Pulmonary alveolar proteinosis: a case report and world literature review

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Abstract
Pulmonary alveolar proteinosis (PAP) is a lung disorder which was first described in 1958 by Rosen et al. and is indeed rare disease with a prevalence of 0.1 per 100,000 individuals. PAP is characterized by abnormal accumulation of pulmonary surfactant in the alveolar space, which impairs gas exchange leading to a severe hypoxemia. Pulmonary surfactant is an insoluble proteinaceous material that is rich in lipids and stains positive with periodic acid–Schiff (PAS). The most common type of PAP is the so-called autoimmune or idiopathic type. It has been hypothesized that deficiency in granulocyte macrophage–colony stimulating factor (GM-CSF), as a result of the anti-GM-CSF antibody production, is strongly related to impaired surfactant recycling that leads to the accumulation of surfactant in the alveolar space. Its clinical course is variable from spontaneous remission in the best case scenario, going through the entire spectrum of disease severity, towards fatal respiratory failure. Whole lung lavage has been the gold standard therapy in PAP until the advent of GM-CSF. Although the first case was reported to be idiopathic, subsequent analysis revealed that Pneumocystis jirovecii, silica, and other inhalational toxins were able to trigger this reaction. In this study, we report the case of a 52-year-old man who developed PAP syndrome following a 2-year exposure to silica dust. Our review of the world literature where 363 cases were found.

Introduction
Pulmonary alveolar proteinosis (PAP) was first described in 1958 by Rosen et al. as an infrequently seen disorder in which an amorphous, insoluble, lipoproteinaceous material tends to accumulate in the alveolar spaces, causing impairment of gas exchange [1]. Although the first reported cases were felt to be idiopathic, there have been subsequent reports suggesting that PAP could be a secondary phenomenon, resulting from exposure to silica, silicates, aluminium, fibreglass particles, and infectious agents such as Pneumocystis jirovecii, Nocardia, and mycobacteria, as well as associated with haematological malignancies. We report the case of a man who developed PAP syndrome following a 2-year exposure to silica dust and subsequently reviewed the world literature where 363 cases were found.

Case Report
A 52-year-old white male with a 60 pack-year history of cigarette smoking presented with progressive dyspnoea on exertion for 18 months. He had worked in an environment where other workers were placing tiles and cutting floors, without wearing a mask. He had a long-standing cough...
with whitish sputum production, but denied fever, chills, weight loss, night sweats, and other symptoms. Physical examination revealed a mildly dyspnoic patient with normal vital signs; heart auscultation was normal; bibasilar fine late inspiratory rales involving half the way up in both lung fields were heard. Laboratory analyses showed haemoglobin (Hb) 17 g/dL, white blood cells (WBC) 8.700/mm³, and routine chemistry results including liver function tests were normal. Arterial blood gases: $\text{PaO}_2$, 76 mmHg; $\text{PaCO}_2$, 35 mmHg; and pH, 7.44. Pulmonary function tests revealed FVC: 4.69 L (89% of predicted), FEV1 3.73 L (92%), FEV1/FVC 80%, TLC 5.76 L (78%), and DLCO 16.8 mL/min/mmHg (54%). Chest radiograph revealed bilateral alveolar infiltrates (Fig. 1). Fiberoptic bronchoscopy failed to reveal any endobronchial lesion but yielded biopsies disclosing alveoli filled with periodic acid of Schiff (PAS)-positive lipoproteinaceous material and refringent particles compatible with silicates, and negative cultures (Fig. 2A, B). A therapeutic whole lung lavage (WLL) was carried out, resulting in an immediate improvement in symptoms as well as in gas exchange.

Figure 1. (A) Chest X-ray and (B) computerized tomography of the chest disclosing bilateral alveolar infiltrates in butterfly distribution, sparing the costophrenic angles characteristic of pulmonary alveolar proteinosis.

Figure 2. (A) High power view of an H&E stain of lung biopsy revealing alveoli filled with periodic acid–Schiff-positive proteinaceous material. (B) Polarized light microscopy showing birefringent particles compatible with silicate deposits in the pulmonary interstitium.
Discussion

This case supports the hypothesis that PAP should not be considered idiopathic until we exclude all the occupational aetiologies. Indeed, the relationship between the occupational exposure and the pulmonary reaction is evident in this patient. The intra-alveolar accumulation of PAS-positive material designated as PAP, has been reported to occur occasionally in workers exposed to high concentrations of fine particulate silica. This condition was first reported in 1969 by Buechner et al. [2].

When humans and animals inhale high concentrations of silica over a short period of time, the lining cells of the airways are damaged and a lipid-rich protein exudate accumulates, obliterating the air spaces. These events are followed by type II pneumocyte hypertrophy and hyperplasia, and increased production of phospholipid. In an experimental model, production of dipalmitoyl lecithin increased threefold, while the elimination of the material decreased. Under these circumstances, phagocytosis and the removal of particles were impaired [3, 4]. Rats exposed to high concentration of quartz dust developed alveolar proteinosis with some foci of desquamative pneumonitis and there was a great deal of aggregated silica in that proteinaceous material [5]. Since 1980 there have been several cases published in the English literature of PAP with silicosis and we think that some cases could have been assumed to be idiopathic PAP [6]. This case report of silica dust exposure coexisting with PAP, and the experimental finding that inhaled fine silica dust in animals can cause a similar disease [7], support the hypothesis that inhaled dust is responsible for the development of PAP, which may not be just a rare idiopathic disease entity, but perhaps a mere, somewhat uncommon pulmonary reaction to a noxious agent. Abraham and McEwen, using scanning electron microscopy, demonstrated the presence of inorganic particulates in histological specimens from patients previously diagnosed with PAP [8], and they also found that the count of birefringent particles was significantly higher in patients with PAP than in control history and accumulation of inorganic particles in the gas spaces of the lungs. Therefore, it is possible that PAP has multiple causes and that inhaled dusts is one of them.

A literature review was done using Medline. Three hundred and sixty-three cases were obtained in 36 manuscripts. The chart was arranged chronologically and contained the number of cases per study, the average age in each study, the type of PAP, the way the diagnosis was made, the treatment given, and the survival.

Table 1 shows the compilation of 363 chronologically arranged cases worldwide from 1988 to 2014. The age at the diagnosis varied from 1 to 79 years. PAP was classified into three groups regarding the aetiology: autoimmune or idiopathic (293 cases of 352 classifiable cases, which represents 83% of the cases), secondary (56 of the 352, which stands for 16% of the classifiable cases), and congenital (only 3 cases reported as such, which comprise 1% of the total). Twelve cases of 363 were not classifiable. PAP was diagnosed on the basis of bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBLB), or open lung biopsy (OLB). Until year 2006, WLL was the only treatment for PAP and the survival was almost 100%. In 2006, oncology researchers discovered serendipitously that knockout mice deprived of granulocyte macrophage–colony stimulating factor (GM-CSF) gene or receptor developed full blown PAP, which was ameliorated by the administration of GM-CSF. Thereafter it was conceptualized that GM-CSF plays an important role in the homeostasis of surfactant production in the alveolar milieu, and then the usefulness of administering GM-CSF to improve this condition was readily acknowledged. Subsequently, a dual therapy consistent in administration of GM-CSF and WLL was established.

WLL had been the standard of therapy since the report by Ramirez [45] and consequently we managed this reported patient using that intervention. The patient was placed under general anaesthesia, and a double lumen endotracheal tube was inserted; the dependent lung was placed down, a bronchoscope was inserted and after wedging it in a distant airway, we started lavage by instilling normal saline and then suctioning intermittently. Initially we obtained a lavageate that was markedly creamy due to the high lipoproteinaceous content and subsequently it became clear. Approximately 20 L had to be suctioned to get to this point. A week later, we performed WLL of the second lung.

The double lumen endotracheal tube is a key factor because we can **obturrate and ventilate one lung and work in the other one. Most of the experts use the ”eyeball technique” to estimate how much of lavage is sufficient. The frequency of lavage has to be individualized.

After the advent of GM-CSF it became a major contributing factor because it was recognized that its deficiency or absence would lead to a significant accumulation of surfactant in the alveolar space. The management of PAP changed forever after this because it became customary to first try GM-CSF and use WLL only for the therapeutic failure of GM-CSF. GM-CSF has been used via inhalational, systemic, or subcutaneous delivery with comparable results.

Finally, it is of utmost importance to analyse and improve the environment of patients. Avoidance of exposure to triggering agents such as silica, mould, or any infective or toxic material is the cornerstone of management of secondary type PAP.
| Reference no. | Year | N  | Ave. age | Autoimmune or idiopathic | Secondary | Congenital | Contrib. factors | Diagnostic method | Treatment | Survival % |
|-------------|------|----|----------|--------------------------|-----------|------------|-----------------|------------------|-----------|------------|
| Bracci [9]  | 1988 | 1  | 49       | 1                        |           |            |                 | OLB              | BAL       | 100        |
| Lopez [10]  | 1991 | 2  | 37       | 2                        |           |            |                 | OLB              | SR        | 100        |
| Chaudhuri [11] | 1996 | 1  | 26       | 1                        | TB        |            |                 | BAL/OLB         | Anti-TB treatment | 100        |
| Kim [12]    | 1999 | 12 |          |                          |           |            |                 | TBLB             | 9 WLL     | 75         |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |
|             |      |    |          |                          |           |            |                 | WLL              | 100       |            |

Table 1. Pulmonary alveolar proteinosis world literature review.
Disclosure Statements

No conflict of interest declared. Appropriate written informed consent was obtained for publication of this case report and accompanying images.

References

1. Rosen S, Castleman B, and Liebow A 1958. Pulmonary alveolar proteinosis. N. Engl. J. Med. 258:1123–1142.
2. Buechner H, and Ansary A 1969. Acute Silico-proteinosis. Dis. Chest. 55:274–284.
3. Silicosis and Silicate Disease Committee 1988. Disease associated with exposure to silica and non-fibrous silicate minerals. Arch. Pathol. Lab. Med. 112:673–720.
4. Heppleston A 1979. Silica and asbestos: contrast in tissue response. Ann. N. Y. Acad. Sci. 330:725–744.
5. Gross P, and de Trebille R 1968. Alveolar proteinosis: its experimental production in rodents. Arch. Pathol. Lab. Med. 86:255–261.
6. Rubin E, Weisbrod G, Sanders D. Pulmonary alveolar proteinosis. Radiology 1980; 135:36–41.
7. Heppleston A, Wright N, and Stewart J 1970. Experimental alveolar lipo-proteinosis following the inhalation of silica. J. Pathol. 101:293–305.
8. Abraham JL, and McEuen D 1986. Inorganic particulates associated with pulmonary alveolar proteinosis. Appl. Pathol. 4(3):138–146.
9. Bracci L 1988. Role of physical therapy in management of pulmonary alveolar proteinosis: a case report. Phys. Ther. 68:686–689.
10. Martínez-Lopez MA, Cerezo G, Villasante C, et al. 1991. Pulmonary alveolar proteinosis: prolonged spontaneous remission in two patients. Eur. Respir. J. 4:377–379.
11. Chaudhuri R, Prabhudesai P, Vaideeswar P, et al. 1996. Pulmonary alveolar proteinosis with pulmonary tuberculosis. Ind. J. Tub. 43:27–29.
12. Kim G, Lee S, Lee H, et al. 1999. The clinical characteristics of pulmonary alveolar proteinosis: experience at Seoul National University Hospital, and review of the literature. J. Korean Med. Sci. 14:159–164.
13. Kokturk N, Oguzgün İ, Haluk T, et al. 2000. A case report: pulmonary alveolar proteinosis. Turk. Respir. J. 1:68–72.
14. Wali SO, Samman YS, Altaf F, et al. 2000. Primary pulmonary alveolar proteinosis: a case report and a review of the literature. Ann. Saudi Med. 20:3–4.
15. Barraclough RM, and Gillies AJ 2001. Pulmonary alveolar proteinosis: a complete response to GM-CSF therapy. Thorax 56:664–665.
16. Beccaria M., Luisetti M., Rodi G., et al. . Long-term durable benefit after whole lung lavage in pulmonary alveolar proteinosis. Eur. Respir. J. 2004; 23:526–531.
17. Abdullhakim K, Prakash SB, and Ifthikar HM 2004. Congenital alveolar proteinosis. Saudi Med. J. 25(10):1474–1477.
18. Ker JM 2004. Pulmonary alveolar proteinosis—a case report and review. SA J. Radiol. 45:46.
19. Kotov PV, and Shidham VB 2006. Alveolar proteinosis in a patient recovering from Pneumocystis cariniiinfection: a case report with a review of literature. CytoJournal 3:22.
20. Kumari I, Rajesh V, Darsana V, et al. 2007. Whole lung lavage: the salvage therapy for pulmonary alveolar proteinosis. Indian J. Chest Dis. Allied Sci. 49:41–44.
21. Thomson JG, Kishima M, Gomes MU, et al. 2006. Pulmonary alveolar proteinosis: four cases. J. Bras. Pneumol. 32(3):261–266.
22. Tazawa R, Nakata K, Inoue Y, et al. 2006. Granulocyte-macrophage colony-stimulating factor inhalation therapy for patients with idiopathic pulmonary alveolar proteinosis: a pilot study; and long-term treatment with aerosolized granulocyte-macrophage colony-stimulating factor: a case report. Respirology 41:S61–S64.
23. Marios E, Koutsopoulos A, Helen P, et al. 2007. Total lung lavage by awake flexible fiberopticbronchoscope in a 13-year-old girl with pulmonary alveolar proteinosis. Respir. Med. 101:366–369.
24. Wylam ME, Ten R, Prakash UBS, et al. 2006. Aerosol granulocyte-macrophage colony stimulating factor for pulmonary alveolar proteinosis. Eur. Respir. J. 27:585–593.
25. Ceruti M, Rodi G, Giulia MS, et al. 2007. Successful whole lung lavage in pulmonary alveolar proteinosis secondary to lysinuric protein intolerance: a case report. Orphanet J. Rare Dis. 2:14.
26. Borie R, Debray MP, Laine C, et al. 2009. Rituximab therapy in autoimmune pulmonary alveolar proteinosis. Eur. Respir. J. 33:1503–1506.
27. Rushi T, Inoue Y, Arai T, et al. 2010. Aerosol GM-CSF therapy of PAP. Am. J. Respir. Crit. Care Med. 181:1345–1354.
28. Hodges O, Zar HJ, Mamathuba R, et al. 2010. Bilateral partial lung lavage in an infant with pulmonary alveolar proteinosis. Br. J. Anaesth. 104(2):228–230.
29. Byun MK, Kim DS, Kim YW, et al. 2010. Clinical features and outcomes of idiopathic pulmonary alveolar proteinosis in Korean population. J. Korean Med. Sci. 25:393–398.
30. Tabataiabi S, Karimi A, Tabataiabi R, et al. 2010. Pulmonary alveolar proteinosis in children: a case series. J. Res. Med. Sci. 15:120–124.
31. Tekgül S, Bilaceroğlu S, Özgaya S, et al. 2012. Pulmonary alveolar proteinosis and superinfection with pulmonary tuberculosis in a case. Respir. Med. Case Rep. 5:25e28.
32. Moreland A, Kijsirichareanchai K, Alalawi R, et al. 2011. Pulmonary alveolar proteinosis in a man with prolonged cotton dust exposure. Respir. Med. CME 4:121–123.
33. Sabeen Yaqub, Michelle S. Harkins. A 39 year old female with progressive dyspnea, dry cough and hypoxia: a case report. Southwest J. Pulm. Crit. Care. 2011; 3:130–140.
34. Bonella F, Ohshima S, Miaotian C, et al. 2013. Serum KL-6 is a predictor of outcome in pulmonary alveolar proteinosis. Orphanet J. Rare Dis. 8:53.
35. Tejwani D, Delacruz AE, Niazi M, et al. 2011. Unsuspected pulmonary alveolar proteinosis in a patient with acquired immunodeficiency syndrome: a case report. J. Med. Case Rep. 5:46.
36. Canellas R, Daniel K, Henrique P, et al. 2012. Spontaneous regression of pulmonary alveolar proteinosis. Radiol. Bras. 45(5):294–296.
37. Khan A, Agarwal R, Aggarwal AN, et al. 2012. Pulmonary alveolar proteinosis in North India. Indian J. Chest Dis. Allied Sci. 54:91–97.
38. Shende RP, Sampat BK, Prabhudesai P, et al. 2013. Granulocyte-macrophage colony stimulating factor therapy for pulmonary alveolar proteinosis. J. Assoc. Physicians India 61:209–211.
39. Hammami S., Harrathi K, Lajmi K, et al. Congenital pulmonary alveolar proteinosis Case Rep. Pediatr. doi: 10.1155/2013/764216.
40. Main S, Somani V, Molyneux A, et al. 2013. Unsuspected pulmonary alveolar proteinosis in a patient with a slow resolving pneumonia: a case report. Respir. Med. Case Reports. 10:1–3.
41. Bansal A, and Sikri V 2013. A case of pulmonary alveolar proteinosis treated with whole lung lavage. Indian J. Crit. Care Med. 17(5):314–317.
42. Rojanapremskul T, Arroyo JE, and Zepeda MR 2013. Case report and review of alveolar proteinosis. Lab Med. 44(2):147.
43. Ishii H, Seymour JF, Tazawa R, et al. 2014. Secondary pulmonary alveolar proteinosis complicating myelodysplastic syndrome results in worsening of prognosis: a retrospective cohort study in Japan. BMC Pulm. Med. 14:37.
44. Fijołek J, Wiatr E, Radzikowska E, et al. 2014. Pulmonary alveolar proteinosis during a 30-year observation. Pneumol Alergol Pol. 82:206–217.
45. Ramirez J, Nyka W, McLaughlin J 1963. Pulmonary alveolar proteinosis: diagnostic technics and observations. N. Engl. J. Med. 268:165–171.
46. Prakash U, Barhan S, Carpenter H, et al. 1987. Pulmonary alveolar phospholipoproteinosis: experience with 34 cases and a review. Mayo Clin. Proc. 62:499–518.