

the development of malakoplakia are an unusual strain of bacteria, an altered immune response, an altered histiocytic response or intrinsically abnormal macrophages [5]. The most common site of infection in females is the urinary tract and it is associated with infection with Gram-negative organisms, mainly *Escherichia coli* and *Klebsiella* sp. The extragenitourinary sites that are involved are the skin and the pulmonary, renal and gastrointestinal tract. Other microorganisms associated with malakoplakia are *Rhodococci equi*, *Mycobacteria* sp., *Pasteurella multocida*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Yersinia* sp., *Staphylococcus aureus* and fungal infection [6–9]. Thus, in cases such as ours where no positive microbiology is obtained, antibiotics covering Gram-positive and -negative organisms should perhaps be used for at least 2 weeks. So far, less than 40 cases of pulmonary malakoplakia have been reported and there is therefore little evidence for definite treatment.

Pulmonary malakoplakia can present as a lung mass with radiological findings consistent with malignancy or infection. Signs and symptoms are nonspecific and clinical presentation depends on the organ system involved. Conservative treatment with antibiotics results in the regression of the disease in most cases.

In this case, the patient was immunocompetent and no positive microbiology was obtained on bronchoalveolar lavage. Diagnosis was confirmed on core biopsy under CT guidance of the lesion extending from the left lower lobe of the lung, through the left hemidiaphragm to the upper pole of the left kidney. Although the PET scan was positive, a biopsy was performed to establish and confirm diagnosis. In this instance, this was of immense importance as the diagnosis changed from a radiological diagnosis of stage IV lung cancer to a potentially curable inflammatory condition. PET results must be interpreted within the clinical context and, where possible, a tissue diagnosis is desirable to confirm diagnosis. Our patient was empirically treated with antibiotics for 4 weeks and a subsequent CT scan showed a decrease in the size of the lesion.

In 1996, OZKÜRÇÜGİL *et al.* [10] reported a case of renal malakoplakia with pulmonary involvement. Diagnosis of malakoplakia was confirmed at nephrectomy. Treatment with antibiotics led to regression of the lung lesion. At present, no

case of malakoplakia extending from the kidney to the lung with possible involvement of the spleen has been reported.

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Interstitial lung disease in a child heterozygous for the 1549C→GAA (121ins2) mutation of surfactant protein B

To the Editors:

The *SFTPB* gene encodes the hydrophobic pulmonary surfactant protein (SP)-B, which is essential for the build-up of the surfactant layer and lowering of surface tension in the airways. SP-B deficiency was the first reported genetic cause of lethal respiratory distress syndrome (RDS) in infants in 1993 [1].

The phenotype of infants with hereditary SP-B deficiency is of a typically full-term neonate with respiratory failure in the

first 24–48 h of life; diagnosis can be delayed, as affected infants may show initially mild symptoms and not require ventilation or further medical support for some time. Chest radiography shows a bilateral, wide ground-glass pattern consistent with a diagnosis of hyaline membrane disease. Typical histological findings are the presence of periodic acid–Schiff-positive eosinophilic material in the alveoli, epithelial cell desquamation, enlarged alveolar macrophages with lamellar inclusions and accumulation of SP-A [2]. Since SP-B

was found to be essential for the proteolytic processing of pro-SP-C, newborns with hereditary SP-B deficiency show aberrantly processed SP-C in the intra-alveolar lumen. Lung disease is rapidly progressive and fatal respiratory failure finally sets in within 3–6 months; lung transplantation is suggested as the only effective treatment. To our knowledge, heterozygous mutation has not previously been reported to cause clinical symptoms.

A 6-month-old male was admitted to the Bronchopneumology Unit (Bambino Gesù Children Hospital and Research Institute, Rome, Italy) in 2008; the patient was a term-born infant, admitted to another hospital at the age of 1 month for acute respiratory failure and pneumonia that required intubation with surfactant administration and mechanical ventilation. Clinical symptoms were consistent with a diagnosis of RDS. A lung computed tomography (CT) scan showed interstitial infiltration. Sweat test, *CFTR* mutations, lymphocyte subsets, α_1 -antitrypsin sampling, bronchoalveolar lavage (BAL) and sputum cultures were negative. The patient was discharged with continuous oral steroid treatment, inhaled salbutamol and ipratropium bromide.

On admission, the patient's general condition was fairly good: weight and height below the third centile; wide crackled on chest auscultation; and arterial oxygen saturation 96% with oxygen ($2 \text{ L} \cdot \text{min}^{-1}$).

Bronchoscopy did not demonstrate anomalies of tracheobronchial tree, and BAL cultures and viral search were negative; $2,000 \text{ cells} \cdot \text{mL}^{-1}$ BAL fluid were counted (differential cell count: 77% macrophages, 16% neutrophils, 6% lymphocytes and 1% eosinophils).

CT scan confirmed the previous findings (fig. 1).

The patient was treated with oral steroids and montelukast, inhaled salbutamol and fluticasone.

In February 2008, the patient underwent an open lung biopsy, which showed a desquamative interstitial pneumonia; electron microscopy revealed anomalies of type 2 pneumocytes, with intracytoplasmic surfactant bodies in numbers and distribution typical of SP anomaly related disease. Immunohistochemical staining for SP-B was negative, consistent with an SP-B deficit.

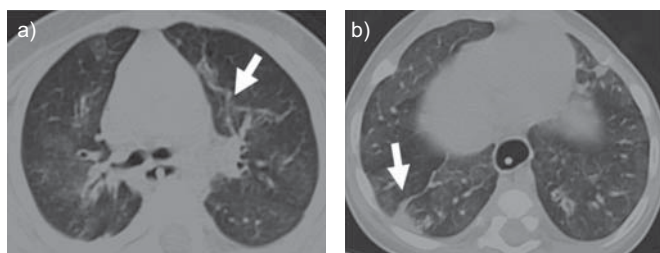


FIGURE 1. Computed tomography scan of the chest: bilateral, patchy lobular and segmental ground-glass attenuation in the lung parenchyma. a) A marked peribronchovascular thickening (arrows) is also present, especially in the central, perihilar structures. b) Subpleural consolidations (arrows) are evident in the lingula and the right lower lobe, associated with distortion of adjacent parenchyma.

The study of anomalies for SP genes showed only a heterozygous mutation of SP-B (1549C→GAA; 121ins2), in blood and BAL fluid, while the analysis of the other known genes encoding SPs (including *ABCA3* and the SP-C gene) was normal. The same mutation was reported in the patient's father, who had no clinical manifestation of lung disease.

The actuarial clinical situation was stable; the patient needed continuous steroid treatment (low dose of prednisone) and had no need of oxygen supplementation.

SP-B deficiency causes fatal respiratory distress in newborn infants. In humans, it is inherited as an autosomal recessive gene that causes respiratory failure in the newborn and death in the first months of life.

Usually, genetic analysis in *STPB* deficit shows homozygosity for a frame-shift mutation in codon 121 (termed the 121ins2 mutation) and this mutation accounts for up to two-thirds of the mutant alleles identified in the SP-B locus, with an estimated allele frequency of one case per 1,000–3,000 individuals [3].

TREDANO *et al.* [4] characterised *SFTPB* 1549C→GAA (1549C→GAA; 121ins2) and 457delC heterozygosity in an infant with severe unexplained respiratory distress and a complete absence of SP-B in BAL fluid. Previous studies on *SFTPB*-haploinsufficient murine lineages demonstrated decreased lung compliance and air trapping at birth. This finding could suggest that infants heterozygous for 121ins2 may have increased risk or severity of RDS. However, it was described that 121ins2 heterozygous healthy siblings and parents of 11 SP-B-deficient infants were completely asymptomatic; only one heterozygous asymptomatic nonsmoking sibling showed a decreased forced expiratory volume in 1 s on spirometry at adult age. These data suggest that these mutations would not cause symptoms in heterozygous individuals [5].

To our knowledge, the patient of the present study is the first paediatric case of symptomatic interstitial lung disease (ILD) with an isolated heterozygous mutation of SP-B (1549C→GAA; 121ins2), as symptoms are usually present only in homozygous patients. Therefore, we speculate that heterozygous individuals may not be "healthy", but that their clinical situation depends on the expression of the mutation, which provokes an abnormal amount of protein production or production of a functionally impaired protein, and/or that this clinical feature could depend on an associated but not yet identified mutation in others genes. For this reason, patients with severe respiratory infections should be investigated for SP deficiency, particularly if other more common diseases are excluded, because infections could reveal the hidden disease. Besides this, heterozygous siblings and parents of SP-B-deficient individuals should be carefully treated if respiratory symptoms are present.

Despite the fact that we do not know all the genes causing ILD in children and that we still miss certain mutations in the known genes, in our case, the identified heterozygous *SFTPB* mutation is linked to the absence of SP-B protein. Previous large cohort studies have found that subjects who are heterozygous for the mutation may be at increased risk of chronic obstructive pulmonary disease if they are smokers in adulthood, but to

our knowledge, ILD has never previously been related to heterozygous *SFTPB* mutation in either adults or children.

The patient's clinical situation was characterised by a normal pulmonary pressure and a transient need for oxygen supplementation; only low doses of oral prednisone were required. Presently, it is not possible to predict the patient's clinical course, as no other similar cases have been reported. Lung transplantation currently represents the only treatment option for this disease, but it is hoped that new treatments will be developed that are based on a better understanding of the disease.

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Ambulatory oxygen in interstitial lung disease

To the Editors:

Interstitial lung diseases (ILDs) are often associated with significant oxygen desaturation on exercise, resulting in exercise limitation, exertional dyspnoea and reduced quality of life. However, surprisingly few data are available on ambulatory oxygen in ILD. The 6-min walk test (6MWT), a self-paced test performed according to standardised protocols, has been shown to be highly reproducible in ILD patients [1], and is felt to be more sensitive than a cycle ergometer test in assessing oxygen requirements [2].

We present a retrospective assessment of the effects of ambulatory oxygen on 6MWT performance in a group of patients with fibrotic ILD seen at the Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK. The 6MWT was performed following a standardised protocol [3, 4]; patients were asked to perform the 6MWT at their habitual walking pace and were allowed to stop if they experienced unacceptable symptoms of dyspnoea and/or fatigue; standardised encouragement to restart the test was given at regular intervals.

A review of the clinical records of ILD patients seen at the Royal Brompton Hospital, from November 2007 to January 2010, identified 52 ILD patients with a fall in arterial oxygen saturation (S_{a,O_2}) $\leq 88\%$ at the end of a baseline 6MWT, who had consented to a second test on ambulatory oxygen during the same session, as part of their routine clinical assessment. All 6MWTs were performed on the same measured corridor and were supervised by the same experienced oxygen technician (A. Montgomery), with a minimum rest period of 20 min between tests.

Measurements included 6-min walk distance (6MWD), S_{a,O_2} , heart rate, and modified Borg dyspnoea score (range 1–10) assessed immediately before and after each 6MWT [5]. Recovery times to baseline S_{a,O_2} , heart rate, and Borg score were also measured at the end of each test. In 32 patients, the baseline 6MWT was performed on room air, whereas the habitual oxygen flow rate at rest was used for the others, and an increased flow rate was used for the second test. Ambulatory oxygen was provided by using the same Sabre cylinder (Aldershot, UK), weighing 6.5 lbs (2.9 kg). To mirror the patient's daily needs, the oxygen cylinder was carried by the patient or by a member of the oxygen assessment team, depending on whether or not the patient was likely to be carrying the cylinder in day-to-day life. The flow rate used during the second test was decided using a semi-quantitative assessment of individual oxygen requirements, based on accumulated local experience. As an approximate guide, in patients of normal build, planning to carry their own cylinder, the required oxygen flow rate was estimated at 2 L·min⁻¹ for desaturations of 86–88%, increasing by 1 L for every three percentage points of desaturation. Patients desaturating <70–75% were offered flow rates >6 L·min⁻¹. The estimated flow rate was increased by 25–50% in patients with body mass index (BMI) >30, while it was reduced by ~0.5 L if the oxygen cylinder was going to be carried by others. Ambulatory oxygen was provided as a continuous flow through nasal cannulae, except for six patients receiving ambulatory oxygen through a Venturi mask (40–60% oxygen).

Lung function tests performed within 3 months of the 6MWT were available for all patients. An echocardiogram performed