Pulmonary Alveolar Proteinosis:

The first South African insight into this rare disease

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Declaration

I Nadia Vorajee, hereby declare that the work on which this protocol and literature is based is my original work (unless otherwise referenced or acknowledged) and that neither part or the whole work be submitted for any other degree at any university.

Signed by candidate

Signature: _____

Date: ____29.06.2021_____

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Pulmonary Alveolar Proteinosis: The first South African insight into this rare disease

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Glossary

6MWT	6min Walk distance/test
CXR	Chest Radiograph
DLCO	Diffusing capacity of carbon monoxide
DM	Diabetes Mellitus
ECMO	Extracorporeal membrane oxygenation
GM-CSF	Granulocyte macrophage – colony stimulating factor
GSH	Groote Schuur Hospital
HIV	Human Immunodeficiency Virus
HPT	Hypertension
HRCT	High Resolution Commuted Tomography of the chest
PAP	Pulmonary alveolar proteinosis
PAS	Periodic Acid-Shiff
RA	Rheumatoid Arthritis
WLL	Whole lung lavage

Abstract

Background: Pulmonary alveolar proteinosis (PAP) is a rare disorder characterized by excessive accumulation of intra-alveolar surfactant related, lipoproteinaceous material. With the exception of a single pediatric case report of PAP, no data exists in Sub Saharan Africa. The aim of the study is to describe the epidemiological and clinical features of patients with PAP treated at Groote Schuur Hospital since May 2009 and their outcome after the first therapeutic whole lung lavage.

Methods: 11 patients with PAP were identified using the Pulmonology whole lung lavage register. A retrospective folder review was undertaken for demographic and clinical data which was captured via a paper data capture sheet and then entered into a REDCap database for ease of statistical analysis.

Findings: The median age at diagnosis was 42 years, with a male to female ratio of 1:1.2 . All the patient's tested negative for HIV. A history of smoking was seen in 63.6% (7) with median pack years of 21.5. Common symptoms at presentation included: dyspnoea (100%), dry cough (45.5%), productive cough (45.5%) and weight loss (54.5%). All patients were hypoxic at diagnosis with an average $Pa0_2$ on room air of 7.75 kPa (±1.59) and, a mean FEV1/FVC ratio of 87.60% (±7.02) of predicted. Although 36.4 % (4) were unable to perform 6 min walk tests at presentation, the remaining patients had a median distance of 287 m. No mortality was seen at 12 months, despite all patients requiring whole lung lavage during this period.

Conclusions: This small, retrospective cohort offers the first insight into the demographic and clinical features of patients in Sub-Saharan Africa with PAP. Interestingly, no patients in this cohort were HIV positive. Within this small cohort

very few statistically significant details can be drawn but rather a description of a rare condition. Future plans to continue data collection prospectively and expand to other centres will improve deductions made.

Complete Article

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disorder, causing a chronic lung disease[1, 2]. It is characterized by excessive accumulation of intra-alveolar surfactant related, lipoproteinaceous material, which is Periodic Acid-Schiff positive (PAS)[1-3]. PAP was first described in 1958, and to date less than 1000 cases have been reported worldwide, with the largest cohorts being described in China and Japan in 2008 and 2009 respectively[1, 2, 4]. Despite its global rarity in literature, it has been estimated to have prevalence of 3.7 cases per million population[2, 4]. Given its prevalence, it is understandably difficult for any single researcher or institution to gather significant experience with the disorder. As a result, 75% of the literature on PAP is made up of single case reports or small case series, with less than 10 studies having more than 20 or more patients[1, 5, 6].

Over the last decade, there has been a revolution in the understanding of PAP pathogenesis. In autoimmune PAP a notable deficiency in Granulocyte Macrophage – Colony Stimulating Factor (GM-CSF), which is produced by pulmonary macrophages[1, 4, 5] is thought to result in poor surfactant clearance and an accumulation of surfactant-related proteinosis debris within the alveoli[1,4]. Despite these advancements in understanding, the mainstay of therapy in PAP remains whole lung lavage (WLL)[5, 7]. Although there are no randomized controlled studies, there is good data showing improvement in exercise tolerance, objective improvements in lung function and arterial oxygenation[5]. The procedure of WLL **(Appendix 1)** is specialized and not carried out by many institutions. In Africa, Groote Schuur Hospital is one such institute.

With the exception 2 case reports of PAP[8,9], no data exists in Sub-Saharan Africa, with most studies having been conducted in European or Asian settings[6]. This void in data has led to much speculation on the incidence, demographics and clinical variants of PAP in Sub-Saharan Africa. With the high rates of Human Immunodeficiency Virus (HIV) and rising non-communicable disease in developing countries, Sub-Saharan Africa would be a unique setting to describe this condition.

The process of WLL can be likened to a large volume, bronchoalveolar lavage, which is used in patients with PAP as a therapeutic technique to clear the lipoproteinaceous material from the alveolar space[10,11] (see **Appendix 1** for full procedure details). The patient is intubated with a double lumen endotracheal tube and while, ventilating one lung, the other is 'washed out' by infusing normal saline into the lung and then slowly draining saline mixed with the lipoproteinaceous material out into bags (See **Figure 1**).

In undertaking this study, we hope to extend the understanding of this condition by describing the epidemiological and clinical features of all patients diagnosed with Primary Alveolar Proteinosis since May 2009, and their outcomes after the first therapeutic whole lung lavage (WLL).

Methods

After ethics approval was obtained under the ethics number, HREC 458/2020 data collection was started. In view of this being a retrospective cohort study with no

identifying data having been captured, no complex ethical considerations were required.

Using the Pulmonology whole lung lavage register at Groote Schuur Hospital's respiratory clinic, patients who underwent WLL from May 2009 to date (an 11-year period), were enrolled into this retrospective cohort study. A folder review was undertaken for demographic and clinical data, which was captured via a paper data capture sheet and then loaded into a secure electronic REDCap database (attached as **Appendix 2**) hosted at the University of Cape Town for ease of statistical analysis and record keeping. Data such as age, gender, comorbidities, and HIV status was captured. Co-morbidities that have been shown to have an association with PAP were looked at, namely underlying malignancy and autoimmune diseases. Regarding presentation symptoms and investigations, these were all captured from patient clerking notes made on review at the Respiratory Clinic.

The outcome of patients was assessed, by measuring the change in pulmonary function tests (American Thoracic Society guidelines where adhered to during spirometry), diffusion capacity for carbon monoxide (DLCO) and six-minute walk test (6MWT) distance pre and post therapeutic WLL at 3, 6 and 12 month follow up clerking notes.

Once the data was captured onto RedCap it was then collated, and comparisons reported in a non-parametric manner due to small sample size.

Results

Of the 11 patients with PAP identified, 54.5% (n=6/11) were females and all (n=11/11) were HIV negative. The median age at diagnosis was 42 years (IQR 22). 36.4% (n=5/11) had existing comorbidities: hypertension 27.3% (n=3/11) and diabetes 18.2% (n=2/11). None of the patients in this cohort had a known malignancy. A history of smoking was seen in 63.6% (n=7/11) with median of 21.5 pack years. Only 18.2% (n=2/11) had exposure to inorganic or organic dusts, but no mining or asbestos and silica exposure was noted.

All 11 (100%) patients presented with dyspnoea as a cardinal symptom. The other common symptoms noted were, 5 patients (45.5%) had a dry cough, 5 (45.5%) had a productive cough and 6 patients (54.5%) reported weight loss. The majority of patients, 54.4% (n=6/11) were noted to have a duration of symptoms prior to diagnosis of 5-10 months. 18.2 % (n=2/11) of patients had symptoms for 1-5 months, while 9.1% (n=1/11) had symptoms for 10-15 months and 18.2%(n=2/11) had symptoms for more than 15 months.

All the patients underwent radiological investigations at diagnosis, with the most common feature on chest radiograph being an alveolar infiltration 54.5% (n=6/11). In addition to a diffuse distribution noted in 27,3% (n=3/11), a butterfly appearance was seen in 18,2% (n=2/11) of the patients. None of the patients displayed a simple consolidation. On high resolution commuted tomography (HRCT) the most common finding was a “crazy-paving” appearance noted in 90% (n=9/11) of patients with 60% of these patients having a diffuse

distribution. The least common finding was that of a pleural effusion, reported in only one patient.

All patients were hypoxic at diagnosis with a median room air saturation of 87% (84-92) and median $Pa0_2$ of 7.2 (6.9-8.6) kPa. Only 9 of the 11 patients, underwent lung function tests at diagnosis. 7 of the 9 (77.78%) patients had FEV1/FVC ratios that would be classified as restrictive. Of note is that the median FVC was 59% (49-67) of predicted with a median FEV1/FVC ratio of 87% (85-89). The remaining two patients were noted to be too dyspnoeic to perform the test. A reduced median diffusion capacity (DLCO) of 34% (27-46) of predicted was noted in the 8 patients who had a DLCO recorded at diagnosis (**Table 2**). Only 7 patients had 6MWTs done at baseline, the median distance was 287m (401-205) (the international normative distance for healthy individual is 460-740m[14]).

9 complete data sets for comparison of preWLL and post 1st WLL were available at presentation and 3m follow up (**Table 2**). Lung function tests done at 3m post WLL showed a median FVC of 62% (60-79) of predicted with an average improvement from presentation of 282ml (11.2%). At 12m post WLL only 8 patients had recorded data to compare, with a median FVC of 69% (62-79) of predicted, with a recorded improvement of 259ml (10.2%). A marked improvement in DLCO (from 9.72 mmol/min/kPa at presentation – 34% of predicted) was seen at both 3m to 60% (38-64) of predicted and to 53% (37-86) of predicted at 12m. In terms of functional state, the 6MWT had improved to median distance of 378m at 3 months post WLL, a marked 91m improvement from the median distance recorded at presentation.

Testing for GM-CSF antibodies was only undertaken in two (18.2%) of patients, and their results were positive. No mortality was seen at 12 months post-diagnosis. 72.7% (n=8/11) of patients required one whole lung lavage during their first year after diagnosis, with 18.2% (n=2/11) patients requiring a second lavage, and only one patient (9.1%) required a third. Of note, is that 2 patients (18.2%) required the use of extracorporeal membrane oxygen (ECMO) during their 1st WLL.

Discussion

Although this study incorporated a small number within its cohort, it offers Africa's first experience with adult PAP, and makes several observations that are in keeping with international reports. Its finding also support the use of WLL as a therapeutic procedure in these patients.

As noted in prior articles [2,3], PAP is more common in males than in females, however, this cohort had a ratio of 1:1.2, with only one more female than male noted; this may speak to the sample size. The median age of diagnosis was within the fifth decade of life, and the same as the median age (42 years) quoted by Xu *et al*.[2]. Unlike a similar cohort of 10 patients published by Du Bouis *et al.*, who noted that all their patients smoked cigarettes[11], only 63.6% (7) of the patients in this cohort had a smoking history, with 4 being life-long non-smokers.

As in other reports, dyspnoea was the most common presenting symptom among patients in this cohort. Goldstien *et al* in 1998 also noted much higher rates of coughing

and weight loss with very few patients complaining of chest pain in comparison to earlier studies[3]. These finding were similar in our cohort, with cough (both productive 45.5% and dry 45.5%) and weight loss (54.5%) being common, and no patients reporting chest pain. Of note is that none of our patients were asymptomatic. This is likely due to selection bias, reflected in the use of the WLL register in identifying patients for the study.

All the patient's tested negative for HIV, and only 36.4% (5) had existing comorbidities; this was similar to the cohort by Goldstien *et al*[3]. None of the patients in our cohort had a known malignancy associated with PAP as noted in other reports[2]. Unlike studies published in the East[5], very few patients (18.2%, 2) had exposure to inorganic dust, with no patients having silica or asbestos exposure. This may be due to underreporting as the study was conducted retrospectively from patient's notes.

The features that were revealed by radiography are consistent with prior published reports. Alveolar infiltrates on chest radiograph (See Figure 2) were most common at 54.5% (6), followed in frequency by a diffuse interstitial involvement 27,3% (3). Prior reports suggest HRCT demonstrates the extent of PAP more clearly than a chest radiograph[2,3]. The review article by Xu *et al.*, noted a rise in the reporting of the "crazy paving" appearance (Figure 3) from reports published after1991[2]. In line with this observation, this feature was the most common finding 90% (9) within our cohort. Also observed by Xu *et al* was the rarity of pleural effusions on HRCT[2], again confirmed in this cohort with only one of our patients having this finding.

Our experience suggests that the median duration of time to diagnosis was 10-15 months, which is similar to median durations quoted in other papers (10 months[2] and 12 months[3]). Despite an improvement from the pre-1990s duration of a median time to diagnosis of 24 months [8], this is still a quite protracted period of symptoms. Given the improvements made in diagnosing this rare disease, this would suggest that it is not commonly considered on initial presentation or may be indicative of our health system and the long delays in referrals to tertiary institutions like Groote Schuur Hospital. Only two of our patients were tested for GM-CSF antibodies, which may speak to the access and affordability of the test in the developing country setting, such as our own.

As stated above and noted in **Table 1**, all patients were mildly hypoxemic at diagnosis with an average $Pa0_2$ on room air of 7.2 (6.9-8.6) kPa. This is similar to Goldstien *et al*'s, cohort of 20 patients who had a mean $Pa0_2$ 8.7 ±1.88[3]. Only 9 patients, underwent lung function tests at diagnosis with a median FEV1/FVC ratio of 87.6% (77.6-98.8) of predicted, and more importantly a FVC of 59% of predicted (49-67), with a diffusion capacity that was disproportionately and severely reduced at 34% of predicted (27-46).

Globally, changes of 10% in FVC and of 15% in DLCO are regarded as significant[12]. Despite missing lung functions for some patient records, comparison of those who had lung functions at presentation and 3 and 12months post WLL, a significant improvement in FVC of 11.2% (282ml) and 10.2%(259ml), at 3 and 12months respectively was noted. DLCO showed a marked increase of 45.2% at 3months and 66.4% increase at 12months. This improvement translated into a functional improvement of 6MWT distance to a median of 378m at 3 months post WLL, a marked 91m improvement. This supersedes the 25m regarded as significant by international standards in patients with chronic lung disease[13].

In the current interventional era, another uncertainty about PAP is the need for whole lung lavage. The variable natural history of the disease can include a spectrum of phenotypes, some going into spontaneous remission and others requiring a number of WLLs and possibly newer therapeutic alternatives, such as biologics[3]. Our series serves as an advocate for WLL, as all 11 patients required at least one WLL during the 12 months post-diagnosis. Although, 72.7% of patients in the cohort went into remission after a single WLL, three patients did not, and required further WLL.

However, it is noteworthy that WLL can be a technically challenging procedure from the perspective of provision of safe anaesthesia, airway management and ventilation[11]. Bearing this in mind, patients are fully assessed pre-operatively for suitability to have the procedure performed under general anaesthesia and to evaluate if they would tolerate single lung ventilation, as these patients already have physiologically difficult airways and a poor tolerance of apnoea. As a result, 2 (18.2%) of the patients in the cohort required ECMO during therapeutic WLL.

An improvement in was seen, as early as, 3 months post WLL with an improvement in 6MWT distance of 91m and an increase in FVC of 282ml (11.2%) this was further reinforced by the improvement of DLCO to 60% (38-64) of predicted at 3m. These improved functional and clinical parameters, are definite advocates for the use of WLL as a therapeutic tool in the treatment of hypoxemic PAP patients in a low resource, developing country setting.

There are several limitations to this study. Firstly, the retrospective nature meant that we failed to collect consistent follow-up data at regular predefined intervals (particularly 3 and 6 months), and that not all data regarding investigations such as lung function tests and diffusion capacity were uniformly available. Secondly, given the small sample size, very few statistically significant comparisons could be made.

Conclusions

This small, retrospective cohort offers the first insight into the demographic and clinical features of adult, patients in Sub-Saharan Africa with PAP. Interestingly, no patients in this cohort were HIV positive. Within this small cohort we cannot draw statistically significant conclusions, but rather offer a description of a rare condition, in a developing country. Despite the sample size, several similarities existed between our cohort and those described in other reports and review articles, which is reassuring. Our use of WLL as a primary therapeutic procedure has shown significant results in the improvement of both functional and clinical measures amongst our patients and is likely to continue to be the mainstay of our therapy due to the cost involved in the use of new biologic agents. Plans to continue data collection prospectively and expand to other centres will improve demographic and outcome data in future data collected.

Acknowledgements

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Appendix legend

Appendix 1: The process of WLL carried out on our patients.

Patients are fully assessed pre-operatively for suitability to have the procedure performed under general anaesthesia and to evaluate if they would tolerate single lung ventilation. Understanding that these patient's capacity to tolerate apnoea is poor and that they have physiologically difficult airways, they are assessed to determine if they will require the procedure done on ECMO.

The procedure entails the isolation of a single lung, by the correct placement of a double lumen tube and single lung ventilation of the other lung. The isolated lung is then lavaged with normal saline (heated to room temperature) and buffered with 4mls of sodium bicarbonate to each litre of saline. Approximately one litre of fluid is instilled into the lung at a time and, with vigorous chest physiotherapy, the fluid is allowed to drain back, passively, with the aid of gravity.

On average each lung would require 10-12 litres of fluid to adequately washout the proteinaceous material. The procedure can last between 4-5 hours, to successfully washout both lungs and invariably the patient requires post-operative ventilation in the ICU for 12-24 before they can be safely extubated. The combined effects of alternating single lung ventilation in these patients, in the supine position; and the cardiorespiratory interactions caused by dynamically changing pulmonary vascular resistance, necessitate invasive monitoring[9,10], a high level of resources and an experienced, highly skilled multi-disciplinary team;

involving pulmonologists, anaesthetists, physiotherapists, and intensivists are needed in the successful management of these patients.

Appendix 2: Data Capture tool downloaded from RedCap to illustrate what demographic data was captured.

Demographics

Study number	_____
Gender	◯ Male ◯ Female
Age	_____
Socioeconomic status	◯ Poor ◯ Middle class ◯ Upper class
Smoking	◯ Yes ◯ No
Pack yr history	_____
HIV positive	◯ Yes ◯ No
CD4	_____
Arvs	◯ Yes ◯ No
Other Co-morbidities	☐ None ☐ Diabetes ☐ Hypertension ☐ Obesity ☐ Malignancy ☐ Rheumatoid Arthritis
Occupational Exposures	◯ None ◯ Inorganic or organic dusts ◯ Gold mining ◯ Asbestos ◯ Silicosis

Presentation

Study number	_____
Symptoms at presentation	☐ Dry cough ☐ Productive cough ☐ Dyspnoea ☐ Chest pain ☐ Weight loss
Duration of symptoms prior to diagnosis (months)	◯ 1 to 5 ◯ 5 to 10 ◯ 10 to 15 ◯ > 15
Finger sats on room air	_____
Pa02 on room air	_____
Chest X-ray report	◯ Alveolar infiltration ◯ Butterfly appearance ◯ Consolidation ◯ Diffuse distribution
CT report	☐ Geographic pattern ☐ Crazy paving ☐ Diffuse distribution ☐ Pleural effusion
Tested for antiGM-CSF antibodies	◯ Yes ◯ No
If tested	◯ Positive ◯ Negative
Lung functions done	◯ Yes ◯ No
Reason	_____
FEV1	_____
FVC	_____
FEV1/FVC	_____
DLCO	_____
6min walk test done	◯ Yes ◯ No
Distance	_____

Outcomes

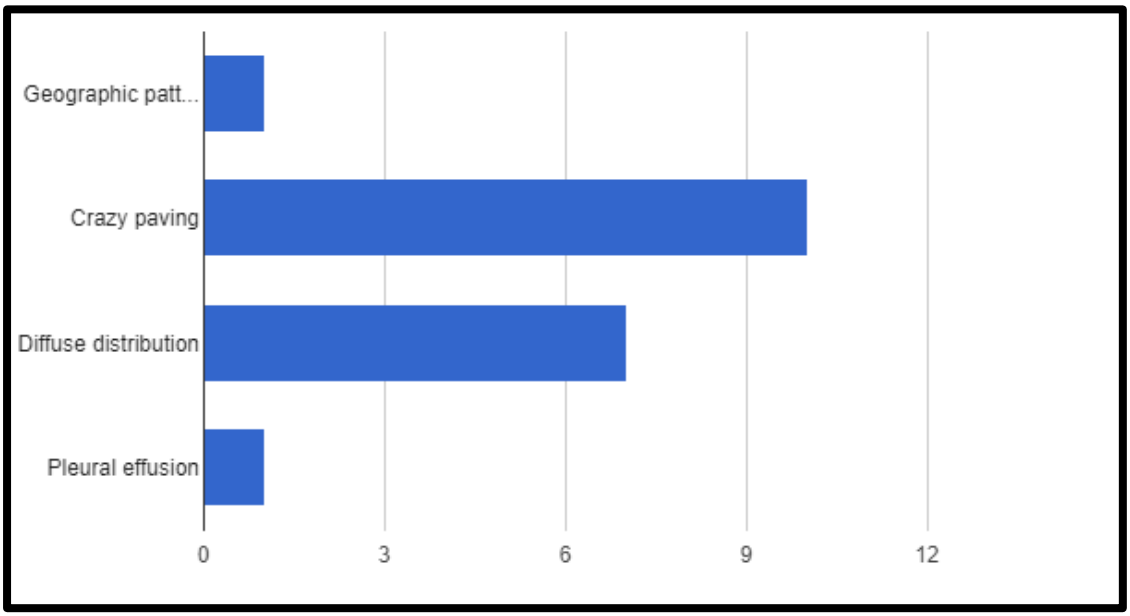
Study number	_____
Outcome at 12months	◯ Alive ◯ Dead
Number of whole lung lavage 12months post presentation	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ >4
Lung functions 3m post whole lung lavage	◯ Yes ◯ No
FEV1	_____
FVC	_____
FEV1/FVC	_____
DLCO	_____
6min walk test done	◯ Yes ◯ No
Distance	_____
Lung functions 6m post whole lung lavage	◯ Yes ◯ No
FEV1	_____
FVC	_____
FEV1/FVC	_____
DLCO	_____
6min walk test done	◯ Yes ◯ No
Distance	_____

Lung functions 12m post whole lung lavage	◯ Yes ◯ No
FEV1	_____
FVC	_____
FEV1/FVC	_____
DLCO	_____
6min walk test done	◯ Yes ◯ No
Distance	_____

Figure legends

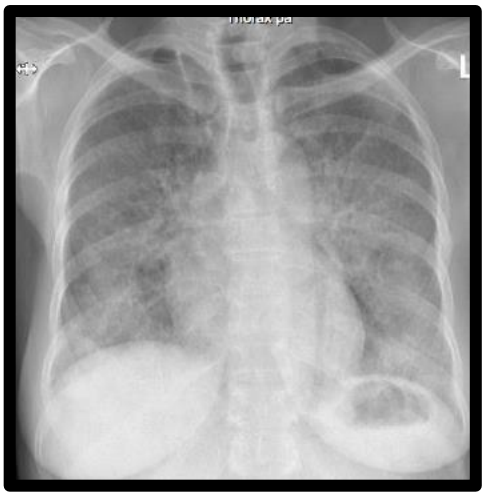
Figure 1: Fluid drained after whole lung lavage of one of our cohort patients showing declining amounts of lipoproteinaceous material (the clearer the fluid the less lipoproteinaceous material mixed with saline). Bag marked with arrow is the first bag of saline infused and drained.

Figure 2: Bar graph showing common CT findings of patients presenting with pulmonary alveolar proteinosis in South Africa.

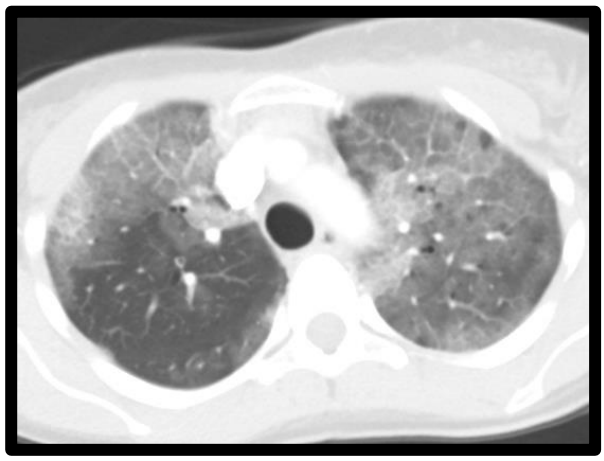


The most common CT findings within our cohort of patients included a Geographic pattern (1, 9,1%), Crazy paving (10, 90,9%), Diffuse distribution (7, 63,6%), Pleural effusion (1, 9,1%)

Figure 3: Typical chest radiograph (CXR) and commuted tomography (CT) scan of one of the cohort patients at presentation.



CXR showing alveolar infiltration (ground glass opacification) in a diffuse distribution.



CT scan showing the typical crazy paving appearance.

Tables

Table 1: Demographic and clinical features upon diagnosis of idiopathic pulmonary alveolar proteinosis

Parameters	No.	Median	Interquartile Range
Age (yrs)	11	42	33-51
Male (%)	5	45.5%	-
Pa02 (kPa)	11	7.2	6.9-8.6
FVC (% of pred)	9	59	49-67
FEV_1/FVC	9	87.6	77.6-98.8
DLCO (% of pred)	8	34	27-46

PaO2, partial pressure of oxygen in arterial blood; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide.

Table 2: Comparison of 9 cohort patients in terms of FVC, DLCO and 6MWT at presentation and post WLL at 3m and 12m

Study no.	FVC(% predicted)				DLCO (% predicted)				6MWT			
	Pres	3m	12m	%	Pres	3m	12m	%	Pres	3m	12m	Imp in m
01	63	62	67	4	34	60	72	38	-	-	-	-
02	59	79	96	37	41	62	96		210	380	395	185
03	***-***	***46***	***73***	***-***	***-***	***25***	***49***	***-***	***-***	***182***	***280***	***-***
04	***67***	***72***	***75***	***8***	***27***	***25***	***28***	***1***	***287***	***234***	***250***	***37***
05	81	97	89	8	46	67	63	17	320	450	432	112
06	43	62	70	27	23	38	43	20	495	528	660	165
07	41	60	62	21	34	38	40	6	-	-	-	-
08	49	51	55	6	56	79	81	25	482	650	644	162
10	115	120	-	-	60	64	-	-	200	378	-	-
11	57	56	62	5	-	28	29	-	100	120	200	100

*participant 09 was removed from the table as there was a significant amount of missing data
*participants 03 and 04 required WLL on ECMO
FVC, forced vital capacity (%of predicted); Pres, investigations at baseline; 3m, 3month follow-up findings; 12m, 12 month follow-up findings; %, percentage improvement at 12m follow-up; imp in m, improvement of 6MWT distance between presentation and 12months