Alveolar proteinosis - an underdiagnosed condition in young people

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Abstract

Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterized by an abnormal intra-alveolar accumulation of surfactant derived lipoproteinaceous compounds, leading to dyspnea and, in severe cases, to respiratory failure. The most common form of PAP is the auto-immune one. Secondary PAP has been recognized in myeloid leukemia, non-hematological neoplasms, lung infections or environmental exposure to noxious particles. Mutations in several genes (such as MARS, SFTPB, TTF1) are responsible for the alteration of surfactant production. Diagnosis tools include high-resolution computed tomography, bronchoalveolar lavage. Although over the past 20 years the pathophysiology of PAP has become more clear, the therapeutic strategies still need improvement. A national programme for patients with PAP might be useful in Romania.

Keywords: pulmonary alveolar proteinosis, surfactant, auto-immune, bronchoalveolar lavage

Definition

Pulmonary alveolar proteinosis (PAP) is a rare disease and was first described in 1958 by Samuel H. Rosen and his team [1]. PAP represents the abnormal accumulation of surfactant and its derivatives in the alveoli of the lungs, having as substrate the defective function of the alveolar macrophages [2]. Over time, the definition and management of this pathology have undergone several changes that have led to a significant decrease in morbidity (Table I).

Epidemiology

The prevalence of alveolar proteinosis was estimated to vary between 3.7-40 cases / 1 million inhabitants, with important geographical variations, and the incidence was set at 0.2 / million inhabitants [3,4]. A study of 15 million people in the United States found a prevalence of 6.87 ± 0.33 cases / million in the general population, with a 1:1 ratio between women and men [5], although previous studies report a predilection for males, with a ratio of 2:1 [6]. Smoking is cited as a risk factor in the adult population, but the disease also affects newborns.

Pathogenesis

The main feature of alveolar proteinosis is the excessive accumulation of lung surfactant in the alveoli of the lungs, due to inadequate clearance of macrophages. The surfactant is composed of a mixture of proteins and lipids, secreted by type II pneumocytes. Its role is to reduce surface tension and prevent alveolar collapse at the end of expiration.

Clinical presentation

Although up to 1/3 of the patients with PAP are asymptomatic, most of the patients present non-specific symptoms such as dyspnea and cough – dry or productive [7]. Other symptoms include: asthenia, fever, weight loss, chest pain, hemoptysis [4,8]. In small children, symptoms are non-respiratory and include vomiting, diarrhea, malaise [9]. The physical examination is frequently normal, but in some patients, crackles, cyanosis and/or clubbing fingers can be found [10]. Opportunistic infection may occur, adding symptoms to the clinical presentation.

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Table I. Classification and risk factors (after Suzuki and Trapnell [2], 2016).

Classification PAP	Risk factors
Primary PAP	Autoantibodies GM-CSF (granulocyte-macrophage colony-stimulating factor) CSF2RA mutations, CSF2RB mutations
Secondary PAP	Hematological disorders (most commonly myelodysplastic syndrome) Non-hematological neoplasms Immune deficiencies (acquired immunodeficiency syndrome, agammaglobulinemia, amyloidosis, Behcet's disease, juvenile dermatomyositis, Fanconi syndrome) Chronic inflammatory and infectious diseases (nocardiosis, aspergillosis) Inhalation of toxic substances: inorganic dust - aluminum, silicon, titanium; organic dust - agriculture, bakery, fertilizers; others - chlorine, cleaning products, gasoline, nitrogen dioxide. SLC7A7 mutations, MARS mutations
Alteration of surfactant production	SFTPB mutations, SFTPC mutations, ABCA3 mutations, TTF1 mutations

Table II. Chest radiographic features in PAP (McCook and Frazier et al. [9,12]).

Findings	Characteristics
Batwing pulmonary opacities	Found in adult patients Symmetrical, bilateral central opacities Could mimic acute pulmonary edema
Diffuse small pulmonary opacities	Frequently found in small children Could mimic a miliary pattern
Extensive diffuse consolidation	Multiple, disseminated different size opacities
Reticulonodular opacities	Suggestive for an interstitial lung disease

Radiographic features

Chest X-ray - In PAP, radiographic features are almost every time more severe than the clinical presentation, and consist of bilateral, symmetric opacities, without air bronchogram. The localization is often in the perihilar area and/or the lower lobes. Chest X-ray is inconclusive, as PAP could mimic acute pulmonary edema, although pleural effusion and cardiomegaly are not present (Table II) [11].

High-Resolution Computed Tomography of the chest – is a major diagnostic tool for PAP. the main findings include smooth thickening of interlobular and interlobular septal lines, ground-glass opacities, and parenchymal consolidation. Reticulations and ground-glass opacities create the crazy-paving pattern, which is characteristic in PAP, but not pathognomonic [13,14]. Lower lobe predominance was observed in most of the cases. Congenital PAP may present with lung cysts, or with a „white-lung" pattern [4].

Pulmonary function testing

Spirometry is not specific in PAP, but is important for monitoring the disease and for therapeutic decisions. Most of the cases present with restrictive ventilatory dysfunction, but an obstructive pattern could also be present, especially in smokers, resulting in mixed ventilatory dysfunction [15]. The diffusion capacity of the lung for carbon monoxide (DLCO) is reduced due to loss of alveolar space and correlates with the severity of the disease [7,16]. Arterial blood gas analysis reveals hypoxemia. An important percentage of patients present important blood oxygen desaturation on the 6 Minute Walk Test [7].

Laboratory blood tests

Anti-GM-CSF antibodies, detected by ELISA method (gold standard) or a functional assay, with a blood concentration over 19 micrograms/millilitre indicate the presence of autoimmune PAP. The serum level of LDH is typically elevated, but it is not a specific test [2]. Decreased serum levels of the surfactant proteins SP-A, SP-B, and SP-D are observed and also correlate with the severity of the disease [7].

Bronchoalveolar lavage fluid (BALF) and lung biopsy

BALF is pathognomonic and presents as a milky, turbid appearance and thick sediment on visual inspection. The cytologic examination shows high cellularity and Periodic Acid Shiff (PAS) stain positive large macrophages [3]. Lung biopsies are not necessary to establish the final diagnosis. If performed, the biopsy will reveal PAS positive lipoproteinaceous material [17].

Evolution and prognosis

The evolution of PAP is unpredictable, from spontaneous remission to death[4]. The use of bronchoalveolar lavage has improved 5-year survival in autoimmune PAP to almost 95% of cases [7]. PAP patients have an increased risk of opportunistic infections, mainly with Aspergillus spp, Candida spp, Mycobacterium (tuberculous and non-tuberculous), Nocardia, Pneumocystis spp. Pulmonary fibrosis occurs in approximately 30% of autoimmune PAP patients [18].

Treatment options

Mild cases of PAP do not require treatment, as spontaneous remission can be seen in some patients. For newborns with severe forms of the disease, immediate lung transplant is mandatory. Whole lung lavage (WLL) represents the gold-standard therapy for PAP since 1960. The initial technique has been improved over the years, resulting in decreased morbidity of PAP. Symptomatic and radiologic improvement occurs, together with better results on the respiratory functional testing [3,4]. Subcutaneous injections of GM-CSF proved to be effective in autoimmune PAP, but not in congenital PAP. Their efficiency is inferior to WLL, but it represents an alternative treatment method [3,17]. Systemic corticotherapy increases the risk of over infections and is not indicated. Rituximab and plasmapheresis, as algternative therapies are controhersial. Extracorporeal Membrane Oxygenation and lung transplants are reserved for severe, selected cases [19]. The recurrence of PAP disease was observed in some patients.

References

1. Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Engl J Med. 1958;258:1123-1142.
2. Suzuki T, Trapnell BC. Pulmonary Alveolar Proteinosis Syndrome. Clin Chest Med. 2016;37:431-440.
3. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med. 2003;349:2527-2539.
4. Borie R, Danel C, Debray MP, Taille C, Dombret MC, Aubier M, et al. Pulmonary alveolar proteinosis. Eur Respir Rev. 2011;20:98-107.
5. McCarthy C, Avetisyan R, Carey BC, Chalk C, Trapnell BC. Prevalence and healthcare burden of pulmonary alveolar proteinosis. Orphanet J Rare Dis. 2018;13:129.
6. Campo I, Mariani F, Rodi G, Paracchini E, Tsana E, Piloni D, et al. Assessment and management of pulmonary alveolar proteinosis in a reference center. Orphanet J Rare Dis. 2013;8:40.
7. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med. 2008;177:752–762
8. Briens E, Delaval P, Mairesse MP, Valeyre D, Wallaert B, Lazor R et al. Pulmonary alveolar proteinosis [Lipoprotéinose alvéolaire pulmonaire]. Rev Mal Respir. 2002;19:166–182. French
9. McCook TA, Kirks DR, Merten DF, Osborne DR, Spock A, Pratt PC. Pulmonary alveolar proteinosis in children. AJR Am J Roentgenol. 1981;137:1023-1027.
10. Goldstein LS, Kavuru MS, Curtis-McCarthy P, Christie HA, Farver C, Stoller JK. Pulmonary alveolar proteinosis: clinical features and outcomes. Chest. 1998;114:1357–1362.
11. Delaval P, Brinchault G, Corre R, Jouneau S, Meunier C, Briens E. Pulmonary alveolar phospholipoproteinosis [Lipoprotéinose alvéolaire pulmonaire]. Rev Pneumol Clin. 2005;61:186–192. French
12. Frazier AA, Franks TJ, Cooke EO, Mohammed TL, Pugatch RD, Galvin JR. From the archives of the AFIP: pulmonary alveolar proteinosis. Radiographics. 2008;28:883-899.
13. Holbert JM, Costello P, Li W, Hoffman RM, Rogers RM. CT features of pulmonary alveolar proteinosis. AJR Am J Roentgenol. 2001;176:1287–1294.
14. Kamboj A, Lause M, Duggirala V. Severe Pulmonary Alveolar Proteinosis in a Young Adult. Am J Med. 2018;131:e199-e200.
15. Presneill JJ, Nakata K, Inoue Y, Seymour JF. Pulmonary alveolar proteinosis. Clin Chest Med. 2004;25:593–613.
16. Hildebrandt J, Yalcin E, Bresser HG, Cinel G, Gappa M, Haghighi A, et al. Characterization of CSF2RA mutation related juvenile pulmonary alveolar proteinosis. Orphanet J Rare Dis. 2014;9:171.
17. McElvaney OJ, Horan D, Franciosi AN, Gunaratnam C, McElvaney NG. Pulmonary alveolar proteinosis. QJM. 2018;111:185-186.
18. Bonella F, Campo I. Pulmonary alveolar proteinosis. Pneumologia. 2014;144:147–155.
19. Wilson CA, Wilmshurst SL, Black AE. Anesthetic techniques to facilitate lung lavage for pulmonary alveolar proteinosis in children-new airway techniques and a review of the literature. Paediatr Anaesth. 2015;25:546–553.