Diffuse Alveolar Hemorrhage Following Allogeneic Peripheral Blood Stem Cell Transplantation: A Case Report and A Short Review

Sanjeev Kumar Sharma · Suman Kumar ·
Avinash Kumar Singh · Tulika Seth · Pravas Mishra ·
Sanjay Sharma · Manoranjan Mahapatra

Received: 28 January 2012 / Accepted: 2 August 2012 / Published online: 21 August 2012
© Indian Society of Haematology & Transfusion Medicine 2012

Abstract Pulmonary complications are one of the most common causes of morbidity and mortality in patients undergoing peripheral blood stem cell transplantation. Both infective and non-infective etiologies can involve the lungs during this period and differentiating them clinically is a challenging task and management differs in each case. We present here a case of acute myeloid leukemia, in whom following allogeneic peripheral blood stem cell transplantation, diffuse alveolar hemorrhage developed.

Keywords Allogeneic stem cell transplant · Pulmonary complications · Diffuse alveolar hemorrhage

Introduction

The lungs are the most common organs involved by infective or non-infective pathologies in post-transplant patients. Clinical, radiological and microbiological parameters are helpful in reaching the diagnosis, but these may not be sufficient at times and supportive management has to be done. Since infective etiologies are now being better managed, non-infective causes of severe pulmonary damage remain a serious concern. Diffuse alveolar hemorrhage (DAH) is one of such a cause which needs a high index of suspicion and carries a high mortality. It needs to be

differentiated from infections like, cytomegalovirus (CMV) and pneumocystis jiroveci pneumonia (PCP), as treatment and prognosis differs. This short review highlights the common causes of pulmonary complications following stem cell transplantation and their management.

Case Summary

A 44-years-old woman was diagnosed as acute myeloid leukemia (FAB, AML M4) with complex cytogenetics and she had received 3 + 7 induction chemotherapy (daunorubicin 60 mg/m² for 3 days and cytarabine 100 mg/m² continuous intravenous infusion for 7 days) and was in remission. Following this she was given one course of high dose cytarabine (HIDAC, 3 g/m² twice daily on days 1, 3 and 5). She had a 6/6 HLA matched sibling and was taken up for sibling matched allogeneic peripheral stem cell transplantation after first HIDAC. Pre-transplant pulmonary function test and computed tomograph (CT) scan of chest were normal. She was given conditioning with busulfan (3.2 mg/kg/day for 4 days) and cyclophosphamide (60 mg/kg/day for 2 days). Graft versus host disease prophylaxis included cyclosporin (5 mg/kg/day in two divided doses, titrated according to serum levels) and methotrexate (15 mg/m² on D + 1 and 10 mg/m² on D + 3, D + 6, D + 11). The total stem cell dosage transfused was 6.26 × 10⁶/kg CD34 + cells. She developed grade 3 oral mucositis, loose stools and fever (101 °F) on day +4. Physical examination was unremarkable except for oral mucositis. She was started on intravenous antibiotics (meropenem 1 g q8H and teicoplanin 400 mg q12H for three doses followed by q24H) as per institutional policy. Blood and urine cultures were sterile and stool was negative for clostridium difficile. She became afebrile on day +7. Though neutrophils engrafted on day +9, she continued to require single donor platelet

S. K. Sharma (✉) · S. Kumar · A. K. Singh · T. Seth ·
P. Mishra · M. Mahapatra
Department of Hematology, All India Institute of Medical
Sciences, New Delhi, India
e-mail: sksanjeev13@yahoo.com

S. Sharma
Department of Radiology, All India Institute of Medical
Sciences, New Delhi, India

(SDP) transfusions for thrombocytopenia. On day +10 she developed mild breathlessness and chest examination revealed fine crackles in the left infrascapular area. Considering engraftment syndrome (ES) she was given furosemide 40 mg twice daily and methylprednisolone 125 mg once daily intravenously. She was also started on anti-fungals (voriconazole 400 mg daily orally). However, breathlessness progressively increased with occasional cough with blood tinged sputum. Arterial blood gas analysis revealed hypoxemia with low arterial oxygen gradient (pH 7.31, PCO_2 34 and PaO_2 76) while on 5 l of oxygen support. Chest radiograph and CT scan showed bilateral pulmonary infiltrates with peripheral sparing (Fig. 1). Sputum and later endotracheal tube aspirate examination for gram staining, fungal elements, pneumocystis jiroveci and CMV inclusion bodies were negative. Because of progressive respiratory failure, patient required ventilatory support and expired after 2 days. Blood CMV-DNA by quantitative PCR (reported later) was negative.

Discussion

There are mainly six main differentials of early pulmonary involvement post-transplant (Table 1). These are (1) pulmonary edema (PE), (2) transfusion associated acute lung injury (TRALI), (3) ES, (4) idiopathic pulmonary syndromes (IPS) including DAH, (5) infections notably pulmonary aspergillosis, CMV and PCP and (6) drug toxicity. Differentiating these conditions may be difficult but definite diagnosis is very helpful in the final outcome of the patient. Certain conditions like PE and ES are easily treatable whereas DAH is highly fatal. PE is treated with diuretics, ES may be treated with steroids, fungal infections with anti-fungals and DAH with supportive treatment. Our patient developed immediate post-transplant pulmonary complications which unfortunately proved fatal. She was already on anti-fungals and did not respond to diuretics and

steroids and required ventilator support. There was no other organ involvement. We discuss here both the non-infective and infective causes of pulmonary complications that can develop in the immediate post-transplant period and the probable cause of death in our patient (Table 1).

Non-infectious Pulmonary Complications in the Immediate Post-transplant Period

Non-infectious causes are a major contributor to the pulmonary complications in the post-transplant setting, and can be PE, TRALI, ES and DAH [1, 2]. PE is reported in up to 65 % patients and is due to fluid overload, which is aggravated by chemotherapy and septicemia and is caused by capillary membrane leakage. It is diagnosed clinically. Chest radiographic findings are typical of PE with bilateral diffuse pulmonary opacities often accompanied by Kerley B lines. Patients usually respond to diuretics and fluid restriction.

Differentiating PE from TRALI may be difficult [3, 4]. TRALI is as an acute lung injury that is related to a transfusion of blood products (fresh frozen plasma and platelets) and usually develops within 6 h of transfusion. Antibodies directed toward human leukocyte antigens have been implicated. Treatment for TRALI is primarily supportive and many patients may need mechanical ventilation, though mortality is low. Our patient was getting SDP transfusions and developed breathlessness about 10 h later which proved fatal. ES—it represents a form of diffuse alveolar damage [5], and is thought to be due to a spurt of cytokine production during engraftment. It is a diagnosis of exclusion and occurs in approximately 30–40 % of patients following BMT. Clinically, the patient presents with skin rash, dyspnea, fever, non-productive cough and hypoxemia and may be treated with steroids. The chest radiographic findings include bilateral pleural effusions, transient pulmonary infiltrates

Fig. 1 The chest radiograph (a) and CT scan (b) showing diffuse alveolar opacities

Table 1 Cause of pulmonary involvement during early post-transplant period

S. no.	Differential diagnosis	Clinical features	Signs	Predisposing factors	Radiology	Usual treatment
1	PE	Breathlessness, orthopnea	Basal fine crackles	Fluid overload	Bilateral pulmonary infiltrates, Kerley B lines	Fluid restriction, diuretics
2	TRALI	Breathlessness	Hypoxia, cytopenias	Anti-bodies to HLA	Bilateral pulmonary infiltrates	Supportive care
3	ES	Fever, skin rash, breathlessness	Rash, effusions	Cytokine release, capillary leakage	Pleural effusions, pulmonary infiltrates	Glucocorticoids
4	DAH	Breathlessness, cough	Hypoxia, tachypnea	Not known	Bilateral diffuse ground glass and patchy consolidation	Supportive, steroids
5	CMV pneumonia	Fever, breathlessness, cough	Hypoxia, tachypnea	Immuno-compromised state, steroids use, T cell depletion	Diffuse GGO and nodules, mainly in the mid and lower zones	Ganciclovir, immunoglobulins
6	PCP	Fever, non-productive cough	Hypoxia, tachypnea, chest signs less	Immuno-compromised state, steroids use, T cell depletion	Bilateral interstitial-alveolar infiltrates	Trimethoprim and sulfamethoxazole
7	Other infections (bacterial and fungal viz. aspergillus)	Fever, chest pain, cough	Bronchial breath sounds	Neutropenia, mucosal injury	Consolidations, halo sign	Antibacterials, anti-fungals (voriconazole, ecinocandins)
8	Drug toxicity	Breathlessness	Occasional crackles	Low FEV1/VC	Non-specific	Supportive

and interstitial PE. Our patient did not have rash or fever and had no response to steroids.

Two types of acute lung injury syndromes—IPS and DAH—can develop post-transplant. Pathogenesis may involve activation of inflammatory cascades by chemotherapeutic conditioning regimens and T cell alloreactivity. DAH is a common entity and has been reported in 2.5–20 % of patients after HSC transplantation with mortality ranging from 50 to 80 % [6, 7]. Clinically, the patient presents with acute dyspnea, non-productive cough and hypoxia [8]. Frank hemoptysis is uncommon and the clinical signs may be slight despite the rapid deterioration in radiographic appearances. Chest radiographic findings are non-specific and include bilateral diffuse ground glass and patchy consolidation, predominantly perihilar and in the lower lung zones. Bronchoalveolar lavage may show a bloodier lavage fluid and hemosiderin laden macrophages. DAH is considered as a subset of IPS. It is associated with poor prognosis and shows variable response to high dose steroids [6, 9]. Our patient had streaks of blood in the sputum and she deteriorated rapidly with no response to steroids. Her CT scan showed bilateral alveolar opacities suggestive of alveolar hemorrhage (Fig. 1). Because of rapid deterioration of general condition, she could not be taken up for BAL. Her endotracheal tube aspirate was blood tinged and she did not have bleeding from any other site.

Drug toxicity though implicated in chronic lung injury, can rarely cause acute lung toxicity and is associated with chemotherapeutic agents such as bleomycin, methotrexate and busulfan. Radiology findings are variable and non-specific [10] and diagnosis is by excluding other causes.

Infectious Pulmonary Complications in the Immediate Post-transplant Period

Though bacterial infections are common in the neutropenic phase, death from these infections has decreased due to the wide usage of broad-spectrum antibiotics. Fungal infections are a common cause of pneumonia following BMT with an incidence of up to 50–70 % [11, 12]. The most common pathogen is aspergillus. In the immunocompromised, aspergillus may be angioinvasive, invading blood vessels and causing hemorrhagic infarction. Clinically, the patient may present with fever, dyspnea, dry cough, pleuritic pain and sometimes hemoptysis. On HRCT, early angioinvasive aspergillosis characteristically shows a “halo sign” which represents hemorrhagic infarction around the consolidated fungal infection.

Cytomegalovirus and PCP may present in the early phase post BMT between 30 and 100 days, or even earlier. CMV infections can occur in up to 70 % of patients following BMT. It is of considerable clinical importance in all

types of allogeneic BMT, and once pneumonitis develops there is a high mortality rate (about 85 %) [13]. Plain radiographic findings include areas of diffuse ground glass change, and nodules, mainly in the mid and lower zones. HRCT findings include multiple micronodules and associated areas of consolidation or ground glass attenuation. BAL can aid in the diagnosis, though CMV culture is positive in 25–29 % of immunocompromised patients [14]. In PCP clinical signs and symptoms are not distinct from other causes of diffuse pneumonia. Chest radiographs usually reveal bilateral interstitial-alveolar infiltrates, although isolated nodules, lobar consolidation, and even normal radiographs have also been reported. The characteristic HRCT finding is ground glass attenuation, which may be diffuse, predominantly perihilar or patchy in distribution with peripheral sparing. Diagnosis is usually confirmed by BAL and prognosis is poor [15]. DAH usually develops within first 30 days of transplantation [6] whereas PCP is generally seen after 30 days [2], though rarely late onset DAH can occur. Sputum and later endotracheal tube aspirate examination of our patient did not show any infective pathogen and was negative for CMV inclusion bodies (Cowdry type A intranuclear inclusion bodies) and *Pneumocystis jiroveci*. The BMT patients who develop pulmonary complications and require mechanical ventilation have a low survival rate [16].

Conclusion

Though there are limited differentials for major pulmonary complications post-transplant, early diagnosis remains a challenge and morbidity and mortality depends on the cause of pulmonary complication with treatment directed accordingly. Because of the immunocompromised state infections can not be entirely ruled out, though they can be effectively treated to a major extent. Strategies predicting occurrence and the management of DAH, which is the most fatal non-infectious pulmonary complication, still need to be evaluated, to improve the outcome of transplant recipients.

Conflict of Interest The authors have declared that no conflict of interest exist.

References

1. Chan CK, Hyland RH, Hutcheon MA (1990) Pulmonary complications following bone marrow transplantation. *Clin Chest Med* 11:323–332
2. Wah TM, Moss HA, Robertson RJH, Barnard DL (2003) Pulmonary complications following bone marrow transplantation. *Br J Radiol* 76:373–379
3. Gajic O, Gropper MA, Hubmayr RD (2006) Pulmonary edema after transfusion: how to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury. *Crit Care Med* 34:109–113
4. Silliman CC, McLaughlin NJ (2006) Transfusion-related acute lung injury. *Blood Rev* 20:139–159
5. Cahill RA, Spitzer TR, Mazumder A (1996) Marrow engraftment and clinical manifestations of capillary leak syndrome. *Bone Marrow Transplant* 18:177–184
6. Afessa B, Tefferi A, Litzow MR, Krowka MJ, Wylam ME, Peters SG (2002) Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. *Am J Respir Crit Care Med* 166: 641–645
7. Sharma S, Nadrous HF, Peters SG, Tefferi A, Litzow MR et al (2005) Pulmonary complications in adult blood and marrow transplant recipients. *Chest* 128:1385–1392
8. Lara AR, Schwarz MI (2010) Diffuse alveolar hemorrhage. *Chest* 137:1164–1171
9. Raptis A, Mavroudis D, Barrett AJ, Suffredini AF, Molldrem J (1999) High-dose corticosteroid therapy for diffuse alveolar hemorrhage in allogeneic bone marrow stem cell transplant recipients. *Bone Marrow Transplant* 24:879–883
10. Abid SH, Malhotra V, Perry MC (2001) Radiation-induced and chemotherapy-induced pulmonary injury. *Curr Opin Oncol* 13: 242–248
11. Leung AN, Gosselin MV, Napper CH, Braun SG, Hu WW et al (1999) Pulmonary infections after bone marrow transplantation: clinical and radiographic findings. *Radiology* 210:699–710
12. Mori M, Galvin JR, Barloon TJ, Gingrich RD, Stanford W (1991) Fungal pulmonary infections after bone marrow transplantation: evaluation with radiography and CT. *Radiology* 178:721–726
13. Sable CA, Donowitz GR (1994) Infections in bone marrow transplant recipients. *Clin Infect Dis* 18:273–281
14. Tamm M, Traenkle P, Grill B, Solèr M et al (2001) Pulmonary cytomegalovirus infection in immunocompromised patients. *Chest* 119:838–843
15. Tuan IZ, Dennison D, Weisdorf DJ (1992) *Pneumocystis carinii* pneumonitis following bone marrow transplantation. *Bone Marrow Transplant* 10:267–272
16. Huaranga AJ, Leyva FJ, Giralt SA, Blanco J, Signes-Costa J et al (2000) Outcome of bone marrow transplantation patients requiring mechanical ventilation. *Crit Care Med* 28:1014–1017