



Bronchoscopic features, associations, and outcomes of organizing pneumonia following allogeneic hematopoietic stem cell transplantation

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Abstract

Organizing pneumonia (OP) is a poorly understood complication of hematopoietic stem cell transplant (HSCT). We identified 15 patients diagnosed with OP following HSCT and described their clinical course. CT chest findings were remarkable for multifocal infiltrates that were predominantly consolidating or ground glass opacities. Bronchoalveolar lavage (BAL) was performed on 14 patients with five having lymphocytosis (> 25% lymphocytes), three with eosinophilia (> 5% eosinophils), three with neutrophilia (> 30% neutrophils), and three with normal cell counts. Flow cytometry was analyzed on BAL fluid in 13 patients with 11 having a CD4/CD8 of ≤ 0.9 . Initial treatment with 0.3–1.0 mg/kg prednisone resulted in improvement in symptoms, in radiographic findings, and in pulmonary function testing for the majority of patients. Six patients had recurrence of OP after completing treatment. Eleven patients had evidence of extra-pulmonary graft-versus-host disease prior to diagnosis of OP, and seven patients were diagnosed with an upper respiratory tract infection (URI) within 8 weeks of OP diagnosis. Most patients respond well to prednisone with significant improvement in pulmonary function, but risk of recurrence is high after cessation of steroid treatment. Risk factors for the development of OP may include prior URI.

Keywords Organizing pneumonia · Stem cell transplant · Bronchiolitis obliterans · Pulmonary infiltrate

Introduction

Advances in the field of allogeneic hematopoietic stem cell transplantation (HSCT) have provided therapies for many people suffering from hematologic malignancies with opportunities for improved long-term survival [1]. Graft-versus-host disease (GVHD) is a multisystem disorder wherein donor immune cells recognize host tissue as foreign and initiate an

immune reaction. GVHD is a significant cause of morbidity and mortality following HSCT [2, 3]. Pulmonary manifestations of GVHD occur in nearly 50% of patients with GVHD, and are associated with higher rates of late mortality [4, 5].

Bronchiolitis obliterans syndrome (BOS), defined as a new onset obstructive pulmonary defect in post-HSCT patients without evidence of infection and at least one extra-pulmonary site of chronic GVHD [2], is the most common pulmonary manifestation of chronic GVHD [6]. Another common post-HSCT pulmonary complication is organizing pneumonia (OP), formerly referred to as bronchiolitis obliterans organizing pneumonia, which may be a manifestation of GVHD in some cases. OP is defined as a diffuse interstitial lung disease that typically afflicts the distal respiratory bronchioles and the alveoli with a patchy distribution in which the background lung architecture is preserved [7]. In OP, there is polypoid intraluminal plugs of proliferation of granulation tissue consisting of fibroblasts, myofibroblasts, and loose connective matrix, involving both the alveoli and the alveolar ducts, which can extend to the bronchioles [8]. OP typically presents with non-specific symptoms including cough,

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malaise, low-grade fever, and dyspnea [9]. On chest CT imaging, OP features diffuse, patchy alveolar opacities which may be consolidating or ground-glass in typical cases, though solitary lesions have been described in focal OP [10–12]. OP can feature a restrictive pattern on pulmonary function testing (PFT) or a combined obstructive and restrictive pattern.

OP following HSCT has a reported incidence of between 1 and 10% patients, with a highly variable time frame from HSCT to development of this condition [13–16]. Potential transplant-related risk factors for development of OP include HLA disparity, peripheral blood stem cell transplantation, and female-to-male HSCT [17]. T cell depletion appears to be protective against the development of both OP and BOS [18]. We sought to review our own cohort of patients diagnosed with post-HSCT OP, with particular interest focused on bronchoscopic findings during the diagnostic workup, potential risk factors for development of OP, and treatment outcomes.

Methods

Patients were identified from the University of Kansas Medical Center Adult Hematopoietic Stem Cell Transplantation Clinic. All patients had a history of allogeneic HSCT and developed OP following HSCT. Diagnosis of OP was based on clinical features, typical radiographic findings, and exclusion of infectious etiologies or other alternative diagnoses that could be assessed by bronchoscopy or serologic testing [8, 13, 17]. Additionally, all of the patients had persistent symptoms or radiographic changes after completing an appropriate course of empiric broad-spectrum antimicrobials before the diagnosis of OP was made.

Diagnostic testing performed to exclude infections include standard bacterial and fungal cultures from serum, serum galactomannan antigen, and serum beta-d-glucan assay. From BAL fluid, standard bacterial, fungal, and acid-fast bacterial cultures, galactomannan antigen, *Pneumocystis carinii* PCR, herpes simplex virus PCR, cytomegalovirus PCR, and grocott stain were all performed. The NxTAG respiratory pathogen panel PCR was also performed on all BAL specimens, and assessed for influenza A, influenza B, respiratory syncytial virus A and B, rhinovirus, parainfluenza virus 1–4, human metapneumovirus, adenovirus, coronavirus, *Bordetella pertussis*, *Chlamydomphila pneumoniae*, and *Mycoplasma pneumoniae*.

Typical symptoms at the time of diagnosis include new onset of respiratory symptoms post-HSCT including cough, dyspnea, or pleurisy. All patients had pulmonary infiltrates on CT imaging of the chest with typical features of OP, including lung consolidation and ground-glass opacities. In all patients, the diagnosis was confirmed by the exclusion of infectious causes, including performing bronchoscopy with

bronchoalveolar lavage (BAL) when indicated. Lung biopsy, either bronchoscopically via transbronchial lung biopsy or open surgical lung biopsy, was typically not performed in this patient population due to risks of complications. Following diagnosis of OP, initial follow-up CT scans ranged from 14 to 60 days and then patients typically followed every 30–60 days with a pulmonologist with additional imaging as clinically indicated.

Data collected included background information, HSCT details, other sites of GVHD occurrence, CT findings, symptoms, BAL findings, treatments, and PFT results. Outcomes collected included time until resolution of symptoms, time until resolution of infiltrates, total duration of prednisone treatment, complications, and survival.

All patients were identified from July 1, 2013 until January 1, 2018. Censorship of all data occurred on June 30, 2018. The study was performed with the approval of the University of Kansas Medical Center Institutional Review board. *p* values were determined using ANOVA analysis.

Results

We identified 15 patients who were diagnosed with OP following HSCT, with a mean age of 48 years (range 24–72 years), 13 of which were males. During this period of time, 716 patients underwent allogeneic HSCT at our institution, giving a prevalence of 2.1%. The patients had various underlying hematologic malignancies, including eight with AML. Ten patients underwent HSCT with unrelated donors. Three patients had a history of underlying lung disease and four patients had a history of tobacco use. Full background characteristics of these patients are described in Table 1.

The mean onset for symptoms was 286 days after transplant. Most patients presented with cough and dyspnea on exertion, but in some, the symptoms also included fever and pleuritic chest pain. Clinical features prior to the diagnosis of OP included history of extra-pulmonary GVHD in 11 of the 15 patients (73%), as opposed to an incidence of 59% in all allogeneic HSCT patients at 1-year-post-HSCT. Seven patients were diagnosed with an upper respiratory tract infection (URI) within 8 weeks of being diagnosed with OP. Twelve patients (80%) of patients with OP had received total body irradiation (TBI) during the conditioning regimen. During the same time frame, 716 patients underwent allogeneic HSCT at our institution, and 330 (46.1%) received TBI.

Full details on symptoms, radiographic characteristics, and bronchoscopic findings are shown in Table 2. CT chest findings at the time of diagnosis were remarkable for multifocal infiltrates in all 15 patients. Infiltrates were described as ground glass opacities in six patients, consolidating in two patients, nodular in four patients and a mixed pattern in three patients. At the time of presentation with OP, the patients had

Table 1 Patient background characteristics

ID	Age	Sex	Diagnosis	Status at Transplant	Type of Transplant	Conditioning Regimen	GVHD prophylaxis	CMV Status (Donor / Recipient)	History of Pulmonary Disease	History of Tobacco Use	Number of Other Sites of GVHD	Active GVHD Time of OP Diagnosis	Treatment at Time of OP Diagnosis
1	36	M	NHL	PR	MUD HSCT	Cyc/TBI	FK/MTX	-/-	Asthma	No	2	FK	FK
2	61	F	AML	CR	MUD HSCT	Bu/Flu	FK/MTX	-/-	No	Yes	2	FK	FK
3	45	M	NHL with 2° AML	CR	MUD HSCT	Cyc/Flu/TBI	CyA/MMF	+/+	Asthma	No	1	CyA/Prednisone	CyA/Prednisone
4	72	M	AML	CR	MUD HSCT	Flu/TBI	FK/MMF	+/+	No	Yes	0	No	No
5	26	M	AML	CR	MSD HSCT	Bu/Cyc	FK/MTX	-/-	No	No	0	No	No
6	39	M	DLBCL	CR	MSD HSCT	ATG/TBI	No Records	-/-	No	No	1	No	No
7	27	M	T cell ALL	CR	MUD HSCT	Cyc/TBI	FK/MTX	-/-	No	No	2	No	No
8	24	M	AML	PIF	MUD HSCT	Cyc/TBI/VP16	FK/MTX	-/+	No	No	1	FK	FK
9	68	M	AML	CR	Haploidentical HSCT	Cyc/Flu/TBI	FK/CyA/MMF	-/-	No	No	2	Prednisone	Prednisone
10	71	M	MDS	Stable	MUD HSCT	Flu/TBI	FK/MMF	-/-	No	No	2	No	No
11	49	M	B cell ALL	CR	MUD HSCT	Cyc/TBI	FK/MTX	+/+	Bronchiectasis	No	1	No	No
12	34	M	NHL	Stable	MSD HSCT	Cyc/Flu/TBI	FK/CyA/MMF	-/-	No	No	2	No	No
13	46	F	AA	Unknown	MUD HSCT	ATG/Cyc/Flu/TBI	FK/CyA/MMF	-/+	No	No	0	FK	FK
14	60	M	AML	CR	Haploidentical HSCT	Cyc/Flu/TBI	CyA/MTX	-/-	No	Yes	0	No	No
15	62	M	AML	CR	MUD HSCT	Bu/Flu	FK/MTX	+/+	No	Yes	2	No	No

AA = aplastic anemia; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ATG = anti-thymocyte globulin; Bu = busulfan; CMV = cytomegalovirus; CR = complete remission; CyA = cyclosporine; Cyc = cyclophosphamide; DLBCL = diffuse large B cell lymphoma; FK = fludarabine; GVHD = graft versus host disease; HSCT = hematopoietic stem cell transplant; MDS = myelodysplastic syndrome; MMF = mycophenolate mofetil; MSD = matched sibling donor; MUD = matched unrelated donor; MTX = methotrexate; NHL = non-Hodgkin's lymphoma; PIF = primary induction failure; PR = partial remission; TBI = total body irradiation.

Table 2 Clinical features of patient's with OP

ID	Time from Transplant to OP (Days)	Diagnosis	Presenting Symptoms	CT Chest Findings	BS Abx Prior to BAL	BAL Cell Count Differentials	BAL CD4/CD8	Associated Infections
1	180	Cough	Multifocal, Consolidations	Yes	Neut: 86%; Lymphs: 2%; Mono: 12%; Eos: 0%	0.2	No	
2	204	Cough, DOE, Pleuritic CP	Multifocal, Consolidations and GGO	No	Neut: 21%; Lymphs: 7%; Mono: 61%; Eos: 11%	0.5	Rhinovirus 8 weeks prior	
3	106	Cough, DOE, Fever	Multifocal, GGO	Yes	Neut 4%; Lymphs: 26%; Mono: 69%; Eos: 1%	3.7	No	
4	400	Cough, DOE	Multifocal, GGO	No	Neut: 1%; Lymphs: 85%; Mono: 12%; Eos: 2%	0.7	Adenovirus 2 weeks prior	
5	181	Cough, DOE	Multifocal, GGO	Yes	Neut: 21%; Lymphs: 0%; Mono: 72%; Eos: 7%	0.7	No	
6	676	Cough, DOE	Multifocal, Nodular	No	Neut: 7%; Lymphs: 32%; Mono: 58%; Eos: 3%	0.1	No	
7	279	Cough	Multifocal, GGO	No	Neut: 10%; Lymphs: 10%; Mono: 71%; Eos: 9%	0.03	Rhinovirus 6 weeks prior	
8	142	Cough, Chills, Fever	Multifocal, Consolidations and GGO	Yes	Neut: 9%; Lymphs: 28%; Mono: 63%; Eos: 0%	0.7	Parainfluenza 2 weeks prior	
9	214	Cough, Fever	Multifocal, Nodular and GGO	Yes	Neut: 8%; Lymphs: 5%; Mono: 85%; Eos: 2%	Not Performed	No	
10	624	Cough, DOE	Multifocal, Nodular	No	Neut: 86%; Lymphs: 4%; Mono: 9%; Eos: 1%	0.7	Parainfluenza at time of diagnosis	
11	303	Cough, DOE, Pleuritic CP	Multifocal, Consolidations	No	Not Performed	Not Performed	No	
12	164	Cough, DOE, Pleuritic CP	Multifocal, Nodular	Yes	Neut: 46%; Lymphs: 12%; Mono: 46%; Eos: 0%	0.9	Parainfluenza 4 weeks prior	
13	172	Cough, DOE	Multifocal, Nodular	Yes	Neut: 1%; Lymphs: 4%; Mono: 95%; Eos: 0%	0.64	Rhinovirus 1 week prior	
14	523	Cough, DOE, Fever	Multifocal, GGO	No	Neut: 3%; Lymphs: 36%; Mono: 61%; Eos: 0%	0.17	No	
15	126	Fever	Multifocal, GGO	Yes	Neut: 0%; Lymphs: 21%; Mono: 79%; Eos: 0%	2	No	

BAL = Bronchoalveolar lavage; BS-Abx = Broad-spectrum antibiotics; CP = Chest pain; DOE = Dyspnea on exertion; Eos = Eosinophils; GGO = Ground glass opacity; Lymphs = Lymphocytes; Mono = Monocytes; Neut = Neutrophils.

Table 3 Treatment and outcomes for patients with OP

ID	Prednisone (mg/kg)	Second-Line Treatments	Time to Symptom Improvement (Days)	Time to Resolution of Infiltrates on CT (Days)	Time on Steroids (Days)	Complications	Recurrence	Recurrence Treatment	Resolution of Recurrence	Survival	Cause of Death
1	2	None	3	24	106	None	Yes	Prednisone	No	No	Septic Shock
2	1	None	14	31	168	None	Yes	Prednisone	Yes	Yes	x
3	1	None	15	50	120	None	No	x	x	Yes	x
4	0.7	None	12	59	107	None	No	x	x	Yes	x
5	0.4	None	6	109	244	None	Yes	Prednisone/Ruxolitinib	Yes	Yes	x
6	1	Rituximab/ Ruxolitinib	12	94	137	Insomnia	No	x	x	Yes	x
7	1	None	7	14	101	None	Yes	Prednisone/Ruxolitinib	Yes	Yes	x
8	1	None	11	43	176	None	Yes	Prednisone/Rituximab	Yes	No	Pneumonia
9	0.7	None	4	68	157	None	No	x	No	No	AML recurrence
10	1	None	14	98	161	Insomnia	Yes	Rituximab/ECP	No	Yes	x
11	0.5	None	30	No F/U CT	203	None	No	x	x	Yes	x
12	0.3	Ruxolitinib	6	154	324	None	Yes	Prednisone/Ruxolitinib	No	No	Pulmonary Embolus
13	0.8	None	8	116	76	None	No	x	x	Yes	x
14	0.7	Ruxolitinib/ECP	7	28	167	None	No	x	x	Yes	x
15	0.8	None	Asymptomatic at diagnosis	Never Resolved	59	DM, Myopathy	Yes	Prednisone	No	No	PulmonaryGVHD

ECP= Extracorporeal photopheresis.

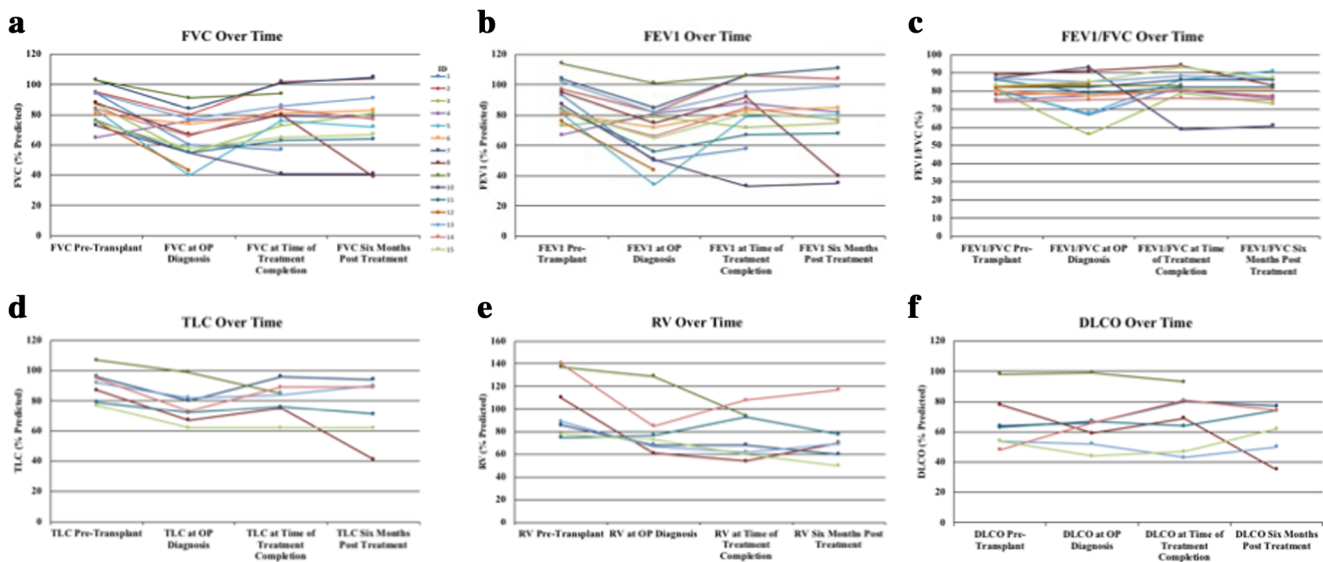


Fig. 1 Dot plot graphs of pulmonary functioning testing (PFT) from pre-transplant testing to testing 6-month-post-treatment following OP diagnosis for **a** forced vital capacity (FVC), **b** forced expiratory volume over 1 s (FEV1), **c** FEV1/FVC, **d** total lung capacity (TLC), **e** residual volume (RV), and **f** diffusion capacity (DLCO). The median time of PFTs at OP

diagnosis was 204-day-post-transplant (range 106–676 days). The median time of PFTs at steroid completion was 147 days following diagnosis of OP (range 42–244 days) and 332 days at 6-month-post-treatment (range 225–427 days)

an average reduction in their FVC and FEV1 of 23.1% (p value < 0.05) and 22.4% (p value < 0.05), respectively, when compared to pre-transplant PFT (Fig. 1). Additionally, there was an average reduction in total lung capacity (TLC), residual volume (RV), and diffusion capacity (DLCO) of 13.8%, 18.2%, and 8.3%, respectively.

Bronchoalveolar lavage (BAL) with cell differentials was performed on 14 patients. Five patients featured lymphocytosis ($> 25\%$ lymphocytes), three with eosinophilia ($> 5\%$ eosinophils), three with neutrophilia ($> 30\%$ neutrophils), and three with normal cell counts. Flow cytometry was analyzed on BAL fluid in 13 patients with 11 having a CD4/CD8 of ≤ 0.9 .

First-line treatment details for OP is shown in Table 3. The average initial dose of prednisone was 0.86 mg/kg/day (range 0.3–1.0 mg/kg/day). Steroid-sparing therapies that were introduced during first-line of treatment included rituximab, ruxolitinib, and retractorporeal photopheresis (ECP), which were prescribed in three patients.

Treatment outcomes are shown on Table 3. Most patients' symptoms improved with treatment, on average 10.6 days after treatment initiation (range 3–30 days). Follow-up CT scans demonstrated an average time to resolution of infiltrates of 68.3 days (range 14–154 days). There was one patient who did not have resolution of infiltrates with treatment.

In average, patients received steroid treatment for 153.7 days (59–324 days). Complications of steroid treatment included development of insomnia, diabetes, and steroid-induced myopathy. PFTs performed at the time of steroid completion showed an increase in FVC and FEV1 of 18.4% and 20.7%, respectively, when compared to PFTs completed

at time of OP diagnosis (Fig. 1). Additionally, over this same period of time, TLC, RV, and DLCO had a 5% increase, no change, and 3% decrease following treatment with steroids, respectively. PFTs remained stable at 6-month-post-treatment in the majority of patients.

In terms of outcomes, eight patients had recurrence of OP. Of the patients that had recurrence, three were treated with prednisone monotherapy, one of which had resolution. Three patients were treated with a combination of prednisone and ruxolitinib, two of which had resolution. One patient was treated with a combination of prednisone and rituximab and had resolution. The final patient was treated with ECP and rituximab and did not have resolution, though he did have improvement in his PFT and imaging. Five patients ultimately died, with one patient's death attributed to respiratory failure secondary to OP.

Discussion

We have reviewed our cohort of patients diagnosed with OP following HSCT, and found variability in underlying hematologic process, conditioning regimens, and pre-existing pulmonary disease. The patients presented with similar symptoms, and seven of the 15 patients had a documented viral URI within 8 weeks of OP diagnosis. While there was variability in the cell counts seen on BAL, a CD4/CD8 ≤ 0.9 was seen in 11 of the 13 patients. We did observe a response to systemic corticosteroids in the majority of patients with improvement in PFTs, though some patients did require second-line therapy.

Bronchoscopy with BAL is a valuable tool in evaluating pulmonary infiltrates of unknown etiology in the immunosuppressed patient [19]. It is of the utmost importance to exclude infectious etiologies in this patient population, with early bronchoscopy providing higher yield and possibly improving survival [20]. While we found a wide variability in alveolar cell counts identified on BAL, the reduced CD4/CD8 ratio that we encountered is a known finding in non-HSCT-related OP [21, 22]. Transbronchial lung biopsy was generally avoided in this patient population due to low associated yield and risks of complications [23, 24]. Whereas open lung biopsy is typically recommended to confirm the diagnosis of OP in the non-HSCT population [25], we feel that by excluding infectious etiologies with BAL and narrowing the differential diagnosis substantially, we can expedite treatment and avoid complications of open-lung biopsy, which is declining in its use in HSCT recipients [26].

Our population was treated with corticosteroids as first-line therapy for OP, which is in line with current recommendations [14, 15]. While the side effect profile of corticosteroids is problematic, their effectiveness in management of OP, both in HSCT recipients and those who have not received HSCT, is accepted as standard of care [15, 25]. The majority of patients were managed with corticosteroids alone for the initial treatment, though eight of the 15 patients did have recurrence of OP. This begs the questions of how long is the optimal duration of steroid therapy for this entity, and can it be beneficial if extended up to one year [27]?

In patients without history of HSCT, common agents employed in persistent or recurrent OP include cyclophosphamide, macrolides, and rituximab [28–30]. In our population of HSCT recipients, the agents that we employed for recurrent disease included ECP, rituximab, and ruxolitinib, either alone or in combination, with mixed results among the group. These agents have been used successfully in treatment of steroid-resistant and steroid-refractory GVHD, including those patients with BOS as a pulmonary manifestation of GVHD [31–35]. Determining the optimal agent to use in recurrent or steroid-resistant OP due to GVHD will require ongoing clinical trials with careful attention to outcomes.

The etiology of post-HSCT OP is unclear at this time. While it is tempting to assume that this is a manifestation of pulmonary GVHD, it is unclear as to why only 11 of our cohort's 15 patients had extra-pulmonary manifestations of GVHD. Previous studies have shown potential associations with the use of irradiation in conditioning regimens [15], which was utilized in 12 of our 15 patients. Another potential cause of OP in these patients includes previous viral infection, which was documented in seven of the 15 patients. Dysregulated airway inflammation may be the mechanism that explains progression of a URI to OP in the HSCT recipient.

Our study has many limitations. First, this is a retrospective study of a single-center of a rare lung disease following HSCT. Additionally, patients were treated in a non-uniform manner, and the use of steroid-sparing agents was varied among the participants in this study. This variation in treatment choices is largely driven by inequities in drug availability in various patients, often driven by managed care decisions. Unfortunately, this is quite a heterogeneous patient population, and many of our limitations are related to the variability in presentation and response to treatment in this inflammatory lung disease. While our population was quite heterogeneous, the common link in this population was an exclusion of alternative diagnoses and a generally steroid-responsive disease.

In summary, OP is a condition that may occur following HSCT. It is diagnosed based on characteristic radiographic patterns and the exclusion of infectious etiologies, typically by BAL. Patients may have decline in lung function at the onset of OP, though this is typically reversible with treatment of OP. Corticosteroids remain the standard first-line therapy, though the use of second-line agents is often required in steroid-resistant or recurrent disease.

Compliance with ethical standards

Local institutional review board gave approval for this study.

Conflict of Interest The authors declare that they have no conflict of interest.

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