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First case report of bacteremia caused by *Haematobacter massiliensis* in Turkey

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ABSTRACT

Background: *Haematobacter massiliensis* is a Gram-negative, non-motile, non-spore-forming, non-fermenting, pleomorphic, and aerobic bacillus. It is rarely isolated from bloodstream infections such as bacteremia, particularly in immunosuppressed patients.

Case presentation: We report the case of a 67-year-old female patient with a recent history of coronary angiography who presented to the Infectious Diseases outpatient clinic in February 2023 with complaints of fever, chills, rigors, and sweating. Blood cultures obtained for fever etiology identified *Haematobacter massiliensis* as the causative agent using MALDI-TOF MS and 16S rRNA gene sequencing. The patient was successfully treated and discharged in good health.

Conclusions: The paper reports the first case of bacteremia caused by *Haematobacter massiliensis* in Turkey. *Haematobacter* species are clinically significant due to their potential to cause bloodstream infections, particularly in immunosuppressed patients, and should be considered in the differential diagnosis. In patients presenting with fever of unknown origin, bacteremia, particularly when atypical growth patterns are observed in cultures, *Haematobacter massiliensis* should be considered a rare but potential pathogen.

Keywords: bacteremia, *Haematobacter massiliensis*, Turkey

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INTRODUCTION

Haematobacter massiliensis, one of the 105 genera within the Rhodobacteraceae family, is a Gram-negative, non-fermenting, pleomorphic, non-motile, non-pigmented, catalase-, oxidase-, and urease-producing aerobic bacillus that is rarely isolated from human infections. It was first identified in 2003 in Marseille, France, from the nasal cavity of a patient with aspiration pneumonia and was initially named *Rhodobacter massiliensis*. In 2007, it was reclassified as *Haematobacter massiliensis* comb. nov [1,2].

The first isolation of *H. massiliensis* in the United States was performed in 2010 from a 65-year-old patient, whereas the first isolation in China was reported in 2017 from a 44-year-old female patient as the causative agent of aortic valve endocarditis. [3,4]. While *H. massiliensis* is predominantly isolated from bacteremia and septicemia cases, it has also been identified as a potential pathogen in endocarditis and other invasive infections [2]. Some studies conducted in China have demonstrated that newly isolated Gram-negative bacilli from soil exhibit high similarity to *H. massiliensis* based on phylogenetic analysis of their 16S rRNA gene sequences [5,6].

In this case, we report a rare bacteremia infection caused by *H. massiliensis* in a 67-year-old female patient with diabetes mellitus, accompanied by hypertension and hypothyroidism.

CASE PRESENTATION

A 67-year-old female patient was admitted to the emergency department in February 2023 with complaints of fever, chills, and sweating that had been rising intermittently for a week. Since her fever was 38.6°C at the time of admission, she was dispatched to the infectious diseases outpatient clinic, to determine the etiologies that would explain the current symptoms.

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A detailed medical history revealed that she had undergone coronary angiography ten days prior and had a history of thyroidectomy performed 13 years earlier. She had known diagnoses of diabetes mellitus, hypertension, and hypothyroidism. In order to investigate the etiology of fever, she was admitted to the infectious diseases service with preliminary diagnoses of urinary tract infection, bloodstream infection, and infective endocarditis. Before empirical treatment was started, a urine culture and two sets of anaerobic/aerobic blood cultures were obtained.

Empirical treatment with piperacillin/tazobactam (3 × 4.5 g IV) and moxifloxacin (1 × 400 mg IV) was initiated. After empirical antibiotic treatment, in the physical examination during follow-up: conscious, oriented and cooperative, fever was measured as 36.3°C, blood pressure was measured as 110/80 mmHg; oropharynx was normal, respiratory sounds were normal, no additional sounds or murmurs were detected in the cardiovascular system examination; the abdominal examination was unremarkable, there was no neck stiffness, and Kerning/Brudsinzki was evaluated as negative. Laboratory tests showed the following results: white blood cell count (WBC) 7.3 × 10^3/µL, hemoglobin (Hgb) 11.4 g/dL, platelet count (Plt) 231,000/µL, urea 33 mg/dL, creatinine 1.18 mg/dL, alanine aminotransferase (ALT) 30 U/L, aspartate aminotransferase (AST) 60 U/L, erythrocyte sedimentation rate (ESR) 53 mm/h, C-reactive protein (CRP) 87 mg/L, procalcitonin 2.5 ng/mL. Laboratory test results throughout hospitalization and in the outpatient clinic visits are summarized in Table 1.

Serological tests for *Brucella* (IgG, IgM, immunocapture, Rose Bengal), *Borrelia burgdorferi* (IgG, IgM), and *Treponema pallidum* (VDRL) were all negative. Chest computed tomography revealed no infiltration, and abdominal ultrasonography findings were unremarkable. No bacterial growth was observed in the midstream urine culture.

Two sets of blood cultures (two aerobic and two anaerobic bottles) were obtained from the patient during febrile episodes and incubated in the BacT/Alert automated blood culture system (bioMérieux, France). A positive signal was observed in only one aerobic bottle after 72 hours of incubation. Samples from the aerobic positive blood culture bottle were inoculated onto 5 % sheep blood agar (bioMérieux, France), Eosin Methylene Blue (EMB) agar (bioMérieux, France), and chocolate agar (bioMérieux, France). Blood and EMB agars were incubated aerobically at 37°C, while chocolate agar was incubated at 37°C in a 5–10 % CO_2-enriched environment for 48 hours. After the incubation period, pure, non-pigmented, non-hemolytic, glistening, stuck, grayish mucoid colonies were observed on blood and chocolate agar, while weak growth was observed on EMB agar. Gram staining of the colonies revealed pleomorphic, varying in length from short to long, serpentine Gram-negative bacilli (Figure 1). Conventional biochemical tests identified the isolates as catalase-positive, oxidase-positive, urease-positive, indole-negative, non-motile, and non-fermenting.

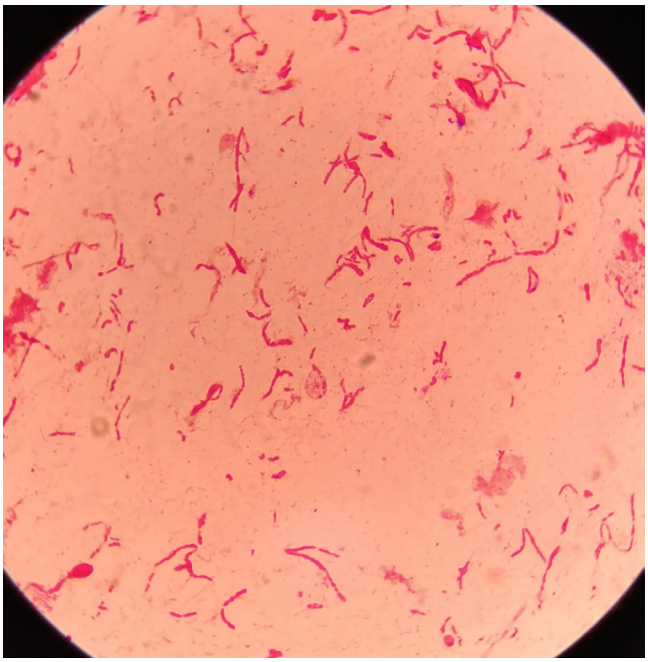

Figure 1. Gram stain of serpentine pleomorphic *H. massiliensis* bacilli (1000x)

Table 1. Changes in the patient's laboratory test results at admission and during follow-up

Parameters (Unit)	17.02.2023 (admission)	20.02.2023 (follow-up)	23.02.2023 (follow-up)	26.02.2023 (discharge)	14.03.2023 (control)	07.04.2023 (control)	Reference range
WBC (10^3/µl)	7300	5900	3900	8000	6500	5330	4.49-12.68
HGB (g/dL)	11.4	11.7	11.3	11.2	11.3	12.4	12-16
PLT (10^3/µl)	231000	180000	168000	153000	196000	209000	150-450
LY (%)	9.2	20.7	50.3	22	24.9	39	18.3-45.7
NEU (%)	82.7	73.2	39.9	69.6	65.3	50.3	42-74.3
Urea (mg/dL)	33	67	56	51	44	36	17-43
Creatinine (mg/dL)	1.18	1.38	1.34	1.31	0.93	1.06	0.66-1.09
ALT (U/L)	30	29	16	12	13	15	7-35
AST (U/L)	60	41	32	15	20	21	5-35
CRP (mg/L)	87	14	3.4	15.9	15	5	0-5
Procalcitonin (ng/mL)	2.5	0.82	0.12	0.13	-	-	0-0.12

Abbreviations: WBC- White blood cell, HGB- Hemoglobin, PLT- Platelet, LY- Lymphocytes, NEU- Neutrophils, ALT- Alanine aminotransferase, AST- Aspartate aminotransferase, CRP- C-reactive protein.

Bacterial identification was performed from blood agar using MALDI-TOF MS (VITEK MS, bioMérieux, France), identifying the isolate as *Haematobacter massiliensis* with 99.9 % accuracy. Gram-negative bacilli were seen in the staining of pure passages of colonies of different sizes grown on blood agar, and the result of the identifications made with MALDI-TOF MS (VITEK MS, bioMérieux, France) was found to be *H. massiliensis*. The VITEK 2 Compact system (bioMérieux, France) identified the isolate with approximately 90 % confidence as *Brucella spp*. Vitek 2 Software Version 9.02.4.531 was used for evaluation. However, due to the colony morphology, Gram stain findings inconsistent with *Brucella spp.*, and the presence of Gram-negative bacilli, *H. massiliensis* was considered the more likely diagnosis. A cardiology consultation was requested to evaluate for possible endocarditis caused by *H. massiliensis*. Echocardiography revealed no vegetation. Although the patient had a fever, high CRP and procalcitonin levels, the microorganism grown in the blood culture was accepted as the causative agent since there was no other focus of infection except blood. However, since the patient was conscious, her general condition was good, her vital signs were stable, and there was no evidence of end-organ involvement, the current clinical picture was evaluated as bacteremia rather than sepsis. The patient's treatment with piperacillin/tazobactam and moxifloxacin and the absence of recurrence of the infection also contributed to our diagnosis.

Antibiotic susceptibility testing was performed using the VITEK-2 AST N420 card (bioMérieux, France) for non-fermenting Gram-negative bacteria. Since *H. massiliensis* was absent in the VITEK-2 compact system database, the microorganism was classified as a non-fermenting Gram-negative bacillus, and minimum inhibitory concentration (MIC) values were determined. The MIC values for the *H. massiliensis* isolate were as follows: piperacillin/tazobactam 1 µg/ml, ceftazidime 2 µg/mL, cefepime 1 µg/mL, aztreonam 4 µg/mL, imipenem 0.5 µg/mL, meropenem ≤ 0.25 µg/mL, amikacin 2 µg/mL, gentamicin 4 µg/mL, ciprofloxacin ≤ 0.06 µg/mL. To determine the MIC values for antibiotics not included in the non-fermenter panel, the microorganism was classified as an aerobic Gram-negative bacillus, and the following additional MIC values were obtained using the VITEK 2 Compact automated system: ertapenem ≤ 0.12 µg/mL, ampicillin/sulbactam ≤ 0.25 µg/mL, amoxicillin/clavulanate ≤ 2.0 µg/mL, trimethoprim/sulfamethoxazole ≤ 20.0 µg/mL. Overall, *H. massiliensis* exhibited low MIC values for most antibiotics.

Given the low MIC values for ciprofloxacin and piperacillin/tazobactam, the empiric treatment regimen of piperacillin/tazobactam (3 × 4.5 g IV) and moxifloxacin (1 × 400 mg IV) was continued for 10 days. The patient's fever subsided during hospitalization, clinical symptoms improved, and laboratory markers showed resolution. She was discharged with oral amoxicillin/clavulanic acid (2 × 1 g) therapy. No recurrence was observed at the follow-up visit two weeks later. Written informed consent was obtained from the patient.

MOLECULAR IDENTIFICATION

DNA isolation of the cultured isolate was conducted using the EZ1 DNA Tissue Kit (Qiagen, Germany) with the EZ1 DNA isolation system (Qiagen, Germany). After extraction, DNA was amplified for the 16S rRNA region using the primers p8FPL (5'-AGTTTGATCCTGGCTCAG-3') and p806R (5'-GACTACCAGGGTATCTAAT-3'). The amplicons were sequenced with the BigDye Terminator v3.1 Cycle Sequencing Kit using an ABI Prism 310 Genetic Analyzer (Applied Biosystems, USA). The obtained sequences were compared with other isolates registered in the database using the BLAST (Basic Local Alignment Tool) server available at the "http://www.ncbi.nlm.nih.gov" website. Sequence analysis revealed that the isolate exhibited 98.55 % homology with *Haematobacter massiliensis* (GenBank accession no: NR_115743.1).

DISCUSSION

Haematobacter massiliensis is a newly identified bacterium that has been isolated from clinical specimens, particularly blood cultures. Previously classified under *Rhodobacter massiliensis*, *Haematobacter* species have gained attention due to their frequent isolation from blood cultures, especially in immunocompromised patients or individuals with underlying health conditions, and their association with invasive infections, including septicemia [2]. In our case, the patient had underlying conditions such as diabetes mellitus, hypertension, and hypothyroidism, which could have contributed to immunosuppression. Additionally, the patient had undergone coronary angiography ten days prior, further raising suspicion of *H. massiliensis* infection.

Helsel et al. [2] analyzed 12 *H. massiliensis* isolates using phenotypic and genotypic methods. The study also investigated the minimum inhibitory concentration (MIC) values of various antibiotics against these isolates. The researchers found that carbapenems, aminoglycosides, tetracyclines, and fluoroquinolones demonstrate remarkable effectiveness against *Haematobacter* species. Similarly, MIC values for amoxicillin-clavulanate and cephalosporins were found to be low. However, MIC values for aztreonam and piperacillin were higher. The authors also highlighted the absence of established clinical breakpoints for these antibiotics.

In a case report by Buscher et al. [3] in 2010, a 65-year-old male patient with a history of smoking and alcohol dependency, initially suspected of having a pulmonary infection, was found to have aortic valve endocarditis. The pathogen was identified via 16S rRNA gene sequencing. The patient was initially treated with vancomycin and piperacillin-tazobactam, which was later switched to ceftriaxone, leading to clinical improvement. This study emphasized the importance of molecular techniques in identifying *Haematobacter* species and diagnosing infections caused by these organisms.

Cheng et al. [4] reported a *H. massiliensis*-related endocarditis, detailing the clinical presentation, diagnostic procedures, treatment, and microbiological characteristics of the pathogen. The MIC values of ampicillin/sulbactam, amoxicillin/clavulanate, ceftazidime, cefoperazone/sulbactam, cefepime, piperacillin/tazobactam, trimethoprim/sulfamethoxazole, ciprofloxacin, and ertapenem were found to be low. The researchers found low MIC values for most antibiotics, highlighting the challenges in diagnosing infective endocarditis and the potential pathogenic role of *H. massiliensis*.

In a 2019 study, the *H. massiliensis* OT1 strain was isolated from human skin (the forehead of a male university student), and its complete genome was sequenced. This study provided significant insights into the adaptation mechanisms of *H. massiliensis* for colonization of human skin [7].

Although different methods were used to find the MIC value, the MIC values we found are similar to the MIC values found by Helsel et al. and Cheng et al [2,4]. Our results align with the literature and were further supported by antibiotic susceptibility testing, leading to the continuation of empiric moxifloxacin and piperacillin/tazobactam therapy after antibiogram results. However, as noted by Helsel et al., no established MIC threshold currently exists to define *Haematobacter* species as susceptible or resistant. Since clinical breakpoint values for *Haematobacter* species are not available in CLSI or EUCAST guidelines, interpretations were performed using the VITEK-2 Nonfermenter/Gram negative AST N420 card and the VITEK 2 Compact system (bioMérieux, France), which are designed for Gram-negative enteric and nonfermenting bacteria. This represents a limitation of our study, as MIC values were determined using these methods. In addition, since we did not have the opportunity to study Microdilution and E-test, we used the VITEK-2 AST N420 card to determine MIC values. This makes it difficult to compare the MIC values obtained in our study with the values obtained with different MIC determination methods used in other studies.

CONCLUSIONS

This is the first case report in Turkey regarding the isolation of *H. massiliensis* from the bloodstream of a patient with bacteremia. *Haematobacter* species are clinically significant due to their potential to cause bloodstream infections in patients with diabetes mellitus, hypothyroidism, recent angiography, and particularly in immunosuppressed patients, as in our case, and should be considered in the differential diagnosis. In such patients, when non pigmented, nonhemolytic, shiny, sticky gray mucoid colonies that are of different sizes on blood agar and can be considered as contamination are seen, *H. massiliensis* should also be considered and passages should be made from all colonies that appear different, while Gram staining and identification should be performed from these passages. The microbiological identification of infections caused by these bacteria is crucial for effective treatment. The literature underscores the importance of molecular identification techniques. Due to the absence of established clinical breakpoints for these bacteria, further studies are needed to define susceptibility and resistance thresholds, which would be beneficial for guiding appropriate treatment strategies.

ABBREVIATIONS

ALT – Alanine aminotransferase

AST – Aspartate aminotransferase

AST N420 – Antibiotic susceptibility testing N420

BLAST – Basic Local Alignment Tool

CLSI – Clinical Laboratory Standard Institute

CRP – C-reactive protein

DNA – Deoxyribonucleic acid

EMB – Eosin methylene blue

ESR – Erythrocyte sedimentation rate

EUCAST – European Committee on Antimicrobial Susceptibility Testing

HGB – Hemoglobin

MALDI-TOF MS – Matrix-assisted laser desorption/ionization- time of flight- mass spectrometry

MIC – Minimum inhibitory concentration

NCBI – National Center for Biotechnology Information

PLT – Platelets

rRNA – Ribosomal ribonucleic acid

USA – United States of America

VDRL – Venereal Disease Research Laboratory

WBC – White blood cell

AUTHORS' CONTRIBUTION

SA – conceptualization, laboratory data acquisition, data interpretation, writing and reviewing the manuscript

BS – conceptualization, clinical data acquisition, data interpretation

MG – conceptualization, laboratory data acquisition, clinical data acquisition

EST – laboratory data acquisition, data interpretation, writing and reviewing the manuscript

BG – conceptualization, data interpretation, writing and reviewing the manuscript

CONFLICT OF INTEREST

None to declare.

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