. 2020;8:739-41. doi: 10.1016/S2213-8587(20)30266-7.
29. Brancatella A, Viola N, Rutigliano G, Sgrò D, Santini F, Latrofa F. subacute thyroiditis during the SARS-CoV-2 pandemic. J Endocr Soc. 2021;5:bvab130. doi: 10.1210/jendso/bvab130.