Case Report

Chronic Rhinosinusitis as a Crucial Symptom of Cystic Fibrosis—Case Report and Discussion on the Sinonasal Compartment as Site of Pseudomonas aeruginosa Acquisition into CF Airways

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Abstract: Cystic fibrosis (CF) is the most frequent congenital lethal disease in Caucasians. Impaired mucociliary clearance causes chronic bacterial rhinosinusitis in up to 62% of patients, and almost all patients exhibit sinonasal pathology in CT scans. Pathogens like Pseudomonas aeruginosa (Pa.) chronically colonize about 70% of the CF adults’ lungs and are the major reason for pulmonary destruction and premature death. In our 34-year-old female CF patient, rhinosinusitis caused massive orbital hypertelorism despite three sinonasal operations. Her sputum samples had always been negative for Pa. Then, Pa. was primarily detected in her sputum and additionally in nasal lavage, which since then persisted in both, her upper and lower airways. The Pa. strains turned out to be genetically identical in both airway levels, indicating early colonization of the entire airway system with Pa. This first report on simultaneous primary Pa. detection in the sinonasal and pulmonary compartments highlights the need to include an assessment of upper airway colonization in the standards of CF care, particularly in patients without chronic Pa. colonization. Both airway levels need to be considered as one united system, and a strong cooperation between ENT and CF specialists should be established. Prospective longitudinal studies should assess the upper airways´role in acquisition and persistence of pathogens and evaluate conservative and surgical therapeutic options.

Keywords: cystic fibrosis; rhinosinusitis; Pseudomonas aeruginosa; upper airways; paranasal sinus; nose; sinus surgery

1. Introduction

Previously, sinonasal involvement in cystic fibrosis (CF) did not receive much attention in the patients with the most frequent life threatening congenital disease in Caucasians. Only four decades ago, CF regularly led to premature death in preschool-age by pulmonary destruction.

Due to improved prognosis, upper airway involvement is coming into focus, and it has been found to have a much higher impact on CF overall health than expected [1,2]. Patients carrying the disease causing defective chloride and sodium channels in sinonasal mucosa are reported to
suffer from symptoms of rhinosinusitis in up to 62% [3–5]. Thereby, sinonasal involvement can play a relevant and underestimated role in colonization of the airway system with pathogens. In early stages, these are *Staphylococcus aureus* and *Haemophilus influenza*. With disease progression, 70% to 80% of adults with CF are chronically colonized with *Pseudomonas aeruginosa* (*Pa.*). This pathogen is ubiquitously present in water and cannot be cleared from CF airways because thick viscous secretions impair mucociliary clearance. With time *Pa.* clones change their phenotype and become mucoid by developing an alginate layer and biofilms that additionally impair eradication by the immune system and antibiotics. In addition to its virulence factors, mucoid *Pa.* stimulates the host to an enhanced but frustrating immune reaction that further damages the airway system. The resulting pulmonary destruction is responsible for 90% of premature death in patients with CF [6].

In this context, evidence of the sinonasal role in airway colonization with pathogens remains scarce as the sampling does not belong to the current standards of CF care [7].

2. Case Report

We present a 34-year-old CF patient with genotype F508del/2789+5G→A who exhibited mild pulmonary disease and pancreatic sufficiency. In her first years of life, chronic rhinosinusitis was her leading early symptom, and she underwent three sinonasal surgeries until 1994. Nevertheless, CF-related chronic sinusitis relapsed soon and led to orbital hypertelorism with a broadening of her nasal bridge (Figures 1 and 2).

![Figure 1](image1.png)

**Figure 1.** CF patient with massive broadening of the nasal bridge because of chronic rhinosinusitis.

![Figure 2](image2.png)

**Figure 2.** (a) T1-weighted MRI sequence: polypous hyperintense structures (arrowhead →) within the left maxillary sinus. Broadening of the ethmoidal segment in correlation to orbital size as cause of hypertelorism (↔ see Figure 1); (b) T2-weighted MRI sequence: thickened mucosa (hyperintense = bright) in maxillary and ethmoidal sinuses; nodular polypos structures in the left maxillary sinus.
In addition to routine sampling of the sputum from the lower airways (LAW), we started including sinonasal sampling by nasal lavage (NL) into our local standards of care in 2005 [8,9]. In our patient LAW and upper airway (UAW) sampling by NL always turned out to be negative for P.a. until October 2007. Then, a non-mucoid P.a. was detected for the first time in both, sputum and NL, whereas P.a.-serum antibodies remained negative. A three-month course with oral ciprofloxacin and bronchial inhalation of colomycin was performed aiming to eradicate the bacterium. Nevertheless, five months later, the sampling of both airways segments again revealed the presence of P.a. UAW and LAW isolates from October 2007, March 2008, and February 2010 were identical in their multi-marker genotype 681A [10], indicating that the patient was chronically carrying the same P.a. clone in both airway compartments since the onset of colonization. The genotyping was performed by a microarray for the typing of P.a. strains in both the conserved core and the flexible accessory genome.

3. Discussion

Our case report shows to which extent sinonasal involvement in CF influences facial morphology [1], albeit typically in a less severe form than in the presented patient. Our CF patient is an extreme case of chronic sinonasal involvement that is detectable in almost 100% of CF patients by computed tomography or MR imaging [11]. Mucoceles and nasal polyps are very frequent in the disease, occurring even in small children and in more than 50% of adults with CF [1,12]. Therefore, detection of nasal polyps in the first years of life should prompt an evaluation for CF by analysis of chloride in sweat or genetic analysis.

Altogether, our report sheds some doubt on the validity of most of the current standards of airway sampling for CF microbiology. P.a. colonization of the patients’ upper airways would not have been detected following the current standards of CF care [7]. Thereby, colonization with the bacterium persisted in both airway segments despite anti-pseudomonas therapy, as proven by identical P.a. genotypes during a period of currently more than nine years. The initial detection of P.a. in both habitats was not accompanied by relevant systemic antibody levels against the pathogen. This indicates that early cross colonization of UAW and LAW segments did not caused a significant systemic humoral response.

The relevance of the UAW concerning P.a. persistence has been previously postulated by Walter et al. [13], who typed P.a. isolates from the lower airways of CF patients prior to and after lung transplantation. It was found that P.a. free donor lungs were colonized by P.a. belonging to the same genotype as pre-transplant isolates of the CF recipient. The authors concluded that the UAW is the reservoir of the pathogen. These results from end-stage CF pulmonary disease were also seen in adults with less advanced lung destruction [14]. Muhlebach et al. [15] also found high concordance of intra-operatively sampled P.a. genotypes from both airway segments in children with CF. Prior, we assessed a large cohort of 182 CF patients of all ages non-invasively for upper and lower airway colonization with P.a. [8]. During routine outpatient visits, we sampled the UAW by nasal lavage or deep nasal swabs and compared the results to sputa or deep throat swabs from the patients. P.a. UAW and LAW isolates from 23 of 24 patients were identical in genotype.

Recently, the Copenhagen CF center [16] published data from longitudinal analysis of sinonasal colonization assessed during surgery or endoscopy guided maxillary swaps. The authors found that the paranasal sinuses can be a site of early colonization with P.a., where the bacteria diversify and evolve pathogenicity, e.g., by antibiotic resistance and adapt to the CF airway. From the sinonasal reservoir, they may intermittently colonize the lungs, ultimately leading to chronic lung infection; thus, sinonasal involvement can be crucial for many CF patients, even those without relevant upper airway symptoms. Repeatedly, sinonasal surgery was discussed as a chance to prevent colonization of the upper airway segment with pathogens such as P.a. [4,17]. However, in the presented patient, three sinonasal operations with an establishment of widely patent maxillary ostia (see Figure 2a,b) did not prevent colonization and persistence of pathogens in this habitat. Additionally, sinonasal...
surgery has recently been reported to represent a risk for pathogen acquisition in a case series of four CF patients with a new *P. a.* colonization after ENT surgery [18].

Whereas the sinonasal niche is not assessed according to most current international standards [7], the very recent German guidelines for prevention of chronic airway colonization with *P. a.* [19] addresses this issue: Additional assessment of the sinonasal niche is recommended at the least when eradication from the LAW does not succeed. Altogether, UAW-sampling in CF patients without chronic *P. a.* colonization can help to prevent or postpone chronic colonization before the pathogen switches to the mucoid persisting phenotype.

After identification of sinonasal pathogen colonization in additional CF patients, we assessed novel therapeutic options: The patients inhaled antibiotics as vibrating aerosols into their paranasal sinuses. Basically, conventional aerosols do not reach the paranasal sinuses when their ostia have not recently been widened by surgery [20]. In contrast, scintigraphic *in vivo* studies proved that vibrating aerosols reach paranasal sinuses [21]. We recently eradicated *P. a.* with such an approach in a CF patient with first-isolated sinonasal colonization with the pathogen [22]. Additionally, we performed a pilot study showing that tobramycin at 1 × 80 mg a day inhaled with the Pari Sinus™ device can reduce pathogen counts and symptoms in CF patients with sinonasal colonization with *P. a.* [23]. For patients with chronic rhinosinusitis (non-CF) who underwent functional endoscopic sinus surgery with the widening of sinus ostia, Bonfils *et al.* showed that nasal inhalation with tobramycin with a mesh nebulizer can be effective [24]. Furthermore, the Copenhagen CF center brought up a program combining sinonasal surgery with 14 days of intravenous antibiotic treatment (e.g., with tobramycin and ceftazidim), with daily nasal lavages containing antibiotics like colomycin for a period of six months [4]. This approach helped to eradicate *P. a.* from the sinonasal reservoir in a subgroup of the included CF patients. Under the assumption that the sinonasal niche is a site of first and persistent colonization with critical pathogens in CF patients, there is a need for routine sinonasal sampling—at least in the patients who are not yet chronically colonized. Furthermore, prospective investigation is required for better understanding the bidirectional communication between upper and lower airway segments [3] and its conservative [2] and surgical [4] therapy.

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Author Contributions: The publication was written by J.G.M., C.A., A.G., J.F.B., and B.T. H.J.M. performed and evaluated the MR, J.R. is responsible for the *P. a.* biobank, B.T. and N.C. genotyped *P. a.* colonies. All authors discussed, edited and approved the final version.

Conflicts of Interest: J.G.M., J.F.B. and C.A. performed investigator initiated studies using vibrating aerosols as cited in References [22] and [23]. Besides, all authors disclose any actual or potential conflict of interest including any financial, personal, or other relationships with other people or organizations that could inappropriately influence the work.

References

4. Aanaes, K. Bacterial sinusitis can be a focus for initial lung colonisation and chronic lung infection in patients with cystic fibrosis. *J. Cyst. Fibros.* 2013, 12, S1–S20. [CrossRef]


