

Non Infectious Pulmonary Complications after Bone Marrow Transplant with a Special Focus on Idiopathic Pneumonia Syndrome

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Abstract

Pulmonary complications are a significant cause of early mortality (up to 100 days) after hematopoietic stem cell transplantation (HSCT). While infectious complications particularly due to opportunistic pathogens are common in these patients, diffuse lung injury is a non-infectious complication occurring in 25-50% of HSCT recipients. The incidence of this complication is higher with allogeneic as apposed to autologous transplants and is largely dependant on the method of graft versus host prophylaxis. The spectrum includes interstitial pneumonitis (IP), bronchiolitis obliterans (BO), diffuse alveolar hemorrhage (DAH) and noncardiogenic capillary leak syndrome (NCLS). In 1993 a panel convened by the National Institutes of Health (NIH) defined widespread alveolar injury following HSCT that occurs in the absence of an active lower respiratory tract infection and cardiogenic causes as the idiopathic pneumonia syndrome (IPS). IPS is a clinical syndrome with

variable histopathologic correlates and several potential etiologies. Peri-engraftment respiratory distress syndrome (PERDS) and delayed pulmonary toxicity syndrome (DPTS) are also included within the definition of IPS. Histopathologic findings associated with IPS include diffuse alveolar damage with hyaline membranes, lymphocytic bronchitis and bronchiolitis obliterans organizing pneumonia (BOOP). The pathophysiology involves four distinct mechanisms, namely: the toxic effects of chemotherapy, immune dysregulation, alloreactive donor cells and host cell responses. The roles of lipopolysaccharide (LPS), monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor (TNF) in the genesis of endothelial cell injury are being defined. Therapy for IPS includes supportive care and immunosuppressive agents. The role of TNF antagonists is being studied in ongoing clinical trials.

Key words: Hematopoietic stem cell transplant, bone marrow transplant, noninfectious, idiopathic pneumonia syndrome, pulmonary toxicity.

Pulmonary complications are a significant cause of morbidity and early mortality (before day 100) after hematopoietic stem cell transplantation (HSCT). The pulmonary complications include infectious and

noninfectious disorders. The spectrum of noninfectious pulmonary complications occurring in HSCT recipients is summarized in **Table 1**. Diffuse lung injury is a major non-infectious complication following HSCT occurring in 25–50% of patients. This syndrome is typically difficult to diagnose antemortem, frequently leading to a delay in diagnosis. Early bronchoscopy allows for the exclusion of infectious complications, however, the therapeutic options for most forms of diffuse lung injury remain limited.

Teshima and colleagues reported significant pulmonary pathology at autopsy in 63 of the 71 patients (89%) who died following HSCT [1]. The results of this study are shown in **Table 2**. Of the 96 pulmonary

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complications identified at autopsy, only 27 (28%) were diagnosed ante mortem. Most of the patients who were being treated for suspected infections did not have the suspected infections at autopsy. Indeed, noninfectious etiologies accounted for 69 of the 96 autopsy findings (72%). Diffuse alveolar damage (DAD) and diffuse alveolar hemorrhage (DAH) were the most common noninfectious pulmonary findings. Bronchiolitis obliterans organizing pneumonia (BOOP) and bronchiolitis obliterans (BO) were rare.

Acute lung injury (ALI) can be present with any of the entities mentioned above. Drug toxicity from the chemotherapy regimen given prior to HSCT, from the conditioning regimen given as part of the HSCT and from various supportive therapies has been described. Arimura and colleagues described a healthy HSCT donor who developed ALI after 4 days of granulocyte colony stimulating factor (G-CSF) administration [2]. The serum interleukin-1 beta (IL-1 beta) level was elevated on day 4 and was implicated pathogenetically in this case. G-CSF is commonly administered to healthy donors to mobilize peripheral blood stem cells for allogeneic HSCT. Adverse events from G-CSF use in healthy donors have been described in approximately 30% of cases, and are comprised predominantly of bone pain, headache, and general fatigue. Pulmonary complications caused by G-CSF include cough, dyspnea, and interstitial or alveolar pulmonary edema with mild-to-severe deterioration of blood oxygen level.

Idiopathic Pneumonia Syndrome (IPS)

In 1993, a panel convened by the National Institute of Health (NIH) in the US defined widespread alveolar injury following HSCT that occurs in the absence of an active lower respiratory tract infection and cardiogenic causes as idiopathic pneumonia syndrome (IPS) [3]. As shown in **Table 3**, diagnostic criteria of IPS include signs and symptoms of pneumonia, lobar radiographic infiltrates, abnormal pulmonary function and the absence of infectious organisms as determined by broncho-alveolar lavage (BAL) or lung biopsy. The panel was careful to stress that they considered this definition to be a clinical syndrome with variable

histopathologic correlates and several potential etiologies. Histopathology findings associated with IPS include DAD with hyaline membranes, lymphocytic bronchitis and BOOP. Risk factors and presumed etiologic agents are shown in **Tables 4** and **5**.

The incidence of IPS after allogeneic HSCT is difficult to determine but ranges from 20% in patients who have undergone conditioning protocols that include total body irradiation (TBI) down to 7.6% in patients for whom irradiation was not included in the conditioning protocol. Kelemen *et al* [4] reported an IPS incidence of 5.5% in their HSCT recipients. Nonmyeloablative conditioning, also referred to as dose reduced conditioning entails less intense conditioning such that the host marrow cells are not completely eradicated prior to HSCT. Presumably the subsequent elimination of malignant cells is achieved by a “graft versus leukemia” effect rather than by total ablation of the host bone marrow. This method of conditioning avoids the prolonged pancytopenia and prolonged immunosuppression observed with conventional myeloablative conditioning. Fukuda *et al* [5] compared the incidence and outcome of IPS among patients who underwent allogeneic HSCT after nonmyeloablative (n=183) and conventional (n=917) conditioning. The cumulative incidence of IPS was significantly lower at 120 days following nonmyeloablative conditioning than after conventional conditioning (2.2 vs. 8.4%; $p < 0.003$). Grades III–IV acute graft-versus host disease (GVHD) was independently predictive for developing IPS after adjusting for other risk factors. In addition, patient age greater than 40 years and diagnosis of acute leukemia or myelodysplastic syndrome (MDS) were associated with significantly increased risks for IPS. Among the older patients who received conventional conditioning, high-dose (X12 Gy) TBI was associated with an increased risk for IPS than were non-TBI-based regimens (16 vs 5.8%; $p < 0.001$). These findings suggest that the intensity of HSCT conditioning plays an important role in the development of IPS. In the study by Fukuda *et al* [5], IPS progressed rapidly once diagnosed and was associated with a high mortality rate (75%) despite aggressive support. Initiation of mechanical ventilation and the presence of renal insufficiency at IPS onset were associated with an

increased risk of death.

Nusair and colleagues reviewed 53 consecutive patients who had undergone HSCT after nonmyeloablative conditioning, of these 49 were fully HLA matched [6]. The conditioning protocol consisted of fludarabine, oral busulfan and anti-thymocyte globulin (ATG) for four consecutive days. Treatment included prophylaxis against GVHD with intravenous cyclosporine. Eleven patients with residual disease or mixed chimerism in the absence of GVHD were treated with donor lymphocyte transfusions to augment the "graft versus tumor effect". All patients received infection prophylaxis against *P. carinii* pneumonitis and screened for cytomegalovirus (CMV) with weekly testing. Fiber optic bronchoscopy (FOB) was performed within 24 to 48 hours in patients who developed focal or diffuse pulmonary infiltrates. Those with nodular infiltrates underwent FOB or CT guided fine needle aspiration. IPS is defined by the presence of diffuse nonlobar radiographic infiltrates accompanied by signs and symptoms of pneumonia and physiological changes such as hypoxemia and an increasing alveolar to arterial oxygen gradient, and bronchoalveolar lavage (BAL) examination results that do not reveal a possible infectious agent. Findings from histological specimens, when obtained, range from interstitial mononuclear infiltrates and edema to diffuse alveolar damage with alveolar epithelial necrosis, intra-alveolar hyaline membranes and type 2 alveolar cell hyperplasia. Of the patients reviewed in the present study, 17 (32%, 95% CI 20-46%) developed pulmonary complications. There were only two (3.8%, 95% CI 0-13%) patients in whom a diagnosis of IPS was made. One patient who had undergone transplantation because of non-Hodgkin's lymphoma developed pulmonary infiltrates and respiratory failure 2 months after transplantation. Notably, this patient had received mediastinal radiotherapy as part of a previous treatment for lymphoma. The other patient, who had undergone transplantation for myelodysplastic syndrome, developed fever and bilateral diffuse pulmonary infiltrates 8 months after transplantation; however, there had been no previous exposure to irradiation. Of the 53 patients 29 patients died, with 35 patients surviving beyond 100 days. Only two of the

deaths were due to IPS.

Peri-engraftment respiratory distress syndrome (PERDS) and delayed pulmonary toxicity syndrome (DPTS) are also included within the definition of IPS. PERDS and DPTS typically occur after autologous HSCT, and both are characterized by fever, dyspnea and hypoxemia [7]. By definition, PERDS occurs within 5 days of engraftment, whereas the onset of DPTS may be delayed for months and commonly occurs following conditioning regimens that contain cyclophosphamide, cisplatin and bischloroethylnitrosurea (BCNU) [7].

Late Onset Noninfectious Pulmonary Complications (LONIPCs)

Late-onset noninfectious pulmonary complications (LONIPCs) occurring beyond 3 months after allo-HSCT may be a life threatening complication that reduces the recipient's quality of life [8]. The spectrum of LONIPCs is undefined. Palmas *et al* proposed that LONIPCs include BO, BOOP, DAD, lymphocytic interstitial pneumonia (LIP), and nonclassifiable interstitial pneumonia (NCIP) [9]. The etiology of LONIPCs is unclear, however, it is presumed to result from alloreactive T cells with GVHD having a protective role.

Palmas *et al* reported the incidence of LONIPCs was 10% after allogeneic bone marrow transplantation, with 5 of 18 patients with LONIPCs succumbing from progressive respiratory failure after a median follow-up of 13.5 months [9]. Duncker *et al* reported that 14.8% of HSCT recipients developed LONIPC with a mortality of 27.5% [10]. Sakaida and colleagues performed a retrospective analysis of 76 patients who had survived more than three months post allogeneic HSCT with no relapse [8]. Among the 76 patients, 18 patients (23.7%) developed LONIPCs at a median interval of 227 days post-transplant (range 91-1105 days). The patients with LONIPCs were further subclassified as having bronchiolitis obliterans (6 patients) or interstitial pneumonitis (12 patients). Eight LONIPC patients (44.4%) died. The duration from the diagnosis of LONIPCs to death ranged from 1.1 to 45.7 months. Overall survival of the LONIPC patients was not longer than that of non-LONIPC patients.

The pathogenesis of LONIPCs is still unclear, but the presence of chronic GVHD has been taken as a risk factor for developing LONIPCs [10,12]. Differences in minor histocompatibility antigens between the donor and recipient has been suggested to be important factor in the pathogenesis of LONIPCs. Sicca syndrome and bronchial gland involvement in LONIPCs may be caused by chronic GVHD. It is postulated that donor allo-reactive lymphocytes attack the bronchial glands and make the respiratory tract dry, decreasing immunoglobulin secretion. In previous reports, other risk factors for LONIPCs were chronic myeloid leukemia, inclusion of busulfan in the conditioning regimen, methotrexate and steroids given as GVHD prophylaxis [11,13,7].

Mechanisms of Lung Injury

The role of chemokines

Chemokines are small (8-14 kd) proteins that regulate leukocyte functioning and migration during inflammation [14]. Following tissue injury the up-regulation of adhesion molecules on endothelial surfaces causes tethering and rolling of circulating leukocytes, adhesion via cell surface integrins, diapedesis and extravasation into the lung tissue. Chemokines act as migratory signals guiding inflammatory cells to the site of injury with the cell surface receptors determining the cellular specificity of the chemokines. IPS is associated with an increase of CC chemokines (MCP-1, MIP-1alpha, RANTES and C10) and a CXC chemokine (IP10) that attracts T cells and monocytes in the lung by day 7 post HSCT. These increases are dependent on the co-infusion of allogeneic T cells with the bone marrow inoculum.

The role of the vascular endothelium

Vascular endothelial cells are the primary barrier separating donor derived cellular effectors and GVHD target organs. Endothelial cell (EC) injury has been observed after allogeneic HSCT has been implicated as a direct contributor to the development of several complications including GVHD, veno-occlusive disease (VOD) and endothelial leak

syndrome (ELS). The adhesion of leukocytes to the micro-vascular endothelium is critical for their infiltration into the tissues. TNF alpha, IL-1, LPS and IFN gamma may directly damage or activate the vascular endothelium. Lung injury after allogeneic BMT is associated with enhanced pulmonary vascular ICAM-1 expression. TNF alpha has been shown to regulate the intrapulmonary expression of ICAM-1 and ICAM-1 has a major role in the development of lung inflammation in various experimental modules. When mice deficient in ICAM-1 were subjected to allogeneic and syngeneic HSCT (as a control) and compared for development of lung injury and systemic GVHD, the absence of ICAM-1 in the host tissues was associated with a dramatic decrease in lung histopathology noted at 4 weeks and persisting through 7 weeks with a decrease in BAL fluid levels of total cells, CD4 and CD8 T cells, TNF alpha and IFN gamma levels. This was independent of cyclophosphamide and total body irradiation conditioning. The administration of an ICAM blocking antibody significantly reduced the severity of lung histopathology at 6 weeks post HSCT [15].

The role of alloreactive T cells

Donor T cells are critical to the early proinflammatory events associated with lung injury that develops within the first week of HSCT across MHC antigens, whereas in minor H antigen mismatch systems, donor lymphocytes continue to respond to host antigens and contribute to physiologically significant lung injury at later time points. Donor T cell clones that recognize CD45 polymorphisms result in a rapidly progressive pulmonary vasculitis within 3 days of their injection into nonirradiated recipients. Despite the experimental data supporting a role for alloreactive donor lymphocytes in the development of IPS, noninfectious lung injury has been reported in patients in whom systemic GVHD is mild or absent, making a causal relationship between the two entities difficult to establish [16].

The role of dendritic cells

Pulmonary dendritic cells play a critical role in the initiation and regulation of immune responses

in the lung, and recent data suggest that they are important to both acute and chronic rejection of lung allografts. The necessity of host APCs for the generation of acute GVHD has been demonstrated in a CD8 β T cell driven GVHD model. These results were recently extended to show that alloantigen expression on host APCs alone is both necessary and sufficient to induce a graft-versus-host reaction and that GVHD target organ damage can be mediated by inflammatory cytokines [1]. Activated donor T cells that can cause progressive lung injury might therefore remain within the pulmonary microvascular circulation because persistent hosts DCs function as a continuing site of allo antigen presentation. This scenario could account for the apparent 'sanctuary' status of the lung with respect to alloreactive donor T cells and may have important implications with regard to the evaluation and treatment of IPS after allogeneic SCT even when clinical GVHD is absent. The role of donor accessory cells A significant body of experimental data suggests that synergistic interactions between cells from the lymphoid and myeloid lineage are critical to the development of GVHD.

The role of neutrophils

Although not traditionally considered essential to the induction of GVHD, neutrophils are consistently identified in target tissues collected from both mice and humans. Neutrophilia is also prominent finding in several forms of immune-mediated lung injury including acute respiratory distress syndrome (ARDS) and in bronchiolitis obliterans syndrome (BOS), characteristic of lung allograft rejection [17-19]. PMN products such as elastase, myeloperoxidase, metalloproteinases and oxidants are abundant in the BAL fluid of patients with ARDS and are believed to contribute to the endothelial and epithelial damage that occurs in this setting. Furthermore, increases in PMN activation markers may also be early indicators of BOS after lung transplant. Neutrophils are likely to play a role in lung injury after SCT as well. PMNs are a major component of the inflammatory infiltrates seen in animals with IPS, and their appearance in the bloodstream is often temporally associated with lung injury in the clinical setting.

The recruitment of leukocytes from the vascular space and into target tissue can be divided into four steps: (1) weak adhesion of WBCs to the vascular endothelium, (2) firm adhesion of WBCs to endothelial cells, (3) transmigration of leukocytes through the vascular wall and (4) migration of cells through the extracellular matrix along a chemotactic gradient [20]. A subset of chemoattractant molecules called chemokines likely contribute to steps 2, 3 and 4 of this process as it relates to the recruitment of leukocytes into GVHD target tissues. Chemokines secreted at the site of tissue inflammation are retained within the extracellular matrix and on the surface of the overlying endothelial cells. Leukocyte rolling is facilitated by selectin molecules and brings WBCs into contact with chemokines present on the endothelial surface. Chemokine signaling activates leukocyte integrin molecules resulting in arrest and extravasation. Once through the vascular wall, the WBC enters the tissue space where it is exposed to an existing chemokine concentration gradient surrounding the inflammatory stimulus.

Compared to syngeneic controls, the pulmonary expression of MCP-1 and CCR2 mRNA was significantly increased after allo-SCT [21]. Transplantation of CCR2-deficient (CCR2 $_{-/-}$) donor cells resulted in a significant reduction in IPS severity compared to SCT with wild-type (CCR2 $^{b/b}$) cells. The reduction in histopathology after CCR2 $_{-/-}$ SCT was associated with decreased macrophages, CD8 β lymphocytes and levels of TNF alpha and TNFRI in the BAL fluid. Similar findings were observed when recipients of wild-type SCT were treated with polyclonal antibodies to MCP-1 from day 10 to 28 after transplant. Importantly, experimental data correlated with preliminary clinical findings; patients with IPS have elevated levels of MCP-1 in the BAL fluid at the time of diagnosis. Use of other non cross-reactive strategies may also hold promise in the future. Injury to the pulmonary vascular endothelium may be critical to both the initiation and propagation of this process. Thus, it is conceivable that strategies that maintain EC integrity may be effective at preventing or treating IPS. The administration of molecules that function as survival factors for ECs has been successful

in preventing endothelial damage and mortality from septic shock and radiation injury [22,23]. Specifically, keratinocyte growth factors (KGF) have been shown to be efficacious in reducing epithelial damage and the severity of acute GVHD and pulmonary injury after allogeneic SCT, as well as protecting pulmonary endothelium from oxygen-induced injury [24]. Phase I/II clinical trials using KGF along with standard GVHD prophylaxis are in progress and the effects of this strategy on the development of IPS is of great interest.

The lung, like the gut and skin, serves as an interface between the sterile body sanctuary and the outside environment, and the pulmonary defense system is well designed to maintain this barrier; the lung is a rich source of histocompatibility antigens and professional APCs and is the site of complex immunologic networks involving cytokine production and lymphocyte activation. As noted above, inflammatory cytokines along with donor-derived T cell effectors, which are known to play a role in acute GVHD, also directly contribute to acute lung injury in animal SCT models and have been identified in the BAL fluid of patients with IPS. Clinically, evidence supporting the concept that the lung is a target organ of acute GVHD is limited, and the major obstacle has been the lack of apoptotic epithelial injury. However, other GVHD target organs such as the thymus do not express this particular form of injury, and recent experimental data demonstrate that direct recognition of alloantigen on host epithelium by cytotoxic effectors is not required for GVHD induction or target organ injury. Moreover, the unique aspects of epithelial anatomy in the lung may significantly contribute to this discrepancy. Since there is no stratification or layering of pulmonary epithelial cells as in the skin or intestine, the histopathologic repertoire of pulmonary damage is very limited making a potential diagnosis of acute GVHD in the lung by histological criteria difficult. As animal models of lung injury after SCT yield further insights, our understanding of this clinical complication should improve.

Role of (NO)

Lung dysfunction post HSCT in mice is

associated with increased BAL levels of nitrite, lactate dehydrogenase and protein. Allogeneic T cells stimulate nitric oxide production whereas cyclophosphamide stimulates the production of superoxide, the combination of which forms the tissue damaging substance peroxynitrite [25].

Treatment of IPS

Therapeutic considerations for IPS are summarized in **Table 6**. Supportive therapy still forms the back-bone of the treatment of IPS. This includes oxygen therapy and mechanical ventilation if necessary. Broad spectrum antibiotics are usually administered as occult infection is thought to be one of the etiological factors in the evolution of IPS although the strict definition of IPS rests on infection being excluded by a bronchoscopy. There is no clear cut rationale for diuretics in the absence of increased extravascular lung water. Immunosuppressive therapy has been tried including corticosteroids [26] and anti-TNF inhibitors without much difference in outcomes. The rationale for anti-TNF strategies included experimental models where this strategy appeared to be effective [27]. In addition, in the early post transplant period, TNF- appears to be generation in the lungs by host monocytes/macrophages and epithelial cells and allogeneic donor T cells. The importance of lung-infiltrating donor T cell-derived TNF- was recently shown by Hildebrandt *et al* [28], who demonstrated significantly reduced IPS severity in recipient mice given allogeneic T cells from TNF- /mice, whereas utilization of TNF- /mice as BMT recipients had no effect on IPS assessed by a histopathological injury score. The interaction of TNF- with TNF receptor activates the cascade pathway, leading to programmed cell death as well as activation of nuclear factor (NF-kappa B), leading to gene expression of inflammatory mediators including inducible nitric oxide synthase (iNOS). In the presence of superoxide, iNOS-derived NO may lead to the formation of peroxynitrite, a potent oxidant and nitrating agent that has been implicated in IPS injury [25]. Etanercept (Enbrel; Immunex, Seattle, WA), a soluble, dimeric tumor necrosis factor alpha-binding protein, was administered to 3 consecutive pediatric allogeneic BMT recipients with IPS [13].

The administration of etanercept, in combination with standard immunosuppressive therapy, was well tolerated and associated with significant improvements in pulmonary dysfunction within the first week of therapy. Clinical trials using etanercept for the treatment of IPS are now ongoing.

Conclusion

There are many different entities that can be included under noninfectious pulmonary complications. Most develop weeks to months after the transplant and result in significant morbidity and mortality. One of these entities is the idiopathic pneumonia syndrome. The pathogenesis includes alloreactive T cells, dendritic cells and proinflammatory cytokines. Usual risk factors include agents used for GVHD prophylaxis, alloreactive T cells and type of immunosuppression. The disease is hard to predict and treat and much of the treatment is experimental at present. It is hoped with refinements in the transplant process and patient selection these complications will be minimized.

Table 1. THE SPECTRUM OF NONCARDIOGENIC, PULMONARY TOXICITY

Interstitial pneumonitis (IP)

- Clinical symptoms: fever, cough, dyspnea, hypoxemia
- Onset: within first 100 days post transplant
- Etiology : infectious (ie CMV, PCP) or noninfectious factors (chemo toxicity: BCNU, bleomycin, busulfan, methotrexate)
- Radiographic findings: bilateral interstitial infiltrates

Bronchiolitis obliterans syndrome (BOS)

- Clinical symptoms: cough, dyspnea, wheezing, lack of fever
- Pulmonary function testing: obstructive findings

(diminished FEV1.0, or FEV1.0/FVC)

- Onset: 3-24 months post transplant
- Radiographic findings: hyperinflation. Otherwise routinely normal
- Computed tomography (CT): bronchiectasis, centrilobular nodules, septal lines, ground glass appearance
- Histology: lymphocytic bronchitis. Bronchiolar inflammation with luminal obliteration

Bronchiolitis obliterans organizing pneumonia (BOOP)

- Clinical symptoms: fever, dry cough, dyspnea
- Onset: 2-12 months post transplant
- Radiographic findings: patchy airspace disease, ground glass appearance, nodular opacities
- Histology: peribronchiolar infiltration and fibrosis and the presence of intraluminal granulation tissue

Diffuse alveolar hemorrhage (DAH)

- Clinical symptoms: progressive dyspnea, cough, rare hemoptysis
- Key finding: progressively bloodier aliquots of lavage fluid
- Onset: early, within first 100 days post transplant
- Radiographic findings: diffuse infiltrates, central appearance initially noted
- Histology: diffuse alveolar damage with alveolar hemorrhage

Periengraftment respiratory distress syndrome (PERDS)

- Clinical symptoms: fever, dyspnea, hypoxemia
- Onset: very early, within 5-7 days of engraftment, classically after autologous SCT
- Radiographic findings: bilateral

- interstitial infiltrates
- Delayed pulmonary toxicity syndrome (DPTS)
- Clinical symptoms: fever, dry cough, dyspnea
 - Onset: late, months to years following autologous HSCT breast cancer
 - Responds to corticosteroid therapy

- Noncardiogenic capillary leak syndrome (CLS)
- Clinical symptoms: dyspnea, cough, weight gain, edema
 - Onset: early, within first 30 days post transplant
 - Radiographic findings: bilateral perihilar infiltrates pulmonary edema and pleural effusions

Table 2. NONINFECTIOUS PULMONARY FINDINGS IDENTIFIED AT AUTOPSY AMONG 71 BMT RECIPIENTS*

Non infectious complications	Autopsy	Antemortem	Months after BMT (Median IQR)
Alveolar hemorrhage	35 (49)	12	1.80 (0.90-5.08)
Amyloidosis	10 (14)	1	3.32 (0.70-7.70)
Pulmonary embolism	9 (13)	0	0.84 (0.40-1.15)
Leukemia/lymphoma	5 (7)	0	0.82 (0.37-1.75)
Bronchiolitis obliterans	4 (6)	0	5.75 (3.40-9.15)
Pulmonary alveolar proteinosis	2 (3)	0	28.5
Bronchiolitis obliterans with organizing pneumonia	1 (1)	0	17.9
Acute and organizing pneumonia	1 (1)	0	11.8
Aspiration pneumonia	1 (1)	0	1.86
Diffuse alveolar damage	1 (1)	0	2.2

* Data are presented as No. (%)

Table 3. DEFINITION OF IDIOPATHIC PNEUMONIA SYNDROME

1. Evidence of widespread lung injury

- Multilobar infiltrates on chest radiograph or computed tomography
- Signs and symptoms of pneumonia (cough, dyspnea, rales)
- Abnormal pulmonary physiology: increased alveolar to arterial oxygen gradient; or new or increased restrictive lung findings

2. Absence of lower respiratory tract infection

- Broncho-alveolar lavage negative for bacterial pathogens and/or lack of improvement with broad-spectrum antibiotics
- Broncho-alveolar lavage negative for pathogenic non-bacterial microorganisms

3. Transbronchial biopsy

4. Ideally, second confirmatory negative test for infection 2-14 days after the initial procedure

Table 4. RISK FACTORS FOR IDIOPATHIC PULMONARY SYNDROME

1. GVHD prophylaxis (methotrexate)
2. Acute GVHD (grades II–IV)
3. Increasing recipient age
4. Total body irradiation
5. Myeloablative conditioning
6. High-dose 1-3 bis chloroethyl-1 nitrosurea
7. Decreased pre-transplant performance status
8. Longer duration from diagnosis to transplant
9. Transplantation for malignancy other than leukemia
10. Transplantation for hematological malignancy
11. HLA disparity (donor/recipient)

Table 5. POSSIBLE ETIOLOGIC FACTORS IN THE PATHOGENESIS OF IPS

1. Toxic effects of chemotherapy and radiation
2. Occult pulmonary infections
3. Immunologic dysregulation

- Enhanced pro-inflammatory cytokine (TNF α)
 - Release of endogenous endotoxin (LPS)
 - Donor-derived cellular effectors
4. Alloreactive T cells, neutrophils and mononuclear cells/macrophages
 5. Endothelial cell apoptosis/activation

Table 6. THERAPEUTIC CONSIDERATIONS FOR IDIOPATHIC PNEUMONIA SYNDROME

Supportive therapy

- Supplemental oxygen, mechanical ventilation
- Empiric broad-spectrum antimicrobial agents pending culture results
- Diuresis: furosemide or thiazide diuretic
- Continuous veno-venous hemofiltration (CVVH)

Immunosuppressive therapy

- Corticosteroids (2 mg/kg/day)

Investigational

- Cytokine inhibitors, including anti-TNF agents
- Use of KGF as an agent to prevent epithelial/endothelial injury
- Use of chemokine receptor antagonists

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