First case of biliary *Aureimonas altamirensis* infection in a patient with colon cancer in China

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***Abstract*—*Aureimonas altamirensis*, first reported in 2006, is an aerobic, gram-negative bacillus. It is usually considered a contaminant from the surrounding environment; however, recent evidences suggest that it may be an opportunistic pathogen in humans, which may cause multiple-site infections. Here, we report the first case of biliary *A. altamirensis* infection in a patient with colon cancer in Guangzhou, China. The *A. altamirensis* strain GZ8HT01 was isolated from the bile culture taken from the patient and identified by 16S ribosomal RNA gene sequencing. Additionally, the bacterial strain was sensitive to all antibiotics tested. The patient was effectively treated with imipenem-cilastatin. These findings are valuable for the early diagnosis and effective treatment of this emerging pathogen.**

Key words: *Aureimonas altamirensis*, Biliary tract infection, 16S rRNA gene sequencing, Phylogenetic tree, Antimicrobial susceptibility, Emerging infection

I.

Aureimonas altamirensis is an aerobic gram-negative bacillus discovered only 14 years ago. It was first isolated in 2006 from the subterranean environment of the Altamira Cave in Spain. Initially, it was designated as *Aurantimonas altamirensis*, before being reclassified as *Aureimonas altamirensis*, belonging to the newly described family of Aurantimonadaceae [1], [2]. The first draft genome of *A. altamirensis* consisted of 13 contigs and a G+C content of 65.2%, with 3594 genes being identified and classified as genes encoding 3523 proteins [3]. Members of the Aurantimonadaceae family have always been regarded as environmental contaminants, usually originating from water-cooling system and air, among other sources [4], [5], [6], [7]. *A. altamirensis* was first isolated from human clinical samples in 2008. Several reports have indicated it to be a potentially opportunistic human pathogen associated with keratitis, dendritic corneal ulcer, pleural effusion, peritonitis, cystic fibrosis-related infection, and bacteremia following scrotal infection (Table 1) [3], [8], [9], [10], [11], [12], [13], [14]. The etiologic role of *A. altamirensis* in human diseases and its transmission remain unclear. Here, we report the first case of biliary *A. altamirensis* infection in a patient with metastatic colorectal carcinoma in China. This study was approved by the Institutional Review Board of Guangzhou Eighth People's Hospital (GZEH) and informed consent of the patient was not required, considering the low ethical load (IRB No.201817108).

A 37-year-old man was admitted to GZEH in February 2019, due to abnormal liver function. On admission, the patient complained of nausea, vomiting, inappetence, abdominal pain, and urine darkening for 7 days after receiving postoperative chemotherapy with two targeted drugs (PD-1 and CTLA-4). The patient's medical history showed that he was diagnosed with descending colon cancer in 2016, but did not have hepatitis or any other chronic liver disease. Prior to hospitalization, the patient received a supplement of sodium and nutrient solution as well as liver protection treatment to reduce inflammation; however, aside from urine color, the symptoms did not improve. Physical examination revealed that the patient had moderate jaundice, with the absence of liver palms and spider nevus. Although his abdomen was soft, a 5×5 cm mass with a medium texture, unclear edge, poor mobility, and tenderness could be palpated in the left upper abdomen. On the second hospital day (HD), laboratory tests revealed the following remarkably elevated liver-associated biochemical indexes and inflammatory indicators: total bilirubin (T-Bili), 134.64 μmol/L; direct bilirubin, 103.83 μmol/L; alanine aminotransferase, 476 U/L; aspartate aminotransferase, 713 U/L; total bile acid, 201.47 μmol/L; glycocholic acid, >80 μg/ml; gamma-glutamyltransferase, 1016 U/L; alkaline phosphatase, 547 U/L; leucine aminopeptidase, 199.9 U/L; lactic dehydrogenase, 471 U/L; 5'-nucleotidase, 77.42 U/L; C-reactive protein, 129 mg/L and procalcitonin, 0.778 ng/mL. All hepatitis and autoimmune liver disease indicators were negative. In addition, radiological examination of the abdomen revealed multiple retroperitoneal lymphadenopathies, as well as slight ascites and pelvic effusions. Thus, the patient was initially diagnosed with drug-induced hepatitis, cholecystitis, cholangitis, bilateral pleural effusion, and a malignant colon tumor. Intravenous cefoperazone/tazobactam (2.25 g; twice a day) was empirically administered for antimicrobial therapy on the third HD, while albumin infusion and diamine glycyrrhizinate were used to improve liver function.

However, after 8 days of treatment, the patient's jaundice worsened and he experienced a dull pain in the right upper abdomen and a slight fever between 37.5 °C and 38 °C, indicating the possibility of obstructive jaundice. He received percutaneous transhepatic cholangiodrainage (PTCD), follow-

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ing which cultures of bile, peripheral blood, urine, and ascites were taken. After aerobic incubation at 37 °C for 24 h, small, circular, convex, smooth, and mucoid colonies were observed on the culture agar of the bile sample, indicating the presence of gram-negative bacteria. No other organisms were detected in these cultures.

Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-ToF-MS) failed to identify the gram-negative bacterium GZ8HT01. Hence, 16S rRNA gene amplification, using primers 5′-AGAGTTTGATCCTGGCTCAG-3′ and 5′-GGCTACCTTGTTACGACTT-3′, and sequencing were performed to identify the bacterium [15]. The cycling parameters were as follows: 94 °C for 3 min; 35 cycles of 94 °C for 30 s, 55 °C for 30 s, 72 °C for 90 s; and a final extension at 72 °C for 5 min. The PCR products were sequenced by the Shanghai Sangon Bioinformatics Company, China. Based on the BLAST algorithm against the GenBank database maintained at NCBI, the isolate GZ8HT01 was found to have the highest homology, with ≥99.93% identity to the corresponding sequences from the *A. altamirensis* strain, thereby confirming its identity. Phylogenetic tree analysis showed that the GZ8HT01 isolate formed a clade encompassed by other *A. altamirensis* strains with a bootstrap value of 99% (Figure 1); the analysis was performed using Clustal W, the neighbor-joining method, and the software MEGA 6.0, based on 16S rRNA sequences [16], [17], [18]. Additionally, the isolate was more closely related to the strains derived from America and the South Asian subcontinent compared to those derived from other regions.

An *in vitro* drug susceptibility test was carried out by broth microdilution using the Vitek2-compact sysmtem (bioMérieux, France), an automatic identification of drug sensitivity system, according to the Clinical and Laboratory Standards Institute guidelines and the results obtained were interpreted based on the same [19]. The results revealed that the GZ8HT01 isolate was susceptible to all antibiotics tested, including amikacin, cefotaxime, cefoperazone/sulbactam, imipenem, levofloxacin, and trimethoprim/sulfamethoxazole (Table 2). Additionally, the MIC of imipenem (≤1) was lower than that of cefoperazone/tazobactam (≤4). Hence, the patient was switched to a 14-day course of imipenem-cilastatin sodium, with less effect on the liver and coagulation function. After administering the new antibiotic treatment, the patient's body temperature returned to normal over 3 days, the abdominal pain disappeared, and the jaundice decreased significantly. He was discharged with almost full recovery of liver function, apart from slight jaundice (T-Bili: 32.75 μmol/L) after discontinuing antibiotics for 2 days.

II. Discussion

A. altamirensis is rarely encountered in clinical specimens, and to date, only 11 cases associated with human infections have been reported in medical literature [3], [8], [9], [10], [11], [12], [13], [14]. However, an increasing number of cases of *A. altamirensis* infections have been reported recently, mostly in immunodeficient patients with cancer or other underlying diseases, suggesting that *A. altamirensis* is a potential pathogen in humans, especially in those that are immunodeficient.

MS is increasingly becoming a promising tool for routine diagnosis that enables rapid and precise identification of causative agents within hours. However, it was difficult to identify this infrequent bacterium in our study due to the incomplete commercial MALDI-ToF-MS database with only a few relevant reports available. Therefore, adding the main spectrum of our isolate to the MS database will lead to better identification of this causative agent in ongoing laboratory diagnostics. Moreover, in such situations, 16S rRNA sequencing should be considered for further characterization. Meanwhile, the 16S rRNA gene, which is the conserved and specific gene in bacteria, can be used to identify clinically unknown bacteria.

A. altamirensis is an aerobic gram-negative bacillus within the newly redefined genus *Aureimonas*, which consists of other species originating from environmental sources, including *A. coralicida*, *A. ureilytica*, and *A. frigidaquae*. It was originally isolated from the subterranean environment of the Altamira Cave (Cantabria, Spain) [1]. Additionally, *A. coralicida* was the causative agent of white plague type II on Caribbean scleractinian corals [20]. Furthermore, *A. ureilytica* was collected from an air sample in South Korea [5], while *A. frigidaquae* was found in a water-cooling system from South Korea [4]. A previous publication review identified *A. altamirensis* as a contaminant found in environmental and water sources, such as metal tools, contact lenses, ophthalmic equipment, and lens-cleansing solution [8]. These sources can act as reservoirs to harbor pathogenic bacteria. In the current study, most of the *A. altamirensis* isolates were originally found in the blood or ascites of the patient. The bacteria have not been previously described in association with biliary system infections; this study is the first to demonstrate their clinical significance. Although the patient did not have a history of trauma or field operation, he had previously been diagnosed with colon cancer and had undergone surgery and chemoradiotherapy, which may have contributed to the invasion of gram-negative bacilli from the environment into the biliary tract by ascending the intestinal tract. The patient complained of gastrointestinal symptoms on admission and rapidly developed deep jaundice, dull pain in the right upper abdomen, and fever. His symptoms improved significantly after PTCD and antibiotic treatment, determined based on the drug sensitivity of *A. altamirensis*. Meanwhile, the cultures taken from the patient, including that of blood, urine, and ascites, were negative for other clinical specimens and the patient did not have any history of hepatitis or any other chronic liver disease. Therefore, our collective observations provide a convincing evidence that *A. altamirensis* may have been the causative agent of the patient's biliary infection. These results also indicated that bile culture should be performed when an individual with compromised immunity due to advanced cancer or chemotherapy experiences unexplained severe jaundice, abdominal pain, and fever. Additionally, the involvement of *A. altamirensis* should be considered.

To date, the mechanism of *A. altamirensis* infection in humans remains unclear. Review of reported literature revealed six clinical cases of *A. altamirensis* infections associated with

TABLE I EARLIER REPORTS OF *A. ALTAMIRENSIS* INFECTION IN HUMANS

Year	Area	Age/ Sex	Diagnosis	Underlying diseases	Isolation sources	Isolate identification			Treatment	Outcome
						Automated/ biochemical methods	Mass spectrometry	16S rRNA sequencing		
2020	USA	68/♂	Bacteremia	Cancer, diabetes, hypertension	Blood	Nm	*Brucella spp.*	*A. altamirensis*	Cefepime, IV Vancomycin	−
2019	Korea	65/♂	Bacteremia	Stroke, diabetes mellitus	Blood	*Acinetobacter lwoffii*	Nr	*A. altamirensis*	Moxifloxacin	+
2015	Canada	Nm	Cellulitis	Nm	Blood	Nr	*A. altamirensis*	*A. altamirensis*	Imipenem, Vancomycin, Clindamycin, Sulfamethoxazole/ Trimethoprim	+
2014	Germany	47/♀	Peritonitis	Liver and lymph nodes metastasis, peritoneal carcinomatosis	Ascites	Nm	*A. altamirensis*	*A. altamirensis*	Levofloxacin	_
2012	Spain	65/♀	Bacteremia	Multiple myeloma	Blood	Nr	Nm	*A. altamirensis*	Levofloxacin	+
2010	Spain	69/♀	Pleural effusion	Gastric adenocarcinoma, chronic ischemic heart disease	Pleural fluid	*Cupriavidus Pauculus*, *Paracoccus yeei*	Nm	*A. altamirensis*	Levofloxacin	+
		81/♀	Pleural effusion	Nm	Pleural fluid/blood					
2009	USA	50/♀	Scrotum infection	Hypertension, hyperlipidemia, hyperthyroidism, diabetes mellitus, congestive heart failure, peripheral neuropathy, chronic renal failure	Blood	*Brucella* spp. CDC group EO-3	Nm	*A. altamirensis*	Vancomycin, Clindamycin, Ciproflfloxacin	+
2008	Canada	Nm	Keratitis	Nm	A contact lens/ lens cleansing solution	*Ochrobactrum anthropi*, *Sphingomonas paucimobilis*, *Shewanella putrefaciens*	Nm	*A. altamirensis*	Nm	Nm
			Penetrating eye injury	Nm	Corneal scrapings				Fluconazole, Trifluridine, Tobramycin-dexamethasone	−
			Cystic fibrosis	Respiratory system infection due to *Staphylococcus aureus* and *Pseudomonas aeruginosa*	Sputum				Ciprofloxacin	+

♂, male; ♀, female; Nm, not mentioned; Nr, no results; +, patient's condition improved/patient was cured; −, patient's condition deteriorated/patient died.

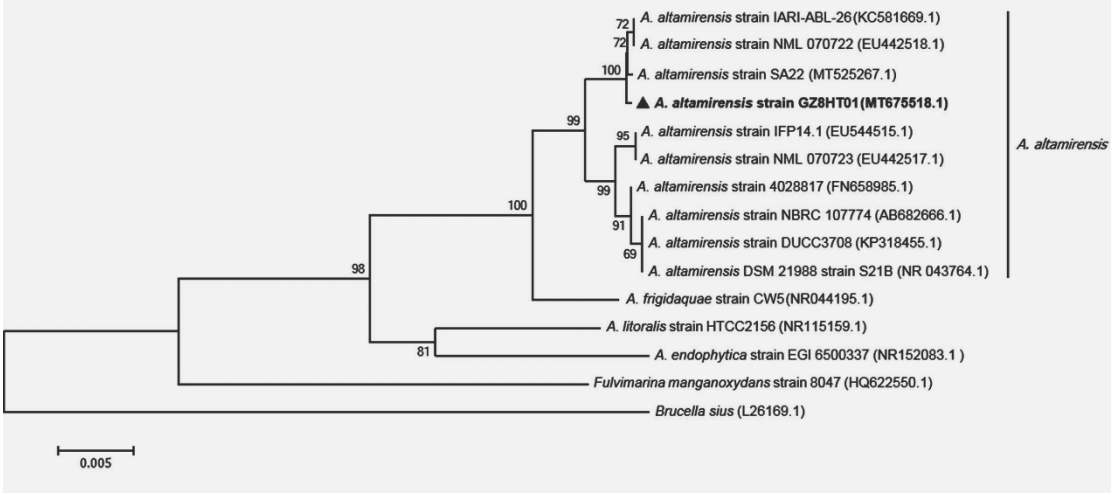

Fig. 1. hylogenetic tree generated based on 16S rRNA gene reference sequences from genus *Aureimonas.* Phylogenetic relationships were inferred using the neighbor-joining method with the Kimura 2-parameter model. The topology of the phylogeny tree was evaluated using 1000 bootstrap replications. The tree was rooted with *Brucella sius* (L26169.1) as the outgroup and *Fulvimarina manganoxydans* strain 8047 (HQ622550.1) was used as a family-level outlier. The GenBank accession numbers are indicated in parentheses and the scale bar represents percentages of substitutions per nucleotide position.

TABLE II
ESULTS OF ANTIBIOTIC RESISTANCE TESTING OF *A. altamirensis* STRAIN GZ8HT01.

Antibiotic	MIC beakpoints (μg/ml)	Susceptibility categories
Amikacin	≤2	S
Colistin	≤1	S
Cefepime	≤1	S
Ceftazidime/avibactam	≤1	S
Cefotaxime	≤2	S
Imipenem	≤1	S
Cefuroxim	≤1	S
Ceftazidime	≤1	S
Cefoperazone/sulbactam	≤4	S
Ertapenem	≤1	S
Levofloxacin	≤1	S
Ciprofloxacin	≤1	S
Chloromycetin	≤2	S
Trimethoprim/sulfamethoxazole	≤1	S

MIC-minimal inhibitoryconcentration; S-susceptible.
Susceptibility tests were performed using standardbroth microdilution and the Kirby-Bauer method. The MIC values generated by thetest can be interpreted based on the established breakpoints.

blood infections, three with hydrothorax or ascites, and two with ocular infections. Most patients responded well to antibiotic treatment determined according to the susceptibility test results; however, the condition of the patients in Schrottner and Bankowski's reports continued to deteriorate after antibiotic treatment, possibly due to the multiple metastases associated with the carcinoma [12], [14]. Most patients presented with immune dysfunction, sometimes accompanied with other underlying conditions, indicating that the enhancement of the immune system is essential for the clinical prevention of *A. altamirensis* infection. However, the pathogenic mechanism and clinical relevance of this infection in humans require further investigation.

Information on the susceptibility of *A. altamirensis* to most antibiotics is still limited; consequently, clinicians have to rely on previous case reports and empirical treatments. Fortunately, most clinical isolates reported, along with the isolate reported in this study were susceptible to the major antibiotics used against gram-negative bacteria, and showed satisfactory treatment responses. Nevertheless, it should be noted that some of the previously reported isolates displayed an antibiotic-resistant phenotype to ciprofloxacin and trimethoprim/sulfamethoxazole [8], [14].

In conclusion, this is the first report to describe the bacterial species *A. altamirensis* as a potential causative agent of human biliary system infection. We propose to consider *A. altamirensis* as an opportunistic pathogen in humans. Further studies are required to elucidate its epidemiology, pathogenic mechanisms, and clinical significance.

Nucleotide sequence accession numbers . All data of the *A. altamirensis* strain GZ8HT01 have been deposited in the NCBI database. The 16S rRNA gene sequence of this bacterium is available in GenBank under the accession no. MT675518.1.

Abbreviations:

16S rRNA, 16S ribosomal RNA; HD, hospital day; T-Bili, total bilirubin; PTCD, percutaneous transhepatic

cholangio drainage; MALDI-ToF-MS, Matrix-assisted laser desorption/ionization-time of flight mass spectrometry; MIC, minimal inhibitory concentration; S, susceptible; Nm, not mentioned; Nr, no results.

III. Competing Interests:

The authors declare that there is no conflict of interest.

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Author Contributions:

Santao Zhao and Linghua Li conceived and designed the experiments and wrote the paper; Santao Zhao, Wanshan Chen and Meijun Chen performed the experiments. Yun Lan assisted in analyzing the data; Jianping Li and Yujuan Guan collected the clinical data. Fengyu Hu, Feng Li and Xiaoping Tang assisted in design and thesis writing. All authors have approved of the final manuscript.

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