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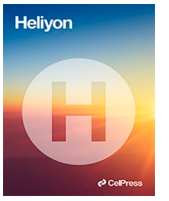

Case report

A case of localized paranasal sinusitis associated with *Burkholderia cenocepacia* ST 1880 in a cystic fibrosis patient

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ABSTRACT

Burkholderia cepacia complex (Bcc) bacteria are considered to be very dangerous players in cystic fibrosis (CF) pathogenesis and are a criterion for negative prognosis in CF cases. In this report, a pediatric case of paranasal sinusitis caused by *Burkholderia cenocepacia* in a CF patient is described. This is an unusual case, since the paranasal sinuses were the only colonization locus of *B. cenocepacia* in this patient for 5 years (2015–2020). The lungs remained microbiologically clear with no clinical or radiological signs of pulmonary function decrease during this time period. The paranasal sinuses were sanitized by endoscopic sinus surgery on the left side (2020). Although having no local or systemic antibiotic treatment from the time of surgery to 2022, no *B. cenocepacia* were detected in the samples. The case shows the possibility of a prolonged remission of Bcc-associated paranasal sinusitis in the absence of systemic antibiotic therapy.

1. Introduction

Cystic fibrosis (CF) is a common genetic disease. Its outcome depends on the severity of the CF-associated lung disease. Bacteria of the *Burkholderia cepacia* complex (Bcc) are a group of opportunistic respiratory pathogens that can cause a severe decrease in the lung function of CF patients [1]. Prolonged Bcc-colonization of the respiratory tract in CF often decreases external respiration, causes fatal septic pneumonia (cepacia syndrome), increases the risk of death, and creates unfavorable conditions for lung transplantation [2]. The first detection of Bcc in a respiratory sample worsens the prognosis for patients with CF and requires the immediate correction of treatment tactics [3]. Bcc-infected CF patients are believed to need personalized antibiotic therapy selected in accordance with the state-of-the-art approaches and considering such criteria as the antibiotic susceptibility profile of the isolate, the duration of the therapy, and whether monotherapy, combination therapy, saline inhalation, and/or antibiotic inhalation, or antibiofilm agents are required [4–6]. The effectiveness of lung transplantation for Bcc-associated lung disease has been discussed, but Bcc-infection should not be considered as an absolute contraindication [7,8]. Among cases of extrapulmonary Bcc-infection in CF, paranasal sinusitis has been described [9]. Antimicrobial therapy in sinusitis can be combined with surgical treatment [10].

This paper describes an unusual clinical case of a favorable course of *Burkholderia cenocepacia* infection in a pediatric patient with follow-up in a CF center in Samara, Russian Federation.

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2. Case presentation

The patient, S., is male, born in 2013. CF was not been diagnosed at birth. He had frequent respiratory episodes during the first year of life. Sweat tests provided an uncertain outcome (42–60 mmol/l) and did not confirm CF. At 8–10 months of age, the typical clinical manifestation of CF developed, including a typical complication of Pseudo-Bartter's syndrome. Electrolyte and acid–base abnormalities (hypochloremia, hyponatremia, hypokalemia, and metabolic alkalosis) are typical signs of Bartter's syndrome, which is a consequence of an inherited tubulopathy of the thick ascending limb of the loop of Henle. Hence, the same symptoms of electrolyte imbalance in CF were designated Pseudo-Bartter's syndrome [11]. In young children, Pseudo-Bartter's syndrome can be the first manifestation of CF [11]. At 10 months of age *Pseudomonas aeruginosa* was detected on the posterior pharyngeal wall. The sample processing, isolation, and identification procedures for the microorganisms are described in the Supplementary Materials. Treatment with dornase alpha and a combination of amikacin and ceftazidime for 21 days led to the eradication of *P. aeruginosa*. At 12 months of age, genetic testing revealed the F508del/3849 + 10kbC-T mutation. From December 2015 (2 years of age) to 2018 *B. cenocepacia* in the amount of 10^2-10^4 colony-forming units was regularly detected in the oropharyngeal bacteriological samples (Fig. 1). From the moment of CF clinical manifestation (2014) to the spring of 2022, regular sputum microbiological examination revealed no presence of *Burkholderia cenocepacia.* The history of the microbiological findings in the respiratory samples is presented in Fig. 1 and in the Supplementary Materials (Table S1 Suppl). From 2016, regular (at least 4 per year) PCRs of the sputum samples for *B. cenocepacia* species-specific genes were conducted; all the results of the sputum samples analyses were negative for.

B. cenocepacia. At different time periods during 2015–2018 the patient received intravenous, inhalation and oral ceftazidime, co-trimoxazole, meropenem, thiamphenicol (inhalations).

In February 2019, for the first time, both the sputum and nasal lavage from the paranasal sinuses' drainage were studied simultaneously. The sputum sample showed no *B. cenocepacia* growth. The nasal lavage fluid, however, showed the growth of 32 colony-forming units/ml. Thus, the main infection reservoir was not in the lungs, but in the paranasal sinuses. Computer tomography confirmed the specific inflammatory alteration of the paranasal sinuses. A decision was then made to alter the treatment plan: cease the systemic antibacterial treatment and administer local antibacterial treatment – thiamphenicol 600 mg once a day, ceftazidime 1 g twice a day, meropenem 1 g twice a day – delivered to the upper respiratory tract by the PARI LC SPRINT® SINUS (PARI GmbH) inhaler in the pulse mode of drug delivery.

From March 2019 to July 2020 the lavage fluid showed the intermittent presence of *B. cenocepacia* (Table S1 in Supplementary Materials). During the follow-up the sputum showed no clinically significant growth of bacteria.

In September 2020, the patient underwent left endoscopic hemisinusotomy with postoperative meropenem treatment for 3 days. After that, no local or systemic antimicrobial therapy was administered because no clinically significant pathogens showed growth in the oropharyngeal samples, the lavage fluid from paranasal sinuses, or the sputum. Since the intervention, there has been no growth in the patient samples through March 2022.

From 2015 to 2022, none of the other pathogens were detected in the sputum, oropharyngeal samples, or the lavage from paranasal sinuses.

From the start of colonization to the present moment, the patient showed no aggravation both in the physical examination and the lung computer tomography. The blood chemistry had no significant deviations, and the vitamin D level was within the normal range.

The *B. cenocepacia* isolates recovered in 2019 and 2020 were subjected to whole genome sequencing. MALDI TOF mass spectrometry, and whole genome sequencing have confirmed the taxonomic affiliation of all the Bcc-isolates to *B. cenocepacia* (the description of the methods is presented in the Supplementary Materials). To analyze the homogeneity of all the *B. cenocepacia* strains,

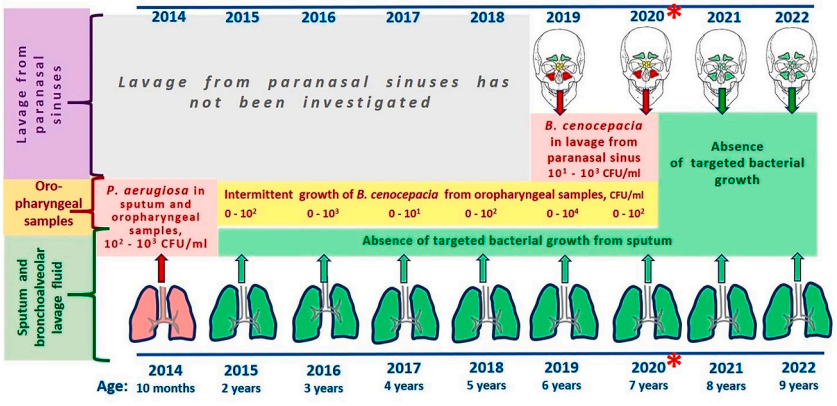

Figure 1 Chronology of *B. cenocepacia* isolation in patient S. with cystic fibrosis, 2015 - 2022. Red asterisk, the time point when the patient was subjected to endoscopic hemisinusotomy.

Fig. 1. Chronology of *B. cenocepacia* isolation in patient S. with cystic fibrosis, 2015–2022. Red asterisk, the time point when the patient was subjected to endoscopic hemisinusotomy. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

isolated from the patient samples at different time periods, a statistical comparison of the mass spectra of their protein profiles with subsequent visualizing was performed using MALDI Biotyper 3.0 Offline Classification software (Bruker Daltonik GmbH, Germany). The results of the comparative analysis, shown in a heat diagram in Supplementary Materials (Fig. 1 Suppl), confirmed the homogeneity of the protein profiles of the *B. cenocepacia* isolates, recovered in 2015–2020 from the nasal lavage and oropharyngeal samples. Thus, the isolates from different years of follow-up are highly likely to belong to a single *B. cenocepacia* strain Bcc1/1.

According to the whole genome sequencing data and PubMLST, the strain belongs to a previously undescribed sequence type *Burkholderia cenocepacia* ST1880 (https://pubmlst.org/bigsdb?page=info&db=pubmlst_bcc_isolates&id=3867). Sequencing results have been deposited in Genbank (JAFIBB000000000). The results of the bioinformatics analysis of the genome differences in *B. cenocepacia* Bcc1/1 in comparison with *B. cenocepacia* ST1880 AU35678 are presented in the Table S2 Suppl. in the Supplementary Materials.

This study was approved by the Bioethics Committee of the Samara State Medical University (No. 151 of 26/11/2014). All procedures performed were in accordance with the ethical standards of the university Bioethics Committee and with the principles of the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from the parents of the patient included in the study.

3. Discussion

The Bcc lesions in CF lungs are often combined with the presence of extrapulmonary Bcc loci. Bcc-associated sinusitis, cutaneous vasculitis, and bloodstream infections are known [12–14]. However, in almost all the described cases, extrapulmonary Bcc pathology was secondary and was associated with an unfavorable course of the lung disease. Prolonged Bcc colonization is considered to cause lung damage and reduce its function [1,2]. The course of Bcc-associated sinusitis can be extremely severe, e.g., a fatal case of sinusitis with intracranial invasion has been reported [15]. The clinical case we describe is an exception that also shows an unusual course of Bcc infection in CF. In particular, there were no signs of damage in the lungs, while the focus of the Bcc infection existed in the paranasal sinuses for years. Sputael V. et al. described a similar case where a Bcc-positive nasopharyngeal aspirate, throat swab, and nasal lavage were combined with normal bronchoalveolar lavage [10]. However, Sputael V. et al. did not describe the duration of the Bcc colonization, and Bcc eradication was performed by a combination of bilateral maxillary and frontal sinus surgery with local and systemic antibacterial treatment for 14 months after surgery. In the presented report, a favorable course of *B. cenocepacia* infection with a prolonged remission and possible eradication of *B. cenocepacia* without extensive systemic and local antibacterial therapy (post-surgery meropenem therapy took 3 days) was observed. Endoscopic sinus surgery for chronic rhinosinusitis is believed to have no advantage over drug therapy [16]. However, the presented case was not subject to this rule.

An important question to address is why the Bcc-infection in patient S. proceeded favorably. One of the possible reasons for the favorable course of the disease may be the low virulence of the strain. The multilocus sequence typing (MLST) determined the strain belonged to a previously undescribed sequence type ST1880. It has been suggested that strains belonging to ST1880 have low-virulence. To confirm or refute this hypothesis, a search and analysis of the genomic characteristics of other ST1880 strains was performed. A subsequent pubMLST DB search revealed another isolate AU35678 (GenBank: JAGSVF000000000) that belonged to ST1880 and was obtained in 2016 in the USA. This strain was isolated from a CF patient's sputum; therefore, ST1880-sequence-type pathogenic potential does not exclude bronchopulmonary system colonization. The *B. cenocepacia* Bcc1/1 ST1880 and ID AU35678 isolate genomes were compared. The most significant difference in the strain obtained from patient S. was the presence of extra genes: the secretion system and phage plasmid, and the total single nucleotide polymorphism (SNP) number made up 50 variants (indels or SNPs). Among them, 6 SNPs were synonymic, 17 non-synonymic SNP variants were detected in intergenic regions, and 6 variants (missense mutations and frameshift) were found in hypothetical proteins with unknown function. Table S2 Suppl. of the Supplementary Materials provides 21 high confidence SNP variants and insertions/deletions in the genes of metabolism, signaling and cellular processes, membrane transport, quorum sensing, cell division, replication and repair, transcription factors, chaperones, and signal transduction. In general, the differences we found did not provide enough evidence for the conclusion that the virulence of our strain was lower than the one of the AU35678 isolate. The influence of the reported mutations on *B. cenocepacia*'s virulence needs to be further studied.

As an alternative theory of the favorable course of the *Burkholderia* infection, one may speculate that our patient has a specific mutation (allele with fourth class mutation, a 'mild phenotype') that did not lead to a severe course of CF. The permanent absence of the microbial contamination of the lungs supports this hypothesis (the sputum had no other pathogens, typical for CF).

4. Conclusion

In conclusion, the presented case yet again shows the diversity of infection courses in CF patients. The main results of the follow-up, which were the absence of lung damage and the prolonged remission of *B. cenocepacia* infection, show the possibility of successful treatment of Bcc-associated sinusitis in the absence of systemic antibiotic therapy. Bcc-infected CF patients need personalized antibiotic treatment selected considering the pathogen features and disease management strategies.

Author statement

Olga Kondratenko: sample acquisition, methodology, data curation; writing - original draft. Artem Lyamin: conceptualization; methodology; validation. Tatiana Savinova: sequencing; bioinformatic data analysis. Yuliya Bocharova: bacteriological investigation;

formal analysis. Elena Vasilyeva: data curation, writing. Igor Chebotar: conceptualization; writing, editing; supervision.

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Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data associated with this study has been deposited at Genbank under the accession number JAFIBB000000000.

Declaration of competing interest

The authors declare no conflicts.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e16618.

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