
Rare cause of dyspnoea: protein accumulation in the lungs

Interstitial or diffuse lung disorders are disorders affecting the spaces between the alveoli and blood vessels (the so-called interstitium) in the lung. It is an umbrella term for a range of rare diseases, including a disease called pulmonary alveolar proteinosis (PAP), which involves accumulation of proteins in the interstitium but also in the alveoli themselves. In the Netherlands there are an estimated 50 to 60 patients suffering from this disorder.

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In a normal lung, the alveoli (pulmonary vesicles) contain air, and its inner surface is covered by a very thin layer of protein. This thin layer consists of a number of proteins, the most familiar of which is surfactant. Important functions of this protein layer include anti-inflammatory action and lowering the surface tension of the alveoli, in order to prevent them from collapsing. There is a balance in the lungs between continuous production and breakdown of surfactant. If this balance is disturbed, surfactant can accumulate in the lungs, making it gradually harder for oxygen to reach the blood circulation from the alveoli. These proteins thus cause a literally breath-taking situation, characterised mostly by dyspnoea, reduced exercise tolerance and fatigue. This illness is known as pulmonary alveolar proteinosis (PAP).¹ Its estimated prevalence is 4 per million inhabitants. Most of the patients are aged between 20 and 50 years. The male-female ratio is 2.7:1 and the incidence is about three times as high among smokers than among non-smokers.^{1,2} The key problem in this disorder is the

reduced function of a cytokine called granulocyte/macrophage-colony stimulating factor (GM-CSF). GM-CSF is required for an adequate function of macrophages in the lungs. Alveolar macrophages play a major role not only in our defence mechanisms, but also in removing excess intra-alveolar proteins such as surfactant. This function is affected in people with PAP, leading to symptoms. A distinction can be made between hereditary PAP, secondary PAP and auto-immune PAP.³

People with hereditary PAP have a defect in the GM-CSF receptor, causing a reduction or even absence of signal transduction after GM-CSF binds to its receptor. These patients develop symptoms in early childhood. Secondary PAP involves the development of PAP associated with underlying disorders such as haematological defects (leukaemia, lymphoma, aplastic anaemia), immunological diseases (IgA deficiency, severe combined immunodeficiency) and infections (Mycobacterium tuberculosis, Nocardia, Pneumocystis jiroveci). An association has also been found between inhaling organic compounds (flour) and inorganic



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substances (silica, aluminium) and the development of secondary PAP, although the pathogenesis behind this association is not yet fully clear. The most common form of PAP among adults is the so-called auto-immune PAP, in which auto-antibodies are formed against GM-CSF. Pulmonary alveolar proteinosis does not occur exclusively in humans: a cat with the disease was recently described.⁴

Establishing the diagnosis

Patients with PAP have nonspecific complaints like dyspnoea, coughing and sometimes pneumonia. The reduced function of GM-CSF causes proteins like surfactant to accumulate in the lungs, so the alveoli fill up with protein. This produces a highly characteristic pattern on a CT scan of the lungs, which is known as "crazy paving" (see Figure 1). Although this CT picture is highly suggestive of PAP, it is not conclusive. After the secondary causes listed above have been excluded in a patient with this CT pattern, and the presence of auto-antibodies against GM-CSF is proven, the diagnosis of auto-immune PAP can be established.

Treatment: whole-lung lavage

The gold standard for treatment of severe PAP with reduced lung function is the so-called whole-lung lavage,⁵ in which one lung at a time is flushed. This procedure is carried out in the operating room, under general anaesthesia. A special ventilation tube with two separate channels is introduced, a so-called double-lumen tube. This allows the patient to be ventilated in one lung while the other is being flushed. The procedure involves a special set-up, with a bag of saline (NaCl)

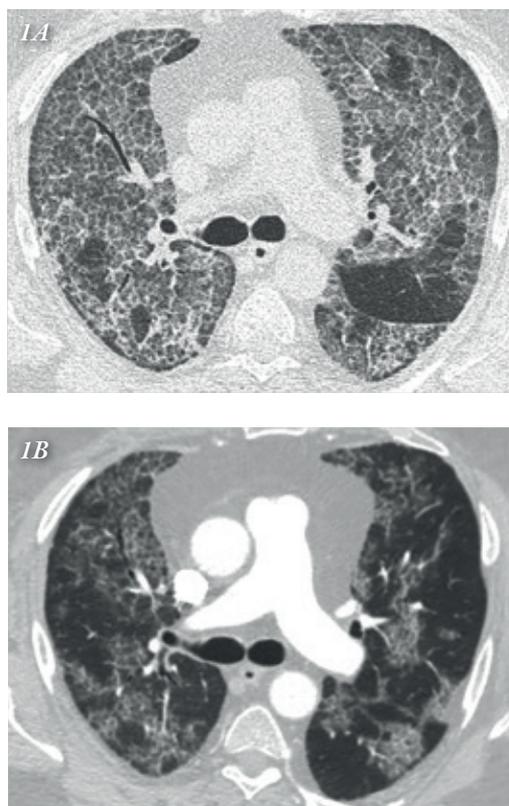


Figure 1. Crazy Paving: a characteristic pattern on a CT scan of the lungs of a patient with pulmonary alveolar proteinosis. These are scans of a patient, panel A. showing the CT pattern before his first pulmonary lavage and panel B. the pattern after his first lavage.

warmed to 37°C suspended high above the patient. A tube leads from this bag to the lung that is to be flushed, through the double-lumen tube. This is called the upper tube. Gravity causes the fluid to gradually fill the lung. After about one litre of the fluid has entered the lung,

the bag of saline is sealed off. Apart from the upper tube that carries fluid to the patient, there is a second tube, which also runs through the special ventilation tube, that leads away from the patient. This is known as the lower tube, and is connected to a receptacle placed on the floor. This lower tube is closed off by a valve while the body-temperature saline is being infused. When the valve in the lower tube is opened up, gravity will cause the fluid to slowly drain from the lung into the receptacle. This fluid contains protein flushed from the lung. After the entire 1-litre quantity of fluid has left the lung, the cycle can be repeated by once again introducing a litre of saline into the lung. On average, this cycle is repeated about 12 to 20 times in each lung, to a total volume of 12 to 20 litres. Placing the successive receptacles side by side clearly shows how the fluid becomes gradually clearer (Figure 2). The protein density in the fluid drained into the receptacles is measured by means of photospectrometry in each cycle. Based on international publications, the procedure is terminated as soon as this protein density has fallen below 0.4 Optical Density (OD).⁶ An important aspect of the treatment is the thoracic percussion that is applied by a physiotherapist during the entire procedure.



Figure 2. Receptacles with fluid obtained during the whole lung lavage. The proteins are clearly visible as they precipitate to the bottom. The beakers in front show the layer of protein on the bottom becoming thinner with each lavage. Behind the beakers are the large receptacles containing the total volume of pulmonary lavage fluid.

This percussion ensures that more protein is evacuated from the lungs. Furthermore, coughing is mechanically induced after every third cycle by means of controlled mechanical ventilation of the lung that is being flushed, using a ventilation bag. A tidal volume of 300ml of room air is delivered by the bag while monitoring the pressure. While the pressure suddenly is decreased manual thoracic compression is applied inducing a mechanical cough. This is performed 10 times consecutively. The subsequent lavage then releases more protein from the lung.

It will be clear from the above description that whole-lung lavage can only be applied by experienced staff. It is crucial to have a team consisting of anaesthesiologists, physiotherapists, pulmonary nurses and pulmonologists who are familiar with the procedure and the complications that might occur. A video about the whole lung lavage as carried out at the ILD Centre of Excellence of the St. Antonius Hospital (Nieuwegein, The Netherlands) is available on www.ildcare.nl.

Treatment: administering GM-CSF

Another treatment for PAP involves giving the patient GM-CSF. Various studies have shown that this therapy is effective in an average of 59% of all patients, the preferred method being nebulisation of the GM-CSF rather than subcutaneous administration.^{7,8}

One major disadvantage is that the GM-CSF preparation used for this indication is often not covered by health insurance. Hence, a worldwide pre-authorisation trial has been started on nebulised GM-CSF, and the ILD Center of Excellence at Nieuwegein, The Netherlands is one of the participating centres (IMPALA trial, <https://clinicaltrials.gov/ct2/show/NCT02702180?term=molgramostim&rank=1>).

An example from practice

A 47-year-old patient presented with symptoms of progressive dyspnoea that had started several months ago. Additional diagnostics revealed a CT pattern showing crazy paving (Figure 1A), and a milky fluid was obtained at broncho-alveolar lavage (BAL). Eventually, auto-immune PAP was diagnosed after auto-antibodies against GM-CSF were identified. The patient was severely short of breath and oxygen-dependent at rest. In view of the perilous pulmonary situation, it was immediately decided to apply whole-lung lavage. This procedure led to a clearly improved status, (Figure 1B), but the patient still showed desaturation upon exertion.

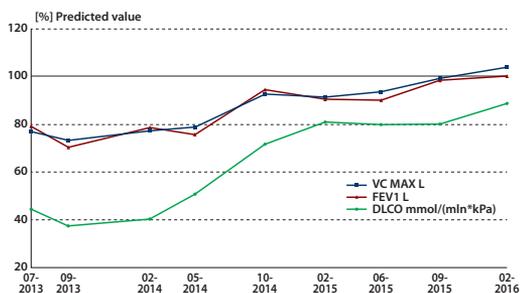


Figure 3. Course of lung function of the patient. VC = Vital Capacity; FEV1 = Forced Expiratory Volume in 1 second; DLCO = CO diffusion capacity.

The patient eventually underwent 6 whole-lung lavages, followed by treatment with nebulised GM-CSF for another 12 months. This management further improved his lung function (Figure 3). Now, 3 years on, his lungs show an almost normal picture (Figure 4) and the patient is symptom-free.

Practice recommendations

Dyspnoea is a very common complaint, and its cause is not always clear. There may occasionally be very rare causes, such as protein accumulation in the lung, called pulmonary alveolar proteinosis (PAP). Over 90% of all adult patients with PAP have auto-antibodies against GM-CSF, a growth factor that is required to stimulate macrophages to remove excess surfactant from the alveoli. The main treatment for severe PAP is whole-lung lavage, which often needs to be repeated several times to obtain a satisfactory result. This technique requires a team of experts and must be carried out at a specialised centre. Milder forms of PAP can be treated with nebulised GM-CSF or a watchful-waiting strategy.



Figure 4. Thorax X-ray at diagnosis (A) and at the final checkup at the outpatient department 3 years later (B).

References

1. Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. *Am J Respir Crit Care Med* 2002; 166(2): 215-35.
2. Huisman P, et al. Pulmonary alveolar proteinosis: a disease caused by surfactant accumulation, and new treatment with sargramostim. *Ned Tijdschr Geneesk* 2008 28; 152(26): 1450-54.
3. Carey B, Trapnell BC. The molecular basis of pulmonary alveolar proteinosis. *Clin Immunol* 2010; 135(2): 223-35.
4. Szatmari V, et al. Pulmonary alveolar proteinosis in a cat. *BMC Vet Res* 2015; 11: 302,015-0613-4.
5. Abdelmalak BB, et al. Therapeutic Whole-Lung Lavage for Pulmonary Alveolar Proteinosis: A Procedural Update. *J Bronchology Interv Pulmonol* 2015; 22(3): 251-58.
6. Bonella F, et al. Wash-out kinetics and efficacy of a modified lavage technique for alveolar proteinosis. *Eur Respir J* 2012; 40(6):1 468-74.
7. Khan A, et al. Effectiveness of granulocyte-macrophage colony-stimulating factor therapy in autoimmune pulmonary alveolar proteinosis: a meta-analysis of observational studies. *Chest* 2012; 141(5): 1273-83.
8. Tazawa R, et al. Duration of benefit in patients with autoimmune pulmonary alveolar proteinosis after inhaled granulocyte-macrophage colony-stimulating factor therapy. *Chest* 2014; 145(4): 729-37.

More information?

Please visit the website of ild care foundation. There you will find a video of how Dr. Marcel Veltkamp - with a team of experts from the ILD Center of Excellence, St. Antonius Hospital Nieuwegein, The Netherlands - performs a total lung lavage. See: <https://vimeo.com/181687565>



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