Subacute Thyroiditis Following the Third Dose of SARS-CoV-2 mRNA (Pfizer-BioNTech) Vaccine for COVID-19 in a Patient with Clear Cell Renal Cell Carcinoma: A Case Report

Amro Nagy[1*], Muhammad Yaqut[1], Doaa Abbas[2] and Amna Mohamed[3]

[1]Department of Medicine, Division of Nephrology, Sultan Qaboos Comprehensive Cancer Care, Muscat, Oman

[2]Department of Medical Oncology, Sultan Qaboos Comprehensive Cancer Care, Muscat, Oman

[3]Department of Pharmacy, Sultan Qaboos Comprehensive Cancer Care, Muscat, Oman

Received: 4 September 2023

Accepted: 14 December 2023

**Corresponding author:* a.nagy@cccrc.gov.om

DOI 10.5001/omj.2026.10

Abstract

Subacute thyroiditis (SAT) following COVID-19 vaccination or infection is a newly recognized complication. Over 160 cases of SAT have been reported in the medical literature thus far. Roughly one-half were attributed to either the first or second dose of the COVID-19 vaccine. Furthermore, SAT in the oncology population remains an extremely rare entity and has been reported only three times to date. The patient is a 47-year-old male with a history of clear cell renal cell carcinoma (ccRCC) and advanced chronic kidney disease (CKD) among other comorbidities, excluding thyroid disease. He received three doses of the Pfizer mRNA vaccine and never contracted COVID-19. We accidentally discovered a deranged thyroid profile during the workup for short-lasting and infrequent palpitations. The patient remained asymptomatic throughout his illness and did not receive specific treatment for this COVID-19-related complication. Thyroid function normalized after 6 months of regular follow-up. This is the first case report of SAT following the third dose of the COVID-19 Pfizer BioNTech Vaccine. It is also the first reported case of SAT following a COVID-19 mRNA vaccine in a patient with ccRCC. SAT post-COVID vaccination is a self-limiting and rare condition that should be considered in the differential diagnosis of silent thyroiditis.

Keywords: Subacute thyroiditis, COVID-19 infection, COVID-19 vaccines, ASIA syndrome.

Introduction

With over 694 million reported cases of infections to date and over 6.9 million COVID-19-related deaths, COVID-19 infections continue to pose significant financial, social, and healthcare threats globally.[1,2] Many cases of subacute thyroiditis (SAT) have been reported following a COVID-19 infection. Following the rapid development and approval of multiple COVID 19 vaccines, cases of SAT are now being reported post-COVID-19 vaccination.

We present a case of subacute (silent) thyroiditis following the administration of the third dose of the mRNA Pfizer BioNTech vaccine in a patient with a history of clear cell renal cell carcinoma (ccRCC) who has been following up in the nephrology clinic for chronic kidney disease (CKD) and hypertension (HTN). We describe the clinical presentation, laboratory results, imaging findings, and the management of the incidental discovery of SAT.

Case Report

A 47-year-old male was diagnosed with ccRCC of the left kidney, along with a left renal vein thrombus extending into the inferior vena cava. He underwent left radical nephrectomy, adrenalectomy, and cavectomy in April 2021. His preoperative COVID-19 PCR test was negative, and no documented COVID-19 infection occurred postoperatively. Postoperatively, his management included regular surveillance every three months by the oncology team. He was not exposed to chemotherapy, anti-angiogenesis, or immunotherapy drugs postoperatively. He was referred to the nephrology team for persistent preoperative CKD and uncontrolled HTN.

The patient presented to the nephrology clinic on Nov. 10th, 2021. He had history of longstanding HTN, and poorly controlled diabetes mellitus (DM). His preoperative HbA1c was 8.6%. Postoperatively, his DM control improved (HbA1c was 6.5%). He did have proteinuric CKD stage IV (urinary PCR 500mg/mmol, eGFR 23.7 ml/min) presumed to be secondary to diabetic nephropathy. The patient was morbidly obese with a body mass index (BMI) of 43kg/m^2. He had obesity-related severe obstructive sleep apnea (OSA) (apnea-hypopnea index (AHI): 41.9) and was not compliant with CPAP. He suffered from cor-pulmonale and heart failure with reduced ejection fraction (HFrEF) with a preoperative EF of 38% (which later improved to 69% postoperatively). He was a cigarette smoker for over 20 years and occasionally consumed alcohol (beer) but could not estimate how much he would drink per day or week. There was no medical history suggestive of prior thyroidal illness. He had been vaccinated twice against COVID-19 with Pfizer BioNTech BNT162B2. The first dose was on June 28th, 2021, while the second was on August 12th, 2021. His third dose was scheduled on December 21st, 2021. His home medications were nifedipine 90mg once daily, labetalol 200mg twice per day, hydralazine 50mg thrice daily, furosemide 40mg once daily, darbepoetin alpha injection 30mcg every three weeks, aspirin 100mg once daily, as well as one Neurobion forte (combination of vitamins B1, B6 and B12) tablet daily.

Despite the elevated automated office blood pressure (AOBP) readings in our clinic (average of 155/66 mmHg), the patient seemed to be in good overall general condition. Thyroid gland palpation revealed a non-tender, normal sized gland with no signs of hyperthyroidism such as tachycardia or fine tremors. He did, however, have mild bilateral leg oedema as well as significant acanthosis nigricans in both legs. The remainder of his physical examination was non-contributory. His full metabolic profile included a thyroid gland profile as part of his HTN and OSA work up. His thyroid stimulating hormone (TSH) was found to be normal in November 2021 [Table 1]. The patient received appropriate care for his CKD and his blood pressure (BP) medications were adjusted accordingly. He had a 24-hour urine protein excretion done in August 2021 which showed 4.6g per day (consistent with a urine protein to creatinine ratio of 500mg/mmol). He was given a follow-up appointment in our clinic after two months.

Table 1: A Summary of his laboratory results are shown below.

	TSH (normal: 0.34 – 5.60 mIU/L)	**Free T4 (normal: 7.9 – 14.4 pmol/L)**	**TSH Receptor Antibodies (normal: <1.8 IU/L)**	**Anti-Thyroid Peroxidase Antibodies (normal: <34 IU/ml)**	**Anti-Thyroglobulin Antibodies (normal: <115 IU/ml)**	**Hemoglobin (normal: 11.5 – 15.5 g/dl)**	**Hematocrit (normal: 0.35 – 0.45 L/L)**	**Ferritin (normal: 24 – 336 mcg/L**
Nov. 9th, 2021	N/A	N/A	N/A	N/A	N/A	11.7	0.372	N/A
Nov. 10th, 2021	3.19 (N)	N/A	N/A	N/A	N/A	N/A	N/A	117
Jan. 4th, 2022	N/A	N/A	N/A	N/A	N/A	11.0	0.355	N/A
Jan. 5th, 2022	0.293 (L)	19.27 (H)	N/A	N/A	N/A	N/A	N/A	131.6
Jan. 6th, 2022	0.279 (L)	21.21 (H)	N/A	N/A	N/A	N/A	N/A	N/A
Feb. 24th, 2022	0.02 (L)	19.10 (H)	N/A	N/A	N/A	N/A	N/A	N/A
March 22nd, 2022	0.021 (L)	21.59 (H)	N/A	N/A	N/A	N/A	N/A	N/A
May 26th, 2022	0.026 (L)	21.89 (H)	N/A	N/A	N/A	N/A	N/A	N/A
May 30th, 2022	N/A	N/A	< 0.2 IU/L (N)	7.46 IU/ml (N)	16.18 IU/ml (N)	N/A	N/A	N/A
July 4th, 2022	0.365 (N)	18.47 (H)	N/A	N/A	N/A	N/A	N/A	N/A

July 19th, 2022	1.30 (N)	16.85 (H)	N/A	N/A	N/A	N/A	N/A	N/A

On January 6th, 2022, the patients attended a follow-up appointment in the nephrology clinic. His BP readings showed some improvement (average of 145/85mmHg) and a mild reduction in his level of proteinuria was observed (24 hours urine protein excretion done on November 11th, 2021 was 2.7g per day). As advised by the oncology team, he received his third dose of the Pfizer-BioNTech vaccine as planned on December 21st, 2021. The patient did not report any medical concerns following his third dose of the vaccine. His repeat thyroid function tests (which were done to screen for thyroidal illnesses in CKD patients) revealed elevated serum free T4 (fT4) with suppressed serum TSH, normal hemoglobin and normal serum ferritin [Table 1]. A repeat thyroid profile was ordered on the following day (January 6th, 2022) which confirmed his prior results (high fT4 and low TSH) [Table 1].

We used the Naranjo Adverse Drug Reaction Probability Scale, a questionnaire designed to evaluate the likelihood of a causal relationship between an adverse drug reaction and a specific medication. Our conclusion, supported by a score of seven, pointed to the Pfizer-BioNTech BNT162b2 COVID-19 mRNA vaccine as the most probable cause of SAT.[3] The patient was referred to the endocrinology team for further assessment. Subsequently, a provisional diagnosis of silent thyroiditis was suspected based on the history of recent exposure to an mRNA vaccine and a matching thyroid profile. No treatment was initiated as the patient was asymptomatic, and the inflammation of the thyroid gland was expected to be transient. The patient was advised to avoid exposure to iodinated contrast materials and iodine-rich foods. A thyroid gland ultrasound conducted on January 23rd, 2022, revealed a normal-looking thyroid gland with a solitary small spongiform nodule in the right lobe, measuring approximately 11x10x7mm, and two small spongiform nodules in the left lobe, with the largest measuring approximately 10x9x8mm. There was no evidence of enlarged cervical lymph nodes.

The patient attended a follow-up appointment at our nephrology clinic on February 24th, 2022, five weeks after receiving the 3rd dose of the Pfizer vaccine. On one hand, he reported a stable overall general condition but persistently high BP readings at home (average systolic BP 145-155 mmHg, average diastolic BP: 90-95mmHg). It was established that he was non-compliant with CPAP use and consumed a higher-than-recommended amount of salt per day. On the other hand, he did not express thyroid disease-related symptoms. A repeat thyroid exam was negative for pain, goiter, or lymph node enlargement. A follow-up thyroid profile continued to exhibit suppressed TSH and elevated fT4 [Table 1]. On March 31st, 2022, a 99-Tc thyroid scan was performed to confirm a diagnosis of thyroiditis. The scan revealed severely reduced uptake, with a total thyroid uptake of 0.1% (Normal range: 1-4%). Testing for thyrotropin receptor antibodies (TRAb), thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TGAb) yielded negative results [Table 1].

On May 26th, 2022, during a routine visit for CKD and HTN review, the patient remained asymptomatic for thyroid dysfunction. He reported no exposure to intravenous iodinated contrast or ingestion of an iodine-rich diet. The patient showed no symptoms or signs of thyroid dysfunction. His home BP readings had improved (average systolic BP 128-135mmHg, diastolic BP 71-78mmHg), but his AOBP remained elevated as he omitted the morning dose of his scheduled BP medications. Additionally, his proteinuria level had improved (24-hour urine protein excretion was 1.68g/d). Repeat thyroid profiling continued to display suppressed TSH and elevated fT4 [Table 1].

On July 4, 2022, during a follow-up visit with the oncology team, another thyroid profile was conducted, revealing normalization of TSH levels. However, his fT4 remained elevated, though to a lesser extent than previous readings. The patient felt reassured that the inflammation in his thyroid gland had subsided. No treatment was initiated for subclinical hyperthyroidism throughout the 6-month follow-up period.

Discussion

SAT is an inflammatory thyroid disease that typically follows viral infection and stands as a common cause of painful thyroiditis. It is usually preceded by an acute symptomatic or asymptomatic viral illness, predominantly an upper respiratory tract infection (URTI). It is more common in females and usually presents with infection-type symptoms (fever, myalgia, asthenia), anterior neck pain radiating to the jaw or ear region, and symptoms of thyroid dysfunction (palpitations, hyperhidrosis, weight loss). The thyroid gland may be enlarged (50%), sensitive, or painful on palpation, but the absence of painful phenomena does not rule out the diagnosis.[4,5]

PD-L1 is responsible for T cell activation, proliferation, and cytotoxic secretion in cancer, leading to the production of anti-tumor immune responses.[6] Additionally, the frequency of PD-1 expression on CD4+ and CD8+ lymphocytes appear to strongly correlate with the outcome of SAT.[7] TGF-β1 and interleukin-10 (IL-10) are key regulators of immune homeostasis with anti-tumor effects.[8,9] An increased serum level of the cytokine IL-10 is a considerable laboratory predictor for severe and fatal COVID-19 disease.[10] RNA vaccines can induce immune responses by activating specific toll-like receptors (TLRs).[11] These receptors play a significant role in the host's defense against microorganisms.[12]

Different pathogenic mechanisms have been hypothesized to explain the development of SAT following the COVID-19 vaccine. It is suggested that viral upper respiratory tract infections may trigger SAT in genetically predisposed individuals with specific HLA haplotypes, such as HLA-B*35, HLA-B67, and HLA-Drw8; however, this test was not conducted in our case. The proposed mechanism involves the infiltration of the virus into the follicular cells of the thyroid gland, leading to cytotoxic T-cell activation, follicular destruction, and subsequent thyroid dysfunction.[13-15]

Another significant pathogenic hypothesis centers around the overactivation of the human immune system, combined with molecular mimicry between thyroid tissue (specifically thyroid peroxidase peptide sequences) and vaccine components, particularly the spike protein.[8,9] Additionally, the ASIA syndrome (autoimmune/autoinflammatory syndrome induced by adjuvants) hypothesis suggests that the vaccine triggers an autoimmune thyroid response. Adjuvants, which are crucial components of vaccines, have been associated with post-vaccination phenomena linked to autoimmune endocrine diseases, especially after HPV, influenza, and hepatitis B vaccines. This response is represented by vaccine-induced higher viscosity status, which may cause an abnormal increase in thyroid hormone levels due to their excessive release from the thyroid, particularly in patients displaying a higher risk for coagulation anomalies.[16-18]

COVID-19 is well-known for causing a wide range of pulmonary and extrapulmonary complications.[17] Among the extrapulmonary manifestations of COVID-19 infection, thyroid gland dysfunction may be included. The clinical spectrum of COVID-related thyroid gland involvement exhibits two patterns: it may accompany severe COVID-19 infections with multi-organ spreading (most frequently associated with lung involvement) or manifest as an asymptomatic infection, with SAT being the sole manifestation or the initial presentation.[16]

Before the introduction of mRNA vaccines against COVID-19 infection, reports of SAT were infrequent after the administration of the influenza vaccine.[5] Cases of SAT have been documented following the administration of the inactivated SARS-CoV-2 vaccine (CoronaVac®) in three healthcare workers in Turkey.[18,19] A systematic review suggested that a prior history of autoimmune thyroiditis might be a risk factor for developing SAT after COVID-19 vaccination.[15]

COVID-19 vaccine-induced thyroiditis can occur hours to weeks post-vaccination, with no clear correlation to the administration of the first or second doses of the vaccine.[20] The largest literature review of SAT cases following COVID-19 vaccines to date includes 80 patients. It concluded that vaccine-related SAT is typically less symptomatic than other types of SAT, with incidents occurring variably following either the first or second dose of the vaccine within an average of 2 weeks. The pathogenic mechanisms are less understood, and there are no clear risk factors that could predispose patients to developing SAT either peri- or post-vaccination.[20]

In general, vaccine-related adverse effects were observed at a lower incidence rate in cancer patients compared to individuals without cancer, possibly attributed to a higher pain threshold in the former. However, challenges in reporting may arise due to an overlap between symptoms related to chemotherapy and those associated with chronic illnesses, potentially leading to underreporting and delayed diagnosis.[21] Another plausible explanation is the lower rates of immunogenicity observed in cancer patients, as documented in the literature. Notably, the SOAP-O2 study found lower incidences of local (52% vs. 36%) and systemic (32% vs. 25%) symptoms following the Pfizer/BioNTech vaccine in cancer patients.[22]

This lower immunogenicity may explain why post-COVID-19 vaccination-induced SAT in cancer patients has only been reported in three cases, all of which occurred after mRNA vaccines. Specifically, one case was documented

in a patient with concurrent papillary thyroid cancer after receiving the Pfizer vaccine, another in an individual with colorectal cancer following the Moderna vaccine, and a third case in a patient with multiple myeloma who received the Pfizer vaccine.[20,23,24]

Conclusion

We present this case to contribute to the growing body of evidence in medical literature indicating that SAT can develop after COVID-19 mRNA vaccination. It should be recognized as a potential side effect of the vaccine and considered in the differential diagnosis for patients presenting with symptoms suggestive of thyroid-related illness or, even if asymptomatic, albeit rarely.

To the best of our knowledge, this is the first reported case of SAT following the administration of the third dose of the SARS-CoV-2 Pfizer BioNTech BNT162b2 vaccine. Furthermore, it represents the first case of SAT following mRNA vaccine administration in a patient diagnosed with ccRCC. Lastly, this marks the fourth reported case of SAT post COVID-19 vaccination in the cancer population at large.

Given the ongoing global mass immunization efforts against COVID-19, vaccine-related adverse events are anticipated. However, SAT following COVID-19 vaccination remains a complication in the general health population and is considered very rare in patients with a prior history of cancer diagnosis. The rarity of SAT occurrence post COVID-19 mRNA vaccines in cancer patients should not dissuade them from receiving mRNA vaccines to protect against COVID-19 infection. The benefits of vaccination in preventing infection far outweigh the minimal risk of developing SAT in these patients.

Learning Points:

- SAT following the administration of a COVID-19 vaccine is a newly discovered and rare complication of mRNA vaccines. Its consideration should be integrated into the differential diagnosis of thyroid dysfunction, particularly in the current era of the COVID-19 pandemic and global vaccination efforts.

- SAT in cancer patients remains an extremely rare occurrence, with only three reported cases to date. This rarity may be attributed to decreased immunogenicity in such patients.

- SAT can manifest after any dose of the COVID-19 vaccine. Clinicians should maintain awareness of the clinical presentation of thyroid dysfunction and specifically inquire about the presence of such symptoms, particularly in oncology patients.

Ethical approval and consent for participation

This research work is approved by our institutional review board.

Consent for publication

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

Availability of supporting Data

The medical data that supports our conclusion and diagnosis in this case will be made available upon request.

Competing Interests

I declare that I have no competing interests below.

Funding

Not Applicable

Authors Contributions

Not Applicable

Acknowledgments

Not Applicable

References

1. Oyibo SO. Subacute Thyroiditis After Receiving the Adenovirus-Vectored Vaccine for Coronavirus Disease (COVID-19). Cureus 2021 Jun;13(6):e16045. .

2. Worldometer. COVID-19 Coronavirus Pandemic [Internet]. [cited date]. Available from: https://www.worldometers.info/coronavirus/

3. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981 Aug;30(2):239-245. .

4. Franquemont S, Galvez J. Subacute Thyroiditis After mRNA Vaccine for Covid-19. J Endocr Soc 2021 May;5(Suppl 1):A956-A957. .

5. Bornemann C, Woyk K, Bouter C. Case Report: Two Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccination. Front Med (Lausanne) 2021 Aug;8:737142. .

6. Abdel Hafeez LA, Mansor SG, Zahran AM, et al. Expression of programmed death ligand-1 (PDL-1) in Acute Myeloid Leukemia Patients and its relation to post induction Response. SECI Oncol J. 2021;9(2):106-111. .

7. Wykes MN, Lewin SR. Immune checkpoint blockade in infectious diseases. Nat Rev Immunol 2018 Feb;18(2):91-104. .

8. Abdel Hammed MR, Ahmed YA, Adam EN, Bakry R, Elnaggar MG. sVCAM-1, and TGFβ1 in chronic phase, chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. Egypt J Immunol 2022 Oct;29(4):163-173. .

9. Mohammed D, Khallaf S, El-Naggar M, et al. Interleukin-10: A Potential Prognostic Marker in Patients with Newly Diagnosed Multiple Myeloma. Resum Oncol 2021;17(1):38-41. .

10. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;pii: S0091-6749:30495-4. .

11. Chung YH, Beiss V, Fiering SN, Steinmetz NF. COVID-19 Vaccine frontrunners and their nanotechnology design. ACS Nano 2020 Oct;14(10):12522-12537. .

12. Abdel Hammed MR, Elgendy SG, El-Mokhtar MA, Sayed D, Mansour SM, Darwish AM. T-lymphocytes Expression of Toll-like Receptors 2 and 4 in Acute Myeloid Leukemia Patients with Invasive Fungal Infections. Mediterr J Hematol Infect Dis. 2022 Mar 1;14(1):e2022022. . PMID: 35444773. doi:10.4084/MJHID.2022.022.

13. Kojima M, Nakamura S, Oyama T, Sugihara S, Sakata N, Masawa N. Cellular composition of subacute thyroiditis. an immunohistochemical study of six cases. Pathol Res Pract 2002;198(12):833-837. .

14. Caron P. Thyroiditis and SARS-CoV-2 pandemic: a review. Endocrine 2021 May;72(2):326-331. .

15. Ippolito S, Gallo D, Rossini A, Patera B, Lanzo N, Fazzino GF, et al. SARS-CoV-2 vaccine-associated subacute thyroiditis: insights from a systematic review. J Endocrinol Invest 2022 Jun;45(6):1189-1200. .

16. 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 (Basel) 2022 Apr;12(4):960. .

17. Jeeyavudeen MS, Patrick AW, Gibb FW, Dover AR. COVID-19 vaccine-associated subacute thyroiditis: an unusual suspect for de Quervain's thyroiditis. BMJ Case Rep 2021 Nov;14(11):e246425. .

18. İremli BG, Şendur SN, Ünlütürk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Postvaccination ASIA Syndrome. J Clin Endocrinol Metab 2021 Aug;106(9):2600-2605. .

19. Şahin Tekin M, Şaylısoy S, Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: a case report. Hum Vaccin Immunother 2021 Nov;17(11):4090-4092. .

20. Plaza-Enriquez L, Khatiwada P, Sanchez-Valenzuela M, Sikha A. A Case Report of Subacute Thyroiditis following mRNA COVID-19 Vaccine. Case Rep Endocrinol 2021 Nov;2021:8952048. .

21. Monin L, Laing AG, Muñoz-Ruiz M, McKenzie DR, Del Molino Del Barrio I, Alaguthurai T, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol 2021 Jun;22(6):765-778. .

22. So AC, McGrath H, Ting J, Srikandarajah K, Germanou S, Moss C, et al. COVID-19 Vaccine Safety in Cancer Patients: A Single Centre Experience. Cancers (Basel) 2021 Jul;13(14):3573. .

23. Alkis N, Baysal M. Subacute thyroiditis after SARS-CoV-2 BNT162b2 vaccine in a multiple myeloma patient. SAGE Open Med Case Rep. 2022 Apr 24;10:2050313X221091392. .

24. Sigstad E, Grøholt KK, Westerheim O. Subacute thyroiditis after vaccination against SARS-CoV-2. Tidsskr Nor Laegeforen 2021 Oct;141(2021-14). doi:10.4045/tidsskr.21.0983.