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Adalimumab-Associated Thyroiditis in a Patient With Pre-existing Hypothyroidism: A Case Report and Literature Review

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Abstract

We present a rare case of adalimumab-associated thyroiditis mimicking acute meningitis in a patient with pre-existing hypothyroidism, without overt thyrotoxicosis. She presented with features of meningitis, such as severe headache, fever, photophobia, and neck pain. Clinical examination revealed mild diffuse thyroid enlargement with some tenderness. Inflammatory markers were markedly elevated. Empirical antibiotic therapy was started for suspected meningitis without any clinical improvement. Cerebrospinal fluid analysis and neuroimaging subsequently excluded meningitis and other intracranial pathologies. Thyroid imaging demonstrated features of thyroiditis with reactive lymphadenopathy. A diagnosis of adalimumab-associated thyroiditis was made based on thyroid imaging, normal CSF analysis, and clinical and biochemical picture. Thyroid hormone levels remained within the reference range in the acute thyroiditis phase. Thyroid peroxidase (anti-TPO) antibodies were elevated, which is atypical for subacute thyroiditis but consistent with pre-existing autoimmune hypothyroidism. The patient was treated with a tapering course of corticosteroids resulting in significant symptomatic improvement. Other published cases showed a more typical clinical presentation but a similar clinical course with a good response to corticosteroid therapy and no long-term thyroid dysfunction. This case highlights that TNF-α inhibitor-associated thyroiditis can present without thyrotoxicosis or typical clinical features, particularly in patients with pre-existing hypothyroidism.

Categories: Internal Medicine, Endocrinology/Diabetes/Metabolism, Dermatology
Keywords: adalimumab (humira), chronic inflammatory diseases, subacute thyroiditis, thyroid pathologies, tnf-alpha inhibitor

Introduction

Tumor necrosis factor-alpha (TNF-α) inhibitors like adalimumab are widely used in the treatment of chronic inflammatory diseases like psoriasis, psoriatic and rheumatoid arthritis, and inflammatory bowel disease. However, uncommon thyroid dysfunction, including subacute thyroiditis, and, more rarely, Graves' disease and Hashimoto's thyroiditis have been reported with the use of TNF-α inhibitors [1]. Patients with subacute thyroiditis normally present with painful thyroid swelling and a transient hyperthyroid phase due to thyroid inflammation and release of preformed hormones. This is usually followed by a hypothyroid phase due to thyroid follicular destruction and hormone depletion.

A literature search of PubMed/MEDLINE and Google Scholar using combinations of the terms "adalimumab", "subacute thyroiditis", "thyroiditis", and "hypothyroidism" did not identify any previously reported cases of adalimumab-associated subacute thyroiditis in patients with pre-existing hypothyroidism. Published cases of subacute thyroiditis associated with adalimumab have largely involved patients without documented pre-existing hypothyroidism [2-7].

We report an unusual presentation of adalimumab-associated thyroiditis with a meningitis-like presentation and without hyperthyroidism in a patient with pre-existing hypothyroidism.

Case Presentation

A 54-year-old woman presented with a two-day history of severe headache, photophobia, neck pain, and vomiting. The patient had a history of chronic headaches, diagnosed as cluster headaches in 2012. She reported that the current headache differed from her usual headaches in its character and distribution, radiating from the occipital region to the forehead and eyes. It was also associated with severe photophobia and neck pain, which were not typical features of her usual headaches. She denied preceding upper respiratory tract symptoms or recent travel.

Her medical history included hypothyroidism diagnosed in 2017 and treated with levothyroxine, psoriasis, psoriatic arthritis, alopecia areata, type 2 diabetes mellitus, sleeve gastrectomy, and hypertension. Her psoriasis and psoriatic arthritis were clinically stable at presentation. Adalimumab had been commenced by her dermatologist four months earlier for psoriatic arthritis. She was receiving 40 mg subcutaneously every

other week, with her last dose administered the week before presentation. Her other medications included methotrexate, folic acid, and levothyroxine.

On admission, the patient was apyrexial, with a temperature of 36.7°C, heart rate of 97 beats/min, blood pressure of 136/90 mmHg, respiratory rate of 20 breaths/min, and oxygen saturation of 97% on room air. Following admission, she developed intermittent pyrexia with temperatures exceeding 38°C. Examination revealed a diffusely enlarged and mildly tender thyroid without overlying erythema. She had pain on neck movement but no neck stiffness. There were no new focal neurological deficits.

Investigations

Blood tests (Table *1*) demonstrated marked systemic inflammation, with a C-reactive protein (CRP) of 152 mg/L, erythrocyte sedimentation rate (ESR) of 62 mm/h, white cell count of 18.4 × 10^9/L, and platelet count of 461 × 10^9/L. Lumbar puncture was performed, with a normal opening pressure of 17 cm H_2O. Cerebrospinal fluid analysis showed no evidence of meningitis, with a white cell count of 0 cells/mm^3, a protein level of 202 mg/L, and no growth on CSF culture. The infectious work-up, including blood cultures, infectious mononucleosis screen, and Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) IgM antibodies, was negative.

Test	Result	Reference range
Activated partial thromboplastin time (APTT)	31.9 s	22.5-28.0 s
APTT ratio	1.3	
C-reactive protein (CRP)	152 mg/L	0-5 mg/L
Erythrocyte sedimentation rate (ESR)	62 mm/h	9-19 mm/h
Haemoglobin	135 g/L	117-149 g/L
White cell count (WCC)	18.4 × 10^9/L	4.3-11.2 ×10^9/L
Platelets	461 × 10^9/L	150-400 ×10^9/L
Red cell count (RBC)	4.00 × 10^{12}/L	3.85-5.15 ×10^{12}/L
Mean cell volume (MCV)	96.0 fL	81-97 fL
Haematocrit (HCT)	0.383 L/L	0.347-0.445 L/L
Mean cell haemoglobin (MCH)	33.8 pg	26.9-33 pg
Mean cell haemoglobin concentration (MCHC)	352 g/L	320-359 g/L
Neutrophils	12.41 × 10^9/L	2.1-7.4 ×10^9/L
Lymphocytes	4.32 × 10^9/L	1.0-3.6 ×10^9/L
Monocytes	1.36 × 10^9/L	0.3-1.0 ×10^9/L
Eosinophils	0.23 × 10^9/L	0.02-0.5 ×10^9/L
Basophils	0.07 × 10^9/L	0.02-0.1 ×10^9/L

TABLE 1: Blood results on admission

Thyroid function remained within the normal range: TSH 3.4 mU/L, free T4 14.3 pmol/L. These results represented an improvement compared with previous tests obtained two months earlier and also several months before the initiation of adalimumab (Table *2*). The patient had previously been over-replaced with levothyroxine, with a TSH of 0.03 mU/L and free T4 of 25.3 pmol/L. Consequently, her GP had reduced the levothyroxine dose from 150 µg to 100 µg daily approximately two months before admission, preceding the onset of her acute symptoms. This dose adjustment may have contributed to the absence of biochemical thyrotoxicosis at presentation. Anti-thyroid peroxidase antibodies were significantly elevated at 600 IU/mL.

Time point	TSH (0.27-4.5 mU/L)	FT4 (11-23 pmol/L)
Before starting adalimumab	0.15	23.8
Two months after starting adalimumab	0.03	25.3
During thyroiditis phase	3.4	14.3
Six months after stopping adalimumab	3.7	18.6

TABLE 2: Thyroid function tests before, during, and after adalimumab.

TSH: thyroid-stimulating hormone, FT4: free T4

Radiological investigations

CT head showed no acute intracranial abnormality.

Ultrasound examination of the neck demonstrated diffuse thyroid enlargement with heterogeneous hypoechoic parenchymal echotexture, multiple hypoechoic micronodules, and increased vascularity. The thyroid isthmus measured 8.6 mm, while the right and left lobes measured 32 × 33 × 69 mm and 28 × 32 × 60 mm, respectively, as demonstrated in Figure *1*. Several small reactive cervical lymph nodes were also identified. This appearance was consistent with underlying autoimmune thyroid disease with superimposed thyroid inflammation, as suggested by the increased vascularity and reactive cervical lymph nodes.

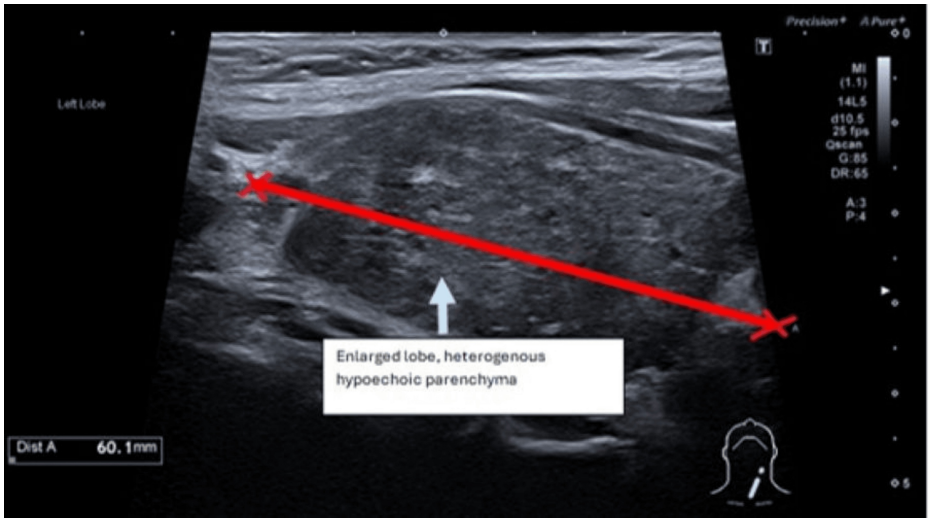


FIGURE 1: Transverse ultrasound image of the thyroid.

Thyroid ultrasound demonstrating diffuse thyroid enlargement with heterogeneous hypoechoic parenchymal echotexture, hypoechoic micronodules and increased vascularity, with bilateral small reactive cervical lymph nodes.

Contrast-enhanced CT of the neck demonstrated uniform diffuse enlargement of the thyroid gland with associated cervical lymphadenopathy. In the context of persistent fever, painful thyroid enlargement, and markedly elevated inflammatory markers, the radiological findings favoured acute thyroiditis.

CT of the chest, abdomen and pelvis showed no alternative source of infection or evidence of malignancy.

CT intracranial angiography and venography were normal. MRI of the brain demonstrated no acute intracranial abnormality. A partially empty sella was noted with no other features suggestive of idiopathic intracranial hypertension.

Thyroid scintigraphy was not performed.

Differential diagnosis

Bacterial and viral meningitis, as well as adalimumab-induced aseptic meningitis, were considered but excluded by normal cerebrospinal fluid analysis. Screening for infectious mononucleosis was negative. Other intracranial causes of headache were considered unlikely given the normal neuroimaging.

A flare of Hashimoto's thyroiditis (autoimmune thyroiditis) was considered in view of the elevated anti-TPO antibody titre and Ultrasound scan findings. However, marked systemic inflammatory response and absence of clinical and biochemical Hypothyroidism made this less likely. Her thyroid function had indeed normalised compared with her previous results, when she appears to have been over-replaced with levothyroxine. This was likely related to the GP reducing her levothyroxine dose from 150 to 100 micrograms daily.

She was also receiving methotrexate. We found no convincing previously published evidence for methotrexate causing subacute thyroiditis, apart from reports of thyroid involvement in methotrexate-associated Lymphoproliferative disorder.

Viral subacute (de Quervain) thyroiditis was also considered in the differential diagnosis. However, the absence of biochemical thyrotoxicosis and the presence of increased vascularity on ultrasonography are not typical features of viral subacute thyroiditis. Although screening for selected viral infections was negative, these results do not exclude all possible viral triggers. Indeed, a viral trigger has previously been proposed as a possible cause of TNF-α inhibitor-associated thyroiditis, as these agents can modulate immune responses and may increase susceptibility to certain infections.

The clinical presentation and radiological findings did not support a diagnosis of thyroid neoplasia or abscess.

We acknowledge that establishing a definitive cause-and-effect relationship between adalimumab and thyroiditis is challenging, as is the case with previously published reports. A viral trigger or an interaction between TNF-α inhibition and pre-existing autoimmune thyroid disease remains possible, although these explanations were considered less likely in this case. Overall, the association of adalimumab therapy with painful diffuse thyroid enlargement, systemic inflammation, imaging features consistent with thyroiditis, along with rapid response to steroid therapy favoured the diagnosis of adalimumab-associated subacute thyroiditis.

Clinical course and management

Given the acute headache, photophobia, and neck pain associated with markedly elevated inflammatory markers, meningitis was initially suspected, and she was commenced on intravenous ceftriaxone. However, there was no clinical or biochemical improvement with antibiotic therapy. Her headache and neck pain persisted, and her inflammatory markers worsened (CRP 300).

Adalimumab was discontinued because we suspected drug-induced thyroiditis. She was reviewed by the endocrinology team and commenced on corticosteroid therapy for presumed adalimumab-associated thyroiditis.

She was treated with prednisolone 40 mg daily for five days, followed by 20 mg for five days and 10 mg for five days. She showed rapid improvement, with resolution of neck pain and progressive improvement in inflammatory markers and systemic symptoms. Following the initiation of corticosteroid treatment, the CRP level decreased from 300 mg/L to 136 mg/L and subsequently to 34 mg/L. Her headache was slow to resolve, and she was referred to the Outpatient Neurology Clinic for chronic headaches. Her case was discussed at the regional endocrinology multidisciplinary team meeting, where the consensus was that adalimumab-associated thyroiditis was the most likely diagnosis. She was discharged with a plan for her GP to repeat the thyroid function tests and refer her to Endocrinology if required. Her thyroid function tests remained unchanged when repeated after a few months.

The patient was recommenced on adalimumab by the Dermatology team 10 months after discharge. She has remained asymptomatic, with no recurrence of thyroid-related symptoms several months after restarting treatment.

Discussion

Adalimumab-associated subacute thyroiditis is rare, but several cases have been reported. Table *3* summarizes the previously reported cases of subacute thyroiditis associated with adalimumab.

Case	Patient/condition, duration of treatment	Clinical presentation	Thyroid status	Thyroid antibodies	Treatment/outcome
Chiriac et al. [2]	54 F, psoriasis. Adalimumab - several months	Fever, neck pain, tender thyroid	Transient hyperthyroidism to transient hypothyroidism	Anti-TPO normal	Responded to NSAIDs
Senlis et al. [3]	50 F, psoriatic arthritis. Adalimumab - 10 months	Fever, painful goitre	Thyrotoxic phase followed by hypothyroidism	Negative except high anti-thyroglobulin Ab	Improved with steroids
Wei et al. [4]	41 F, psoriasis. Adalimumab - seven months	Fever, neck tenderness	Hyperthyroid	Not available	Improved with steroids
Nakagawa et al. [5]	71 F, psoriatic arthritis. Adalimumab - five days after the first dose	Fever, neck pain, tender thyroid	Thyrotoxic phase followed by hypothyroidism	Negative	Improved with steroids
Jobira et al. [6]	43 F, psoriasis. Adalimumab - three years	Fever, painless goitre	Clinically euthyroid	Negative, high thyroglobulin	No treatment given. Goitre persisted on follow-up.
Kuşkonmaz et al. [7]	42 F, ankylosing spondylitis. Adalimumab -seven years	Fever, neck pain, tender thyroid	Hyperthyroid	Anti-TPO negative	Improved after steroids
Present case	54 F, known hypothyroidism. Adalimumab - four months	Meningitis-like presentation	Euthyroid	Elevated anti-TPO	Good response to steroids

TABLE 3: Reported cases of subacute thyroiditis with adalimumab

TPO: thyroid peroxidase, NSAID: nonsteroidal anti-inflammatory drug

Most reported cases occurred in women. The time to onset of thyroiditis following initiation of adalimumab appears to be highly variable, ranging from a few days to several months or years. Most previously described patients presented with painful thyroid enlargement, fever, and elevated inflammatory markers characteristic of viral/drug-induced subacute thyroiditis. The majority of cases reported mild transient hyperthyroidism during the acute phase. Some cases were followed by a hypothyroid phase. Ultrasound findings of hypoechoic areas and increased thyroid vascularity have also been described in many cases, consistent with the findings in our patient. Antithyroid antibodies were generally not helpful and were negative or nonspecific in many cases. Jobira et al. [6] reported a case of a 43-year-old lady who presented with fever, painless goitre, and normal thyroid function tests three years after treatment with adalimumab. Most patients showed a good response to corticosteroid therapy. Thyroid function subsequently remained stable in most cases, except in Nakagawa et al. [5], in which levothyroxine was started after five months of prednisolone treatment for subclinical hypothyroidism. In the case reported by Chiriac et al. [2], adalimumab was restarted after one year, with no recurrence of thyroid dysfunction.

Two other published cases of thyroid involvement associated with adalimumab are worth mentioning. Kawashima et al. [8] described a 56-year-old man who developed subacute thyroiditis-like symptoms following infliximab treatment for Crohn's disease. The symptoms resolved following discontinuation of Infliximab and corticosteroid therapy but recurred after subsequent treatment with adalimumab. The symptoms again settled with discontinuation of adalimumab and prednisolone therapy. However, the patient's thyroid swelling persisted, and fine-needle aspiration cytology (FNAC) demonstrated amyloid goitre. Van Lieshout et al. [9] described a 70-year-old woman with rheumatoid arthritis who developed significantly elevated thyroid function tests without clinical symptoms after long-term adalimumab treatment. She had elevated thyroid antibodies and increased uptake on thyroid scintigraphy, leading to a final diagnosis of Graves' disease. Thyroid function normalised following treatment with thiamazole and propranolol.

The mechanism by which TNF-α inhibitors induce thyroiditis remains poorly understood. They can increase susceptibility to viral infections, which could potentially trigger subacute thyroiditis. However, viral screening is frequently negative in these cases. TNF-α has an important role in cytokine signalling, T-cell regulation, and maintenance of immune tolerance. Suppression of this pathway may paradoxically alter immune homeostasis, promoting autoantibody formation and loss of self-tolerance in genetically susceptible individuals [10]. This phenomenon has been implicated in several autoimmune complications

associated with biologic therapies [11].

Adalimumab potentially acted as an immunological trigger for an acute inflammatory episode occurring on a background of chronic autoimmune thyroid disease. The absence of biochemical thyrotoxicosis may be attributable to the patient's limited thyroid reserve secondary to underlying Hashimoto's thyroiditis. The recent reduction in levothyroxine dose by the GP may also have contributed.

Conclusions

Drug-associated thyroiditis should be considered in patients receiving adalimumab who develop thyroid enlargement and systemic inflammation, even in the absence of typical symptoms or significant changes in thyroid function tests. This case is particularly unusual because of the patient's pre-existing hypothyroidism, preserved thyroid function, and meningitis-like presentation. Recognizing thyroid inflammation in this setting will facilitate timely diagnosis, appropriate treatment, and symptomatic relief for the patient. Nevertheless, given the marked systemic inflammatory response, other causes should be carefully excluded before attributing the presentation to thyroiditis. Infectious, autoimmune, and structural causes of thyroiditis should be excluded where appropriate before attributing thyroiditis to adalimumab or other TNF-α inhibitors. In this case, pre-existing autoimmune hypothyroidism, changes in levothyroxine dosing, and the patient's history of chronic headaches may have influenced the clinical presentation and complicated the diagnostic assessment. This case highlights the importance of clinicians being aware of the potential for thyroid involvement in patients receiving TNF-α inhibitors, including adalimumab, particularly in those with pre-existing thyroid disease.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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