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Case Studies

Sinonasal persistence of *Pseudomonas aeruginosa* after lung transplantation

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ABSTRACT

We report on two CF patients who received double lung transplantation (LTX) due to *Pseudomonas aeruginosa* related pulmonary destruction. Prior to LTX we detected *P. aeruginosa* in nasal lavages (NL) and sputum cultures from both patients. Donor lungs of patient 1 became colonized within four weeks with *P. aeruginosa* identical in genotype with isolates from his pre-transplant sputum cultures and pre- and post-transplant NL.

In contrast, patient 2 remained *P. aeruginosa* free in lower airway samples (bronchial lavage/sputum) for now up to 30 months, despite persistent detection of *P. aeruginosa* that was identical in genotype with pre-transplant NL and sputum isolates in NL and even in throat swabs. For prevention of pulmonary re-colonization patient 2 has continuously inhaled Colomycin 1 MIU once daily during the preceding more than 36 months with the novel Pari Sinus™ nebulizer, which in scintigraphic studies was shown to deliver vibrating aerosols into paranasal sinuses, additional to bronchial antibiotic inhalation.

Discussion: Pulmonary colonization of transplanted donor lungs with identical clones previously colonizing the explanted lungs has been described previously and the upper airways were postulated as reservoir for descending colonization. However, this remained speculative, as upper airway sampling which does not belong to current standards, was not performed in these studies.

Our report demonstrates persistence of identical *P. aeruginosa* genotypes in CF upper airways prior to and after LTX underlining risks of descending colonization of transplanted lungs with *P. aeruginosa*, which increases risks of graft dysfunction. Therefore, we recommend regular assessment of sinonasal colonization prior to and after LTX. Sinonasal inhalation with antimicrobials should be investigated in prospective trials.
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Keywords: Cystic fibrosis; Paranasal sinus; Sinonasal; *Pseudomonas aeruginosa*; Genotype; Lung transplantation; BOS

1. Introduction

1.1. Case reports

Patient 1, a F508del homozygous male, was diagnosed to suffer from CF by the age of three years because of respiratory and gastrointestinal symptoms. After the respiratory tract had become chronically infected with *Pseudomonas aeruginosa* about the age of eight years, pulmonary function deteriorated continuously. Additionally, he had symptoms of chronic rhinosinusitis despite sinonasal surgery had been performed by the age of nine years.

By the age of 20 years a spontaneous pneumothorax occurred which did not stabilize with conventional drainage. Thoracoscopy was followed by serious complications including pulmonary leakages, infection and acute respiratory distress syndrome leading to mechanical ventilation and finally extracorporal membrane ventilation (ECMO). After four weeks of ECMO double lung transplantation was performed. Despite the need of prolonged intensive treatment including re-operation

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for hemorrhage, renal failure and symptomatic transitory psychotic syndrome the patient recovered considerably well. Pulmonary function improved from FEV 1.1 l (24% predicted) to presently 3.2 l (71%).

Already during the critical circumstances of post transplant treatment at the intensive care unit *P. aeruginosa* was detected in his BAL fluid samples from the transplanted lungs, which had not been colonized with the pathogen prior to LTX. The *P. aeruginosa* isolates were identical in their multimarker genotype [1] with isolates from his explanted lungs and NL sampled prior and after LTX (Figs. 1a and 2) and the pathogen persisted despite repeated intravenous antibiotic cycles and oral inhalation of Colomycin.

Patient 2, a F508del homozygous female, was diagnosed to have CF by the age of five months because of failure to thrive and recurrent bronchitis. She was fairly stable with CF standard therapy until an episode of distal intestinal obstruction syndrome required surgical intervention by the age of six years. During the stay at the hospital the patient acquired a persistent airway colonization with *P. aeruginosa*. Despite aggressive antipseudomonal chemotherapy lung function deteriorated substantially over the years so that she required double LTX with resection of the lingula of the donor organ by the age of 20 years. LTX was successful and FEV1 increased from 1.8 l (30% predicted) to 3.2 l (102%) at present.

P. aeruginosa has not been detected in post-LTX bronchoealveolar lavages or in sputum until now, despite of regular detection of the pathogen in sinonasal lavages and in three deep throat swabs (Fig. 1b). For the prevention of the colonization of the donor lung with *P. aeruginosa* from the sinonasal segment, we instructed the patient to continuously inhale Colomycin 1 MIU twice daily into the lower airways and to administer Colomycin 1 MIU once daily into the upper airways (UAW). The utilized device is the Pari Sinus™ nebulizer which has been shown to deposit vibrating aerosols into the paranasal sinuses [2,3].

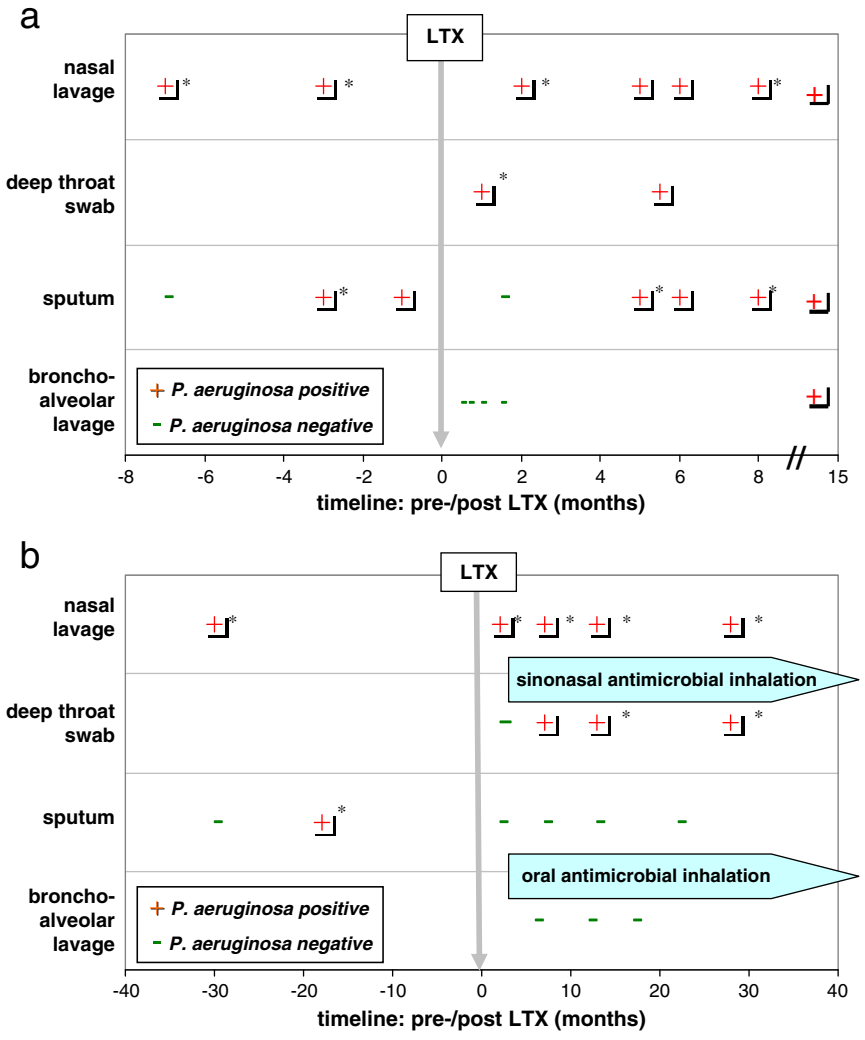

Fig. 1. a and b: Colonization of different airway levels with *P. aeruginosa* prior and after lung transplantation (LTX). Chronic sinonasal and bronchial inhalation of antipseudomonal agents since 2 months post LTX ( ). (a: patient # 1; b: patient # 2). (*) Genotypes of selected indicative *P. aeruginosa* clones from pre- and post LTX periods from each patient were assessed and in each patient they resulted to be identical in genotype.

Fig. 2. (screenshot): Genotypes of selected indicative *P. aeruginosa* clones from pre and post LTX periods from patient #1. Identical clones which prior to LTX colonized the patients' upper and lower airways persisted sinonasally and they colonized the *P. aeruginosa* free donor lung.

1.2. Nasal lavage

At our centre the sinonasal UAW segment is sampled by diagnostic NL from patients elder than 6–8 years [4]. In brief, 10 ml of sterile isotonic saline is applied to each nostril using a 10 ml syringe, with the head in a slightly reclined position and the soft palate occluded. After 10 s, nasal fluid is drained into a sterile cup by anteflection of the head and any material from the mouth is discarded into a basin.

1.3. Genotyping of P. aeruginosa

P. aeruginosa isolates were typed with a custom-made microarray as described previously [1]. In brief, DNA amplified from the bacterial colony by cycles of multiplex primer extension was hybridized onto the microarray to yield an electronically portable binary multimarker genotype.

1.4. Sinonasal inhalation

Hitherto, surgical enlargement of sinus orifices was postulated to permit conventional nebulizers to deliver drugs to the sinus mucosa, as paranasal sinuses are cavities communicating with the nose only via narrow ducts [3]. Now, pressure gradients induced by vibrating air flows were shown to facilitate deposition of significant amounts of aerosols into sinus cavities [3] and this principle is implemented in the novel PARI SINUS™ (Pari Corp, Starnberg, Germany) nebulizer, with a frequency of approximately 44.5 Hz. Sinonasal inhalation with the device is performed as described previously [5–7], in brief, medication is aerosolized into one nostril, while the contralateral nostril is occluded and the soft palate elevated as recommended for nasal lavage [8]. Study medication is administered into both nostrils for 4–6 min each side during arrest of breathing.

Recently, we assessed the effect of sinonasal inhalation of dornase alfa delivered with the device compared to placebo in a cross-over pilot study including five CF-patients. We found that dornase alfa significantly ($p=0.043$) improves rhinosinusitis related symptoms within the Sino-Nasal Outcome Test-20 (SNOT-20) [7]. We are performing further investigations including a further trial with dornase alfa as well as pilot studies with Tobramycin 80 mg respective Colomycin 1 MIU once daily with the device. Endpoints of the pilot studies with sinonasal nebulization of antibiotics are *P. aeruginosa* quantification in nasal lavage fluid of the CF patients who are chronically infected with the pathogen as well as effects of therapy on disease-specific, health-related quality-of-life for rhinosinusitis, and safety and tolerability of the novel therapy.

2. Discussion and conclusions

Pulmonary colonization and infection with *P. aeruginosa* remain one major reason for lung deterioration in CF. Additionally, in patients who successfully underwent lung transplantation, *P. aeruginosa* colonization of the transplanted organs was identified as a risk factor to develop the bronchiolitis obliterans syndrome (BOS) that is the major cause for chronic graft dysfunction [9].

Already in 1997 Walter et al.[10]. found that *P. aeruginosa*-free lungs transplanted in CF patients became infected with *P. aeruginosa* clones that were identical in genotype with the isolates from the explanted CF lungs. The authors reasoned that colonization occurred from the patients' upper airways and the sinonasal space. However, this conclusion could not be proven in this and subsequent publications [11–13] because upper airway sampling had not been performed.

The potential role of the upper airways as the reservoir and the first site of the colonization of the respiratory tract with *P. aeruginosa* has only recently be systematically explored: First, Krogh Johansen et al. found *P. aeruginosa* biofilms in samples taken during sinonasal surgery even if CF patients had only been intermittently colonized with the pathogen [14]. Second, prospective and non-invasive simultaneous sampling

of the upper and lower airways in a cohort of 187 CF patients revealed that upper and lower airways *P. aeruginosa* isolates were identical in genotype in 23 of 24 *P. aeruginosa*-positive patients [4]. Co-colonization of the two airway compartments probably arose from cross-infection. Third, Hansen et al. [15] recently showed by assessment of intraoperatively taken material that the paranasal sinuses are a potential niche for *P. aeruginosa* clones to adapt and diversify for subsequent chronic lung infections.

This report proves the persistence of *P. aeruginosa* in the UAW and paranasal sinuses in two LTX recipients with CF. In patient 1 the *P. aeruginosa* free donor lungs became soon colonized from this reservoir during prolonged mechanical ventilation and ECMO. In contrast, concomitant sinonasal and bronchial inhalation of antibiotics appear to have prevented pulmonary colonization with *P. aeruginosa* in patient 2. This novel therapeutic option may be of special interest since *P. aeruginosa* colonization of transplanted lungs is a risk factor to develop BOS. However, longitudinal studies are required to verify the supposed UAW's role as the site of first infection and reservoir of colonization of lower CF airways with pathogens and prospective trials are needed to assess the potential of sinonasal inhalation of antimicrobials.

Competing interests

All authors confirm that they are not involved in any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this manuscript.

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