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LETTER TO THE EDITOR

WILEY

Can COVID-19 immunisation cause subacute thyroiditis?

To the Editor,

Subacute thyroiditis is often triggered by viral infections. In the current global pandemic of COVID-19 infection, there are several case reports of COVID-19-related subacute thyroiditis.[1,2] Moreover, the rate of vaccination against COVID-19 had risen worldwide with over 1 billion people being vaccinated with some form of the vaccine to date.[3] We now report a case of subacute thyroiditis probably related to immunisation with the COVID-19 AstraZeneca vaccine.

A 75-year-old male presented with pain and tenderness around the front of his neck some 14 days following immunisation against COVID-19 with the AstraZeneca vaccine (ChAdOx1, *Vaxzevria*). Following his initial immunisation, his first dose, he reported a slight headache, pain around the back of the neck and mild pyrexia for 48 h. Although these symptoms gradually improved during the next couple of days, approximately 14 days following the vaccination he developed severe pain and tenderness around the front of the neck associated with shortness of breath, intermittent palpitations, insomnia and generalised anxiety. He noted a stable weight and no change in his regular bowel habit. There was no significant past medical history, including no history of COVID-19 infection, and there was no family history of thyroid disease. His original investigations by his GP 4 weeks postimmunization revealed an elevated free T4 of 28.2 pmol/L (normal, 9.0–22.0) and free T3 of 7.8 pmol/L (normal, 2.63–5.70) respectively, with a suppressed thyroid stimulating hormone (TSH) of less than 0.01 μIU/ml (normal, 0.35–4.94).

When seen in the clinic 12 weeks after immunisation, he had very slight tenderness of the neck, sinus tachycardia with a pulse rate of 110 beats per minute and blood pressure of 110/70 mmHg. There was no tremor and no goitre. His thyroid function tests had slightly improved: The free T4 was 21.8 pmol/L, free T3 6.05 pmol/L, with a maintained suppressed TSH. The TSH receptor antibodies, thyroid peroxidase antibodies and thyroglobulin antibodies were all negative. Furthermore, the anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-S antibody titre was elevated at 1232 U/ml as an expected result of the recent immunisation; a viral antibody screen showed the presence of influenza A and chlamydia pneumonia immunoglobulin G levels indicative of the previous infection. A pertechnetate thyroid scan showed a marked reduction of uptake at 0.08% (normal uptake: 0.4%–3.5%) suggestive of subacute thyroiditis. He was treated symptomatically with ibuprofen, and his symptoms gradually resolved. One month later, he had normal thyroid function.

Our patient had symptoms and some signs of thyrotoxicosis, confirmed biochemically, with no family history and negative thyroid antibodies, including the TSH-receptor antibodies. This, together with his negative pertechnetate scan, renders the diagnosis of subacute thyroiditis highly probable. His neck pain has now settled. We feel that his case should be reported at this juncture due to the temporal association with his COVID-19 immunisation.

It is now well established that subacute thyroiditis may be associated with COVID-19 infection, albeit rarely.[1,2] To date, there is a reported case of subacute thyroiditis following the Pfizer-BioNTech messenger RNA vaccine for COVID-19[4] and three cases of subacute thyroiditis following CoronaVac® which contains inactivated SARS-CoV-2 virus.[3] There are further two cases of new-onset of Graves' disease following COVID-19 Pfizer-BioNTech immunisation, possibly due to an autoimmune inflammatory syndrome induced by adjuvants (ASIA).[5] Adjuvants are an essential part of the vaccine, and postvaccination phenomena have been described with autoimmune endocrine diseases (mostly after HPV, influenza and hepatitis B vaccine).[6] The clinical spectrum regarding thyroid disease includes both Hashimoto's thyroiditis and Graves' disease, but reports include ovarian failure and type 1 diabetes.[7]

Although ASIA might explain the mechanism of thyroiditis by adjuvants, the AstraZeneca vaccine contains recombinant replication-deficient chimpanzee adenovirus vector encoding the SARS CoV-2 spike glycoprotein, produced in the genetically modified human embryonic kidney 293 cells,[8,9] and other mechanisms may be involved in immunisation-induced thyroiditis. SARS CoV-2 spike protein enters cells via the angiotensin-converting enzyme 2 (ACE-2) receptor, and there is evidence to suggest that thyroid cells express the ACE-2 at a very higher concentration, presumably potentiating the entry of the SARS CoV-2 spike protein into thyroid cells.[10,11] This might mediate immunisation-induced damage. In a similar manner, the binding of spike protein to the ACE-2 receptor in endothelial cells induces inflammation of the endothelial cells, with downregulation of ACE-2 leading to a reduction of nitric oxide production and secondary mitochondrial damage.[12] In addition, it is also known that antibodies against the SARS CoV-2 react with cellular antigens including that on the thyroid.[13] Furthermore, the spike protein shows molecular mimicry towards thyroid peroxidase. Thus, the induction of antibodies to COVID-19 may interact with the thyroid surface receptors to cause transient thyroiditis which spontaneously recovers.

Although there is no definitive proof, we note that our patient's symptoms and signs occurred at a time when there is potent immune responsivity, and we suggest a possible cause-and-effect relationship. Although this is clearly not a major cause for concern in light of the relatively mild illness, and especially at a time when the COVID-19 epidemic is raging and there is high international mortality, we suggest that clinicians should be aware of this putative association with this report of

the first case of subacute thyroiditis probably triggered by this specific viral vector DNA vaccine in this period of increasing COVID-19 vaccine roll-out across the world.

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