review

Secondary pulmonary alveolar proteinosis in hematologic malignancies

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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