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How to cite

BONDEELLE, Louise et al. Bronchiolitis obliterans syndrome following SARS-CoV-2 infection in an allogeneic hematopoietic stem cell recipient. In: American journal of transplantation, 2023, vol. 23, n° 6, p. 844–847. doi: 10.1016/j.ajt.2023.03.015

This publication URL: https://archive-ouverte.unige.ch/unige:171543

Publication DOI: 10.1016/j.ajt.2023.03.015

American Journal of Transplantation 23 (2023) 844–847

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Case Report

Bronchiolitis obliterans syndrome following SARS-CoV-2 infection in an allogeneic hematopoietic stem cell recipient

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ARTICLE INFO

Keywords:
COVID-19
lung graft-versus-host disease
obstructive lung disease
late-onset noninfectious pulmonary complication (LONIPC)

ABSTRACT

Peripheral allogeneic hematopoietic stem cell transplant recipients are the most vulnerable patients to community-acquired respiratory viruses such as respiratory syncytial virus, influenza virus, or others. These patients are likely to develop severe acute viral infections; community-acquired respiratory viruses have also been identified as triggers of bronchiolitis obliterans (BO). BO is a manifestation of pulmonary graft-versus-host disease, most often leading to irreversible ventilatory impairment. To date, there are no data on whether Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could be a trigger for BO. Here, we report the first report of a case of bronchiolitis obliterans syndrome following SARS-CoV-2 infection occurring 10 months after allogeneic hematopoietic stem cell transplant with a flare of underlying extra thoracic graft-versus-host disease. This observation provides a new perspective and should be of particular interest to clinicians, suggesting the need for close monitoring of pulmonary function test (PFTs) after SARS-CoV-2 infection. The mechanisms leading to bronchiolitis obliterans syndrome after SARS-CoV-2 infection require further investigation.

Abbreviations: BOS, Bronchiolitis obliterans syndrome; CARV, Community-acquired respiratory viruses; CML, Chronic myeloid leukemia; CNL, Chronic neutrophilic leukemia; COPD, Chronic obstructive pulmonary disease; CRP, C reactive protein; CT, Computed tomography; FEV1/ VC, Forced expiratory volume in 1 second/vital capacity; GVHD, Graft-versus-host disease; HSCT, Hematopoietic stem cell transplant; ICS, Inhaled cortico steroids; LT, Lung transplant; MRC, Modified Medical Research Council; NIH, National Institutes of Health; PFT, Pulmonary function test; SARS CoV 2, Severe acute respiratory syndrome coronavirus 2; TLC, Total lung capacity.

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https://doi.org/10.1016/j.ajt.2023.03.015
Received 31 October 2022; Received in revised form 20 March 2023; Accepted 20 March 2023
Available online 25 March 2023

1. Case

In December 2020, a 69-year-old man with a history of untreated atypical chronic myeloid leukemia or chronic neutrophilic leukemia received an allogeneic hematopoietic stem cell transplant (HSCT) from a matched unrelated donor after reduced intensity conditioning. He received tacrolimus and methotrexate for graft-versus-host disease (GVHD) prevention and was in complete remission after HSCT. IgA and IgG levels were 1.46 g/L and 11.50 g/L, respectively; CD4+ T cell, CD8+ T cell, and B cell counts were 182/μL (410-1590/μL), 47/μL (13-41/μL), and 74/μL (90-660/μL), respectively. In February 2021, he presented with acute gut GVHD stage 1 grade II and was successfully treated with prednisone 1 mg/kg, tacrolimus, and budesonide until June 2021. In July 2021, he presented with oral mild chronic GVHD and was treated with topical steroids until August 2021.

The patient had smoked cigarettes until 2018 and had a pretransplant pulmonary function test (PFT) in which the forced expiratory volume in 1 second (FEV1)/vital capacity ratio was 0.59 with a postbronchodilatator FEV1 of 2360 mL (74% of the predicted value), consistent with asymptomatic and untreated mild chronic obstructive pulmonary disease (COPD). In June 2021, PFTs were performed systematically in the absence of any respiratory or infectious symptoms and showed an FEV1 of 2540 mL (80% of predicted).

In September 2021, he presented with fever, productive cough, dyspnea, and inflammatory syndrome, with a C reactive protein (CRP) value of 100 mg/L, lymphocytes of 2460/mm^3, and neutrophils of 5487/mm^3. He was diagnosed with SARS-CoV-2 infection with a positive polymerase chain reaction. The lung computed tomography (CT) scan (Fig. 1A, B) showed some localized ground-glass opacities in the upper and lower left lobes related to acute SARS-CoV-2 infection but no other lung abnormalities. Notably, his lung CT scan performed prior to HSCT was normal. On clinical examination, the room air saturation was 96%, and auscultation showed some localized crackles. He did not present any signs of acute GVHD or flare of chronic extrathoracic GVHD and was not receiving any systemic immunosuppressive drugs at that time. He was briefly hospitalized with no need for oxygen supply or systemic steroids. He received 1 dose of a specific SARS-CoV-2 antibody cocktail (REGN-COV2, Regeneron). No other specific treatment was administered. He was empirically treated with antibiotics. He had previously been vaccinated with 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (last dose received end of July 2021), and a serology performed at the beginning of September 2021 demonstrated 540 U/mL (positive >0.80 U/mL) of IgG against the SARS-CoV-2 spike protein (EUROIMMUN Anti-SARS-CoV-2 assays).

The patient's respiratory symptoms partially resolved after hospitalization, and approximately 1 month after the viral infection, it progressively worsened, with persistent cough and onset of grade 2 dyspnea according to the modified Modified Medical Research Council (MRC) index.[1] He presented with a grade 1 chronic cutaneous GVHD, according to the National Institutes of Health (NIH) classification,[2] and was treated with topical steroids. PFT showed a severe obstructive ventilatory defect with an FEV1 of 1052 mL (33% of the predicted value) and an FEV1/vital capacity ratio of 0.38, associated with lung distension and a residual volume of 164% of the predicted value (Fig. 2), leading to the diagnosis of bronchiolitis obliterans syndrome (BOS) according to the NIH criteria.[3] Combined inhaled steroids and long-acting bronchodilators were introduced (budesonide and formoterol 200/6 μg twice a day), and treatment with oral corticosteroids was started (1 mg/kg). In December 2021, 3 months after viral infection, while the patient was still complaining of dyspnea, the coronavirus disease 2019 (COVID-19) polymerase chain reaction was negative. PFT performed 5 months after viral infection highlighted worsening of the obstructive ventilatory defect, with a FEV1 of 798 mL (25% of predicted) associated with a residual volume of 191% of the predicted value and a total lung capacity (TLC) of 7040 mL (100% of predicted). The patient also presented with a slight drop in oxygen levels (92%) during the

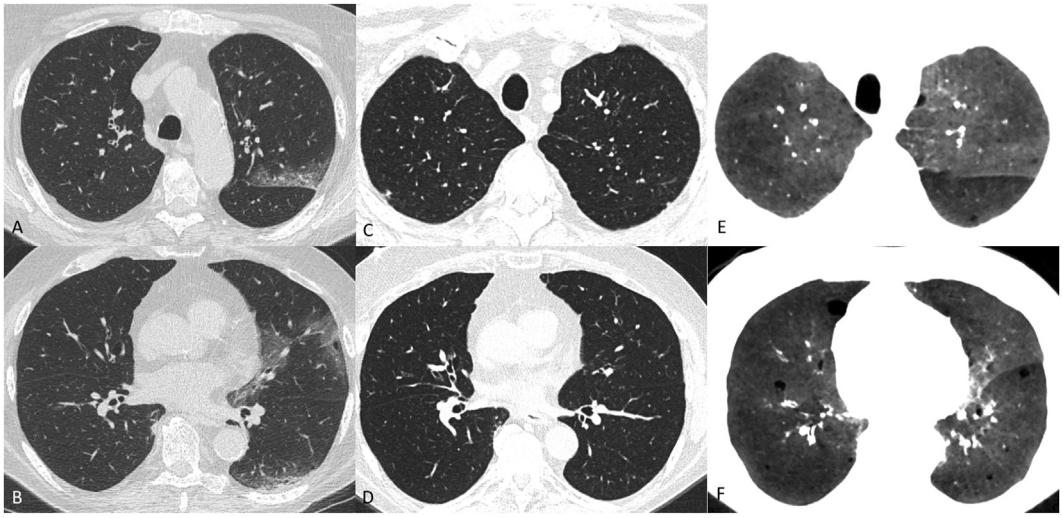

Figure 1. Lung computed tomography (CT) scans of the patient at the time of SARS-CoV-2 infection. (A and B) during SARS-CoV-2 infection and 3 months after COVID-19 (C-F). In A and B, the CT scan shows ground-glass opacities in the upper and lower left lobes, whereas in C and D, the CT scan shows the abnormalities disappeared 3 months later. In E and F, the CT scan shows air trapping using a minimum-intensity projection.

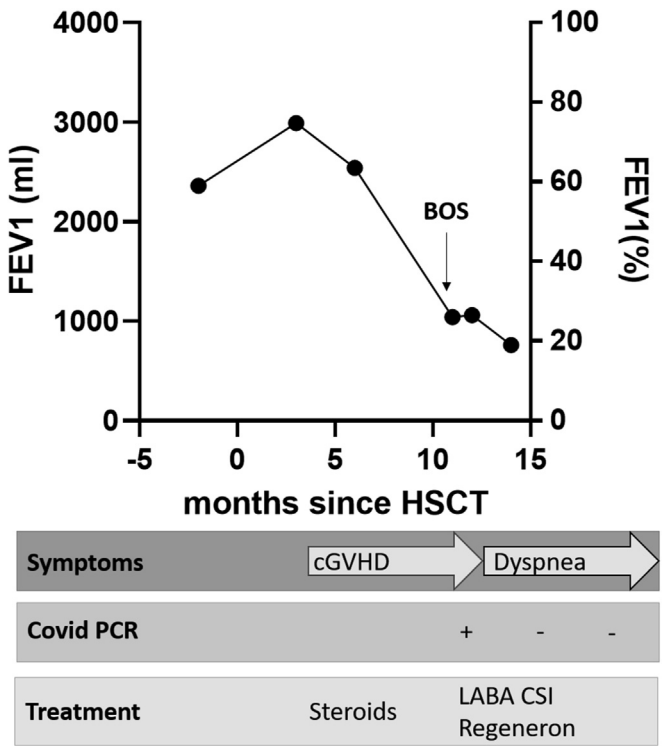

Figure 2. Evolution of forced expiratory volume in 1 second (FEV1) (in ml left Y axis, in % right Y axis) over time. Evolution before allogeneic hematopoietic stem cell transplantation (HSCT), at the moment of SARS-CoV-2 infection (9 months after HSCT) and after infection. Severe decrease of FEV1 illustrating the persistent obstructive ventilatory defect after infection. The clinical course of events cGVHD diagnosis, COVID-19 PCR, treatments, and BOS diagnosis are presented on the bottom of the figure. Forced expiratory volume in 1 second (FEV1), graft-versus-host disease (GVHD), hematopoietic stem cell transplantation (HSCT), Long-Acting Beta-Agonist (LABA), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2.

6-minute walking test, with no need of oxygen. The oxygen level was at 94% at rest and in room air. Three months after COVID-19, a lung CT scan was performed and showed full regression of the ground-glass opacities (Fig. 1C, D). The expiratory cuts showed air trapping, consistent with BOS CT scan criteria (Fig. 1F, G).[3] No other sequelae of COVID-19 were found, including interstitial inflammation and scarring illustrated by parenchymal fibrosis (Fig. 1C, D). At that time, the oral corticosteroids were progressively stopped within a month. At the last follow-up in October 2022, the patient still had exertional dyspnea with dry cough and squeaks on auscultation despite the treatment. PFTs showed a persistent obstructive ventilatory defect, with an FEV1 of 650 mL (21% of predicted) (Fig. 2), consistent with the diagnosis of BOS.

To our knowledge, this is the first report of a case of BOS following SARS-CoV-2 infection occurring 10 months after allogeneic HSCT with a flare of underlying extrathoracic GVHD. BOS is a chronic impairment of lung function that leads to a fixed obstructive ventilatory disorder. BOS is the manifestation of lung chronic GVHD, with a prevalence of 10%.[4] BOS mainly occurs beyond the third month and within the first 2 years following allogeneic HSCT, usually in patients experiencing extrapulmonary GVHD.[5] It has a high association with both mortality and morbidity, even more so when it occurs promptly after HSCT.[6] No curative treatment is currently available.[4] Neither systemic steroids nor immunosuppressive treatments given for BOS were associated with significant improvement in PFT. However, immunosuppressive treatments are associated with increased infectious complications, which are the main cause of death in patients with BOS. Community-acquired respiratory viral infections are considered a risk factor for BOS in HSCT recipients,[7,8] although the mechanisms triggering persistent respiratory dysfunction remain elusive. However, although BOS probably shares some pathophysiological mechanisms with post-viral bronchiolitis, there are major differences. First, postinfectious obliterative bronchiolitis has been described, primarily in children, after adenovirus infection, measles virus infection, or mycoplasma infection.[9] Second, in the setting of HSCT, deep immunosuppression due to conditioning, graft, and immunosuppressive drugs for GVHD prevention delays viral clearance from the respiratory tract. Sustained viral replication,[10] along with alterations in mucociliary clearance and respiratory epithelial innate defenses usually observed in HSCT recipients, might induce a persistent inflammatory state, host microbiota imbalance, and subsequent impairment of respiratory function and lead to chronic bronchial obstruction.

Some scarce studies have shown that the prognosis of HSCT recipients with COVID-19 infection is worse than that of the general population,[11,12] and especially in cases of active GVHD.[13] To our knowledge, no data exist regarding the impact of SARS-CoV-2 on PFT in patients with HSCT. In the overall population, impairment of lung function is mainly related to pulmonary interstitial inflammation and scarring sequelae of COVID-19, leading to a restrictive ventilatory defect on PFT.[14]

In our patient, both the absence of lung parenchymal abnormalities on CT and the restrictive ventilatory patterns on PFT exclude the hypothesis of significant fibrosis secondary to SARS-CoV-2 infection.[15] Conversely, the CT scan found indirect signs of small airway disease. In a retrospective study, 80% of the patients had air trapping on the CT scan between 3 and 6 months after the infection, consistent with the involvement of the small airways.[16] Among these patients, only 20% had an obstructive ventilatory disorder on PFTs, and 35% had a restrictive ventilatory disorder. This suggests a bronchiolar tropism of SARS-CoV-2, corroborating its involvement in the occurrence of BOS. SARS-CoV-2 has been associated with BOS in a lung transplant recipient.[17] This reported case, together with ours, shows that SARS-CoV-2 could be a trigger for BOS following transplantation.

To note, early in the pandemic, it was observed that patients with asthma or COPD were underrepresented among those with COVID-19. Evidence indicates that the inhaled cortico steroids (ICS) routinely taken for asthma and COPD could have had a protective role in preventing severe COVID-19.[18] These data would encourage clinicians not to hesitate to prescribe ICS in cases of BOS occurrence in HSC recipients, even in the current context of the COVID-19 pandemic.

This observation provides a new perspective and should be of particular interest to clinicians, suggesting the need for close monitoring of PFTs after SARS-CoV-2 infection. The mechanisms leading to BOS after SARS-CoV-2 infection require further investigation.

Author contributions

L.B. and A.B. wrote the manuscript. F.G., Y.C., C.T., J.L.G., L.B., and A.B. revised it critically for important intellectual content. All authors approved the final version of the manuscript; moreover, all authors agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the American Journal of Transplantation. Y.C. reported consulting fees from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen, AstraZeneca, and Servier and travel support from MSD, Roche, Gilead, Amgen, Incyte, Abbvie, Janssen, Astra-Zeneca, and Jazz. F.G., C.T., J.L.G., L.B., and A.B. have no conflicts of interest to disclose as described by the American Journal of Transplantation.

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References

1. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest*. 1988;93(3):580–586. https://doi.org/10.1378/chest.93.3.580.
2. Carpenter PA, Kitko CL, Elad S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant*. 2015;21(7):1167–1187. https://doi.org/10.1016/j.bbmt.2015.03.024.
3. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21(3):389–401.e1. https://doi.org/10.1016/j.bbmt.2014.12.001.
4. Bergeron A, Chevret S, de Latour RP, et al. Noninfectious lung complications after allogeneic haematopoietic stem cell transplantation. *Eur Respir J*. 2018;51(5):1702617. https://doi.org/10.1183/13993003.02617-2017.
5. Gazourian L, Rogers AJ, Ibanga R, et al. Factors associated with bronchiolitis obliterans syndrome and chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Am J Hematol*. 2014;89(4):404–409. https://doi.org/10.1002/ajh.23656.
6. Pham J, Rangaswamy J, Avery S, et al. Updated prevalence, predictors and treatment outcomes for bronchiolitis obliterans syndrome after allogeneic stem cell transplantation. *Respir Med*. 2020;177:106286. https://doi.org/10.1016/j.rmed.2020.106286.
7. Erard V, Chien JW, Kim HW, et al. Airflow decline after myeloablative allogeneic hematopoietic cell transplantation: the role of community respiratory viruses. *J Infect Dis*. 2006;193(12):1619–1625. https://doi.org/10.1086/504268.
8. Sheshadri A, Chemaly RF, Alousi AM, et al. Pulmonary impairment after respiratory viral infections is associated with high mortality in allogeneic hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant*. 2019;25(4):800–809. https://doi.org/10.1016/j.bbmt.2018.11.022.
9. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. *N Engl J Med*. 2014;370(19):1820–1828. https://doi.org/10.1056/NEJMra1204664.
10. de Lima CR, Mirandolli TB, Carneiro LC, et al. Prolonged respiratory viral shedding in transplant patients. *Transpl Infect Dis*. 2014;16(1):165–169. https://doi.org/10.1111/tid.12167.
11. Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. *Lancet Haematol*. 2021;8(3):e185–e193. https://doi.org/10.1016/s2352-3026(20)30429-4.
12. Bondeelle L, Chevret S, Cassonnet S, et al. Profiles and outcomes in patients with COVID-19 admitted to wards of a French oncohematological hospital: a clustering approach. *PLOS ONE*. 2021;16(5), e0250569. https://doi.org/10.1371/journal.pone.0250569.
13. Lim YJ, Khan U, Karpha I, et al. COVID-19 outcomes in haematopoietic cell transplant recipients: a systematic review and meta-analysis. *EJHaem*. 2022;3(3):862–872. https://doi.org/10.1002/jha2.465.
14. Laveneziana P, Sesé L, Gille T. Pathophysiology of pulmonary function anomalies in COVID-19 survivors. *Breathe (Sheff)*. 2021;17(3):210065. https://doi.org/10.1183/20734735.0065-2021.
15. McDonald LT. Healing after COVID-19: are survivors at risk for pulmonary fibrosis? *Am J Physiol Lung Cell Mol Physiol*. 2021;320(2):L257–l265. https://doi.org/10.1152/ajplung.00238.2020.
16. Garg A, Nagpal P, Goyal S, Comellas AP. Small Airway Disease as long-term sequela of COVID-19: use of Expiratory CT despite Improvement in Pulmonary Function test. *medRxiv*. 2021. https://doi.org/10.1101/2021.10.19.21265028, 10.19.21265028.
17. Wein AN, Liu J, Lin CY. Evolution of pathological findings in surveillance biopsies of lung transplant recipients infected with SARS-CoV-2. *Transpl Infect Dis*. 2022;24(3), e13823. https://doi.org/10.1111/tid.13823.
18. Bafadhel M, Faner R, Taillé C, et al. Inhaled corticosteroids for the treatment of COVID-19. *Eur Respir Rev*. 2022;31(166). https://doi.org/10.1183/16000617.0099-2022.