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Case Report

Case Report: Subacute Thyroiditis triggered by Sinovac and Oxford-AstraZeneca vaccine

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Abstract

Background: A two-dose regimen of COVID-19 vaccination (inactivated whole virion SARS-CoV-2 followed by adenoviral vector) has been widely used and while the incidence of side effects is very low, several adverse effects have been reported.

Methods: A 40-year old female patient, with a previous history of thyroid goitre, developed severe neck pain, headache, nausea and fatigue 7-days after receiving second vaccination with Vaxzevria® (Oxford-AstraZeneca). Clinical and laboratory findings, including thyroid function tests and ultrasound of thyroid glands, were performed.

Results: Her left thyroid gland was enlarged and multinodular, and severely tender on palpation. She had difficulty in swallowing and had tachycardia but no signs of hyperthyroidism. Laboratory results supported a diagnosis of subacute thyroiditis. She was prescribed NSAID (Ibuprofen 400 mg) and dexamethasone for 3-days and her symptoms resolved.

Conclusions: Although this is an extremely rare event, physicians may encounter more cases of this condition due to the extensive vaccination program using this combination of vaccines.

Keywords: SARS-CoV-2, adenoviral vector vaccines, vaccination, subacute thyroiditis

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and several vaccines have been developed (1). These include: inactivated whole virion SARS-CoV-2 (CoronaVac®, Sinovac, SV); adenoviral vectors (e.g. ChAdOx1, (Vaxzevria®, Oxford-AstraZeneca, AZ); mRNA vaccines (e.g. Pfizer-BionTech and Moderna Biotech). These vaccines have been very widely distributed across many worldwide populations, and generally adverse side effects are relatively uncommon (2).

Several reports have shown that subacute thyroiditis (SAT) which causes damage to the thyroid glands, is observed following natural infection of SARS-CoV-2 (3,4), or other viral infections (5). Clinical symptoms of SAT include anterior neck pain radiating to the jaw, ear and upper mediastinum, fever, fatigue, malaise and muscle pain (6). The thyrotoxicosis phase is more common in the first stages of SAT and

when pain and fever disappears, and the hypothyroid phase usually follows (7). Laboratory findings of SAT include low levels of thyroid-stimulating hormone (TSH), increased erythrocyte sedimentation rate (ESR) and elevated C-reactive protein (CRP). In addition to reports of SAT following viral infections, influenza vaccination (8), and more recently COVID-19 vaccinations (9), particularly with mRNA-based vaccines (10), are rported to induce this condition. It has been suggested that the adjuvants in these vaccines may trigger immune responses leading to SAT (11).

In this report, we describe a case of SAT that developed in a healthy female individual 7days after completion of a 2-dose regimen of SV followed by AZ.

Case Presentation

A 40-year-old female patient presented with severe anterior neck pain, fever, headache, nausea and fatigue. She reported that symptoms started 7-days after completing a 2-dose regimen of a first dose of SV followed by the second dose with AZ approximately 4-weeks apart. She had a previous history of thyroid goiter and had undergone right thyroidectomy 16-years ago. Her histopathology from the first surgery was thyroid goiter. She had no history of using any medication to treat thyroid dysfunction and had no symptoms of upper respiratory tract infections prior to admission to hospital. Upon examination, her left thyroid gland was multinodular enlarged and severely tender on palpation. She had difficulty swallowing and had tachycardia but no signs of hyperthyroidism. Thyroid function tests revealed slightly elevated Free T3 (4.67 ng/ml) and low serum TSH (0.056 μIU/ml). Laboratory tests for thyroid peroxidase (Anti-TPO) and thyroglobulin antibodies (Anti-Tg) were negative. Thyroglobulin levels were elevated, and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were elevated at 130 mm/h and 96 mg/L, respectively. WBC results revealed leukocytosis with elevated neutrophil counts (90.3%). Nasopharyngeal swab PCR screening for SARS-CoV-2 pre-admission was negative. Ultrasound analysis of the thyroid showed a 3.6x3.1x4.6 cm well-defined cystic-solid nodule at the mid-left thyroid gland and a 2.8x2.1x1.9 cm well-defined spongiform hyperechoic nodule at the lower pole of the left thyroid gland, nodules without calcification and extrathyroid extension (Figure 1). No significant cervical lymphadenopathy or residual thyroid parenchyma at the right thyroid bed were detected. Therefore, subacute thyroiditis (SAT) with multinodular goiter was provisionally diagnosed. The patient was admitted to hospital and treated with NSAID (Ibuprofen 400 mg) and dexamethasone (4 mg intravenous every 12 h) for 3-days. Her symptoms disappeared within 2-days after treatment. Prednisolone (20 mg daily for 7-days) was prescribed upon discharge from hospital.

Outcome and follow up

The patient was followed up 3-weeks after discharge from hospital, and she reported no anterior neck pain and the size of her left thyroid gland had decreased. Laboratory tests at this time (3-weeks post-discharge) revealed a normal range of thyroid function tests. Repeat tests for thyroid peroxidase (Anti-TPO) and thyroglobulin antibodies (Anti-Tg) were negative. Erythrocyte sedimentation rate (ESR) was normal.

The results of thyroid ultrasound analysis at 20-weeks after discharge from hospital showed a 2.1x1.5x2.0 cm well-defined cystic-solid nodule at the mid left thyroid gland and a 1.8x1.4x1.7 cm well-defined spongiform hyperechoic nodule at the lower pole of the left thyroid gland, nodules without calcification and extrathyroid extension (Figure 2). These were significantly decreased in size compared to measurements at initial diagnosis.

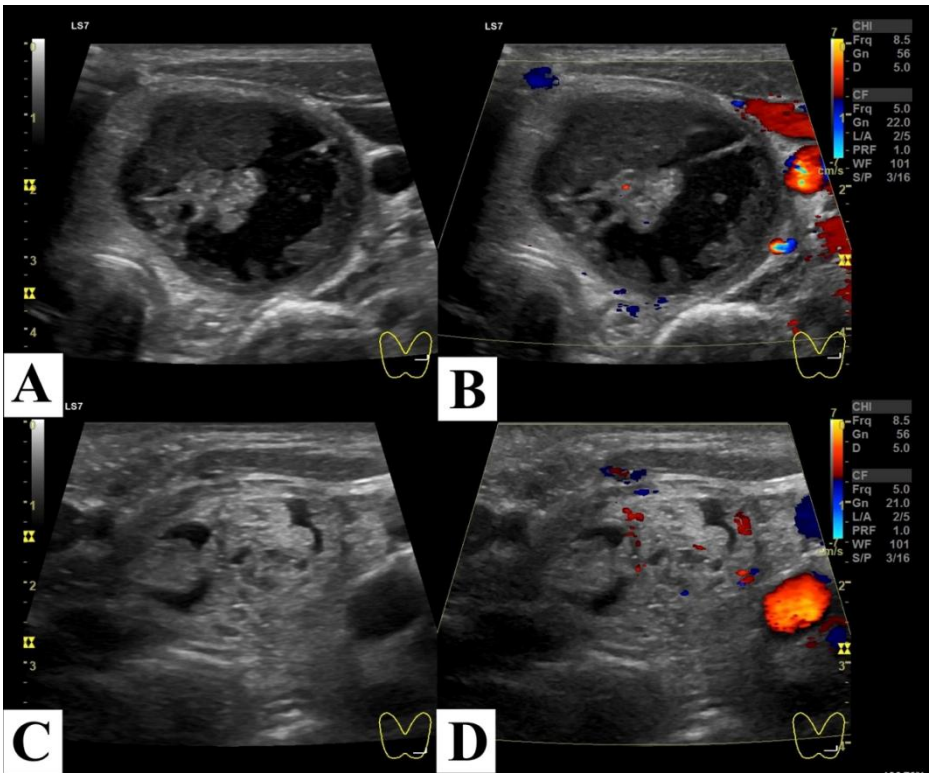

Figure 1 Ultrasound of thyroid gland (at initial admission)

(A) shows a 3.6x3.1x4.6 cm well-defined cystic-solid nodule at the mid left thyroid gland. **(B)** Doppler studies of the left thyroid nodule (A) showed reduce vascular flow. **(C)** A 2.8x2.1x1.9 cm well-defined spongiform hyperechoic nodule at the lower pole of left thyroid gland, nodules without calcification and extrathyroid extension. **(D)** Doppler studies of left thyroid nodule showed increase vascular flow**.**

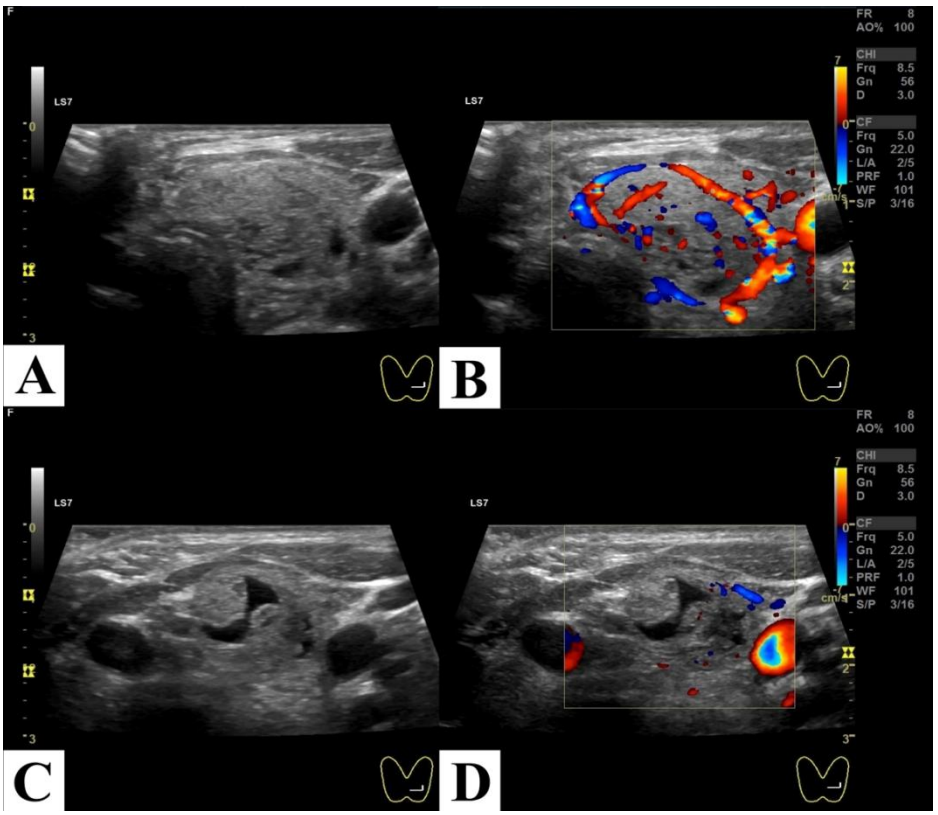

Figure 2 Ultrasound of thyroid gland (Follow up at 20th weeks)

(A) 2.1x1.5x2.0 cm well-defined cystic-solid nodule at mid left thyroid gland. **(B)** Doppler studies of left thyroid nodule (A) showed increase vascular flow. **(C)** A 1.8x1.4x1.7 cm well-defined spongiform hyperechoic nodule at lower pole of left thyroid gland, nodules without calcification and extrathyroid extension**. (D)** Doppler studies of left thyroid nodule showed increase vascular flow.

Discussion

Subacute thyroiditis (SAT) is an inflammatory disease that causes damage to the thyroid glands (6,7). The disease can resolve within weeks to months if left untreated and the most common cases are found in middle-aged women (6). It is known that the disease can be triggered by viral infection (5), including after COVID-19 infections (3,4) and recently increased numbers of reports of SAT cases, have been identified after SARS-CoV-2 vaccination (9,10). These cases are a very low percentage of the total numbers of individuals vaccinated, and a recent review (10), identified 51 patients, 74.5% women with a median age of 39.5 years with this condition. Of these, 70% developed SAT after receiving one or two doses of mRNA vaccines, while 6 individuals of Asian background developed SAT after one dose of inactivated virus (Sinovac) (10). However, it cannot be concluded that this observation indicates an increased susceptibility of Asians to inactivated virus vaccines because this vaccine has been widely distributed to Asian populations and is not licensed in many other countries. It has been shown, however, that those with the co-presence of HLA-B*35 and HLA-C*04.01 significantly increases their susceptibility to COVID-19 induced SAT (12,13). Therefore, genetic backgrounds affect susceptibility to this condition.

Our case was a 40-year old Asian female who developed SAT after completion of a 2-dose regimen of heterogenous vaccines (SV followed by AZ). This has, to our knowledge, not been reported previously. The case was diagnosed as SAT with multinodular left thyroid goiter due to a severe anterior neck pain, fever and other systemic symptoms with prominent raised ESR and CRP, leukocytosis and elevated neutrophils, that differentiate SAT from other diseases, such as acute suppurative thyroiditis and malignancy of thyroid. Laboratory testing for thyroid peroxidase (Anti- TPO) and thyroglobulin antibodies (Anti-Tg) were negative, findings that differentiate SAT from Hashimoto's thyroiditis, Graves' disease (6).

The molecular pathogenesis of thyroid dysfunction might involve either direct viral infection or abnormal inflammatory immune responses to infection. For direct viral infection, SARS-CoV and SARS-CoV-2 utilise the Angiotensin -converting enzyme 2 (ACE-2) as a cellular receptor to infect cells (14, 15), and ACE-2 is also expressed in follicular thyroid cells (15), suggesting that the thyroid might be a direct target for SARS-CoV-2. However, the presented case began symptoms 7-days after completing the second of a 2-dose regimen of the SV and AZ vaccines, and had no evidence of viral infection. This suggests that the SARS-CoV-2 vaccine may be the actual trigger of SAT. A number of SAT cases after COVID-19 vaccination have been reported, for instance three cases following AZ (16), four cases following SV (17), two cases for Pfizer-BionTech and one case for Moderna Biotech vaccine (18), however the precise mechanism remains unexplored.

One possible mechanism to explain these effects may be molecular mimicry between the SARS-CoV-2 spike protein and thyroid cell antigens. In case of SAT, antibodies against SARS-CoV-2 spike protein may cross-react with thyroid cell antigens that have shared molecular components via molecular mimicry (19,20). Among other self-antigens, thyroid peroxidase (TPO) reacts strongly with SARS-CoV-2 spike protein antibodies (21), suggesting a potential mechanism for damage to the thyroid glands through abnormal autoimmune responses against TPO.

It has also been proposed that SAT may be an autoimmune/inflammatory syndrome in response to adjuvant (ASIA syndrome). It has been shown that post SARS-CoV-2 vaccination, autoimmune thyroid diseases such as Hashimoto's thyroiditis, Graves' disease (22) and SAT (11) may develop. However, all of these symptoms occurred after completion of 2-doses of the same vaccine. In our case, the 2-dose regimen of the SV and AZ can also cause such a disease. Therefore, another plausible causative factor might be due to the adenoviral vector of AZ that acts carries the antigenic cargo. Although, active viral infection has been reported to be a key factor in the development of SAT, our patient's history of absence of viral infection and the timing of the onset of

symptoms after second dose vaccination (7 days) argues for the likelihood of the association of the adenoviral vector of the vaccine and development of SAT. However, a limitation of our study is the lack of information or test for active viral infection (other than SARS-CoV-2) to rule out infection with other viruses.

Conclusion

Our case reports a likely association between a 2-dose regimen (SV and AZ) COVID-19 vaccination and rapid development SAT, an outcome that has not been previously demonstrated for this particular combination of vaccines. In this case, the patient completely recovered within 3-weeks after discharge from hospital. Although this is an extremely rare event, it may become more prominent in the future in light of the extensive and ongoing vaccination campaign and use of heterologous vaccines for booster programmes.

Authors' Contributors

Conceptualization: Ratchaneewan Salao and Kanin Salao; Data collection, data interpretation and figure: Ratchaneewan Salao; Investigation and methodology: Ratchaneewan Salao; Writing-original draft: Ratchaneewan Salao and Kanin Salao; Writing-review and editing: Ratchaneewan Salao, Kanin Salao, Kiatichai Faksri, Steven Edwards. All authors read/approved the final version of the manuscript and confirm authorship.

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