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Original Article

COVID-19 and Thyroid Illness

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Abstract

Objective: We present a case series of three cases of thyroid dysfunction such as Hashimoto thyroiditis, Graves' disease and sub acute thyroiditis presenting in few weeks after resolution of acute phase of COVID -19 infection in patients with no prior thyroid disease. Physicians should be acquainted with possible relationship of COVID-19 and thyroid dysfunction.

Methods: We discuss clinical manifestation, diagnostic evaluation and ensuing management and follow-up in each patient having thyroid dysfunction after getting positive for covid-19.

Conclusion: The temporal relationship highlights the association of different forms of thyroid dysfunction with COVID-19 calling for further research to clarify the connections and answers to many questions.

Keywords: COVID-19, thyroid dysfunction, various non-thyroidal illness syndrome, subacute thyroiditis, Graves' disease, hashimoto thyroiditis

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Introduction

COVID-19, caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus, was first reported in Wuhan,China and later declared as a pandemic.[1] It invades the body via upper respiratory mucous membrane mainly affecting the lungs. COVID-19 has varied presentation ranging from mild to moderate disease with fever, cough, myalgias, fatigue or severe viral pneumonia leading to ARDS and respiratory failure requiring mechanical ventilation. Along with that some patients experience serious extra-pulmonary manifestations like sepsis, myocarditis, and acute kidney injury leading to multi-organ dysfunction.[2] Evidence of involvement of hypothalamic-pituitary-thyroid axis because of inflammatory response by COVID-19 is also there.[3,4] However, endocrinological manifestations of COVID-19 are yet to be explored and identified. The receptor-binding domain of SARS-COV2 operates on angiotensin-converting enzyme 2 (ACE2) as a receptor. A number of endocrine organs like pancreas, thyroid, testis, ovary, adrenal glands, and pituitary exhibit ACE2 receptors[5] providing grounds of endocrinological system involvement in patients with SARS-COV-2.

Presence of a thyroid disease like hypothyroidism or hypothyroidism doesn't increase the risk of contracting COVID-19 or developing complications. Neither thyroxine nor antithyroid drugs impart any risk of contracting COVID-19 for not being immunomodulators. The virus is confined to the blood vessels passing through thyroid gland with no direct effect on thyroid gland by the virus itself but there are chances of indirect effects of the cytokine storm by COVID 19.[6] Though it is hard to differentiate thyroid illness from non thyroidal illness syndrome in acute phase of COVID-19 caused by indirect effect of systemic inflammatory response but post-viral thyroiditis like any other viral illness is possible. Little is known about the comprehensive sequel of COVID-19 in parallel with autoimmune endocrine disorders, though it is being reported at a high rate.[7-9] A handful of interrelations have been described between COVID-19 and inflammatory diseases e.g; subacute thyroiditis, Guillain-Barre syndrome, graves' disease, hashimoto thyroidits, multisystem inflammatory syndrome along with surfacing reports of autoimmune thyroid disease. In this case series, we describe patients who had autoimmune thyroid disease, Hashimoto thyroiditis, Graves' disease, along with subacute thyroiditis few weeks after clearance of acute phase of COVID-19 infection having no prior thyroid disease.

Case Series

Case Report 1: Graves' disease and hyperthyroidism

A 49 years old Hypertensive , non-smoker Healthcare worker Presented with Progressive, continuous fever and severe myalgias beside loss of taste and smell for 15 days, with no obvious focus of fever (like sore throat, cough, diarrhoea, burning micturation). Intensity of fever responded to intra-venous antibiotics, antipyeretics and muscle relaxant for few days. However a week later, he again started having Fever, followed by Shortness of breath which was Gradual in onset, Progressed from grade 1 to grade 3, associated with bouts of dry cough, interfering with daily life activities with No specific aggravating or relieving factor. Previous medical record was unremarkable for productive cough, dysnea, seasonal variation, atopy , chest pain, wheezing, orthopnea, Paroxysmal nocturnal dysnea and haemoptysis. At that time His CXR and HRCT revealed COVID-19 pneumonia while rt-PCR for COVID-19 was negative and a repeat sample the other day turned to be positive.

Symptoms improved for almost 2 weeks. After that he again started complaining of dysnea and easy fatigability limiting his daily activities. He also complained of palpitations and marked weight loss of around 7kg this time despite not being anorexic. No history of joint pains, ankle swelling, and eyelid swelling or frothy urine was there. There was no history of tremors, diaphoresis, hot or cold intolerance, diarrhea and irritability.

General physical Examination of this dysneic man revealed a small 2*3 cm sized lymph node in right anterior triangle of neck, and no other lymph nodes were palpable in the neck or other parts of body. Thyroid wasn't tender or enlarged .Rest of the general and systemic examination was unremarkable.

His Labs revealed a normal CBC with an ESR of 100 mm/1st hr initially and on other day it was 74mm/1st hr. CRP level were of 67mg/dl. Baseline LFT's, RFT's, LDH, D-dimers were normal. T-spot test was negative too. Ultrasound neck revealed a nodule in left lobe of thyroid which turned out to be a HOT NODULE on thyroid scan. Thyroid function tests showed serum TSH <0.05 mIU/L(range 0.30-5.0) Free T4 19 pmol/L (range 11.5-23.0), total T3 216 ng/dl (range 76–181), serum anti-thyroglobulin antiboies (TGAb) >1000 IU/ml (normal value <4) , serum anti-thyroid peroxidase antibodies (anti-TPO) <3IU/ ml (normal <4). An electrocardiogram (ECG) showed sinus tachycardia. Patient was started on propranolol, steroids and carbimazole 30 mg with clinical improvement within few days. propranolol and steroids were discontinued shortly and a follow up Thyroid function tests at 45 weeks revealed a normal report with values of TSH 4.65 mIU/L (normal range 0.30-5.0) Free T4 11.8 pmol/L (normal range 11.5-23.0).

Case Report 2: Sub-Acute Thyroiditis:

A 56-year-old retired male who is known case of ischemic heart disease and hypertension developed low grade fever, headache, fatigue, loss of appetite along with mild dysnea and was diagnosed with COVID-19. He recovered at home over a period of 3 weeks with off n on low flow oxygen therapy and steroids for 2 weeks.

Six week later he again developed low grade fever with severe myalgias and insomnia. He experienced anterior neck discomfort along with difficulty in swallowing too. He did endorse pressure like symptoms over the anterior part of the neck which was tender on examination too. Laboratory evaluation revealed serum TSH 0.008 mIU/L, free T4 1.9 ng/dL and positive thyroid peroxidase antibodies 54 IU/mL (normal value less than 9). His thyroid scan revealed an abnormal 24-hr thyroid radioiodine uptake, congruent with the diagnosis of thyroiditis. Four weeks later, he developed signs and symptoms of hypothyroidism having a serum TSH value of 41.0 mIU/L, hence given thyroid hormone supplementation with levothyroxine. Six weeks later he started developing symptoms of hyperthyroidism because of levothyroxine which was gradually withdrawn and patient regained euthyroid status.

Case Report 3: Hashimoto Thyroiditis and Hypothyroidism

A 36-year-old lady who was a school teacher developed fever, sore throat dry cough with loss of smell and taste, diarrhea and lack of appetite. She was tested positive for COVID-19 via RT-PCR along with three other family members. Her symptoms improved with stmptomatic supportive care at home over three weeks and she joined her school after complete recovery. four weeks later she started having dysnea, generalized malaise, fatigue and hair loss along with anterior neck discomfort and noticed some swelling in front of the neck. She was unable to beat that fatigue with rest or any kind of pain killers.

Labs revealed serum TSH value of 73 mIU/L (normal range 0.34–5.6), free T4 level 0.3 ng/dL (normal range 0.93–1.7), anti-thyroid peroxidase antibody level >1000 IU/mL (normal value less than 9) and anti-thyroglobulin antibodies level >600 IU/ml (normal value less than 1). Thyroid ultrasound was significant for thyromegaly along with heterogensity. Granulomatous inflammation without clear lymphocytic infiltration was obtained on fine needle aspiration biopsy of the gland. She was started on thyroid hormone replacement therapy along with steroids. Her symptoms of malaise n fatigue improved over the course of two weeks along with painful thyroid swelling.

Discussion

SARS-COV-2 AND THYROID GLAND

The interaction between covid-19 and thyroid gland

tissue is multiplex and bidirectional. Approximately 15% of patients with mild to moderate intensity illness and 10% of the severe cases of COVID-19 were found to have thyroid dysfunction. The spike proteins over the corona virus bind to angiotensin-converting enzyme receptors-2 (ACE2) which is variably present in human organs, maximum number being in the small intestine, followed by the testis, heart, thyroid, kidney, adipose tissue, and lungs, rendering them vulnerable to infection.[10] This extensive expression of the ACE2 receptor may explain the diverse spectrum of involvement of different organs in patients with COVID-19.

Though present in endocrine organs including parathyroid, pituitary, pancreas and adrenal gland however SARS-CoV-2 presence was not established in the thyroid, testis, ovary and uterus.[11] Different studies showed involvement of thyroid follicular and Para-follicular epithelium. But SARS-COV-2 wasn't found in thyroid gland by tissue immune-histochemistry or PCR.[12,13] Direct molecular analysis of thyroid tissue revealed that ACE-2 receptor mRNA is expressed in thyroid follicular cells, making them susceptible to SARS-COV-2 invasion.[14]

Even slight increase in thyroid hormone in patients with COVID-19 is linked with an increased mortality because of above mentioned mechanism[15]. Keeping in view this pandemic of COVID-19, it is pertinent for clinicians to conserve a high index of suspicion for thyroid illnesses like sick euthyroid, hypothyroidism, autoimmune thyroiditis and especially thyroid storm in toxic-appearing patient, signs and symptoms of which overlap with covid-19 illness.[16,17] For this reason, routine thyroid function testing in all critically ill covid-19 patients should be recommended.[18]

COVID-19 cases have presented with various forms of thyroid illnesses, including hypothyroidism, thyrotoxicosis, nonthyroidal illness syndrome,[9] autoimmune thyroiditis and subacute thyroiditis.[19] Thyrotoxicosis observed during the initial phase of subacute thyroiditis and Graves' disease can be caused by COVID-19 as well.[19,20] Only a few cases of thyroid storm have been reported with covid -19.

COVID-19 and thyroid dysfunction including non-thyroidal illness syndrome (NTIS):

Different studies supports the evidence of thyroid dysfunction as a non-thyroidal illness syndrome (NTIS) in patients with COVID-19 admitted in an intensive care unit. Cytokines released in cytokine release syndrome of covid-19 are thought to be the main culprit because of their numerous effects on the hypothalamic-pituitary-thyroid (HPT) axis and thyroid hormone-binding proteins.[21] Studies revealed an association of high interleukin-6 levels with thyrotoxicosis.[22] Data also supported the evidence of NTIS as the most often observed alteration in thyroid diseases. There was an association between the low TSH and T3 levels with severity of the disease. While T4 levels remained stable and unchanged in most of the patients[23].

Hashimoto thyroiditis is common thyroid disorder in which both humoral and cell-mediated autoimmunity is involved. Prence of antithyroid antibodies such as anti-thyroid peroxidase (anti- TPO and anti-thyroglobulin antibodies (anti-Tg)in serum of most patients confirms the diagnosis.

Graves' disease(GD) is an autoimmune disorder, hallmark of which is the presence of thyroid stimulating immunoglobulins (TSI) resulting in thyroxine overproduction leading to hyperthyroidism or overactive thyroid. Evidence from reported cases of hyperthyroidism with COVID-19 infection suggested that a destructive viral thyroiditis contributed to clinical presentation of subacute thyroiditis, with prompt recovery with steroids (prednisone) and resolution of biochemical abnormalities (TSH normalization).[24] Our case report of new onset Graves' disease soon after resolution of COVID-19 infection in a healthcare worker with significant exposure to COVID-19 during the peak of the coronavirus pandemic in April joins few other case reports published so far[25]. Treatment of critically ill COVID-19 patients with steroids may provide a mortality benefit and is also recommended in the treatment of thyroid storm.

Subacute thyroiditis (SAT) is a self-limited inflammatory thyroid disease of viral or post-viral origin. Also known as de Quervain thyroiditis,it occurs most often in middle aged women and is characterized by a three-stage clinical course of thyrotoxicosis, hypothyroidism then euthyroid status within three months . SAT presents with neck pain typically with radiation to jaw and ears because of swollen and inflamed thyroid gland and a wide spectrum of systemic symptoms like fever, asthenia, difficulty swallowing, hoarseness of voice and malaise. Clinic features of SAT and COVID-19 may overlap in many aspects. High circulating levels of C-reactive protein (CRP), and, more specifically, erythrocyte sedimentation rate (ESR) represent the most predominant biochemical finding at presentation.[26]

Conclusion

Infection with SARS-CoV-2 has been linked with different organ systems along with thyroid. Not much evidence is there regarding pathology of thyroid illness with COVID-19 infection. patients with uncontrolled thyroid disease e.g. thyrotoxicosis may be at a higher risk of complications like thyroid storm from any infection like COVID-19 but there is a lack of much data about the prevalence and determinants of thyrotoxicosis with COVID-19 in patients without prior thyroid disorder. Clinicians should consider performing thyroid

function testing in critically ill patients admitted with COVID-19. Our case of hyperthyroidism and concomitant COVID-19 infection suggests that SARS-CoV2 infection may be a trigger for the patient´s thyrotoxic crisis.

More studies are needed to determine the pathological role played by COVID-19 in causing thyroid dysfunction. Usually Thyroid function test is not routinely performed in context of COVID-19 infection. Though the SARS-CoV-2 virus itself is novel but the approach to this virus in reference to thyroid is likely the same as with any other virus. Sound clinical acumen should form the basis of testing and treatment. More data is required to form the basis of some recommendations to be made for early diagnosis and management of thyroid illness caused by COVID-19.

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