review

Secondary pulmonary alveolar proteinosis in hematologic malignancies

Chakra P Chaulagain [a,*], Monika Pilichowska [b], Laurence Brinckerhoff [c], Maher Tabba [d], John K Erban [e]

[a] Taussig Cancer Institute of Cleveland Clinic, Department of Hematology/Oncology, Cleveland Clinic in Weston, FL, USA,
[b] Department of Pathology, Tufts Medical Center Cancer Center & Tufts University School of Medicine, Boston, MA, USA,
[c] Department of Surgery, Tufts Medical Center Cancer Center & Tufts University School of Medicine, Boston, MA, USA,
[d] Division of Critical Care, Pulmonary and Sleep Medicine, Tufts Medical Center Cancer Center & Tufts University School of Medicine, Boston, MA, USA, [e] Division of Hematology/Oncology, Tufts Medical Center Cancer Center & Tufts University School of Medicine, Boston, MA, USA

[*] Corresponding author at: Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd., Weston, FL 33331, USA. Tel.: +1 954 659 5840; fax: +1 954 659 5810. · chaulac@ccf.org · Received for publication 29 January 2014 · Accepted for publication 1 September 2014

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Abstract Pulmonary alveolar proteinosis (PAP), characterized by deposition of intra-alveolar PAS positive protein and lipid rich material, is a rare cause of progressive respiratory failure first described by Rosen et al. in 1958. The intra-alveolar lipoproteinaceous material was subsequently proven to have been derived from pulmonary surfactant in 1980 by Singh et al. Levinson et al. also reported in 1958 the case of 19-year-old female with panmyelosis afflicted with a diffuse pulmonary disease characterized by filling of the alveoli with amorphous material described as ''intra-alveolar coagulum''. This is probably the first reported case of PAP in relation to hematologic malignancy. Much progress has been made on PAP first described by Rosen which is currently classified as idiopathic or primary or autoimmune PAP. Idiopathic PAP occurs as a result of auto-antibodies directed against granulocyte–macrophage colony stimulating factor (GM-CSF) impeding the surfactant clearing function of alveolar macrophages leading to progressive respiratory failure. Whole lung lavage and GM-CSF therapy has improved outcomes in patients with idiopathic PAP. Despite major advancement in the management of hematologic malignancy and its complications, little is known about the type of PAP first described by Levinson and now known as secondary PAP; a term also used when PAP occurs due to other causes such as occupational dusts. In this article we review and analyze the limited literature available in secondary PAP due to hematologic malignancies and present a case of PAP associated with chronic lymphocytic leukemia successfully treated with bendamustine and rituximab.

KEYWORDS: Secondary pulmonary alveolar proteinosis; Hematologic malignancy; Bronchoalveolar lavage; Opportunistic infections; Hematopoietic stem cell transplantation

Pulmonary alveolar proteinosis (PAP) is a rare disorder in which excess surfactant accumulates within pulmonary alveoli, causing cough, progressive dyspnea and respiratory insufficiency.[1,2] PAP was first reported in 1958 as a series of 27 cases collected from multiple institutions over a period of five years.[1] PAP occurs in three clinically distinct forms: congenital, secondary, and primary (idiopathic or autoimmune). Congenital PAP is the rarest form, occurring due to mutations in the genes encoding the granulocyte–macrophage colony stimulating factor (GM-CSF) receptor or the surfactant proteins.[3,4] Primary PAP is the most common form (≈90% of PAP cases) and is considered an autoimmune disease due to its association with a high titer of anti-GM-CSF autoantibodies. The autoantibodies neutralize the biologic activity of GM-CSF and impair the clearance of pulmonary surfactant by alveolar macrophages, leading to the accumulation of surfactant proteins and cellular debris in the alveolar space, and thus diminishing gas exchange.[2,4] Secondary PAP occurs in association with cancers (most

commonly hematologic malignancies), inhalational exposure to certain occupational dusts (silica, aluminum, titanium, indium), within the setting of immunosuppression after solid organ transplant or allogeneic hematopoietic stem cell transplantation (allo-SCT), or in relation to certain infections such as human immunodeficiency virus (HIV).[2–6] In 1958, Levinson et al. reported the case of a 19-year-old female with myeloproliferative disorder dying from a progressive respiratory illness compounded by pulmonary aspergillosis with pre-mortem biopsy and autopsy of the lungs showing distended alveoli described as "non-cellular acidophilic intra-alveolar coagulum," consistent with PAP by today's standard.[7] This is probably the first reported association of hematologic malignancy to PAP and opportunistic infection. This report was followed by a description in 1963 of two autopsy cases by Doyle et al.[8] and a more systematic autopsy series of five cases by Carnovale et al.[9] in 1977 indicating that the association of PAP, hematologic malignancies and opportunistic infection was more than just a coincidence. In 1980, Singh and Katyal proved that lipoproteinaceous intra-alveolar accumulation in primary PAP is derived from the surfactants produce by the type II pneumocytes.[10] The modern pathogenesis of primary PAP is based on the discovery that bi-allelic GM-CSF knocked down mice (GM-CSF−/−) had normal hematopoiesis but developed a pulmonary disease strikingly similar to PAP, which established the pivotal role of the GM-CSF signaling pathway for the pathogenesis of PAP.[11,12] However, the GM-CSF pathway appears to be uninvolved in PAP secondary to hematologic malignancy (HPAP), and its exact pathogenic mechanism remains unknown.

HPAP remains a rare disorder of unclear etiology limited to case reports and small series. HPAP has been reported in association with a wide range of hematologic disorders (Table 1), with a majority of cases occurring in association with hematological malignancies of myeloid origin.[2–6] Why this disorder has a predilection for myeloid neoplasms and myelodysplastic syndrome (MDS) is unknown, but one hypothesis includes reduced macrophage number or function due to the primary disease or its therapy or both.[5,6] Unlike the primary form, the PAP in hematologic malignancy (HPAP) is not associated with development of GM-CSF auto-antibodies.[5,6] The exact incidence of HPAP is unknown. However, one small, retrospective series showed that it could be responsible for up to 5% of pulmonary symptoms in hematologic malignancies.[6] A large database of 404 patients with PAP in Japan showed that 40 patients (~10%) had HPAP secondary to underlying hematological malignances and all of the 40 cases were negative for anti-GM-CSF antibody.[6] This suggests the existence of a non-antibody mediated and possibly a cellular immune mechanism of HPAP. In most reported cases of HPAP, the diagnosis was often missed prior to autopsy because PAP was rarely suspected prior to the death of patients.[5,6] Thus, PAP is usually considered a lethal complication of hematologic malignancies, though its transient and reversible nature has been reported in association with remission of underlying hematologic malignancy, either from chemotherapy or after hematopoietic stem cell transplants.[5,6] Resolution is thought to result from immune reconstitution and recovery of alveolar macrophage function after treatment of hematologic malignancy, and recovery of leukopenia and tapering or discontinuation of immunosuppressive therapy. Here we present a case of PAP in the setting of chronic lymphocytic leukemia (CLL) and review the limited literature available in patients with HPAP.

Table 1. Reported secondary PAP in association with hematological disorders/malignancies.

Myeloid disorders
• Myelodysplastic syndrome (MDS): most common
• Chronic myeloid leukemia (CML): second most common
• Overlap myeloproliferative neoplasm (MPN/MDS)
• Chronic myelomonocytic leukemia (CMML)
• Acute myeloid leukemia (AML)
• Primary myelofibrosis
• Polycythemia vera (PV)
• Essential thrombocytosis (ET)
Lymphoid disorders
• Acute lymphoid leukemia (ALL)
• Lymphoma (Hodgkin's and Non-Hodgkin's)
• Adult T cell leukemia/lymphoma
• Thymic alymphoplasia
• Cutaneous T cell lymphoma
• Chronic lymphocytic leukemia
Miscellaneous hematologic conditions
• Fanconi's anemia
• Aplastic anemia
• Congenital dyserythropoietic anemia
• Multiple myeloma/plasmacytoma
• Idiopathic thrombocytopenic purpura (ITP)
Non-hematologic malignancies
• Glioblastoma
• Lung cancer
• Mesothelioma

CASE PRESENTATION

A 69-year-old man was diagnosed with CLL during a routine clinical evaluation at an external hospital. He was asymptomatic, but was managed expectantly over the next four years, until he presented with fevers, exertional dyspnea, and night sweats. He was diagnosed with atypical, community-acquired pneumonia based on a chest X-ray that showed bilateral, interstitial and parenchymal opacities for which he received a two-week course of levofloxacin. The symptoms improved somewhat, but a repeat chest X-ray after six weeks showed no improvement. The patient then presented to Tufts Medical Center (TMC) with high grade fever, biopsy-proven leukemia cutis causing nodular skin lesions, a swollen right knee joint with synovial fluid growing *Pseudomonas aeruginosa*, and pseudomonal sepsis. Complete blood count revealed WBC 13,500/mm^3, hemoglobin 9.6 g/dL, platelets 64,000/mm^3, absolute neutrophil count, 200/mm^3, absolute lymphocyte count 12,200/mm^3, and absolute monocyte count 0/mm^3. Computed tomography (CT) scan of thorax revealed bilateral parenchymal pulmonary opacities (Figure 1A) and bronchoscopy with bronchoalveolar lavage (BAL) revealed 12 cc of pinkish fluid that was negative for bacteria, fungi, mycobacteria, *Pneumocystis jiroveci* and cytomegalovirus. BAL fluid differential cell count showed 83% lymphocytes, 12% neutrophils and 5% monocytes/macrophages. The patient remained febrile with persistent left upper quadrant abdominal pain even after completing a course of cefepime for pseudomonal bacteremia, prompting an abdominal CT scan that revealed hepatosplenomegaly and multiple splenic hypodensities suspicious for visceral candidiasis. He was additionally treated with IV micafungin followed by maintenance fluconazole with subsequent defervescence. A bone marrow biopsy showed extensive involvement (>90%) by a monotypic population of B cells expressing CD19, dim CD20, dim CD5, CD23, lambda light chains, and negative for CD5 and CD38. Cytogenetic analysis by florescent in situ hybridization (FISH) demonstrated trisomy 12.

Once the infections were controlled, the patient was treated with bendamustine and rituximab (B–R) for CLL. After two cycles of B–R, he responded with clearing of CLL in the peripheral blood, and resolution of hepatosplenomegaly and generalized lymphadenopathy. However, he experienced interval worsening of pulmonary parenchymal disease with increasing linear and ground glass densities throughout both lungs (Figure 1B). Serology for aspergillus galactomannan antigen index in both blood and BAL was 0.1 (<0.5 is considered negative).

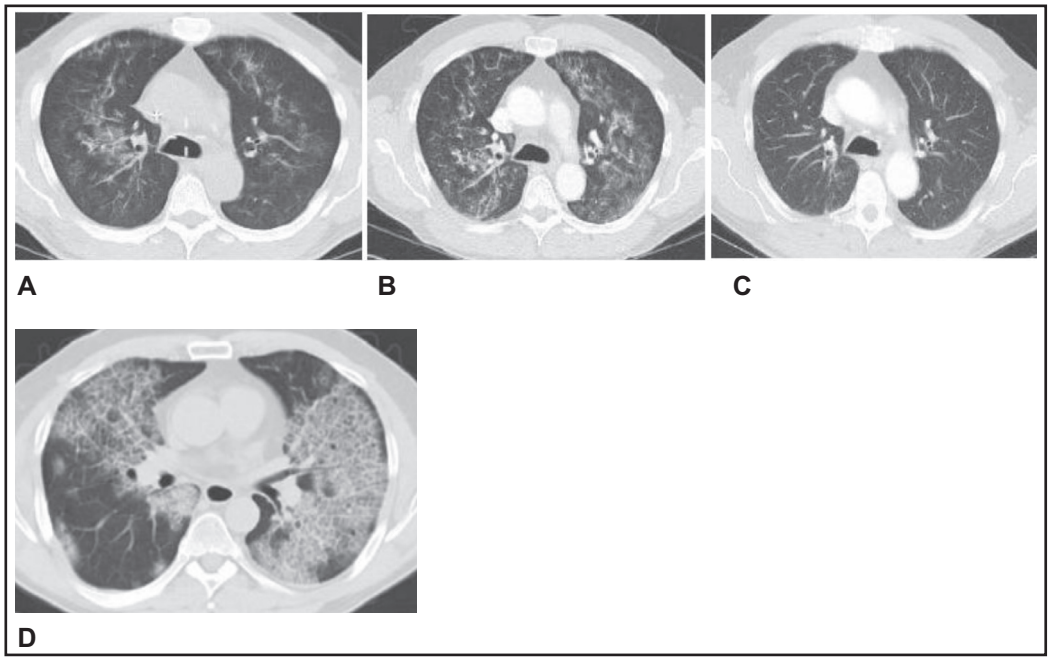

Figure 1. A. Thoracic CT scan at presentation showing ground-glass opacities reported as multifocal pneumonia. B. Thoracic CT scan after 2 cycles of bendamustine and rituximab showing interval worsening of pulmonary parenchymal disease with increasing linear and ground-glass densities throughout both lungs. C. Thoracic CT scan 6 months post-bendamustine and rituximab showing generalized improvement in the pulmonary densities. D. Thoracic CT scan of a different patient with idiopathic (autoimmune) PAP showing bilateral geographic ground-glass opacities (GGO) with inter-lobular septal thickening, creating a characteristic mosaic or so called ``crazy paving pattern'' in both lung fields.

Pulmonary function test (PFT) showed mild restrictive ventilatory defect with normal diffusion capacity. Though the patient was feeling better and had only mild dyspnea on exertion, a repeat flexible bronchoscopy with BAL of right middle lobe was performed. Approximately 30 cc of milky fluid analyzed revealed no neoplastic or infectious process but showed large aggregates of cast-like granular material, staining positively for periodic acid-Schiff stain (PAS) and resistant to diastase, highly suggestive of pulmonary alveolar proteinosis (PAP). GMS stain was negative for fungus or *P. jiroveci* and FITE stain was negative for *Nocardia*. BAL differential cell counts showed lymphocytes 39%, neutrophils 3% and monocytes/macrophage 56%. Video-assisted thoracoscopic surgery (VATS) and wedge biopsies of right upper, middle and lower lobes were performed. Morphologic examination of the lung tissue revealed panlobular diffuse areas of intra-alveolar granular material consistent with PAP (Figure 2 arrow). In addition, a small focus with intra-alveolar fungal hyphae morphologically consistent with aspergillus species and associated areas of organizing pneumonia pattern of lung injury possibly secondary to tissue invasion by the aspergillus was identified. In limited areas predominantly in subpleural location, very small aggregates of CD20 positive B-cells co-expressing CD5 were present. This is consistent with minimal residual involvement by the patient's known CLL. Neutralizing autoantibody against GM-CSF in the serum was not detected and the serum GM-CSF level was not elevated (<3 pg/ml).

Throughout the course of B–R therapy, the patient was supported by exogenous G-CSF, pneumocystis pneumonia prophylaxis with trimethoprim/sulfamethoxazole and immune prophylaxis with intravenous immune globulin for depressed IgG level of 334 mg/dL (normal range 562–1585 mg/dL). The patient continued to do well following four cycles of B–R and a six-month course of voriconazole for pulmonary aspergillosis, with complete resolution of dyspnea. A CT scan obtained six months (Figure 1C) following completion of four cycles of B–R showed marked improvement of the lung abnormalities. He is currently two years post-chemo-immunotherapy (B–R) and remains asymptomatic. It is possible that the patient's presenting symptoms and the radiographic findings of "atypical pneumonia" may have been due to PAP but infiltration by CLL or opportunistic infection with or without coexisting PAP cannot be ruled out.

DISCUSSION

This case illustrates several important features of PAP in hematologic malignancy (HPAP). First, though PAP is predominantly associated with myeloid malignancies,[5,6] it can also – though rarely as in this case – occur in association with lymphoid malignancies including CLL (Table 1). Second, HPAP can be mistaken for atypical pneumonia, but persistent symptoms and non-resolving radiologic infiltrates after appropriate antibiotic therapy should raise suspicion for HPAP. Third, HPAP can have

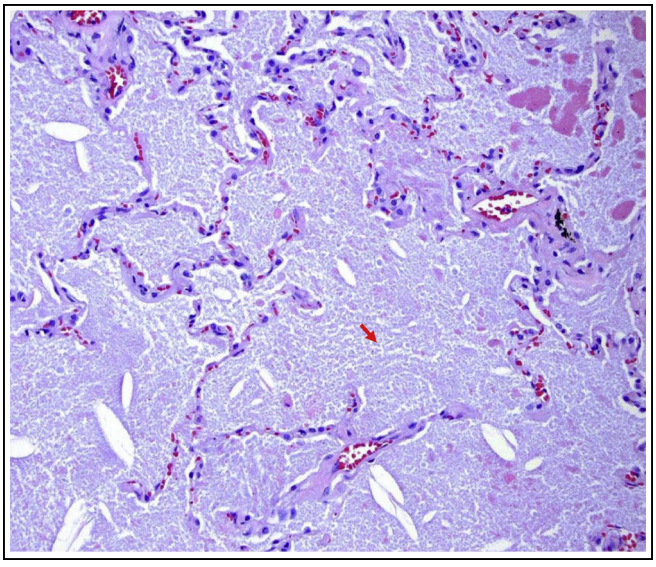

Figure 2. Morphologic examination of the lung tissue derived from video-assisted transthoracic surgery (VATS) reveals alveolar filling with acellular, granular, eosinophilic, periodic acid-Schiff-positive (PAS positive) material (arrow) and preserved alveolar septal architecture, consistent with a diagnosis of pulmonary alveolar proteinosis (PAP).

onset prior to starting chemotherapy, and therefore is not always due to the direct toxicity of chemotherapy as has been proposed.[5,6] Fourth, HPAP can improve with treatment of underlying hematologic malignancy, suggesting that this is a reversible complication and is sensitive to the immunomodulatory effects of therapy. Fifth, this case also highlights the importance of including HPAP in the differential diagnosis of progressive respiratory symptoms and radiographic changes in patients with hematologic malignancies and underscores the importance of alerting the pathologist to include appropriate staining (PAS staining) of BAL fluid or lung biopsy specimens to confirm the diagnosis. Sixth, CLL, HPAP and opportunistic infections (e.g. pulmonary aspergillosis) often coexist, and making a diagnosis of HPAP should not preclude the search for an associated pathogen. Every attempt should be made to identify and treat such an infection. After two cycles of B-R, our patient had excellent response to CLL but developed worsening pulmonary CT findings. We continued both CLL directed and aspergillosis-specific therapy until gradual improvement of dyspnea and eventual clearing of the infiltrates. This case sheds light on the importance of addressing both the hematologic malignancy and the opportunistic infection for successful outcome. Seventh, the fairly sensitive and specific serum galactomannan assay with utility for early diagnosis and prognostic value for pulmonary aspergillosis can be falsely negative in patients with HPAP.[13] Whether the opportunistic infection is a cause or consequence of PAP is unknown. Finally, lymphocytes were the predominant cell type in the first BAL, but monocytes/macrophages were the main type of cells in the second BAL. The difference of predominant cell types between the first and the second BAL is interesting, and could reflect lymphocyte infiltration of alveolar spaces by untreated CLL in the first BAL and possible immune reconstitution of alveolar monocytes/macrophages by chemoimmunotherapy after two cycles of B-R. Rituximab immunotherapy is also known to cause depletion of lymphocytes.

CLINICAL, LABORATORY, PATHOLOGIC AND RADIOGRAPHIC MANIFESTATIONS OF PULMONARY ALVEOLAR PROTEINOSIS SECONDARY TO HEMATOLOGIC MALIGNANCIES (HPAP)

A search of our internal database in this referral center (TMC) for diagnosis and management of hematologic malignancies revealed one additional case of HPAP occurring in association with an MDS patient in the last 15 years. Others have estimated that as many as 5% of hematologic malignancy patients with pulmonary symptoms can have HPAP, while the frequency increases to 10% in such patients with myeloid disorders,[6] suggesting that HPAP is not a rare cause of respiratory illness in this patient population. Thus, HPAP should be considered in the differential diagnoses of all patients with hematologic malignancies accompanied by pulmonary symptoms or abnormal radiographs in asymptomatic patients.[14] HPAP is often diagnosed during the treatment of underlying hematologic disorder coinciding with a prolonged period of cytopenias. However, it is known to occur up to several years before[8] development of a hematologic disorder and while in complete remission for several years after completion of treatment for underlying hematologic malignancy.[9] The common symptoms of cough, dyspnea and fever are non-specific and can easily be mistaken as pneumonia. As high as a quarter of these patients can be asymptomatic.[6]

While the level of lactate dehydrogenase (LDH) can be elevated, this is non-specific and can be due to underlying hematologic disease or infections. No lung-specific biological markers can be used to make diagnosis, track disease progression or predict clinical outcomes. One study demonstrated that the levels of pulmonary surfactant protein D (SP-D) was elevated in sera and BAL fluid of primary PAP patients compared to healthy volunteers.[15] Interestingly, SP-D levels were also associated with disease activity in PAP patients. However, serum SP-D levels are also elevated in other pulmonary diseases such as idiopathic pulmonary fibrosis (IPF) and interstitial pneumonia with collagen vascular disease (IPCD) making it a non-specific marker. On the other hand, SP-D level in BAL fluid could be more specific for PAP because high levels of SP-D in BAL fluids is seen only in patients with PAP, but not with IPF and IPCD.[15,16] No study has yet evaluated the SP-D levels in blood or BAL in patients with HPAP and such correlative biomarker studies are highly desirable. In the absence of a sensitive and specific biomarker, the diagnosis of HPAP continues to rest on invasive procedures such as bronchoscopy, BAL, or lung biopsy. In a series of 40 HPAP patients with hematologic malignancy, the definitive diagnosis of secondary PAP was made using BAL in 21 cases, transbronchial lung biopsy in 9 cases, and VATS in 10 cases.[6] This means BAL can miss the diagnosis (as was the case with our first BAL) in a significant proportion of patients and further invasive procedures such as transbronchial lung biopsy or video-assisted lung biopsy may be

required for diagnosis. The clinical course of the disease is often unpredictable due to its association with an underlying malignancy, cytopenias from chemotherapy, or immunosuppressive therapy in the setting of allo-SCT. In general, the response of an underlying disease to therapy is associated with response to the PAP.

An important feature of HPAP is its high susceptibility to a wide range of usual pathogens and unusual opportunistic pulmonary and extra-pulmonary infections (Table 2). Opportunistic pathogens that have a high degree of association with HPAP include aspergillosis (pulmonary and disseminated), nocardiosis (pulmonary, cerebral and disseminated) and pulmonary and disseminated mycobacteria (mainly non-tubercular). It is important to note that opportunistic infections can precede, coincide or follow a diagnosis of PAP,[17] requiring continuous vigilance and high index of suspicion and prompt intervention. The risk of infections comes from a combination of the immunodeficient state of the hematologic malignancy, chemotherapy-related cytopenias and deranged pulmonary local immunity in the setting of PAP. In addition, no distinctive clinical feature exists to differentiate between PAP secondary to hematologic malignancy, and PAP secondary to opportunistic infection that can occur in the setting of an immunocompromised state such as HIV or hematologic malignancy.

In addition, typical radiographic findings seen in primary PAP can be absent in HPAP. Chung et al. analyzed CT scans of the chest in seven patients with HPAP and reported geographic ground-glass opacities (GGO) combined with septal thickening (so-called "crazy paving") as predominant pattern similar to the pattern of CT findings in primary PAP[18] (Figure 1D). However, Ishii et al. showed that the most common CT finding in secondary PAP is diffuse ground-glass opacities (GGO) as opposed to patchy GGO seen in primary PAP.[19] In patients with hematologic malignancies, these CT findings are not diagnostic, can easily be misinterpreted as opportunistic infections, particularly pneumocystis or viral pneumonia. Other possibilities for similar CT findings include pulmonary edema, diffuse alveolar damage, diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, bronchoalveolar carcinoma, and graft-versus-host disease in the setting of allo-SCT. It is important that physicians suspect secondary PAP when encountered with unexplained pulmonary opacities on chest radiograph or computed tomography in patients with pre-existing hematological diseases. CT scan of the chest (preferably high resolution CT scan-HRCT) is a useful tool to follow up and monitor PAP.

Table 2. Reported pulmonary and extra-pulmonary opportunistic infections in patients with PAP secondary to underlying hematologic malignancies.

Bacterial infections
Pseudomonas aeruginosa
Mycobacterium tuberculosis
Non tuberculous *Mycobacterium avium* complex (MAC)[a]
Mycobacterium scrofulaceum
Mycobacterium abscessus
Nocardia (limited and disseminated)
Legionella pneumophila
Acinetobacter baumannii
Bacillus cereus
Staphylococcus epidermidis
Corynebacterium species
Enterococcus faecium
Enterobacter cloacae
Clostridium difficile (with toxic megacolon reported)
Viral infections
Cytomegalovirus (CMV)
Human immune deficiency virus (HIV)
Herpes simplex virus (HSV)
Parainfluenza virus
Varicella zoster virus (VZV)
Fungal infections
Pneumocystis jiroveci (*carinii*)[a]
Aspergillus fumigatus[a]
Cryptococcus
Histoplasma
Mucorales
Cladosporium
Trichosporon

[a]Indicates commonly described pulmonary infection in association with HPAP.

THERAPEUTIC APPROACHES AND OUTCOMES OF PAP SECONDARY TO HEMATOLOGIC MALIGNANCIES (HPAP)

In symptomatic patients with primary PAP, whole lung lavage to physically remove the lipoproteinaceous material is considered the traditional standard of care leading to improved symptoms and durable prolongation of patients survival based on retrospective data.[20] Subcutaneous recombinant GM-CSF and, more recently, inhaled GM-CSF have shown responses less complete than can be obtained with whole lung lavage. The GM-CSF investigational modality may be considered in patients who cannot tolerate or do not respond to whole lung lavage.[21–25] Neither whole lung lavage nor GM-CSF administration has been uniformly effective in HPAP but the effective treatment of underlying malignancies either by chemotherapy or by hematopoietic stem cell transplantation may lead to resolution of PAP as in our case.[6,18,25,28]

PAP has been described after autologous hematopoietic stem cell transplantation (autoSCT),[26] and following allo-SCT utilizing matched unrelated donor (MUD),[27] matched related donor (MRD),[28] and unrelated umbilical cord blood transplantation (UCBT).[29] HPAP diagnosed prior to stem cell transplantation has reported response to the successful treatment of underlying myeloid malignancies using autoSCT,[30] reduced intensity conditioning (RIC) allo-SCT using MRD[28] and MUD,[31,32] and myeloablative unrelated UCBT.[33] Though conditioning regimens have long been suspected to play a contributory role in PAP, these observations suggest that neither autologous nor allogeneic transplantation lead directly to the development of PAP, but can induce remission for both conditions in selected patients. Therefore, PAP should not be considered a contraindication for hematopoietic stem cell transplant, and this potentially curative treatment should not be withheld due to concomitant PAP. However, it is important to recognize PAP as a co-morbidity that can increase morbidity and mortality during and following transplant. Elimination of the malignant clone by a conditioning regimen and replacement of impaired alveolar macrophages with donor stem cell-derived normal alveolar macrophages might correct the underlying cause of PAP. However, the safety and efficacy of allo-SCT for patients with documented PAP should be further studied. In patients with HPAP, RIC-allo-SCT is probably more desirable over myeloablative conditioning regimen due to minimal pulmonary toxicity and lower risk of pulmonary infections following RIC-allo-SCT.[31,32] Based on the limited number of small retrospective observational case series, it appears that the presence of HPAP adversely affects outcomes of patients with hematologic malignancies with median survival of less than two years, with most deaths occurring within one year of diagnosis[5,6,18,31] (Table 3), and several deaths attributed to respiratory failure from underlying PAP.

Optimal management of patients with PAP while also treating a malignant blood disorder and dealing with the complications of cancer treatment is challenging. Apart from symptomatic and supportive respiratory care and therapy directed toward the underlying hematologic malignancy, no specific therapy has been identified for the treatment of HPAP. Isolated reports on utilizing whole lung lavage and GM-CSF while awaiting transplant or after the transplant have shown only modest effect.[32] Due to the invasive nature of whole lung lavage and need for frequent lavages, it is unclear if this intervention is feasible and safe in hematologic malignancy and bone marrow transplant patients. In primary PAP, there are reports of response using rituximab[34] to decrease production of GM-CSF autoantibodies, or plasmapheresis[35] to remove autoantibodies. There is practically no literature on using rituximab or plasmapheresis in HPAP. Our patient was treated with a regimen that contained rituximab leading to improvement in PAP, but the improvement is most likely due to the clearing of the underlying CLL and pulmonary aspergillosis rather

Table 3. Reported survival of patients with PAP and hematologic malignancies (most deaths occur within 12 months of diagnosis).

Reference	Reported year	Number of patients (*n*)	Reported survival
Cordonnier et al.[5]	1994	10	50% at 2 months
Chung et al.[18]	2009	6	50% at 15 months
Ishii et al.[6]	2011	35	46% at 2 years
Sturgess et al.[31]	2011	3*	33% at 2 years

*All 3 patients had GATA2 deficiency.

than immune effect of rituximab. Corticosteroids and other immunosuppressant are generally tapered or discontinued due to their immune suppressive effects and increased risk of opportunistic infections. However, this approach needs to be finely balanced with the potential flare up of graft-versus-host disease (GVHD) in the case of allo-SCT.

RECENT ADVANCES AND FUTURE DIRECTIONS OF PAP SECONDARY TO HEMATOLOGIC MALIGNANCIES (HPAP)

While the cause of HPAP remains poorly understood, a recent discovery of heritable GATA2 mutation associated with early onset, sporadic and autosomal dominant familial MDS and acute myeloid leukemia (AML) has shed some light on the understanding of this disease. Up to a third of patients who are carriers of GATA2 mutations are also affected by PAP.[28,36–38] Interestingly, GATA2 mutated patients who developed PAP neither had mutations in the GM-CSF receptor, nor had anti-GM-CSF autoantibodies. GATA2, a zinc finger master transcription factor, is indispensable for terminal differentiation of immature hematopoietic cells and also plays crucial role in the regulation of endothelial nitric oxide synthesis in pulmonary epithelium.[39,40] It is possible that some of the pulmonary changes seen in GATA2 deficiency may result from a defective endothelial nitric oxide synthase expression, but impaired alveolar cellular immunity appears to be the central etiology for causation of PAP in this setting. GATA2 deficiency is characterized by severe monocytopenia, B & NK-lymphocytopenia and disseminated infections with intramacrophagic organisms (e.g. mycobacteria, histoplasma).[38] Interestingly, bone marrow transplant was curative for PAP in these patients, presumably from reconstitution of the monocyte/macrophage compartment post-SCT. Holland and Spinner assembled a cohort of 57 patients with GATA2 deficiency. Ten (≈18%) of them developed biopsy-proven PAP and 9/10 of these PAP patients had underlying hematologic malignancies in the form of MDS (the majority), AML, or chronic myelomonocytic leukemia (e-mail communication, March 2013, with Dr. Michael Spinner and Dr. Steven M. Holland; National Institutes of Health, Bethesda, MD, USA).[41] These findings highlight the possibility of other not yet identified genetic susceptibilities for phenotypic expression of PAP in hematologic malignancies not associated with mutated GATA2.

GATA2-mutated patients may serve as potential platform for prospective study directed to understand the biological events leading to the development of PAP in a significant proportion of these patients. The newly opened prospective observational study *Natural History Study of GATA2 Deficiency and Related Disorders* represents a new avenue for further research, potentially leading to better understanding of GATA2 deficiency and hopefully will also be instrumental in providing further insights into PAP in such patients.[42] The recent discovery that most cases of GATA2 deficiency are also accompanied by a severe NK cell lymphocytopenia and marked functional impairment of NK cells may also challenge the traditional thinking of monocyte/macrophage dysfunction alone as the sole cause of PAP in patients with hematologic malignancies and questions whether other cellular dysfunctions (e.g. NK cell or dendritic cell insufficiency) and humoral defects (e.g. cytokines other than GM-CSF) may play a role in the development of HPAP.[43] An ongoing phase II study is evaluating allo-SCT in patients with mutated GATA2, and in which presence of PAP is not an exclusion criteria (e-mail communication, May 2013, with Dennis Hickstein, MD; NIH, Bethesda, MD, USA).[44] Mutational testing for GATA2 and appropriate consultation with the specialists at the referral center of excellence should be considered in patients with HPAP.

CONCLUSION

HPAP remains a diagnostic challenge for hematologists, oncologists, transplant physicians, and allied specialists. No guidelines exist regarding its diagnosis and management. Most of the available literature extrapolates diagnostic and treatment decisions based on the literature in idiopathic PAP. Anti-GM-CSF antibody is a valuable biomarker with high diagnostic accuracy in idiopathic PAP, but its level is normal in HPAP. The diagnosis of HPAP, therefore, continues to rest on invasive modalities such as bronchoscopy, BAL and, less commonly, lung biopsy. Though the mechanism of HPAP remains unclear, it is important to emphasize the reversibility of all or most pulmonary function abnormalities and improved survival with successful treatment of the underlying hematologic malignancy and opportunistic infection. Research to address the questions raised is limited by low incidence and infrequent recognition of this condition. Prospective multinational clinical or registry-based studies may enhance reporting and systematic analysis of clinicopathologic characteristics and outcomes in this patient population.[6,41]

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CONFLICT OF INTEREST

None.

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