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Post-COVID Subacute Thyroiditis and Bronchiolitis in a Lung Transplant Recipient: A Case Report

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ABSTRACT

Lung transplant recipients are at risk for life-threatening infections including severe acute respiratory syndrome coronavirus 2-associated COVID-19. Several viral infections have been associated with the development of chronic lung allograft dysfunction. Long-term outcomes of COVID-19 on graft function are not known.

A 53-year-old female patient, who underwent bilateral lung transplantation 3 years before because of stage IV sarcoidosis and secondary pulmonary hypertension was admitted in the second wave of the pandemic because of COVID-19 with symptoms including dry cough. Chest computed tomography showed ground glass opacities affecting 25\% to 50\% of the lung parenchyma. She was admitted to the COVID-19 Unit of our clinic. She received oxygen via nasal cannula, remdesivir, and low-dose methylprednisolone while mycofenolate acid administration was stopped. Her clinical condition improved. The first follow-up visit 1 month after the infection demonstrated deterioration in lung function. Computed tomography scan showed almost complete resolution; transbronchial biopsy was performed and proved acute allograft rejection. During the hospitalization a new onset atrial fibrillation was confirmed. In the background of atrial fibrillation and simultaneous neck pain, severe hyperthyroidism was proven. Because of thyroiditis and lung allograft rejection, high-dose steroid treatment was initiated and everolimus was added to the immunosuppressive therapy. Donor specific antibodies were also detected, hence plasmapheresis was indicated and continued with photopheresis. On the follow-up spirometry the values were stable; however, they did not reach pre-COVID levels.

In lung transplant recipients COVID-19 might trigger allograft rejection in addition to virus-related thyroid disease.

COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is one of the most important health challenges of our time [1]. The SARS-CoV-2 RNA virus epidemic has so far (January 2022) infected 298 million people worldwide and the disease has claimed a total of more than 5.5 million deaths [2]. The infection can often be accompanied by mild influenza-like symptoms. In more severe cases, COVID-19 pneumonia and systemic inflammatory reaction may occur causing respiratory failure [3]. In addition, COVID-19 may present with cardiac, hematological, gastrointestinal, neurologic, psychiatric, endocrine, or renal complications [4]. Solid organ transplant recipients receiving lifelong combined immunosuppressive therapy are considered high risk for viral infections including SARS-CoV-2 [5,6]. In addition to the direct lung effects of the viral infection, graft dysfunction may develop, which can impair long-term survival and quality of life [7].

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CASE REPORT

A 53-year-old female patient underwent bilateral lung transplant in May 2018 because of end-stage respiratory failure as a result of stage IV sarcoidosis combined with pulmonary hypertension. She received alemtuzumab induction. The donor and the recipient were cytomegalovirus IgG positive. During post-transplant surveillance bronchoscopies transbronchial biopsies showed no signs of rejection. In the first month of the post-transplant period the patient was treated because of *Pseudomonas aeruginosa* pneumonia. Donor specific antigen results were negative throughout. Ten months after transplantation, long-acting beta agonist and inhaled corticosteroid (LABA-ICS) combined inhalation treatment, later leukotriene receptor antagonist (montelukast), was initiated because of decreased small airway parameters; after the first year mycophenolate acid was introduced to tacrolimus and prednisolone immunosuppression. Lymphopenia was observed despite a reduced dose of mycophenolate. In November 2020 a close family member was confirmed with SARS-CoV-2 infection, later our patient also reported dry cough. Antigen rapid test was positive and SARS-CoV-2 was confirmed with real-time polymerase chain reaction (PCR) test. Chest computed tomography showed ground glass opacities affecting 25% to 50% of the lung parenchyma (Fig 1A). Because of the COVID-19 pneumonia, she was admitted to the COVID-19 Unit of our department on November 25, 2020. She received oxygen supplementation via nasal cannula, remdesivir, low dose methylprednisolone, azithromycin, thrombotic and ulcer prophylaxis. Metoclopramid for intermittent nausea and metamizole for fever and headache have been used. During COVID-19 mycophenolate administration was stopped. Her clinical condition improved, oxygen demand ceased, and finally she was discharged on December 10, 2020 after multiple negative real-time PCR and antigen rapid tests, and mycophenolate was restarted.

On the first follow-up visit after COVID-19 (on January 14, 2021) she reported significant fatigue and dry cough. Repeated COVID-19 real-time PCR was negative. Chest computed tomography showed almost complete remission of COVID-19 pneumonia (Fig 1B). However, there was a significant decrease in forced expiratory volume in one second in spirometry. Because of elevated inflammatory markers and decreased spirometry values bronchoscopy was performed and the patient was readmitted to our unit. The histologic findings of the transbronchial biopsy were capillaritis in the area of the alveolar septa, while elsewhere lymphoid cell infiltration showed CD3 positivity without typical perivascular layout. The sample was negative with C4d immunohemistry. From bronchoalveolar lavage (BAL) *Candida albicans* was detected at 10^2/. Bronchoalveolar lavage aspergillus antigen test (Plateia Aspergillus) and serum cytomegalovirus PCR were negative.

During the hospital treatment the patient reported pressing sensation around her neck and palpitation as new symptoms. ECG confirmed novel atrial fibrillation with high ventricular frequency. Metoprolol as a rate-controlling agent and low molecular weight heparin in therapeutic dose as anticoagulation was introduced, and after 24 hours sinus rhythm returned. Additional diagnostic confirmed acute hyperthyroidism with extremely low thyreoglobulin stimulating hormone and elevated antithyroglobulin and thyreoglobulin levels. Based on the ultrasound examination, the thyroid gland was moderately enlarged, echo poor, inhomogeneously structured, and moderately hypervascularized (Fig 2). Thyroid scintigraphy showed low activity, and the diagnosis of subacute thyroiditis was established.

Because of thyroiditis and acute lung allograft rejection high-dose steroid treatment (250 mg of methylprednisolone) was initiated beside antibiotic, antiviral, and antifungal protection. We did not find any sign of infection during this period. As the result of treatment, thyroid function normalized. On March 2021 we initiated mammalian target of rapamycininhibitor everolimus treatment for chronic lung allograft dysfunction. Repeated donor-specific antigen tests detected donor-specific antigens, hence plasmaexchange was indicated and was continued with extracorporal photopheresis. During treatment, donor-specific antigen levels significantly decreased. On regular follow-up visits the patient’s spirometry values were stable but in a lower level (Fig 3). Her quality of life worsened and was associated with a moderate depression episode.
DISCUSSION

Thyroid diseases are less frequently discussed complications of SARS-CoV-2 infection. Based on literature to date the virus enters the thyroid cells via angiotensin-converting enzyme 2 receptor and transmembrane protease serine 2 enzyme [8]. The SARS-CoV-2 virus can also trigger and maintain inflammation of the thyroid gland indirectly through hyperactive T helper 1/T

Fig 2. On ultrasound the thyroid gland was moderately enlarged, echo poor, inhomogeneously structured, and moderately hypervascularized.

Fig 3. Chronology of lung function parameters and treatment modalities since the COVID-19 pneumonia diagnosis.
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helper 17 cell mediated immune responses and cytokine storm. SARS-related thyroid disease can also develop secondary to damage to the cells in the hypothalamus and adenohypophysis.

Other viral infections have also been observed to have complex interactions between hormonal and immunomodulatory signaling molecules. Thyroid hormones also modulate innate and adaptive immune responses. At physiological concentrations, T3 and T4 stimulate the production and release of cytokines, and potentiate the antiviral effect of interferon gamma. On the other hand, in decompensated hyperthyroidism, respiratory viral infections can trigger thyroid storm. COVID-19-associated thyroid diseases may take the form of thyrotoxicosis (subacute thyroiditis, painless thyroiditis, thyroxine thyrotoxicosis, and Graves’ disease), hypothyroidism, or nonthyroidal illness syndrome. Subacute thyroiditis is a self-limited disease caused by viral infection (including adenovirus, orthomyxovirus, Ebstein-Barr virus, and cytomegalovirus) or postviral inflammatory process. The most characteristic symptom is neck pain [8,9], as also observed in our case.

In the background of the worsening condition of the patient and the significantly deteriorating respiratory function values, allograft rejection has been confirmed via histology, and donor-specific antigens could be detected from peripheral blood. Capillaritis and lymphocytic infiltration from histologic specimen taken during transbronchial biopsy confirmed the suspicion. Cause of lung allograft dysfunction may be respiratory viral, bacterial and fungal infections, gastroesophageal reflux, or autoimmunity [10,11]. In this case no persisting infection or condition was found other than previous COVID-19. Multiple episodes of A1 rejection as well as even a single episode are also associated with increased risk of bronchiolitis obliterans syndrome [12].

The high-dose steroid treatment used slowed the worsening of the respiratory function. Later plasmapheresis and extracorporeal photopheresis had to be initiated, which based on control studies was beneficial [13].

Although the World Health Organization’s clinical management guidelines do not include monitoring of thyroid function, as this case shows, it may be particularly important as thyroid diseases can lead to the development of sever clinical conditions [14]. As we often see, SARS-CoV-2 infection can also cause long-term complications, and in susceptible lung transplant recipients this can even be allograft dysfunction.

The key message is: in case of lung transplant recipients SARS-CoV2 infection may cause chronic lung allograft dysfunction, regular spirometry control is necessary. As consequence of COVID-19 thyroid dysfunctions may also develop, we suggest monitoring thyroid function.

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