CASE REPORT

Exploring the possibilities: airspace disease in the postallogeneic haematopoietic stem cell transplant period

Talal Hilal,¹ Zartash Gul²

¹Department of Internal Medicine, University of Kentucky, Lexington, Kentucky, USA

²Division of Hematology, University of Kentucky, Lexington, Kentucky, USA

Correspondence to

Dr Talal Hilal,
talal.hilal@uky.edu

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SUMMARY

A 50-year-old man with a history of myelodysplastic syndrome status postallogeneic haematopoietic stem cell transplantation (HSCT) in July 2013 presented in January 2014 with a 6-week history of worsening shortness of breath and dry cough. Chest imaging revealed scattered groundglass opacities in the upper lobes bilaterally and two areas of focal consolidation on the left side. Bronchoscopy with bronchoalveolar lavage grew methicillin-resistant *Staphylococcus aureus* and the patient was treated with a prolonged course of vancomycin without improvement in symptoms or oxygenation. Image-guided core biopsy of an area of consolidation revealed histological findings of acute fibrinous and organising pneumonia. The patient was diagnosed with what appeared to be a manifestation of chronic graft-versus-host disease of the lung and started on high-dose corticosteroids with resultant improvement in symptoms. The response was short-lived and the patient expired 2 months later.

BACKGROUND

Acute fibrinous and organising pneumonia (AFOP) is a rare but potentially under-recognised clinical entity. The diagnosis is based on the hallmark intra-alveolar fibrin deposition on a background of organising pneumonia on pathological examination. The presentation is variable with acute to subacute symptoms. The illness can range from mild, self-limited to severe, causing respiratory failure and death. The aetiology is unclear, but multiple conditions have been associated with AFOP. This case reports the association in an allogeneic haematopoietic stem cell transplantation (HSCT) recipient.

CASE PRESENTATION

A 50-year-old man was diagnosed with myelodysplastic syndrome, subtype refractory anaemia with excess blasts-2 (RAEB-2) in March 2013. He underwent a 9/10 human leucocyte antigen-matched unrelated donor allogeneic haematopoietic stem cell transplantation (HSCT) in July 2013 following conditioning chemotherapy with busulfan and fludarabine. He was given graft-versus-host disease (GVHD) prophylaxis with thymoglobulin (days -3, -2, -1 before transplantation), mini-dose methotrexate (days 1, 3, 6 and 11 after transplantation) and tacrolimus. His post-transplant course was complicated by hyperacute cutaneous and ocular GVHD over the ensuing month requiring immunosuppression with oral prednisone and azacitidine, in addition to the tacrolimus.

He presented to clinic in January 2014 for regular follow-up and reported a 6-week history of persistent shortness of breath and a dry cough. His respiratory symptoms were stable over that period, but he noticed a significant worsening in shortness of breath, a change in the character and severity of cough which has become productive of yellow sputum, and left-sided pleuritic chest pain over the preceding 2–3 days.

Physical examination revealed tachycardia, tachypnoea and hypoxia with oxygen saturation of 84% on ambient air that improved to low 90 s with a 3 L/min flow via a nasal cannula. Chest auscultation revealed normal vesicular breath sounds without added sounds. He was admitted to the hospital for further workup of new onset hypoxia.

INVESTIGATIONS

Owing to the patient's history of allogeneic HSCT and chronic immunosuppression, a high-resolution CT (HRCT) of the chest was obtained to further assess the lungs. The HRCT showed scattered groundglass opacities in the upper zones and two focal areas of consolidation (figure 1). The patient then underwent a bronchoscopy with washings to rule out opportunistic infections, the results of which grew methicillin-resistant *Staphylococcus aureus* (MRSA). Blood and urine studies for fungal and viral infections were negative.

DIFFERENTIAL DIAGNOSIS

The clinical presentation was most consistent with an infectious process, the aetiology of which was unclear. The typical bacterial pathogens associated with community-acquired pneumonia were on the list, but so were the viral and fungal pathogens that needed to be ruled out. The 1 month history of shortness of breath and dry cough pointed towards the possibility of a different underlying pathology. This included interstitial lung disease, obstructive lung disease and pulmonary hypertension.

TREATMENT

The patient was started on vancomycin and discharged home on day 10 with supplemental oxygen to complete a 14-day course.

He was seen in clinic 7 days after discharge and was requiring continuous oxygen supplementation with persistent symptoms of shortness of breath and cough despite completion of directed antimicrobial therapy.

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Figure 1 High-resolution CT of the chest showing an area of consolidation in the left lower lobe.

OUTCOME AND FOLLOW-UP

A repeat CT of the chest without contrast revealed a largely unchanged airspace disease with minimal improvement in the left upper zone consolidation and worsening in the left lower zone mass-like lesion (figure 2). The decision was made to perform a CT-guided core biopsy of the left lower zone lesion to better assess the nature of the disease. Microscopy of the lung tissue showed air spaces filled with balls of organising fibrin undergoing collagenisation (figure 3). The associated interstitium had a mixed infiltrate of lymphocytes and plasma cell with rare eosinophils and neutrophils. Alveolar wall sparing was noted. The findings were consistent with AFOP, a rare variant of diffuse alveolar damage (DAD) characterised by intra-alveolar fibrin deposition and organising pneumonia in a patchy distribution.

The illness appeared to be a manifestation of chronic GVHD of the lung with a superimposed pneumonia that brought the subtle symptoms to our attention. The patient was started on high-dose corticosteroids at 1 mg/kg orally with a slow taper. He reported significant improvement in symptoms within 2 days and was discharged home.

Figure 2 CT of the chest 3 weeks later showing enlargement of the area of consolidation in the left lower lobe.

Pulmonary function testing (PFT) in June 2013 prior to allo-HSCT showed normal pulmonary function with an forced expiratory volume in 1 s (FEV₁) of 3.22 L (86% predicted), FEV₁/forced vital capacity (FVC) of 0.70, TLC of 7.34 L (109% predicted) and diffusing capacity divided by alveolar volume (DLCO/VA) 90% predicted. Repeat PFTs in February 2014, at 1 week following discharge, revealed severe airflow obstruction with air trapping, FEV₁ of 0.87 L (24% predicted), FEV₁/FVC of 0.40, total lung capacity (TLC) of 6.66 L (99% predicted) and DLCO/VA 82% predicted.

The response to corticosteroids was not prolonged and the patient deteriorated further within the following month with worsening respiratory failure. He expired 2 months after the diagnosis.

DISCUSSION

The background history of an HSCT recipient who presents to the hospital is essential to guide appropriate workup and differential diagnosis. This includes the type of transplant (eg, autologous vs allogeneic), indication (eg, multiple myeloma, acute myelogenous leukaemia, myelodysplastic syndrome, lymphoma, etc), conditioning chemotherapy (eg, myeloablative vs reduced intensity) and post-transplant course (eg, infectious complications, GVHD). Our patient had a complicated immediate post-transplant course with the development of acute GVHD despite appropriate prophylaxis, which increased his risk for further organ involvement.

In addition to the background historical details of the patient with HSCT, the post-transplant day is important as well. The post-transplant period is divided into three phases—phase I is termed the pre-engraftment phase (0–30 days) and is characterised by neutropenia, mucositis and acute GVHD; phase II is termed the post-engraftment phase (30–100 days) and is characterised by impaired cellular immunity and acute GVHD; and phase III is termed the late phase (>100 days) and is characterised by impaired humoral and cellular immunity and chronic GVHD.¹ The patient presents with respiratory symptoms in the late phase, and in addition to impaired immunity, he is further immunosuppressed with steroids and tacrolimus for 6 months, which puts him at risk for a variety of infectious complications.

The differential diagnosis in our case included two major categories—infectious and non-infectious pulmonary conditions. Our patient's symptoms appeared to be subacute with recent worsening, which pointed towards an exacerbation or

Figure 3 Microscopy of a biopsy specimen showing airspaces filled with balls of fibrin and interstitial infiltrate with alveolar wall sparing.

progression of an underlying process, or an infection unmasking an underlying disease.

Pneumonia in the post-HSCT period is an important cause of non-relapse mortality, especially in allogeneic transplant recipients. In this case, some atypical pathogens need to be considered in addition to the typical bacterial pathogens associated with community-acquired pneumonia. This includes encapsulated bacteria, *Nocardia*, viruses (eg, herpes simplex virus, cytomegalovirus) and fungi (eg, *Aspergillus*, *Pneumocystis*).

Bacterial pneumonia is particularly prevalent during the pre-engraftment period of profound neutropenia with an incidence of approximately 15%, half of which occur within the first 100 days.² Gram-negative organisms predominate during the first 100 days, while Gram-positive organisms cause a majority of late infections. With the institution of prophylaxis, *Pneumocystis jirovecii* has become a rare complication of allogeneic transplants. It usually presents late in patients on immunosuppressive therapy for GVHD and not receiving adequate prophylaxis. Treatment is a prolonged course of trimethoprim-sulfamethoxazole, but mortality remains high, approaching 50%.² Invasive pulmonary aspergillosis is the most common fungal infection with an incidence of 5–30% in allogeneic HSCT.³ It occurs most commonly in the pre-engraftment and late phases, and prophylaxis with the newer azoles is recommended for patients who are neutropenic for >2 weeks and those on immunosuppressive therapy for GVHD.^{2,3}

Cytomegalovirus (CMV) pneumonia occurs in the post-engraftment and late phases with an incidence of approximately 20–35% in allogeneic transplants.² It typically requires tissue biopsy for diagnosis, but pre-emptive diagnosis can be made via bronchoalveolar lavage and PCR. The standard of care for the treatment of CMV pneumonia is ganciclovir and CMV immunoglobulin. Mortality is high, especially if respiratory failure ensues.⁴

Non-infectious pulmonary complications in the post-HSCT period should be divided into early, acute lung injury syndromes such as periengraftment respiratory distress syndrome (PRDS), diffuse alveolar haemorrhage (DAH) and idiopathic pneumonia syndrome (IPS); and late such as bronchiolitis obliterans (BO), cryptogenic organising pneumonia (COP), post-transplant lymphoproliferative disorder and pulmonary veno-occlusive disease.¹ The development of late-onset pulmonary complications is associated with reduced overall survival.⁵ If pneumonia was not the cause of our patient's dyspnoea and hypoxic

respiratory failure, late non-infectious pulmonary complications were considered next.

BO has an insidious presentation including dry cough and dyspnoea. Diagnosis requires meeting several criteria including: allogeneic transplant recipient, chronic GVHD in other organs, evidence of airflow obstruction with FEV1/FVC <0.7 and FEV1 <75% predicted, and air trapping or small airway thickening on HRCT; in the absence of infection. Pathological confirmation is not required if all criteria are met. Overall estimated mortality is 12% at 5 years and 18% at 10 years.⁶ Some patients will have rapid deterioration in lung function leading to respiratory failure within a few months while others stabilise or even have improved lung function with treatment. Similar to the lung transplant population, where BO is thought to equal chronic allograft rejection, BO in the patient who has undergone HSCT may represent a continuum of chronic GVHD with acute GVHD being an important risk factor.⁷

COP is an idiopathic form of organising pneumonia, which presents in a manner similar to BO, but is characterised pathologically by excessive proliferation of granulation tissue within small airways and alveolar ducts associated with chronic inflammation in the surrounding alveoli. The incidence is lower (<2%), and it can occur in autologous and allogeneic transplant recipients compared to BO. Furthermore, pulmonary function testing usually shows a restrictive pattern with low diffusion capacity.⁸ In this case, the possibility of chronic GVHD of the lung manifesting as BO, COP or other less common forms became the most likely diagnosis.

AFOP is a rare but potentially under-recognised clinical entity. It was first described in 2002 by Beasley *et al*⁹ as a possible variant of DAD. It has been reported in association with connective tissue diseases, adverse drug reactions and inhalational injury. A few case reports described AFOP in the post-allogeneic HSCT period and suggested that this pathological entity is a manifestation of chronic GVHD of the lung, and should be treated as such.^{10,11} The diagnosis of BO as a form of chronic GVHD of the lung was inferred from data on lung transplant recipients, as seems to be the case with AFOP.¹²

The presentation is variable with acute to subacute symptoms. The illness can range from mild, self-limited when described in association with other conditions such as connective tissue disease, drug-related or idiopathic; to severe, causing respiratory failure and death when described in association with allogeneic transplant recipients. The diagnosis is based on the hallmark

Table 1 Pulmonary complications at different phases of the post-stem cell transplant period

Pulmonary complications	Phase I—pre-engraftment (0–30 days)	Phase II—postengraftment (30–100 days)	Phase III—late (>100 days)
Infectious	Gram (–) bacteria Gram (+) bacteria (eg, Staph, Strep) <i>Aspergillus</i> <i>Candida</i> <i>Pneumocystis</i> HSV Respiratory viruses (eg, RSV, influenza, adenovirus)	Gram (+) bacteria <i>Aspergillus</i> <i>Candida</i> <i>Pneumocystis</i> CMV Respiratory viruses	Encapsulated bacteria <i>Nocardia</i> <i>Aspergillus</i> <i>Candida</i> <i>Pneumocystis</i> CMV HZV Respiratory viruses
Non-infectious	ADHF PRDS DAH	IPS DAH PVOD COP	COP BO PVOD PTLPD

ADHF, acute decompensated heart failure; BO, bronchiolitis obliterans; CMV, cytomegalovirus; COP, cryptogenic organising pneumonia; DAH, diffuse alveolar haemorrhage; HSV, herpes simplex virus; HZV, herpes zoster virus; IPS, idiopathic pneumonia syndrome; PRDS, periengraftment respiratory distress syndrome; PTLPD, post-transplant lymphoproliferative disorder; PVOD, pulmonary veno-occlusive disease; RSV, respiratory syncytial virus.

intra-alveolar fibrin deposition on a background of organising pneumonia on histopathology.⁹ Owing to its rarity, there are no consensus guidelines for therapy but immunosuppression has been used in case reports with variable response rates.¹³ This form of therapy holds true when the condition is treated as a manifestation of chronic GVHD of the lung.¹¹

Classically, the most common pathological diagnosis in chronic GVHD of the lung is BO, which is characterised by airway obstruction on PFT. This seems to be seen with AFOP as well, as evident in studies from lung transplant recipients with biopsy-proven AFOP. The results showed that out of 87 patients who developed chronic allograft rejection, 25% had AFOP, and a minority of them had an obstructive pattern. The study also showed that survival was significantly worse in patients who developed AFOP than in those who developed BO (median time to death 101 vs 294 days, $p < 0.02$).¹²

The mainstay of therapy for GVHD is immunosuppression using systemic steroids, usually prednisone 1 mg/kg/day followed by a slow taper.¹⁴ Alternatively, pulse dosing of prednisone with 10 mg/kg/day for 3 days at 4-week intervals for a total of two cycles has been used, and showed improvement or stabilisation of disease. However, treatment response often does not persist, and other agents have been used as second-line and third-line options including mTOR inhibitors (eg, everolimus), calcineurin inhibitors (eg, tacrolimus), mycophenolate mofetil, imatinib and azithromycin.¹⁴

Experimental drugs that have been used include tumour-necrosis factor α (TNF- α) inhibitors (eg, infliximab, etanercept), but the role of TNF in the development of pulmonary GVHD is not well understood, and any evidence to support their use comes from case reports. Specifically for AFOP, Lee Simmons *et al*¹¹ reported successful treatment with etanercept 25 mg SQ twice weekly for 4 weeks in addition to pulsed methylprednisolone and tacrolimus. Finally, clinical trials examining the use of bortezomib for the treatment of chronic GVHD are underway and show initial promise.¹⁵

Reflecting on this case highlights the difficulty in discerning the exact pathology causing respiratory failure in allogeneic HSCT recipients (table 1). What remains clear is that infection should always be considered first, especially in the

pre-engraftment phase and only when that is ruled out should other non-infectious complications be investigated.

Chronic GVHD of the lung remains a poorly understood entity with variable manifestations, but should be considered in all patients presenting with respiratory symptoms in the post-HSCT period. AFOP is a distinct histological variant that appears to be a manifestation of chronic GVHD of the lung. Immunosuppression with systemic steroids is the mainstay of treatment, but the prognosis remains poor, especially in hypoxic respiratory failure. Clinical trials targeting TNF- α and proteasomes are underway and show initial promise.

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Learning points

- ▶ Chronic graft-versus-host disease (GVHD) of the lung remains a poorly understood entity with variable manifestations, but should be considered in all patients presenting with respiratory symptoms in the posthaematopoietic stem cell transplantation setting.
- ▶ Acute fibrinous and organising pneumonia (AFOP) is a histological variant associated with chronic GVHD of the lung.
- ▶ Immunosuppression with systemic steroids is the mainstay of treatment, but clinical trials targeting tumour-necrosis factor α and proteasomes are underway and show initial promise.

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