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Antithyroid arthritis syndrome in a case of post-COVID-19 subacute thyroiditis

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1. Introduction

Albeit primarily a disease of the respiratory tract, the coronavirus infectious disease 2019 (COVID-19) has causal associations with multiple endocrine complications [1]. Specifically, post-COVID-19 thyroid dysfunctions, including thyrotoxicosis or thyroiditis, are increasingly being reported [2–6].

Antithyroid arthritis syndrome (AAS) is an under-recognized entity, which occurs within eight weeks of initiation of antithyroid drugs (either propylthiouracil or carbimazole/methimazole) [7–9]. Clinical spectrum of AAS includes arthralgia, arthritis, myalgia, fever and rash [7–9]. It is an immune-mediated idiosyncratic adverse drug reaction, which resolves following the withdrawal of the offending drug [7–9]. However, the clinical picture may persist for years when misdiagnosed as either connective tissue disorders (CTD) or anti-neutrophil cytoplasmic antibodies (ANCA)-positive vasculitides [7–16].

We herein report a non-comorbid man with additive inflammatory polyarthritis after the inapt introduction of carbimazole to manage post-COVID-19 subacute thyroiditis. After revising clinical history and with relevant tests, a final diagnosis of AAS was established. Cessation of carbimazole prompted the disappearance of symptoms.

2. Case report

A 50-year-old previously healthy Indian male presented with complaints of acute onset progressive intense pain and swelling in his feet, ankles, wrists, thumbs and fingers for one week. He also complained of continuous low-grade fever for the last three days,

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which was not associated with any other systemic symptoms except arthralgia. He had been recently treated for COVID-19. After discharge, he complained of irritability, restlessness, malaise, weakness, heat intolerance, diarrhea, sweating, tremulousness and subtle pain in front of his throat for which he consulted multiple physicians. Finally, he was diagnosed with hyperthyroidism and put on carbimazole (30 mg/day). Over the next two weeks, symptoms gradually abated until recently when he came with crippling polyarthritis and fever. Other personal, family and addiction history were unremarkable.

General physical examination was remarkable for fever (37.9 °C) and tachycardia. Systemic examination suggested asymmetric inflammatory arthritis involving peripheral small, medium and large joints, enthesitis, fasciitis and Achilles' tendinitis (Fig. 1) without the involvement of axial-joints. Joint deformity, malar/discoid rash, photosensitivity, alopecia, Raynaud's phenomenon, uveitis, mucosal ulcerations, keratoderma blenorrhagicum, vasculitic rashes, lymphadenopathy, goiter, exophthalmos, weight loss, balanitis, urethritis and organomegaly were absent.

Keeping post-COVID-19 triggering of CTD associated with dysthyroidism as a working diagnosis, he was put on acetaminophen (2.5 g/day) for analgesia. Blood analysis revealed elevated total leukocyte count (13,000/cm^3), c-reactive protein (36 mg/L) and erythrocyte sedimentation rate (52 mm/hr), and normal hepatic and renal function; urinalysis was otherwise normal. Thyroid function tests revealed hypothyroidism, for which carbimazole was stopped. Rheumatoid factor, anti-cyclic citrullinated peptide, antinuclear antibodies profile, angiotensin-converting enzyme (ACE), HLA-B5, HLA-B27 and serologies for hepatitis B, hepatitis C and human immunodeficiency virus were negative. Serum uric acid and ferritin levels were normal as well as relevant tests for other infection-mediated arthropathies. Synovial fluid analysis refuted infective and crystal-deposition arthropathies. Anti-thyroid peroxidase antibody was mildly positive. Doppler study of vessels of lower limbs was normal. However, a previous ultrasound of the thyroid had hypoechoic heterogeneity and indistinct margins with an absolute lack of internal vascular flow before prescribing carbimazole for hyperthyroidism. Subsequent imaging showed that vascular flow tended to improve in those affected areas. Based on the clinical course of illness and results of investigations, a list of differential diagnoses was considered (Table 1).

After a two-week-follow-up, his symptoms substantially reduced. He was put on levothyroxine supplementation (37.5 mcg/day) for correction of hypothyroidism. In the sixth week of follow-up, he had no residual symptoms and levothyroxine requirement was reduced (12.5 mcg/day). Subsequently, in the tenth week of follow-up, levothyroxine was stopped. At the 18th week of follow-up, a drug-free euthyroid state (recovery phase of subacute thyroiditis) was established. Fig. 2 summarizes the timeline of events.

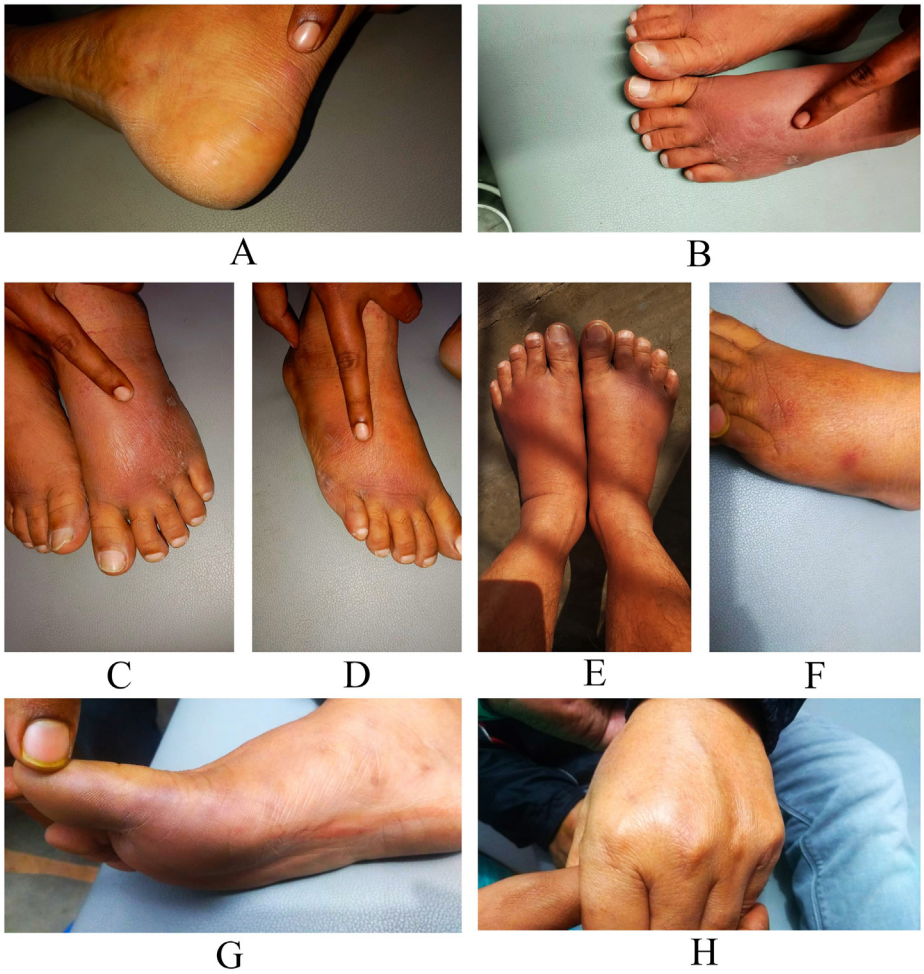

Fig. 1. Inspection of joints and periarticular structures revealed signs of inflammation involving the right Achilles tendon insertion (A), tarso-metatarsal, mid-tarsal and metatarsophalangeal joints of left foot (B, C,E, F) and metatarsophalangeal joints of right foot (D,E,G) and metacarpophalangeal joints of left hand (H).

Table 1
Differential diagnoses based on clinical and laboratory features.

Differential diagnoses	Odds
Rheumatoid arthritis (triggered by SARS-CoV-2 infection itself or related hypercytokinemia)	➢ Anti-cyclic citrullinated polypeptide-antibody and rheumatoid factors were negative ➢Florid enthesitis and tendinitis from the beginning of illness ➢Proximal inter-phalangeal joints were spared ➢Short duration ➢Recovery without disease modifying anti rheumatoid drugs and steroids
Post-COVID-19 reactive arthritis	➢Though he had a history of diarrhea in the post-hospital-stay period it was evidently that it was due to excess thyroid hormones ➢No history of urethritis-like illness ➢No mouth ulcers, uveitis, conjunctivitis, circinate balanitis, keratoderma blennorrhagicum, erythema nodosum, pyoderma gangrenosum, apthous ulceration, psoriatic plaques, and psoriatic nail changes, ➢Negative urine, stool samples for Chlamydia trachomatis ➢Negative HLA-B27 ➢No evidence of sacroilitis or other axial joint involvement ➢Improvement with stoppage of anti-thyroid drug
Systemic lupus erythematosus (SARS-CoV-2 triggered or drug induced)	➢No other clinical features suggestive of systemic lupus erythematosus or drug induced lupus except arthritis ➢Negative tests for, anti-nuclear antibodies, anti-histone antibodies, anti-ssDNA antibodies and other anti-bodies detected in systemic lupus erythematosus or drug-induced lupus
Post-viral (non-COVID-19) arthritis	➢Tests for dengue, mumps, chikungunya, parvovirus B19, rubella, adenovirus, coxackievirus, Epstein Barr virus and cytomegalovirus were negative
Vasculitis (virus associated or drug associated)	➢No characteristic vasculitic rash ➢Anti-neutrophil cytoplasmic antibodies negativity ➢Improvement without immunomodulatory therapy
Bechet's disease (triggered by COVID-19)	➢No oro-genital ulcerations ➢No eye lesions ➢Negative pathergy test and HLA-B5
Primary Sjogren's syndrome triggered by SARS-CoV-2 infection	➢Absence of dryness of mouth and eyes ➢Anti-SSA/B antibodies tested negative ➢Sjögren's International Collaborative Clinical Alliance ocular staining score and Schirmer's test were negative
Adult onset Still's disease	➢No rash, sore throat, high-grade fever, lymphadenopathy or splenomegaly, ➢Normal liver function tests and ferritin ➢Improvement with stoppage of carbimazole
Palindromic rheumatism	➢No similar previous episode
Remitting seronegative symmetrical synovitis with pitting edema	➢No similar previous episode ➢Asymmetric pattern of involvement ➢Large joints are affected in this case (not only small joints) ➢Steroid therapy was not required
Carcinomatous polyarthritis	➢No cancer was found
Infective endocarditis	➢No high-grade fever ➢Normal cardiac examinations
Polyarticular gout and calcium pyrophosphate dihydrate deposition disease	➢Usually seen in late stages of an established disease ➢Synovial fluid analysis was negative for crystals ➢No past history of classic monoarticular illness
Acute sarcoid arthritis	➢Normal angiotensin converting enzyme levels ➢No other stigmata of sarcoidosis such as lupus pernio, bilateral hilar lymphadenopathy, erythema nodosum or neurological deficits.

3. Discussion

The entire hypothalamo-pituitary-thyroid axis and the thyroid gland, in particular, may be affected by the SARS-CoV-2 via ACE-2 receptor and TMPRSS2 mediated entry to thyrocytes, resulting in subacute thyroiditis, thyrotoxicosis, hypothyroidism and sick-euthyroid syndromes [1–6,17].

In our patient, it was difficult to say whether it was a case of 'true' post-COVID-19 thyrotoxicosis or a case of 'thyrotoxic phase' of post-COVID-19 subacute thyroiditis, because of unavailability of the ^{99m}Tc pertechnetate scan. However, the natural history of the illness pointed towards the diagnosis of post-SARS-CoV-2 subacute thyroiditis, which had been initially misdiagnosed as post-COVID-19 hyperthyroidism. Our case is the first one of AAS following mismanagement of subacute thyroiditis following SARS-CoV-2 infection.

AAS, an adverse idiosyncratic drug reaction, has remained an underappreciated clinical entity [7–9]. This syndrome has a female preponderance and is characterized by inflammatory arthritis that may range from apparently benign-looking arthralgia to persistent continuously progressive incapacitating inflammatory polyarthritis mimicking CTD and vasculitides [9]. AAS generally subsides with the withdrawal of offending drug within a few weeks [9], but there are instances where clinical picture persisted for years or even decades [18,19]. Exact pathogenesis and specific therapy remain unknown but plausible hypotheses are disturbed glutathione metabolism and release of inflammatory cytokines, triggering of abnormal immune function by inhibiting DNA synthesis and immunogenic hapten production [8].

Post-COVID-19 transient hyperthyroidism/thyrotoxicosis and post-COVID-19 "thyrotoxic phase" of subacute thyroiditis can evoke diagnostic-dilemma. "Masterly inactivity", here, could avoid mistakes. Physicians who prescribe anti-thyroid medications should recognize new-onset distressing polyarthritis as a possible adverse reaction to these drugs. The drug should be withdrawn swiftly during follow-up if such a complaint arises. Finally, our report highlights the importance of differentiating between thyroiditis and thyrotoxicosis in patients with a suppressed thyroid-stimulating hormone and a raised T4. A radionuclide thyroid scan is of great importance in differentiating between these two conditions.

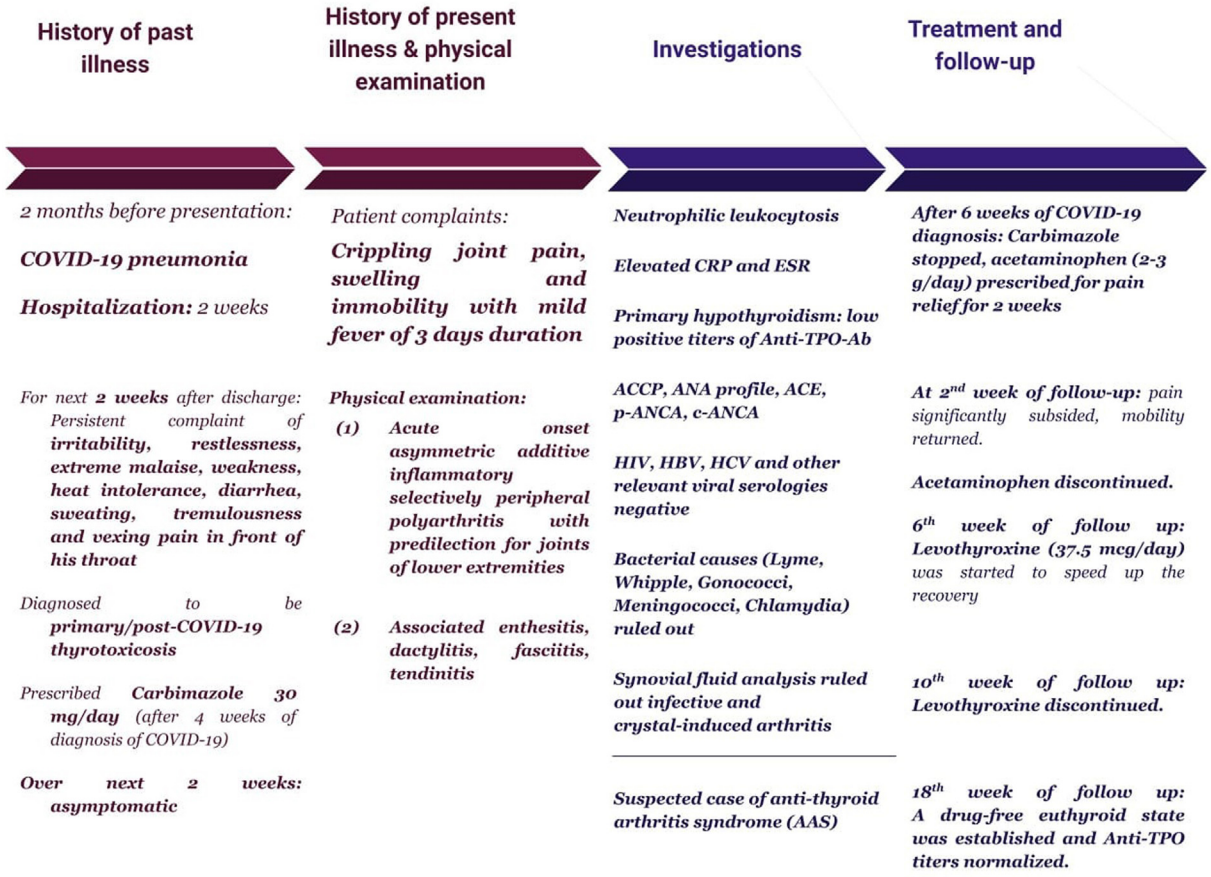

Fig. 2. A schematic flow of the timeline of events in this case. Footnote of the figure: Angiotensin-converting enzyme (ACE); anti-cyclic citrullinated peptide (ACCP); anti-neutrophil cytoplasmic antibodies (ANCA); anti-nuclear antibodies (ANA); anti-thyroid peroxidase antibody (anti-TPO-Ab); c-reactive protein (CRP); erythrocyte sedimentation rate (ESR); hepatitis B (HBV); hepatitis C (HCV); human immunodeficiency virus (HIV).

Author contributions

All authors contributed significantly to the creation of this manuscript; each fulfilled criteria as established by the ICMJE.

Declaration of competing interestCOI

The authors declare that they have no conflict of interest.

References

[1] Chatterjee S, Ghosh R, Biswas P, et al. COVID-19: the endocrine opportunity in a pandemic. Minerva Endocrinol 2020;45:204–27.
[2] Rotondi M, Coperchini F, Ricci G, 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 2020:1–6.
[3] Ruggeri RM, Campennì A, Siracusa M, Frazzetto G, Gullo D. Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic. Hormones (Basel) 2020:1–3.
[4] Mattar SAM, Koh SJQ, Rama Chandran S, Cherng BPZ. Subacute thyroiditis associated with COVID-19. BMJ Case Rep 2020;13.
[5] Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. Rev Endocr Metab Disord 2020:1–13.
[6] Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G. Thyrotoxicosis in patients with COVID-19: the THYRCOV study. Eur J Endocrinol 2020;183:381–7.
[7] Helfgott SM, Smith RN. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 21-2002. A 21-year-old man with arthritis during treatment for hyperthyroidism. N Engl J Med 2002;347:122–30.
[8] Modi A, Amin H, Morgan F. Antithyroid arthritis syndrome. BMJ Case Rep 2017;2017.
[9] Takaya K, Kimura N, Hiyoshi T. Antithyroid arthritis syndrome: a case report and review of the literature. Intern Med 2016;55:3627–33.
[10] Chen M, Gao Y, Guo XH, Zhao MH. Propylthiouracil-induced antineutrophil cytoplasmic antibody-associated vasculitis. Nat Rev Nephrol 2012;8:476–83.
[11] Cooper DS. Antithyroid drugs. N Engl J Med 2005;352:905–17.
[12] Cao X, Lin W. Clinical study of renal impairment in patients with propylthiouracil-induced small-vessel vasculitis and patients with primary ANCA-associated small-vessel vasculitis. Exp Ther Med 2013;5:1619–22.
[13] Aloush V, Litinsky I, Caspi D, Elkayam O. Propylthiouracil-induced autoimmune syndromes: two distinct clinical presentations with different course and management. Semin Arthritis Rheum 2006;36:4–9.
[14] Taguchi T, Nakayama S, Fujimoto S, Terada Y. Lupus nephritis with positive myeloperoxidase/proteinase 3-antineutrophil cytoplasmic autoantibody that developed after 17 years of propylthiouracil therapy. Endocrine 2014;46:357–9.
[15] Haq I, Sosin MD, Wharton S, Gupta A. Carbimazole-induced lupus. BMJ Case Rep 2013;2013.
[16] Wang LC, Tsai WY, Yang YH, Chiang BL. Methimazole-induced lupus erythematosus: a case report. J Microbiol Immunol Infect 2003;36:278–81.
[17] Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 2020;9:45.
[18] Gruber CN, Finzel K, Gruber BL. A case of methimazole-induced chronic arthritis masquerading as seronegative rheumatoid arthritis. J Clin Rheumatol 2014;20:229–32.
[19] Tosun M, Güler M, Erem C, Uslu T, Miskioglu E. Intermittent polyarthritis due to propylthiouracil. Clin Rheumatol 1995;14:574–5.