Fibrotic Cystic Lung Disease Post Hematopoietic Stem Cell Transplant: Who is the Culprit?

Clinical Medicine Insights: Case Reports
Volume 15: 1–6
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/11795476221097317

Walid Alam[1], Rayan Mohamad[2], Maysoun Koubaissi[3] and Salwa A Koubaissi[2]

[1]Department of Emergency Medicine, American University of Beirut Medical Center, Beirut, Lebanon. [2]Pulmonary and Critical Care Division, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon. [3]Department of Internal Medicine, Lebanese University, Beirut, Lebanon.

ABSTRACT: Pulmonary complications post hematopoietic stem cell transplant (HSCT) are associated with poor outcomes and require extensive management depending on the etiology. They usually present in the form of bronchiolitis obliterans syndrome, interstitial pneumonitis, or drug toxicity that can lead to fibrosis. Scant data exists regarding diffuse cystic lung disease following HSCT, and the existing literature only mentions mild cystic changes. We present the case of a 25-year-old man with stage IVB Hodgkin's lymphoma post allogeneic HSCT, who developed progressive traction bronchiectasis, with the appearance of extensive pulmonary cysts that followed significant fibrotic changes and discuss the possible etiologies behind it.

KEYWORDS: Lung diseases, interstitial, bronchiolitis obliterans, hematopoietic stem cell transplantation, graft versus host disease

RECEIVED: October 28, 2021. **RECEIVED:** April 7, 2022

TYPE: Case Report

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Salwa A Koubaissi, American University of Beirut, Riad El-Solh, Beirut, 1107 2020, Lebanon. Email: sk162@aub.edu.lb

Introduction

Pulmonary cysts are either regular or irregular spherical parenchymal lucencies bordered by a thin wall (usually <2 mm). These cysts are usually filled with air, though they may rarely contain fluid or internal debris. Their etiologies are varied and can range from infectious to noninfectious complications.[1]

Pulmonary complications have been shown to occur post hematopoietic stem cell transplant (HSCT).[2] They are classified into infectious or non-infectious, early or late, and can involve any lung anatomic area including bronchi, parenchyma, vessels, and pleura. Bronchiolitis obliterans syndrome (BOS) remains the most commonly described late and non-infectious complication.[3,4]

In this paper, we present a rare case of diffuse extensive cystic lung disease on a background of progressive pulmonary fibrosis as a late complication of allogeneic HSCT in a patient with a history of Hodgkin's Lymphoma (HL).

To our knowledge, no similar cases have been previously reported in the literature.

Case Description

A 25-year-old gentleman, diagnosed at the age of 16 years in 2012 with stage IVB nodular sclerosing Hodgkin's Lymphoma (HL), was treated with 6 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine, followed by complete remission. He then had recurrence twice, the first time in 2013, for which he received salvage therapy with dexamethasone, high dose cytarabine, and cisplatin, and then in 2014, at the age of 18 years, when he received ifosfamide, carboplatin, and etoposide, followed the same year by autologous HSCT.

In 2017, he started having night sweats, back pain, and weight loss, and his positron emission tomography (PET) scan showed disease recurrence in supra and infradiaphragmatic regions as well as bone marrow lesions without evidence of lung involvement. The patient then received 6 cycles of brentuximab vedotin and bendamustine and underwent his second HSCT in the form of haplo-HSCT (half-matched) from his sister in April 2018, at the age of 22 years, and continued his maintenance on brentuximab.

In July 2018, he started having waxing and waning oral and cutaneous erythematous papules over the torso and extremities, with biopsy of the papules confirming it as cutaneous graft versus host disease (GVHD). He was given topical treatment and was started on dexamethasone syrup gargle and spit 10 mg 3 times daily for 1 month for oral cavity lesions with significant improvement. Meanwhile, he was still maintained on brentuximab.

In November 2018, he presented to the clinic for dyspnea and nonproductive cough, for which a computed tomographic (CT) scan of the chest was done and showed scattered ground glass opacities (GGO) in the lung bases bilaterally and mild diffuse bronchiectasis in all lobes (Figure 1). A spirometry was done which showed a new decreased forced vital capacity (FVC) of 67%, compared to a normal baseline prior to the transplant, and a low forced expiratory volume in 1 second (FEV1) of 40% and a low FEV1/FVC of 52% (Table 1). To note that all prior lung imaging and lung function testing was normal. In view of the spirometry results and findings of wheezing on lung examination, he was prescribed a short course of oral prednisone 40 mg that was tapered down then

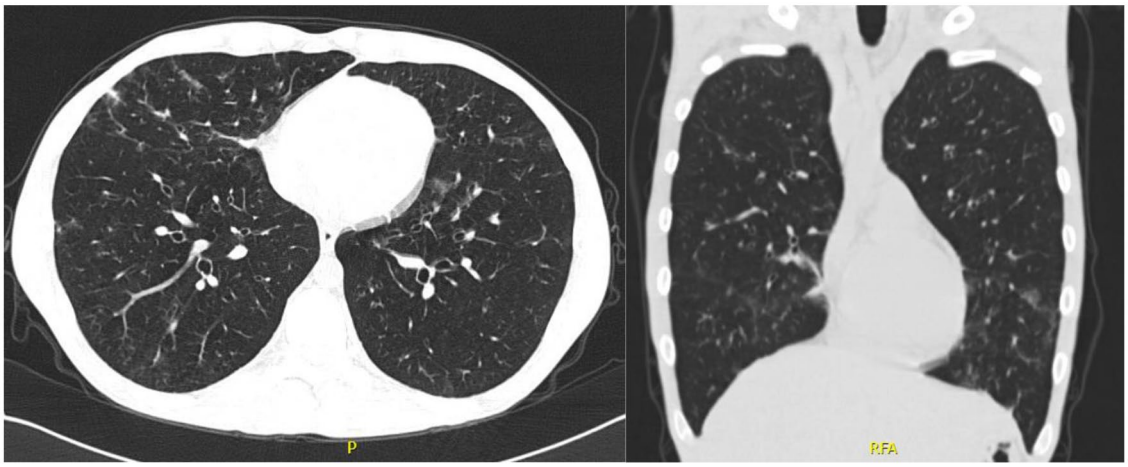

Figure 1. Date: 11-2018: Transverse (left) and coronal (right) views of chest computed tomographic (CT) scan showing scattered ground glass opacities (GGO) in the lung bases bilaterally and mild diffuse bronchiectasis in all lobes, as first radiological changes after both hematopoietic stem cell transplants.

Table 1. Pulmonary function test results showing a normal pattern in 04/2018, a mixed restrictive-obstructive pattern 7 on 11/2018, with further worsening on 11/2019.

DATE	04/18		11/18		11/19	
PFT VARIABLE	PATIENT	%PREDICTED	PATIENT	%PREDICTED	PATIENT	%PREDICTED
FVC	6.21	103	3.63	67	2.44	42
FEV1	4.79	102	1.88	40	1.71	36
FEV1/FVC	77	98	52	65	70	84
Peak flow	10.69	99	7.09	64	5.49	52
FEF25-75%	4.04	82	0.70	14	1.04	21
TLC	-	-	-	-	4.13	55
SVC	-	-	-	-	2.46	43
RV	-	-	-	-	1.67	99
RV/TLC	-	-	-	-	40	178
FRC	-	-	-	-	2.80	83

Abbreviations: FEF25-75%, forced mid-expiratory flow; FEV1, forced expiratory volume in the first second; FRC, functional residual capacity; FVC, forced vital capacity; PFT, pulmonary function test; RV, residual volume; SVC, slow vital capacity; TLC, total lung capacity.

stopped over 2 weeks, oral moxifloxacin, along with vilanterol/fluticasone furoate and tiotropium bromide puffs with partial improvement. Upon follow-up on March 2019, he had persistent dyspnea, but denied the presence of cough or fever. A repeat CT scan of the chest showed development of new lower lobe predominant bilateral, peripheral, peribronchovascular consolidations in the areas of previously seen GGOs, with worsening traction bronchiectasis and evidence of a new architectural distortion (Figure 2), and a suspicion of organizing pneumonia was raised in the radiology report, with a suggestion of chronic pulmonary GVHD, and less likely infection or medication side effect. A list of the medications he was on, along with their pulmonary side effects is shown in Table 2. The patient refused to undergo a lung biopsy as advised to decide for immunosuppression or steroid course, and was prescribed a new course of levofloxacin.

In May 2019, he presented back with fever, worsening dyspnea and a new productive cough of yellowish sputum. His procalcitonin level was also elevated of 9.4 ng/mL (normal laboratory value <0.05 ng/mL). A new CT scan of the chest showed further worsening in bilateral, mid-lung predominant consolidations and ground glass opacities, with changes of traction bronchiectasis and appearance of new cystic changes (Figure 3). A bronchoscopy with broncho-alveolar lavage (BAL) was done and detected the following: Para-influenza virus 2 on respiratory polymerase chain reaction (PCR) panel, gram negative rods on Gram stain, and one colony of Aspergillus species on fungal culture. Serum Aspergillus galactomannan

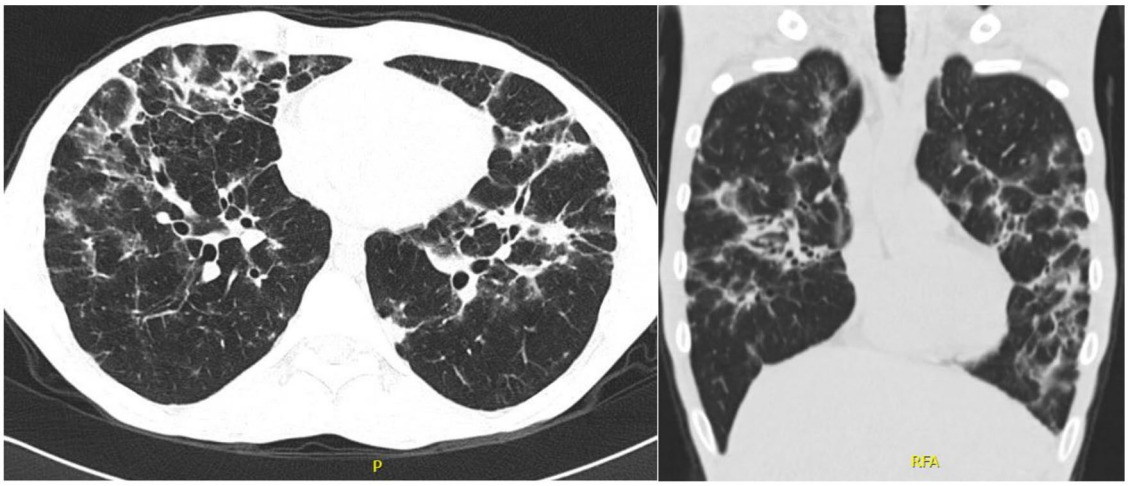

Figure 2. Date 03-2019: Follow-up chest computed tomographic (CT) scan showing (Left: Transverse view; Right: Coronal view) progression of the bilateral lower to mid lobe predominant, peripheral and peribronchovascular consolidations with worsening traction bronchiectasis and evidence of a new architectural distortion. These changes were previously visualized, only 4 months earlier, as scattered ground glass abnormalities with a milder form of diffuse traction, as shown in Figure 1.

was positive with a high index of 1.1 (normal laboratory index expected to be less than 0.5). In addition, the BAL cytology was reported as chronic inflammation with >90% lymphocytes and no malignant cells. Of note that Tuberculosis (TB) and Cytomegalovirus (CMV) PCR, Pneumocystis Jirovecii (PJP) PCR, mycobacterial culture, and Aspergillus galactomannan taken in BAL were all negative. Intravenous (IV) meropenem was given for 7 days for bacterial pneumonia and voriconazole 200 mg orally twice daily for 8 weeks was given for possible pulmonary aspergillosis. Both prophylactic Trimethoprim/sulfamethoxazole and Valacyclovir were added and his home inhalers were continued with significant improvement upon hospital discharge. He also finished his consolidation treatment with brentuximab the same month and his lymphoma was in complete remission.

At this point, the diagnosis of pulmonary fibrosis secondary to recurrent pulmonary infections versus chronic pulmonary GVHD in the form of organizing pneumonia was entertained, however, systemic steroid treatment was deferred in view of his active pulmonary fungal infection.

In August 2019, he was admitted again for fever and worsening dyspnea, found to have worsening upper lobes predominant pulmonary fibrotic changes and Influenza B infection for which he was treated with Oseltamivir, IV Piperacillin-tazobactam, and Levofloxacin. He was also started on oral prednisone 1 mg/kg daily with slow taper by 10 mg every 1 month, for a presumed diagnosis of organizing pneumonia, and he was maintained on prednisone for several months with inability to wean them off due to recurrence of dyspnea.

Subsequent pulmonary imaging over the following year showed a steady progression of his consolidations and traction bronchiectasis, significant decrease in ground-glass abnormalities throughout both lungs, a decrease in FDG uptake indicative of decrease in the inflammatory process and formation of scar tissue with a remarkable spatial shift to the mid and upper lung zones and progressive appearance of new cystic lesions in the upper lobes bilaterally (Figure 4). His pulmonary function test (PFT) also showed further significant drop in his FEV1, and to a greater extent, his FVC (Figure 1).

Discussion

Pulmonary complications following allogeneic transplantation has been estimated to occur in 40% to 60% of patients and is responsible for 10% to 40% of transplant-related deaths.[5] These complications can be infectious or non-infectious and are classified as early or late based on a cut-off of 100 days following the transplant.[5]

Late post allogeneic HSCT pulmonary complication include interstitial lung disease (ILD) in the form of diffuse alveolar damage, nonspecific interstitial pneumonia (NSIP), or lymphocytic interstitial pneumonia (LIP)[6]; the patient's extensive pulmonary cystic disease, however, remains atypical for LIP, usually mild in nature.[7] Late-onset noninfectious pulmonary complications have been reported in 10% to 26% of patients with post stem-cell transplant pulmonary complications.[8] A recent study found that bronchiolitis obliterans syndrome and ILD were the most common non-infectious complications, and that these complications most commonly occurred with 2 years post allogeneic HSCT. Follow-up of allogeneic HSCT recipients over 3 years showed cumulative incidence of 10% and 5% for BOS and ILDs, respectively. The reason behind these diseases seem to be related to recurrent lung injury, such as a chest radiotherapy and early pneumonia after HSCT, which triggers uncontrolled inflammation.[8] In another study, 61 lung biopsies were reviewed in patients post allogeneic HSCT, and showed bronchiolar or alveolar/interstitial pathologies or both. Around 40% of interstitial pathologies were associated with bronchiolar lesions. However, the

Table 2. List of medications taken by the patient along with potential respiratory adverse events..

MEDICATIONS	YEAR OF ADMINISTRATION	POSSIBLE SUB-ACUTE/CHRONIC PULMONARY ADVERSE EFFECTS
Doxorubicin	2012	- Organizing pneumonia: migrating consolidations, nodules, or masses - Pulmonary fibrosis: In general, develops insidiously with dyspnea and bibasilar or diffuse reticular opacities, and can develop late after completion of therapy
Bleomycin	2012	- Pneumonitis: bilateral, symmetrical, and gradual with a cellular NSIP pattern - Pulmonary fibrosis: In general, develops insidiously with dyspnea and bibasilar or diffuse reticular opacities, and can develop late after completion of therapy - Drug induced pulmonary nodules - Eosinophilic pneumonia - Organizing pneumonia: migrating consolidations, nodules, or masses
Vinblastine	2012	- Bronchospasm, de novo, or exacerbation of a preexisting asthma - Pneumonitis: bilateral, symmetrical, and gradual with a cellular NSIP pattern - Drug induced pulmonary nodules
Dacarbazine	2012	Pneumonitis: generally acute, bilateral, and diffuse lung involvement
Dexamethasone	2013	NA
Cytarabine	2013	NA
Cisplatin	2013	- Eosinophilic pneumonia - Acute/chronic VTE
Ifosfamide	2014	- Pneumonitis: bilateral, symmetrical, and gradual with a cellular NSIP pattern - Pulmonary fibrosis, UIP, or NSIP pattern: In general, develops insidiously with dyspnea and bibasilar or diffuse reticular opacities, and can develop late after completion of therapy
Carboplatin	2014	Bronchospasm, de novo, or exacerbation of a preexisting asthma
Etoposide	2014	- Bronchospasm, de novo, or exacerbation of a preexisting asthma - Focal, nodular organizing pneumonia
Bendamustine	2017	Opportunistic pulmonary infections, including PJP and CMV pneumonitis
Brentuximab vedotin	Since 2017	- Pneumonitis: bilateral, symmetrical, and gradual with a cellular NSIP pattern - Eosinophilic pneumonia - Bronchospasm, de novo, or exacerbation of a preexisting asthma - Opportunistic pulmonary infections, including PJP
Esomeprazole	Since 2018	NA
Vilanterol	Since 2018	NA
Fluticasone furoate	Since 2018	NA
Tiotropium bromide	Since 2018	NA
Valaciclovir	Since 2018	NA
Trimethoprim-Sulfamethoxazole	Since 218	- Eosinophilic pneumonia - DRESS with lung involvement (cough, dyspnea, wheezing, pleural effusion, pulmonary infiltrates) - Pulmonary vasculitis secondary to auto-immune antibodies development (+ANA, +Anti-dsDNA, +ANCA)
Ursodeoxycholic acid	Since 2018	NA

Abbreviations: ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; Anti-dsDNA, anti-double stranded DNA; CMV: cytomegalovirus; NSIP: nonspecific interstitial pneumonia; PJP: pneumocystis jiroveci pneumonia; UIP: usual interstitial pneumonia; VTE: venous thrombo-embolism.
Reference: Pneumotox » Drug [Internet]. Pneumotox.com. 2021 [cited 11 May 2021]. Available from: https://www.pneumotox.com/drug/index/.

study found that non-infectious pulmonary complications more than likely present as a spectrum of histopathological patterns involving different lung areas rather than only 1 histopathological feature. The reasons behind these complications is still unclear but could be attributed to smoking history, conditioning regimen, GVHD prophylaxis type, or episodes of respiratory infection.[9]

Our patient started having pulmonary symptoms with radiological and PFT changes approximately 200 days following his second haploidentical transplant, with completely normal

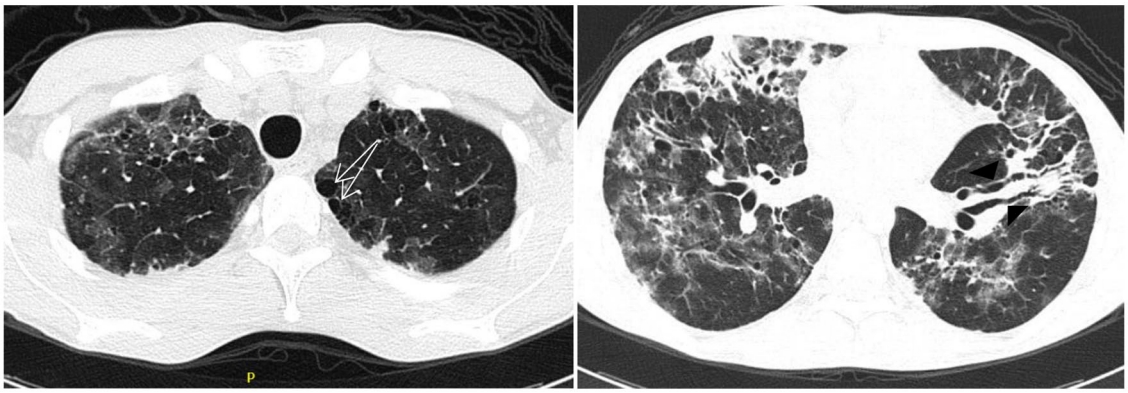

Figure 3. Date 05-2019: Follow-up chest computed tomographic (CT) scan, transverse view, showing the appearance of the first pulmonary cystic changes (white arrows) in bilateral upper lobes, with associated mild traction bronchiectasis (black arrowheads) suggestive of a fibrosing and progressive pulmonary pathology.

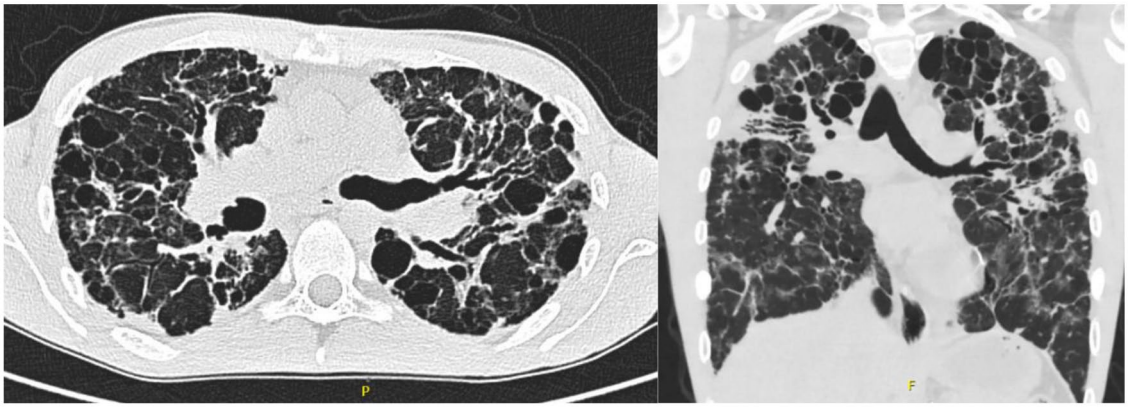

Figure 4. Date: 08-2020: Transverse (Left) and Coronal (Right) of chest computed tomographic (CT) scan, done 14 months after the second transplant, and showing severe upper and mid-lung zones predominant bronchiectatic changes in peri-bronchovascular and peripheral distribution, along with bilateral and extensive upper lobe predominant cysts. The significant decrease in ground glass opacities visualized on previous imaging is indicative of the decrease in inflammatory component of the patient's progressive lung damage.

imaging before, during, and multiple years following his first autologous transplant. This timing is important as it allows us to narrow the wide differential diagnosis of the pathology we are facing to a late pulmonary complication following allogeneic transplantation, and its associated risk factors. Also, given that the time elapsed since his last cycle of bleomycin was more than 1 year, and based on previous studies showing that pulmonary toxicity due to bleomycin begins from the time of administration up to 6 months post therapy, with the longest delayed injury being reported to be 2 years, bleomycin induced lung injury causing pulmonary fibrosis in this case can be ruled out.[10]

Our patient was maintained on brentuximab vedotin (BV) as post-transplant consolidation therapy, a monoclonal antibody therapy used for post-transplant consolidation therapy in patients with HL at high risk for relapse.[11] Unlike bleomycin and other chemotherapy medications commonly known to cause pulmonary fibrosis,[10] pulmonary toxicity related to BV has been reported to occur in only 5% of patients receiving the medication, and it included pneumonitis, interstitial lung disease, and acute respiratory distress.[11,12] In addition, severe acute pulmonary toxicity secondary to BV has been reported with radiological changes of bilateral diffuse GGO around the bronchovascular bundle, and treated successfully with steroids.[13] However, it is still unclear whether BV can lead to advanced pulmonary fibrosis followed by chronic cystic lung changes as in our patient, secondary to repetitive exposure causing ongoing pneumonitis, as such long term side effect has not been reported before. For this reason, BV induced pulmonary toxicity remains very high on the differential, but unfortunately, an adequate treatment with steroids could not be given due to concomitant infection.

Moreover, our patient's post-transplant course was also complicated by multiple pulmonary infections (atypical bacterial, viral, and fungal) requiring multiple hospital admissions for appropriate antibiotic, antifungal, and antiviral therapies. These infections were isolated through cultures and BAL. It is known that respiratory viral infections can lead to multiple acute and chronic pulmonary complications, including lung fibrosis.[14] Nevertheless, underlying infections as a culprit for such extensive pulmonary distortion is unlikely, with the only exception being PJP, an infection that was ruled out with a negative BAL.

Another late non-infectious pulmonary complication following allogeneic HSCT, and its subtype half matched haploidentical

HSCT, is pulmonary GVHD, manifested histologically by bronchiolitis obliterans syndrome (BOS), an irreversible obstructive disease that affects the terminal bronchioles and characterized by air trapping on PFTs and mosaic pattern on CT chest.[14] These changes are not consistent with our patient's presentation.

Additionally, cryptogenic organizing pneumonia (COP), the idiopathic form of organizing pneumonia that was formerly called BOOP, has also been reported to occur in 1% to 10% of patients undergoing allogeneic HSCT, usually between 2 and 15 months after transplant.[14] It consists of infiltration of inflammatory cells that result in the formation of intra-alveolar buds of granulation tissue, and manifests as restrictive ventilatory defect on PFTs, consolidations and GGO on chest CT, along with BAL lymphocytosis.[6,14] These features shows some similarities with our patient's findings.

Conclusion

Our patient's case represents a medical dilemma. Not only he suffered from progressive fibrosing cystic lung disease post HSCT, but he also had multiple active pulmonary infections preventing us from offering a steroid therapy trial, that would have otherwise helped treating most of the possible underlying inflammatory lung diseases he might have experienced. The unavailability of tissue biopsy added more challenge to his treating physicians.

In this challenging case, BV induced pneumonitis remains the first on the differential, followed by COP and then other post HSCT ILDs including LIP as possible pathologies.

It is also likely that our case could have represented 2 or more different pathologies occurring simultaneously: BV induced ongoing pneumonitis leading to fibrosis, an atypical form of undertreated LIP with extensive cystic changes, and/or advanced stage COP. A new pathologic process described for the first time is also possible.

Author Contributions

WA and SK were responsible for conceptualization and management of the project. WA, RM, MK and SK for manuscript preparation, editing and interpretation of findings. All authors have read and approved the manuscript.

Ethical Consent

Our study did not require an ethical board approval because our institution provides waivers for case report write-up. Nevertheless, a written informed consent was obtained from the patient prior to write-up and submission of this paper.

ORCID iDs

Walid Alam https://orcid.org/0000-0002-3714-6674
Salwa A Koubaissi https://orcid.org/0000-0002-0245-9267

REFERENCES

1. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner society: glossary of terms for thoracic imaging. *Radiology*. 2008;246:697-722.
2. Baldi BG, Carvalho CRR, Dias OM, Marchiori E, Hochhegger B. Diffuse cystic lung diseases: differential diagnosis. *J Bras Pneumol*. 2017;43:140-149.
3. Bondeelle L, Bergeron A. Managing pulmonary complications in allogeneic hematopoietic stem cell transplantation. *Expert Rev Respir Med*. 2019;13:105-119.
4. Bergeron A. Late-onset noninfectious pulmonary complications after allogeneic hematopoietic stem cell transplantation. *Clin Chest Med*. 2017;38:249-262.
5. Patriarca F, Skert C, Sperotto A, et al. Incidence, outcome, and risk factors of late-onset noninfectious pulmonary complications after unrelated donor stem cell transplantation. *Bone Marrow Transplant*. 2004;33:751-758.
6. Grønningsæter IS, Tsykunova G, Lilleeng K, Ahmed AB, Bruserud, Reikvam H. Bronchiolitis obliterans syndrome in adults after allogeneic stem cell transplantation-pathophysiology, diagnostics and treatment. *Expert Rev Clin Immunol*. 2017;13:553-569.
7. Cha SI, Fessler MB, Cool CD, Schwarz MI, Brown KK. Lymphoid interstitial pneumonia: clinical features, associations and prognosis. *Eur Respir J*. 2006;28:364-369.
8. Bergeron A, Chevret S, Peffault de Latour R, et al. Noninfectious lung complications after allogeneic haematopoietic stem cell transplantation. *Eur Respir J*. 2018;51:1702617.
9. Meignin V, Thivolet-Bejui F, Kambouchner M, et al. Lung histopathology of non-infectious pulmonary complications after allogeneic haematopoietic stem cell transplantation. *Histopathology*. 2018;73:832-842.
10. Uzel I, Ozguroglu M, Uzel B, et al. Delayed onset bleomycin-induced pneumonitis. *Urology*. 2005;66:195.
11. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in Lancet. 2015;386(9993):532]. *Lancet*. 2015;385:1853-1862.
12. Clifford K, Copeland A, Knutzen G, Samuelson E, Grove L, Schiavo K. Brentuximab Vedotin: a nursing perspective on best practices and management of associated adverse events. *Clin J Oncol Nurs*. 2018;22:E103-E114.
13. Sabet Y, Ramirez S, Rosell Cespedes E, et al. Severe acute pulmonary toxicity associated with brentuximab in a patient with refractory Hodgkin's lymphoma. *Case Rep Pulmonol*. 2016;2016:2359437.
14. Haider S, Durairajan N, Soubani AO. Noninfectious pulmonary complications of haematopoietic stem cell transplantation. *Eur Respir Rev*. 2020;29:190119.