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Microbiota of nasal cavity in sinusitis following hematopoietic stem cell transplantation

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Summary

Hematopoietic stem cell transplantation (HSCT) is often accompanied by infectious complications. The aim of this study was a comparative evaluation of facultative anaerobic microbiota members of nasal and paranasal cavity in sinusitis, which often develops in immunocompromised patients, due to intensive chemotherapy and massive antibiotic treatment followed by hematopoietic cell transplantation (HSCT).

Materials and methods

The study involved 194 patients with various myelo- and lymphoproliferative diseases aged 1 to 62 years who underwent intensive chemotherapy and allogeneic HSCT. As based on appropriate clinical indications, the biomaterial was taken from patients (washings from the paranasal sinuses and/or nasal swabs) within the time period of +100 to +180 days after allogeneic HSCT. We studied 124 samples from maxillary sinus punctures of 97 patients and 973 scrapings from the nasal cavity. Seeding of biological material and isolation of the microorganisms were performed by classical bacteriological techniques. Antibiotic susceptibility of clinical isolates was determined by disk diffusion methods. The data on microbial sensitivity were interpreted by the EUCAST criteria.

Results

In the samples from nasal cavity and paranasal sinuses, *S. epidermidis* was most often detected (34.7%, 377/1097); *S.viridans* (2.2%, 24/1097); *S. aureus* (1.91%, 21/1097); *Klebsiella spp* (1%, 11/1097). Detection frequency of *S.epidermidis* and *S.viridans* was minimal in the younger age group (up to 5 years), and increased in older groups (>15 years old). Profound suppression of *S.epidermidis* growth was noted, especially in paranasal sinuses, within 1 month after HSCT in presence of massive antibiotic therapy. High frequency of *Klebsiella spp* detection was noted in the samples from maxillar sinuses at later terms (2-3 months) after HSCT, at low detection frequency of the pathogen in the specimens from nasal cavity (average 16.3% *vs* 2.1%, p=2×10^14). In addition, we have estimated frequency of bacterial inoculation within +30 days upon the diagnosis of sinusitis. At the same time, an increased frequency of *Pseudomonas spp* isolation (1/378 *vs* 7/217) was revealed in the material from paranasal sinuses.

Conclusion

Bacteriological study of biological samples from maxillary sinuses is of limited value during the 1st month after HSCT accompanied by massive antibiotic therapy which was followed by selection of resistant strains of *Klebsiella spp, Pseudomonas spp, E. coli, S. aureus*, mainly at the terms of >2 months after HSCT.

Keywords

Hematopoietic stem cell transplantation, paranasal sinuses, microbiota, antibiotic resistance.

Introduction

Hematopoietic stem cell transplantation (HSCT) is used as an efficient therapeutic approach for treatment of oncohematological diseases. This mode of treatment causes profound immunosuppression affecting non-specific and specific immunity. This temporary disorder results into frequent infectious complications over post-transplant period, which have been sufficiently studied. However, bacterial and fungal paranasal sinusitis, which is common in general population, has been scarcely studied in immunocompromised patients after HSCT [1].

According to numerous studies, sinusitis affects approximately 5-44% of all the patients in post-transplant period, mainly, at early terms after HSCT. In this regard, searching for bacteria which colonize nasal cavity and paranasal sinuses during the sinusitis seems to be an urgent task. In general excessive microbiota at the surface of nasal mucosa, paranasal sinuses and upper respiratory tract is of similar composition. Bacteriological studies of cultivable microbiota from the nasal cavity and aspirates of maxillary sinuses in chronic rhinosinusitis were carried out in different clinics of Russian Federation and revealed 154 isolates of aerobic bacteria belonging to 32 species, and 90 anaerobic lines, with predominance of *Streptococci*, *Prevotella* in aspirates, less often *S.pneumoniae, H.influenza*, and *S.aureus* [2]. Although many other microbial species were isolated from these samples, the authors did not reveal their clear relations to pathogenesis of chronic rhinosinusitis.

Over the last decade, the microbiota of paranasal sinuses has also been studied by molecular biology techniques (quantitative PCR, microarray methods, like as by NGS studies of polymorphisms in 16S rRNA gene which is universal to bacterial microbiota), thus making it possible to identify a lot of non-cultivable and previously unknown types of bacteria [3]. The authors have shown that, along with *S.epidermidis, S.aureus, Corynebacteria spp*, maxillar sinuses in the patients may harbor, e.g., *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*, as well as *Stenotrophomonas maltophilia, Enterobacter* which may be associated with chronic rhinosinusitis. Significant differences in the composition and diversity of the microbiota of the paranasal sinuses largely depend on the methods used in distinct studies. E.g., analysis of the microbiota at these sites by means of next-generation sequencing (NGS) showed persistence of *Staphylococci, Streptococci, Neisseria, Corynebacteria* and reduced biodiversity of local microbiota in chronic rhinosinusitis [4]. In general, however, bacteriological evaluation of biological samples retains its diagnostic value because of its ability to assess antibiotic resistance of microbial isolates. The aim of this study was a comparative assessment of aerobic and facultative anaerobic microbiota components of nasal and paranasal cavities in sinusitis, which is often observed in immunocompromised patients after intensive chemotherapy, antibiotic therapy and subsequent HSCT.

Patients and methods

The study involved 194 patients with various myelo- and lymphoproliferative diseases aged from 1 to 62 years treated at the R. M. Gorbacheva Memorial Research Institute of Pediatric Oncology, Hematology and Transplantation under the protocols of intensive chemotherapy and allogeneic HSCT over the period of 2016 to 2021 as described in our previous work [5]. During HSCT, patients received an antibiotic prophylaxis regimen that included intravenous administration of fluoroquinolones (sometimes switching to oral administration) from D+1 to D+60. To this purpose, amoxicillin was also prescribed, in particular to pediatric patients. In febrile neutropenia, broad-spectrum antibiotics were empirically administered. Later on, upon occurrence of resistant microbial strains, the patients were treated with antibiotics, orally or systemically, as guided by the *in vitro* sensitivity testing of the microbial isolates.

As indicated by consulting specialist (ORL clinician), according to clinical indications, the biomaterial was taken from patients (nasal swabs or washings from the paranasal sinuses) at the terms of -100 to +180 days after the day of allogeneic HSCT. Of these specimens, we have examined 124 samples of the maxillary sinus punctures from 97 patients, and 973 scrapings from nasal cavity of the patients from general HSCT group.

Seeding and isolation of bacteria from the biological samples were made by classical bacteriological techniques, The isolated microorganisms were identified by means of commercial biochemical test systems (BBL Crystal), as well as with MALDI-TOF mass spectrometry using VITEK MS instrument. The sensitivity of clinical isolates to antibiotics was determined by means of disk diffusion test systems. The results of microbial sensitivity tests were interpreted according to the Guidelines of European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. For statistical analysis, the groups of patients were also divided by age: 0-5 years (group 1); 6-14 children (2); 15-21 years old (3); >22 years (4). Moreover, the results of bacteriological examination were classified by terms post-transplant, starting from <100 days before HSCT (point 0); during the 1st month (point 1); 2nd month (point 2); 3rd month (point 3), etc., up to 6 months after HSCT (point 6). Statistical analysis of the data was carried out by means of parametric and nonparametric statistics, concerning individual types of inoculated microorganisms, and for distinct microbial associations at different times after HSCT using the STATISTICA 10 program.

Results

The detection frequency of cultured bacteria from nasal cavity and maxillary sinuses in the oncohematological patients with ORL disorders was as follows: *S.epidermidis*, 34.7% of biological samples (377/1097); *S.viridans*, 2.2% (24/1097); *S.aureus*, 1.91% (21/1097); *Klebsiella spp.*, 1% (11/1097); *Corynebacteria spp.*, 0.9% (10/1097); *Pseudomonas spp.*, 0.54% (6/1097); *E. coli*, 0.36% (4/1097); *Neisseria spp.*, 0.36% (4/1097); *E.faecalis*, 0.18% (2/1097). Meanwhile, *Proteus, M.luteus, Citrobacter* isolates were not revealed. Seeding rates for the most common bacterial species by the age groups are shown in Fig. 1A and 1B.

As seen from Fig. 1, the frequency of *S.epidermidis* detection was minimal in younger age group and increases at the age of

>15 years (1A). Also, the occurrence of S.viridans is minimal among younger patients, with a maximum in the older group (>15 years). Moreover, we assessed the dynamics for these species at various times after HSCT (Fig. 2A and 2B).

As seen from Fig. 1, the frequency of *S.epidermidis* detection was minimal in younger age group and increases at the age of >15 years (1A). Also, the occurrence of *S.viridans* is minimal among younger patients, with a maximum in the older group (>15 years). Moreover, we assessed the dynamics for these species at various times after HSCT (Fig. 2A and 2B).

As seen from Fig. 2A, the detection rate of *S.epidermidis* is sharply reduced over the first 2 months after HSCT, thus confirming significant depletion of this microbial population due to antibiotic prophylaxis and anti-infectious therapy at the early stages after HSCT. At the same time, frequency of *S.viridans* did not change significantly during the post-transplant period (up to 6 months).

Separate analysis in adjacent infection loci (nasal and maxillar cavities) showed that the most profound suppression of *S.epidermidis* growth was observed in paranasal sinuses, especially, within 1 month after HSCT (Fig. 3). Of interest, the frequency of *S.epidermidis* isolation in the presence of clinically sound sinusitis was even more reduced during the 1st month after HSCT, as well as in later periods (>4 months after HSCT), as shown in Fig. 4.

High frequency of *Klebsiella spp.* isolation in the samples from maxillar sinuses proved to be the most pronounced feature of pathogenic microbiota in the patients at the late terms after HSCT (an average of 16.3% (20/123) *versus* 2.1% (18/864), p=2×10^14), along with low frequency detection in nasal swabs (Fig. 5). Similarly, high seeding rates from sinus washes were shown for Pseudomonas spp. (8.1%, 10/123 *versus* 0.7%, 5/864, p=1.5×10^10).

As can be seen from Table 1, *S.epidermidis*, the most common microflora for the nasopharynx, is found in material from the nose much more often than in swabs from the maxillary sinuses (Fig. 4). Meanwhile, inoculation with *S.epidermidis* from the maxillary sinuses is minimal during 1 and 5 months after HSCT. At the same time, opportunistic pathogens (*E. coli, Klebsiella spp., Pseudomonas spp.*) in the lavage from maxillary sinuses of the patients with sinusitis were detected more frequently than in nasal cavity lavage.

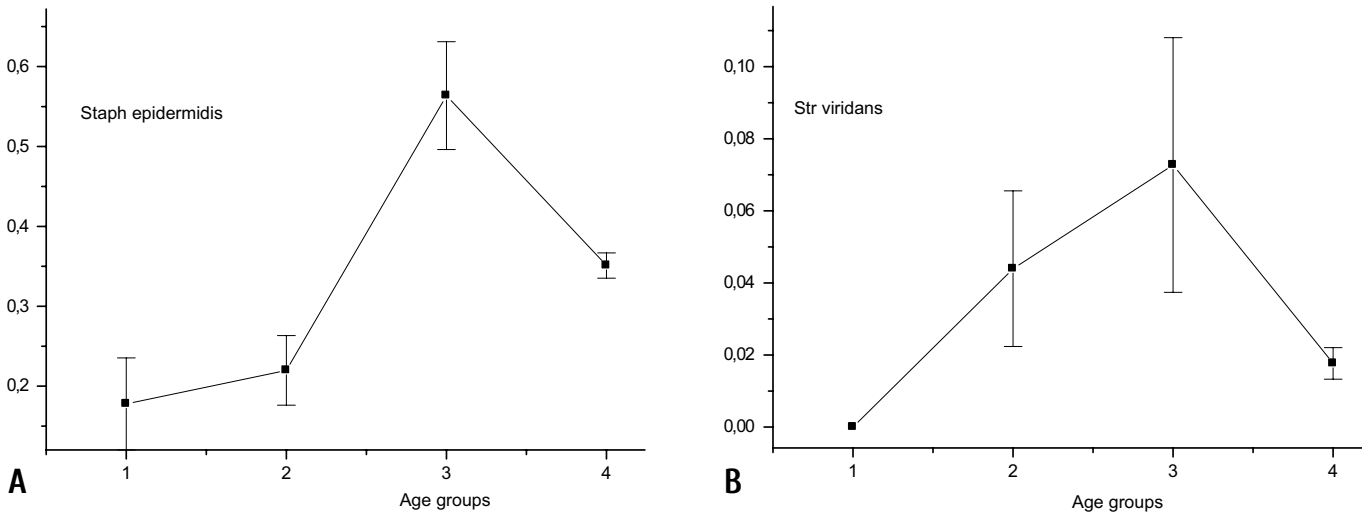

Figure 1. Age dependence of bacterial seeding rates for the dominant bacterial species in oncohematological patients (group 1: 0–5 years; group 2: 6–14 years; group 3: 15–21 years; group 4: >22 years)

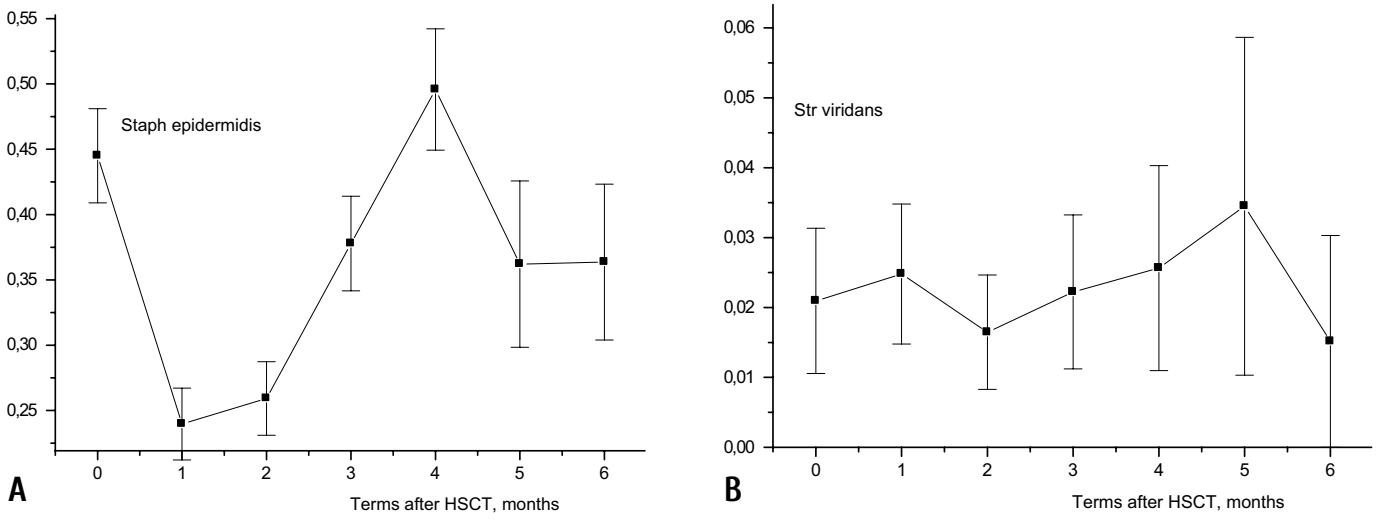

Figure 2. Dynamics of detection for the main types of bacteria at different terms after HSCT

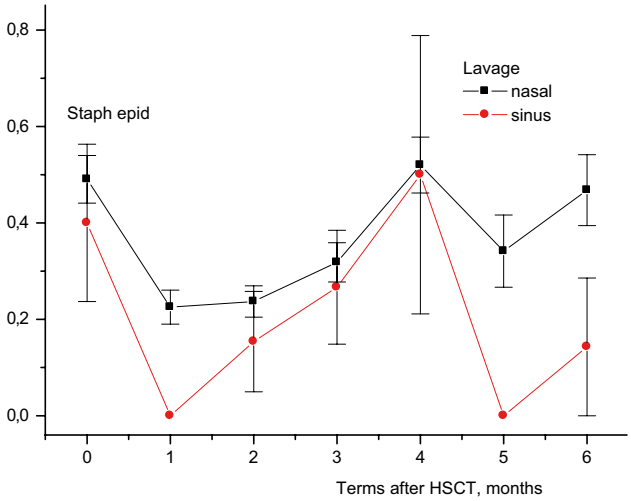

Figure 3. Frequency of *S.epidermidis* detection in nasal swabs (squares) and maxillary sinuses (circles) at various terms after HSCT

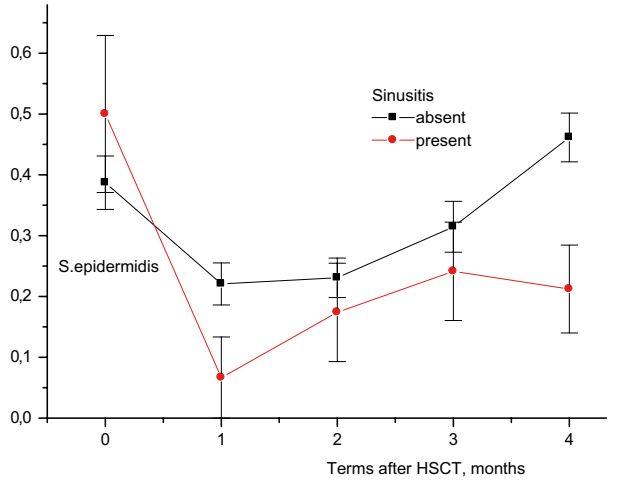

Figure 4. Detection frequency for *S.epidermidis* in the specimens from nasal cavity and maxillar sinuses in sinusitis-free cases (black squares), and in presence of clinical sinusitis (red circles) at various times after HSCT

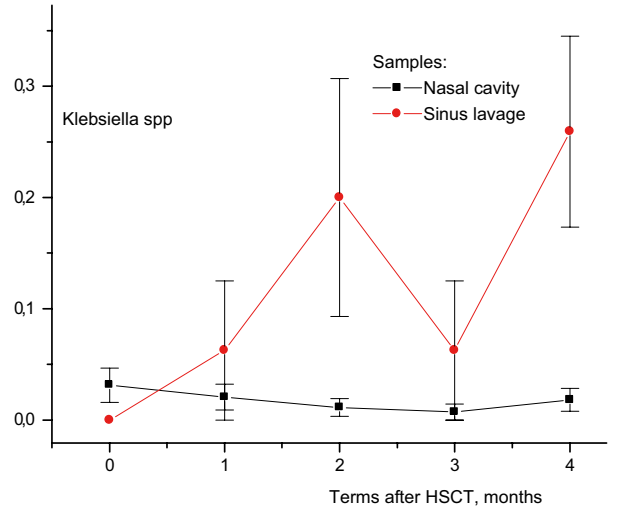

Figure 5. The frequency of detection of *Klebsiella spp.* in the samples from nasal cavity and sinuses in absence of clinical symptoms (black squares), and in presence of clinical sinusitis (red circles) over the terms of 0 to >4 months following HSCT

This confirms the diagnostic significance of the bacteriological analysis of the exudate obtained by sinus puncture and, possibly, the protective function of *S.epidermidis* on the skin and mucous membranes.

Next, we determined the isolation frequency of distinct microbes from the general data massive (nasal cavity + maxillary sinuses) and found that *Klebsiella spp.* with symptoms of sinusitis occurs significantly more often than in patients free of these symptoms, respectively, 6/102 (5.9%) *versus* 8/501 (1.6%), p=0.009. A similar increase was shown for *Pseudomonas spp.* and *E.coli* (see Table 2). A higher frequency of detection of *Klebsiella spp.* in the punctures from maxillary sinuses was noted in cases of clinical sinusitis at the 1st, 2nd month, as well as from the 4th month and later post-HSCT.

Moreover, we estimated the frequency of bacterial findings within +30 days since clinical diagnosis of sinusitis. Higher frequency of *Pseudomonas spp.* (1/378 *vs* 7/217) was revealed in the samples from paranasal sinuses in 5 patients within 3 weeks after clinical diagnosis of sinusitis.

Antibiotic resistance

Several resistant bacterial strains were isolated from nasal cavity and paranasal sinuses in the patients with sinusitis, mostly, at later terms (>2 months post-transplant).

Over the entire period of time (2019 to 2021), the clinical staphylococcal isolates were tested for their sensitivity to cefoxitin, erythromycin, clindamycin, gentamycin, norfloxacin, tetracycline, tigecycline, and linezolid. According to the expert Guidelines of European Committee on Antimicrobial Susceptibility Testing (EUCAST). Cefoxitin is considered a screening drug in order to discriminate between the categories of methicillin-resistant staphylococci (MRS) and methicillin-sensitive strains (MSS). Throughout the observation terms, the methicillin-resistant *S.aureus* (MRSA) were isolated in 4% of lavage and puncture samples obtained from maxillar sinuses in the patients with oncohematological disorders. Over this period of time, we did not reveal any *S. aureus* strains resistant to linezolid or tigecycline. 31% of *S.aureus* isolates were resistant to erythromycin. The revealed category of erythromycin sensitivity, in accordance with EUCAST rules, is also extended to clarithromycin and roxytromycin. Norfloxacin resistance was shown for 5% of *S.aureus* strains. The norfloxacin-sensitive staphylococci are regarded as sensitive to moxifloxacin and, at higher doses (or with prolonged infusion), to levofloxacin and ciprofloxacin. Tetracycline resistance of *S. aureus* strains was shown in 10%. The tetracycline-sensitive staphylococci are also considered sensitive to doxycycline and minocycline. Maximal percentage of antibiotic resistance for staphylococcal strains was found with gentamycin (24%). Gradient diffusion tests for vancomycin resistance were applied to methycillin-resistant staphylococci (E-test). All the MRSA strains proved to be vancomycin-sensitive.

All the *E.faecalis* isolates obtained from nasal cavity of the patients treated for oncohematological disorders who suffered from sinusitis have shown good sensitivity level with antibacterial drugs, i.e., 100% to ampicillin, linezolid, vancomycin and tigecycline.

Table 1. Comparative detection frequency of main bacterial species in the samples from nasal cavity and paranasal sinuses in the patients with ORL disorders after HSCT

Bacterial species	Lavage from maxillar sinus, %	Lavage from nasal cavity, %	Significance levels, p
E.coli	2.9+2.1	0.26+0.19	0.002
E.faecalis	1.5+1.5	1.07+0.37	0.75
Klebsiella spp	8.8+3.5	1.32+0.42	0.00002
Pseudomonas spp	5.9+2.9	0.53+0.03	0.0002
Acinetobacter spp	0	0.26+0.19	0.07
Corynebacter	2.9+2.1	1.2+0.39	0.23
Neisseria	1.5+1.5	0.79+0.32	0.56
S. epidermidis	20.5+4.9	34.4+1.7	0.02
S.viridans	7.4+3.2	3.2+0.6	0.07
S.aureus	4.4+2.5	2.6+0.6	0.39

Table 2. Incidence of different bacterial species in the samples from nasal cavity and/or maxillary sinuses in the patients with sinusitis compared with sinusitis-free patients subjected to HSCT

Bacterial species	Seeding frequency, %		Significance levels, p
	Sinusitis (+)	Sinusitis (-)	
S.epidermidis	25/102 (24.9%)	150/501 (29.9%)	0.27
S.viridans	6/102 (5.9%)	16/501 (3.2%)	0.19
S.aureus	4/201 (3.9%)	11/501 (2.9%)	0.31
Neisseria spp.	1/102 (1.0%)	4/501 (0.8%)	0.85
Klebsiella spp.	6/102 (5.9%)	8/501 (1.6%)	0.009
Pseudomonas spp.	5/102 (4.9%)	3/501 (0.6%)	0.0005
E.coli	2/102 (2%)	1/501 (0.2%)	0.02

100% of *S.pneumoniae* strains isolated in this study were sensitive to oxacillin, and therefore, to all β-lactam antibiotics. Among them, 90% showed sensitivity to norfloxacin and, hence, to moxifloxacin. Over the study period, we have not revealed any *Pneumococcus* strains resistant to vancomycin and linezolid. Resistance to tetracycline and erythromycin was detected for 70% of *S.pneumoniae* strains.

The species of *Enterobacterales* exhibited different patterns of antibiotic resistance. E.g., all *E. coli* strains were sensitive to amikacine, 3rd-generation cephalosporins (cefotaxim, ceftazidim, ceftriaxone), protected aminopenicillines, and meropenem. Meanwhile, resistance of *Klebsiella pneumoniae ssp pneumoniae*, the actual nosocomial pathogen, proved to be increased over this observation period, being as high as 85% to cephalosporins (III generation) and to meropenem (60%).

Discussion

Acute sinusitis is a common complication following HSCT, and several studies addressed this issue [6, 7]. Immunosuppressive drugs, chemotherapy, radiation treatment, prolonged antibiotic therapy, autoaggressive graft-versus-host disease (GVHD), and long periods of hospitalization are predisposing factors for the upper respiratory tract infections. Current clinical diagnostics of sinusitis, both before and after HSCT, is often based on computed tomography (CT) findings, which in many cases correlate with history and clinical examination data [8]. The authors have shown that the severity of pre-transplant sinus lesions revealed on CT scans correlated with clinical and radiological signs of sinusitis later post-transplant, having been associated with a trend for reduced survival. Therefore, the clinical background before HSCT is also important for assessing further risks of developing ORL disorders. Our results of bacteriological testing are based on the clinical cohort treated at the R.M. Gorbacheva Memorial Research Institute of Children Oncology, Hematology and Transplantation [5]. Infectious complications in allogeneic HSCT are significantly more common than in autologous HSCT, with respect to cytopenic period and rates of hematopoietic recovery. Our data refer to the patients who received allogeneic HSCT. Acute symptoms of rhinosinusitis may be registered at any term after HSCT, reaching 5.3% (95% CI 5.0%-5.6%) at the stage before transplantation; 3.01% (95% CI 2.8%-3.2%) in the course of engraftment, and 8.13% (95% CI 7.67%-8.60%), post-engraftment. From this comparison, one may suggest that massive antibiotic therapy after HSCT appears to prevent some of infectious conditions at the early stages post-transplant. However, later recolonization of pathogenic microorganisms is possible, including *Klebsiella spp., S. aureus, S.pneumoniae*, at a high risk of resistant strain selection, which was confirmed by us in the present work. One should note, however, that these 3 types of pathogenic bacteria were detected in a total of 13% of patients with sinusitis, i.e. the pathogen remained unknown in most cases. For additional diagnos-

tics, along with search for pathogenic fungi and viruses, the extended diagnostics, e.g., of strictly anaerobic microbiota, are needed. In this aspect, implementation of advanced sequencing (NGS technique) will be of great importance, thus making it possible to assess biological diversity and the ratio of main microbiota classes in complex clinical samples, e.g., from mucosal surfaces.

Conclusions

1. The studies of relationships between the presence of facultative anaerobic, opportunistic microbiota in maxillar punctures and nasal cavities, and clinical course of sinusitis in the patients undergoing allogeneic HSCT did not reveal any significant correlations with severity of the disease (mild *versus* moderate grade).

2. Standard bacteriological testing aimed for detection of facultative anaerobic microorganisms in the maxillary sinus punctures after HSCT is of limited value within 1 month after HSCT, due to massive antibiotic therapy and suppressed growth of antibiotic-sensitive bacteria.

3. Massive antimicrobial therapy leads to the selection of resistant strains of *Klebsiella spp., Pseudomonas spp., E.coli, S.aureus*, mainly within 2 or more months after HSCT.

4. Low frequency of cultivable potentially pathogenic microorganisms in sino-nasal exudates cultures suggests reduced detection efficiency for the etiologically important bacteria which may cause sinusitis.

5. More sensitive and specific methods for detecting bacteria on the oropharyngeal and nasopharyngeal mucosa could be based on DNA diagnostics and multiplex PCR techniques, especially due to possible contamination of these sites with anaerobic bacteria of intestinal origin.

Conflict of interest

None declared.

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Микробиота полости носа при синуситах после трансплантации гемопоэтических стволовых клеток

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Резюме

Трансплантация гемопоэтических стволовых клеток (ТГСК) часто сопровождается инфекционными осложнениями. Целью настоящего исследования была сравнительная оценка состава факультативно-анаэробных представителей микробиоты полости носа и его придаточных пазух при синусите, который нередко развивается у иммунокомпромиссных пациентов после интенсивной химио- и антибиотикотерапии и трансплантации гемопоэтических клеток (ТГСК).

Материалы и методы

В исследовании участвовали 194 пациента с различными миело- и лимфопролиферативными заболеваниями в возрасте от 1 до 62 лет, проходившие интенсивную химиотерапию и аллогенную ТГСК. При наличии клинических показаний у пациентов забирали биоматериал (смывы из околоносовых пазух и/или назальные мазки) в сроки от -100 до +180 суток после аллогенной ТГСК. Исследовано 124 образца пунктатов верхнечелюстных пазух от 97 пациентов и 973 мазка-соскоба из полости носа. Посев биоматериала и выделение микроорганизмов проводили классическими бактериологическими методами. Чувствительность клинических изолятов к антибиотикам определяли диско-диффузионным методом. Интерпретацию результатов чувствительности осуществляли согласно критериям EUCAST.

Результаты

В биоматериале из полости носа и околоносовых пазух наиболее часто высевали *S.epidermidis* – 34,7% (377/1097); *S.viridans* – 2,2% (24/1097); *S. aureus* – 1,91% (21/1097); *Klebsiella spp* – 1% (11/1097). Частота выявления *S.epidermidis* и *S.viridans* была минимальной в младшей возрастной группе (до 5 лет) и возрастала в группах от 15 лет и выше. Глубокое подавление роста *S.epidermidis* отмечалось (в особенности – в околоносовых синусах) в течение 1-го мес. после ТГСК на фоне массивной антибиотикотерапии. Отмечена высокая частота выявления *Klebsiella spp* в материале из синусов в поздние сроки (2-3 мес.) после ТГСК при малой частоте выявления в материале из полости носа (в среднем 16,3% против 2.1%, p=2×10^14). Кроме того, мы оценили частоту высеваемости бактерий в сроки +30 сут. от постановки диагноза синусита. При этом была выявлена повышенная частота выделения *Pseudomonas spp* (1/378 *vs* 7/217) в материале из придаточных пазух.

Заключение

Бактериологические исследование материала из гайморовых пазух имеет ограниченную ценность в течение 1-го мес. после ТГСК в связи с массивной антибиотикотерапией, которая сопровождается селекцией резистентных штаммов *Klebsiella spp, Pseudomonas spp, E.coli, S.aureus*, главным образом – в сроки 2 и более мес. после ТГСК.

Ключевые слова

Трансплантация гемопоэтических стволовых клеток, околоносовые пазухи, микробиота, антибиотикорезистентность.