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Clinical characteristics, antibiotic susceptibilities, treatment characteristics and outcomes in pediatric patients with *Sfingomonas paucimobilis* bacteremia

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ABSTRACT

Objective: This study aimed to examine the clinical and laboratory features, antibiotic susceptibilities, treatment characteristics, and outcomes of pediatric patients with *Sphingomonas paucimobilis* bacteremia.

Material and Methods: This single-center, retrospective study included patients aged between 1 month and 18 years who were treated for *Sphingomonas paucimobilis* bacteremia between September 2019 and December 2022.

Results: The study population included 12 pediatric patients with *S. paucimobilis* bacteremia. The median age of the patients was 28.5 months (range 7-215 months) and 50% were male. All patients had hospital-acquired infections (HAIs). The presence of comorbidities such as hematological-oncological malignancies, neurological disorders, burns and immunological disorders, the presence of a central venous catheter and a history of hospitalization within the last 12 months were prominent risk factors. Bacterial isolates were susceptible at different rates to antibiotics used as follows: piperacillin-tazobactam (83.3%), ceftazidime (91.7%), cefepime (91.7%) and meropenem (100%). The patients were treated with meropenem, cefepime, ceftazidime and piperacillin-tazobactam and the median duration of systemic antibiotic treatment was 10 days (range 10-14 days). Central venous catheters (CVCs) were removed in 3 patients who developed catheter-related bloodstream infections (CRBSIs). Persistent bacteremia, recurrence and 30-day mortality were not observed in any patient.

Conclusion: *Sphingomonas paucimobilis* remains an important opportunistic pathogen of hospital-acquired bacteremia, especially in children with risk factors. Successful treatment seems possible with systemic antibiotic therapy and removal of CVC in the presence of CRBSI.

Keywords: Antibiotic susceptibility, Bacteremia, Children, *Sphingomonas paucimobilis*, Treatment

INTRODUCTION

Sphingomonas paucimobilis (*S. paucimobilis*) is a non-fermentative, yellow-pigmented, aerobic opportunistic gram-negative bacillus (1). *S.paucimobilis* can be found in nature, on the skin, among oropharyngeal flora, and on surfaces and medical equipment in hospital environments (2-4). Community or hospital-acquired *S.paucimobilis* infections may occur (3). It is a common cause of hospital-acquired infections because it colonizes in hospitalized patients. The source of nosocomial infections may be previous colonization of the patient or biofilm formation in various contaminated medical equipment and water distribution systems (5,6). Although it rarely causes serious life-threatening infections, it may be the responsible infectious agent in bacteremia, sepsis, septic shock, endocarditis, peritonitis, meningitis, ventriculitis, adenitis, gastroenteritis, visceral abscesses, respiratory and urinary tract infections, septic arthtitis, osteomyelitis, spondylodiscitis and among them, bacteremia ranks first (3,4,7). Risk factors for *S.paucimobilis* bacteremia include predominantly malignancy, immunosuppression, comorbidities such as diabetes mellitus, end-stage renal disease, and use of central venous catheters (8-10). *S.paucimobilis* is generally resistant to penicillins and first-generation cephalosporins due to the formation of beta-

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lactamases (11). There is no definite guideline for antimicrobial treatment of *S.paucimobilis* infections. There are sporadic case reports (12-14), case series (1,8,9) and outbreak notification studies (15-17) related to *S.paucimobilis* infections in the pediatric age group. This study evaluated clinical and laboratory characteristics, antibiotic susceptibilities, treatment characteristics and outcomes of pediatric patients with *S.paucimobilis* bacteremic.

MATERIALS and METHODS

Study design and participants

This retrospective, single-center study included 12 pediatric patients with *S.paucimobilis* bacteremia at Ankara Bilkent Children's Hospital between September 2019 and December 2022.

Data collection

Data on demographic, clinical, laboratory and treatment characteristics and clinical outcomes were obtained from the hospital's electronic medical records. The study included patients aged 1 month to 18 years with complete data but without polymicrobial bloodstream infection, patients with *S.paucimobilis* bacteremia, and patients who received appropriate antibiotic therapy after the onset of bacteremia. Patients aged <1 month to >18 years with polymicrobial bloodstream infections or missing data and patients referred from another hospital were excluded from the study.

Definitions

S.paucimobilis bacteremia was defined as a single blood culture positivity for *Sphingomonas paucimobilis* in a patient with clinical findings consistent with bacteremia. Bacteremia was considered community-acquired (CA) if detected within the first 48 hours of hospitalization and hospital-acquired (HA) if detected after the first 48 hours of hospitalization (18). Duration of hospitalization was defined as the number of days from the day of the patient's first hospitalization until discharge. Duration of hospital stay associated with bacteremia was defined as the time from the initial detection of *Sphingomonas paucimobilis* bacteremia during hospitalization to completion of antibiotic therapy and treatment of complications. The duration of antibiotic therapy received was measured as the time from the first positive blood culture to the administration of the last dose of effective antibiotic therapy. Duration of bacteremia was defined as the number of days between the first positive and first negative blood culture for *S. paucimobilis*. In a patient with a central venous catheter (CVC), a catheter-related bloodstream infection (CRBSI) was considered if the time to growth signal positivity in the catheter hub sample was detected at least 2 hours before the differential positivity time (DTP) in the peripheral vein sample (19).

Microbiological methods

Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) system and VITEK® MS v3.2.0 (bioMerieux, Marcy-l'Etoile, France) database were used for identification of the causative pathogen and antibiotic susceptibility testing. Since there were no standard clinical cut-off values for *S.paucimobilis*, the pharmacokinetic and pharmacodynamic breakpoint values of the Clinical and Laboratory Standards Institute (CLSI) for other non-Enterobactereles species specified on the Vitek 2 (Biomerieux Inc., France) were used (20). Considering the differences that occurred over the years due to changes in the panel content and antibiotics used, piperacillin-tazobactam, ceftazidime, meropenem, amikacin, gentamicin, ciprofloxacin and trimethoprim-sulfamethoxazole antibiotics were evaluated.

Statistical analysis

Statistical analysis were performed using SPSS software, version 26.0 (IBM Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. Results were reported as median (min-max). A p-value of <0.050 was considered statistically significant.

RESULTS

S. paucimobilis was identified in the bacterial culture media of 12 patients. The median age of the study population was 28.5 months (range 7-215 months) and 50% were male. Risk factors included hematologic-oncologic malignancy in 8, a neurologic disorder in 2, a burn in 1, an immunologic disorder in 1, a history of central venous catheter insertion in 7, and hospitalization within the previous 12 months in all patients. The median duration of hospitalization before bacteremia was 20 days (range 10-124 days). All patients had hospital-acquired infections (HAIs). Demographic and clinical characteristics of patients with *S.paucimobilis* bacteremia and laboratory findings are shown in Tables I and II, respectively.

Antimicrobial susceptibilities

The antimicrobial susceptibilities of the reported isolates are shown in Figure 1. Multidrug resistance was not observed.

Systemic treatments

Patients received antibiotherapies with meropenem (n=4), cefepime (n=2), ceftazidime (n=2) and piperacillin-tazobactam (n=4). The median duration of systemic antibiotic treatment was 10 days (range 10-14 days). Three patients with CRBSI had their infected CVC removed.

Outcomes

The median duration of infection-related hospital stay was 10 days (range 10-14 days), and the duration of bacteremia was 3 days (range 2-3 days). None of the patients experienced

Table I: Demographic and epidemiologic laboratory characteristics of patients with Sphingomonas paucimobilis bacteremia

Patient no	Age (months)	Gender	Underlying diseases	Hospital stay before the onset of bacteremia (days)	Presence of CVC	Sources of infection	Hospital stay within the previous 12 months
1	26	M	Surgical morbidity (burn)	34	No	Primary bacteremia	Yes
2	12	F	Hematologic-oncologic malignancy (rhabdomyosarcoma)	16	implantable port	CRBSI	Yes
3	72	F	Hematologic-oncologic malignity (neuroblastoma)	19	Non-tunnelled central venous catheter	Primary bacteremia	Yes
4	66	M	Hematologic-oncologic malignancy (neuroblastoma)	6	implantable port	CRBSI	Yes
5	215	M	Hematologic-oncologic malignancy (Ewing sarcoma)	8	No	Primary bacteremia	Yes
6	70	F	Hematologic-oncologic malignancy (acute lymphoblastic leukemia)	94	implantablel port	Primary bacteremia	Yes
7	161	M	Hematologic-oncologic malignancy (Hodgkin lymphoma)	21	No	Primary bacteremia	Yes
8	30	M	Hematologic-oncologic malignancy (acute lymphoblastic leukemia)	42	implantable port	Primary bacteremia	Yes
9	84	F	Hematologic-oncologic malignancy (acute lymphoblastic leukemia)	16	Tunneled central venous catheter	CRBSI	Yes
10	27	M	Immunologic disorder (common variable immunodeficiency)	51	No	Primary bacteremia	Yes
11	16	F	Neurologic disorder (hypotonic infant, epilepsy)	25	No	Primary bacteremia	Yes
12	7	F	Neurologic disorder (hydrocephalus, epilepsy)	5	Non-tunneled central venous catheter	Primary bacteremia	Yes

M: *Male,* ***F:*** *Female,* ***CRBSI:*** *Catheter-related Bloodstream Infection*

Table II: Laboratory characteristics of the patients with Sphingomonas paucimobilis bacteremia

	WBC at the onset of bacteremia × 10^9/L	ANC during bacteremia × 10^9/L	CRP levels during bacteremia (mg/dL)
1	13760	5610	26
2	2160	920	10
3	40	20	98
4	4810	1960	28
5	290	30	120
6	3620	3010	90
7	20	0	84
8	970	230	100
9	2700	2120	91
10	9910	7620	52
11	25250	14420	30
12	6520	2140	46

WBC: *White Blood Cell,* ***ANC:*** *Absolute Neutrophil Count,* ***CRP:*** *C-reactive Protein*

Table III: Antibiotics are given to patients with Sphingomonas paucimobilis bacteremia and treatment outcomes

Case no	Antibiotics used	Duration of antibiotic therapy (days)	Removal of CVC	Hospital stay after the onset of bacteremia (days)	Total duration of hospital stay	Duration of bacteremia (days)
1	Piperacillin-tazobactam	10	No	20	136	3
2	Cefepime	10	Yes	24	40	3
3	Meropenem	14	No	20	39	2
4	Piperacillin-tazobactam	10	Yes	11	17	3
5	Meropenem	14	No	16	24	2
6	Piperacillin-tazobactam	10	No	17	111	3
7	Meropenem	14	No	55	76	2
8	Meropenem	14	No	124	166	2
9	Cefepime	10	Yes	10	26	3
10	Piperacillin-tazobactam	10	No	32	83	3
11	Ceftazidime	10	No	95	120	3
12	Ceftazidime	10	No	10	15	2

CVC: *Central venous Catheter*

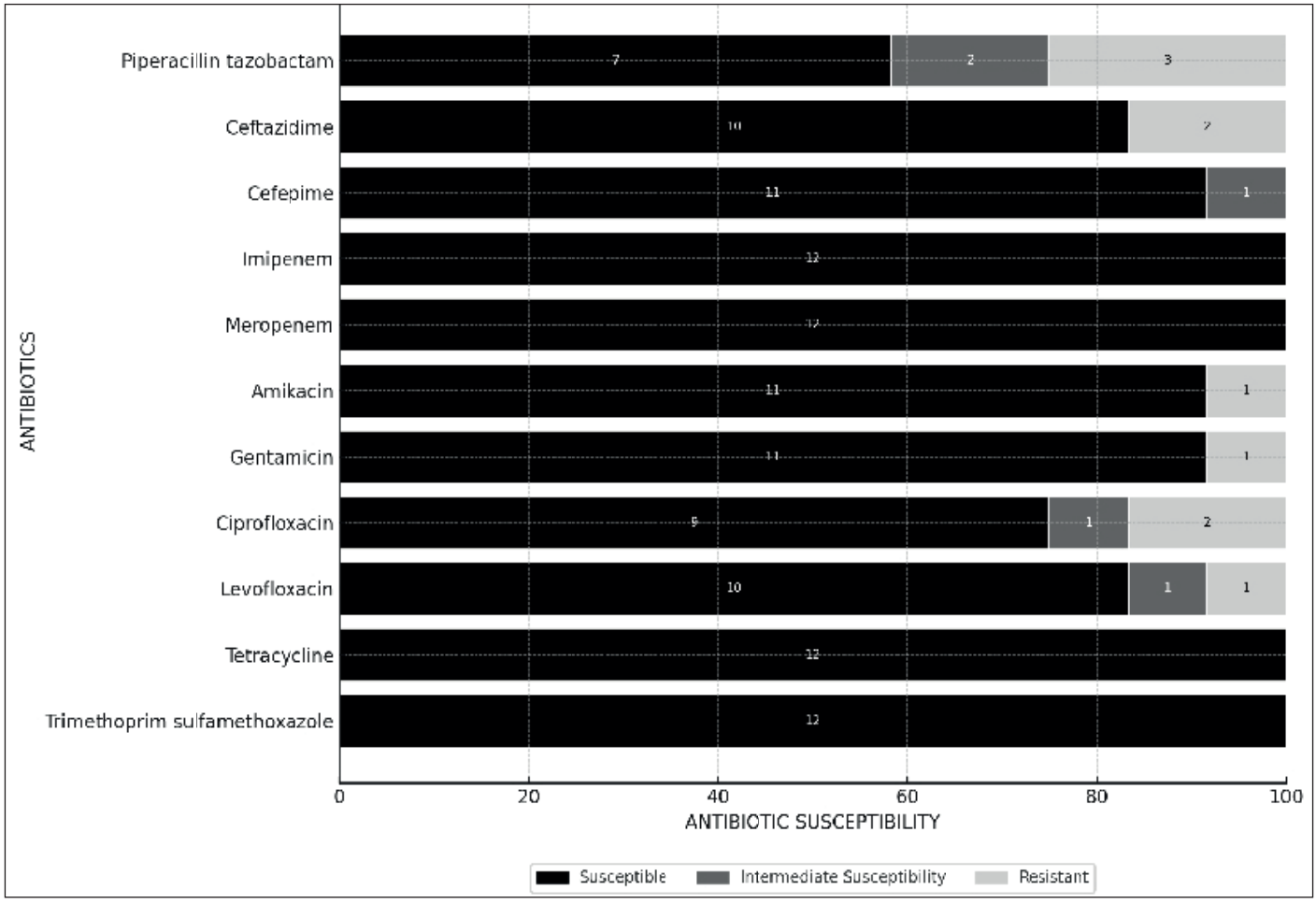

Figure 1: Antimicrobial susceptibilities of blood isolates obtained from patients with Sphingomonas paucimobilis bacteremia

persistent bacteremia, recurrence, *S. paucimobilis* bacteremia or death. Table III presents the treatment characteristics and results of patients with *S.paucimobilis* bacteremia are presented in Table III.

DISCUSSION

Although case reports, case series and outbreak reports of *S.paucimobilis* infection in pediatric patients have been published, the clinical features, treatment options and clinical outcomes of *S.paucimobilis* infections are still poorly known. Therefore, we retrospectively evaluated the clinical features, treatment options and outcomes in our pediatric cases of *S.paucimobilis* bacteremia.

S.paucimobilis can infect all age groups, from neonates to adults. In the literature, sporadic case reports, case series and outbreak reports in the neonatal age group have also been published (9,12,15,16). *S.paucimobilis*-associated infections, such as bacteremia as well as mastoiditis and peritonitis in previously healthy children with comorbidities, have been reported as sporadic case reports, as have pediatric case series and pediatric outbreak studies (1,8,9,13,15,16). During an *S.paucimobilis* bacteremia outbreak in a pediatric hematology-oncology ward, the median age of the patients was 5 years (1 year-17 years). In another case series, pediatric patients were between 6-12 years of age (1,16). In pediatric series, the male ratio varies between 57.1% and 58.3% (8,9). The median age of our study population was younger than the median age in the pediatric case series reported in the literature, and the gender ratios were similar to the values reported in other studies. Since our study did not include the neonatal age group, there were no patients in this population.

In patients infected with *S.paucimobilis*, primary bacteremia rates vary between 35.7% and 66% and catheter-related bloodstream infection (CRBSI) rates vary between 12.7% and 33% (1,8,9,14,16). In a pediatric case series, 20 of 24 patients had primary bacteremia and 2 had CRBSI (9). Most of the *S.paucimobilis* infections reported in the literature are hospital-acquired infections (4,8). However, in contrast to recent publications, most of the infections in this study were community-acquired infections. In a pediatric case series, community-acquired *S.paucimobilis* infections were detected in 54.2% of previously healthy children (9). In an adult case series, the rate of community-acquired cases reportedly varied between 52.7% and 77% (3,21,22). Patients with community-acquired disease were younger on average, had fewer comorbidities and were less likely to have polymicrobial infections. In particular, comorbid diagnoses of cancer and renal disease were not frequently seen in cases with hospital-acquired infections (21). In our study, the incidence rates of primary bacteremia and catheter-related bloodstream infections (CRBSI) were similar to those reported in the literature. Although community-acquired (CA) *S.paucimobilis* bacteremia cases have also been reported in the literature, all of our cases were hospital-acquired (HA) infections and we had no community-acquired (CA) cases. Risk factors for *S.paucimobilis* bacteremia have been reported as hematologic-oncologic malignancies (ALL, solid tumors, lymphomas), immunosuppression, immunodeficiency, surgical diseases, burns, prematurity, diabetes mellitus, alcoholism, end-stage renal disease, permanent intravenous device use, Down syndrome, intensive care unit hospitalization, and use of contaminated water (1-3,8,15,16). The time from hospital admission to the development of *S.paucimobilis* bacteremia varies between 4-47 days and the median time was reported to be 12 days (9). In the pediatric case series, the median length of hospital stay was 7 days, ranging between 4 and 22 days (8,9). In various case series, bacteremia was the most common hospital-acquired infection, while skin soft tissue and lower respiratory tract infections were the most common community-acquired infections (3,9,21,22). In our study, all patients had a history of hospitalization within the last 12 months, suggesting that *S.paucimobilis* colonization may also be an important risk factor for *S.paucimobilis* bacteremia. However, the effect of hospitalization on *S.paucimobilis* colonization is beyond the scope of our study. Although the risk factors in our study are similar to those reported in the literature, the presence of patients with immunological and neurological disorders suggests that these may also be risk factors for *S.paucimobilis* bacteremia.

S.paucimobilis is generally sensitive to carbapenems, aminoglycosides, fluoroquinolones, trimethoprim-sulfamethoxazole and piperacillin/tazobactam (2). Due to chromosomally encoded beta-lactamase production, this microorganism resists penicillin and the first generation of cephalosporins (9). In a pediatric case series (37.5%), isolates resisted at least one antibiotic (9). The highest resistance rate was detected against 3rd generation cephalosporins (20.9%). In this case, series rates of resistance against ampicillin (12.5%), amikacin (8.3%), piperacillin (8.3%) and cefuroxime (8.3%) were as indicated. All isolates were susceptible to imipenem, ciprofloxacin and trimethoprim/sulfamethoxazole (9). In a pediatric study, all isolates were susceptible to cefoperazone-sulbactam, as revealed using the disc diffusion method (16). Very different antibiotic susceptibility rates to various antibiotics used for the treatment of *S.paucimobilis* have been reported in the literature as follows: meropenem (67-100%), imipenem (81.3-100%), ciprofloxacin (81.3-100%), levofloxacin (92.9-100%), piperacillin-tazobactam (42-100%), cefepime (89.2-100%), ceftazidime (68.8-100%), cefoperazone-sulbactam (100%), trimethoprim-sulfomethoxazole (75-100%), tigecycline (100%), amikacin (59-100%), gentamicin (59-90.6%) (3-6,8,21). *S.paucimobilis* has a natural resistance to colistin (1,15). Multidrug-resistant (MDR) strains of *S.paucimobilis* have also been indicated (2). In our study, antibiotic susceptibility rates for meropenem, ceftazidime, cefepime and piperacillin-tazobactam were high and no multidrug-resistant (MDR) isolates were detected.

There is no standardized and recommended treatment for S. paucimobilis infections, especially *S.paucimobilis* bacteremia (2). Therefore, antibiotic treatment is individualized according to the susceptibility pattern of bacterial isolate (2). In studies reported in the literature, the central venous catheter was replaced, removed or not in the presence of catheter-related bloodstream infections caused by *S.paucimobilis* (5,14,16). The reason why removal of the central venous catheter is not necessary may be explained by the low virulence of S. paucimobilis (23). *S.paucimobilis* shows low virulence due to its different glycosphingolipid structure in the cell wall and the absence of lipopolysaccharide components (2). The duration of treatment in *S.paucimobilis* bacteremia usually varies between 7-14 days, depending on the clinical response (9,24). In some cases, 21 days of intravenous treatment was administered (25). In complicated patients, patients who received treatment for up to 6 weeks have been reported (26,27). Antibiotherapies for *S.paucimobilis* bacteremia were reportedly performed with ciprofloxacin and cefepime in adults, cefoperazone-sulbactam in pediatric, with meropenem, levofloxacin, piperacillin-tazobactam, ceftazidime, ceftriaxone, cefuroxime, ampicillin-sulbactam, aminoglycosides in combination with other beta-lactam antibiotics in adult and pediatric patients (5,8-10,14-16,23-28). In our study, meropenem, ceftazidime, cefepime and piperacillin-tazobactam were used, as in pediatric studies, which have been observed to have high antibiotic susceptibility rates. Although the use of cefoperazone-sulbactam, ceftriaxone, cefuroxime, and ampicillin-sulbactam in pediatric patients has been reported in the literature, they were not used in the treatment of patients because they were not studied in our antibiotic susceptibility tests.

While no mortality has been reported in some case series of pediatric *S.paucimobilis* bacteremia (9), mortality rates ranging between 3.9% and 7.7% have also been indicated in some other case series (16). In these studies, two pediatric patients with acute lymphocytic leukemia (ALL) died in the intensive care unit due to sepsis (16) and one premature patient died in the neonatal intensive care unit due to septic shock (29). There is also a report of pediatric sporadic mortality (13). Sporadic mortality cases have been reported in adults (1,2). In addition, adult infection-related mortality ranges from 0% to 5.5% (3,8,21). The development of septic shock has also been reported (8). In one study, recurrence was not observed after resolution of *S.paucimobilis* bacteremia (5).

The study's limitations include its single-center retrospective design, the scarce number of cases included in our study population, and the lack of colonization status. However, the study's strengths include considering immunological and neurological disorders and other risk factors as potential risk factors for *S.paucimobilis* bacteremia in the pediatric age group. All patients had hospital-acquired infections (HAIs) and a history of hospitalization within the previous 12 months. The antibacterial susceptibility tests were performed, and successful treatment regimens that could be used to treat HAIs were mentioned.

In conclusion, it should remembered that *S.paucimobilis* bacteremia may lead to hospital-acquired (HA) bacteremia in immunocompromised pediatric patients with comorbidities, in the presence of central venous catheters and pediatric patients with a history of previous hospitalization. Although *S.paucimobilis* bacteremia has low virulence, it should be kept in mind that it can lead to serious conditions such as septic shock. To treat *S.paucimobilis* bacteremia, removing the infected central venous catheter and applying systemic antibiotic therapy are important. In pediatric patients, piperacillin-tazobactam, ceftazidime, cefepime and meropenem are antimicrobial agents that can successfully treat *S.paucimobilis* bacteremia.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Ankara City Hospital Clinical Research Ethics Committee (Date: 01.03.2023, Decision number: E2-23-3575).

Contribution of the authors

Güneş Ö: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***Özkaya Parlakay A:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, , Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Güney AY***: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experimentsTaking responsibility in necessary literature review for the study. ***Coşkun ZN:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***Üçkardeş F:*** Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study. Yahşi A: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study. ***Özen S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***Erat T:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study. ***Gülhan B:*** Organizing, supervising the course of progress and taking the responsibility

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Conflict of interest

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