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Human Pneumonia Caused by *Bordetella hinzii*: First Case in Asia and Literature Review

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Dear Editor,

The genus *Bordetella* comprises 12 species, some of which cause human diseases. *Bordetella hinzii* widely exists in poultry and rodents and has occasionally been reported in humans wherein it has been confirmed as a causative agent of pulmonary and digestive infection, and bacteremia, almost invariably in patients with immunodeficiency [1,2]. Only 11 cases of human *B. hinzii* infection have been reported to date, and none has been found in Asia (Table 1). However, the clinical and epidemiologic characteristics of *B. hinzii* infection remain to be determined. Here, we describe the first Asian case of *B. hinzii* pneumonia to highlight the pathogenicity of this bacterium. As this case was identified during a routine surveillance organized by the Centers for Disease Control and Prevention, the need for ethical approval for the present study was exempted by the Institutional Review Board of Chengdu Fifth People's Hospital, China; verbal consent was obtained from the patient for case presentation.

A 67-year-old woman was admitted to the Neurological Intensive Care Unit in Chengdu Fifth People's Hospital on January 8, 2013 because of fatigue and loss of the abilities to stand, walk, and speak clearly. Computed tomography (CT) showed spontaneous intracerebral hemorrhage involving the ventricles of the brain. The patient had been suffering from type 2 diabetes in the past year but had no other remarkable medical history. After admission, she received symptomatic treatment, supplementary fluids, and antihypertensive treatment. She developed fever on the third day. Her vital signs included a temperature of 38°C; blood pressure, 148/70 mm Hg; pulse, 84 beats/min; and respiratory rate, 27 breaths/min. Routine blood examination showed a leukocyte count of 9.27×10^9/L; neutrophil percentage, 88.1%, lymphocyte percentage, 6.5%; platelet count, 91×10^9/L; and high sensitive C-reactive protein level, 28.9 mg/L. Chest CT examination showed scattered turbidity in both lungs. Therefore, a pulmonary infection was suspected and intravenous cefmetazole (1.5 g daily) was empirically selected and initiated. The patient's

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Table 1. Previous cases of human infection caused by *Bordetella hinzii*

Year	Country	Clinical diagnosis	Gender	Age	Epidemiology	Immunosuppression status	Method of strain identification	Antibiotics treated	Outcome	Reference
1957	France	NR	NR	NR	NR	NR	Identification of new species through PAGE of whole-cell proteins, Fatty acid methyl ester analysis, DNA-DNA and DNA-rRNA hybridization	NR	NR	[2]
1992	Switzerland	Pulmonary symptoms	Male	51	NR	None	API 20 NFT (NE) system, alkali production from malonate and PAGE of whole-cell proteins	Amoxicillin-clavulanic acid, ciprofloxacin	Recovered	[3]
1994	United States	Bacteremia	Male	42	NR	Immunosuppressed (AIDS)	API NFT, whole-cell fatty acid analysis and DNA-DNA hybridization	Vancomycin; ceftriaxone; ceftriaxone, rifampin	Recovered	[4]
1999	United States	Cholestasis and bacteremia	Male	69	Had attended a cookout at a farm 2 weeks before admission	None	Traditional biochemical testing and 16S rRNA gene sequence analysis	Ampicillin-sulbactam, cefotetan; ampicillin, gentamicin, metronidazole; ticarcillin-sulbactam, ciprofloxacin	Died	[5]
2000	Spain	Respiratory tract infection	NR	NR	No avian exposure	Immunosuppressed (AIDS)	Traditional biochemical testing and 16S rRNA gene sequence analysis	NR	NR	[6]
2001	Germany	Chronic cholangitis	Male	29	NR	Immunosuppressed (liver transplant recipient)	Traditional biochemical testing and 16S rRNA gene sequence analysis	Piperacillin-tazobactam, gentamicin; amphotericin B, flucytosine, vancomycin, and meropenem	Died	[7]
2007	United Kingdom	Flu-like symptoms	Male	79	NR	Immunosuppressed (myelodysplastic syndrome)	Genotypic methods and gene sequence analysis (ompA, 16S rRNA gene)	Amoxicillin, clavulanic acid; vancomycin, ceftazidime	Recovered	[8]
2008	United States	Fevers, full-body rash, fatigue; respiratory distress	Female	36	NR	Immunosuppressed (Epstein–Barr virus viremia and lymphoma)	Cellular fatty acid analysis and 16S rRNA gene sequence analysis	Amoxicillin-clavulanic acid, oxacillin, vancomycin, trimethoprim–sulfamethoxazole, doxycycline, linezolid, meropenem, itraconazole.	Died	[9]
2013	Spain	Respiratory symptoms	Female	85	NR	NR	MALDI-TOF–MS; 16S rRNA gene sequence analysis	Amoxicillin-clavulanate	Unclear	[10]
2013	France	Pulmonary infection	Male	43	Avian exposure	Immunosuppressed (leukemia, diabetes, vascular hypertension, and non-symptomatic chronic bronchiectasis before the allograft)	MALDI-TOF-MS; 16S rRNA gene sequence analysis	Ciprofloxacin; trimethoprim/sulfamethoxazole; piperacillin/tazobactam, ciprofloxacin; vancomycin	Recovered	[1]
2014	France	Chronic obstructive pulmonary disease	Male	74	No recent exposure to pets and poultry	Immunosuppressed (vascular hypertension, dyslipidemia, prostate cancer, ischemic heart disease)	MALDI-TOF-MS; 16S rRNA gene sequence analysis	Piperacillin/tazobactam, vancomycin	Recovered	[1]
2013	China	Pneumonia	Female	67	No avian exposure	Cerebral hemorrhage	MALDI-TOF-MS; 16S rRNA gene sequence analysis	Cefmetazole	Recovered	This study

Abbreviations: NR, not reported; PAGE, polyacrylamide gel electrophoresis; AIDS, acquired immune deficiency syndrome; MALDI-TOF–MS, matrix-assisted laser desorption/ionization-time of flight mass spectrometry; rRNA, ribosomal RNA.

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condition improved, and she was discharged on January 15, 2013.

The blood culture result was negative. Direct gram staining and microscopic examination of the sputum revealed gram-negative rods in the neutrophils. After 18 hours incubation at 35°C, colorless colonies were detected on blood, chocolate, and MacConkey agar plates, which were all gram-negative rods. One isolate from each plate was selected for identification. Initial identification performed using the API 20NE strip (bioMérieux, Lyons, France) classified the isolate as *Bordetella avium* with a 96.6% confidence, which could not be used to distinguish species in the genus *Bordetella*. The selected isolate from the blood agar plate, designated strain A2799, was subject to further identification using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) (Bruker, Leipzig, Germany) and 16S rRNA gene sequencing. Both methods classified this strain as *B. hinzii*. Antibiotic susceptibility testing was performed using the Kirby-Bauer method. The strain was found to be susceptible to the most commonly used antibiotics, and our patient recovered well through therapy with cefmetazole, which is similar to cefoxitin and ceftazidime, to which the strain was found to be susceptible.

Furthermore, the whole-genome sequence of A2799 (GenBank accession no. SRP081450) was obtained. Phylogenetic trees were constructed using a distance matrix based on the presence or absence of genes (pan-genome tree) and single nucleotide polymorphisms in the core genome (core-genome tree) for A2799 and 27 other *Bordetella strains* (Fig. 1). In both trees, A2799 clustered with two *B. hinzii* strains and with *B. pseudohinzii*, further suggesting that A2799 is *B. hinzii*. The three "classical" *Bordetella* species, *B. pertussis, B. parapertussis*, and *B. bronchiseptica*, were closely associated in both the pan-genome and core-genome phylogenetic trees, indicating that these three species were derived from a recent common ancestor (Fig. 1).

Our patient had been suffering from cerebral hemorrhage but had no history of physical injury or trauma on admission. In patients with *B. hinzii* infections, the medical history often reveals a recent exposure to poultry. However, there was a history of avian exposure for this patient. Thus, the exact nature of the exposure in our patient remains unknown.

The identification of *B. hinzii* was inconclusive or inaccurate with a biochemical identification system, consistent with a previous case [1]. 16S rRNA gene sequencing and routine MALDI-TOF-MS are reliable for identifying *B. hinzii* [1]. Furthermore, whole-genome sequencing is increasingly being applied to identify clinical microorganisms. Therefore, it is likely that some species that could not previously be identified by traditional biochemical methods will increasingly be discovered. *B. hinzii* infection is rare but potentially fatal. However, antibiotic therapy often re-

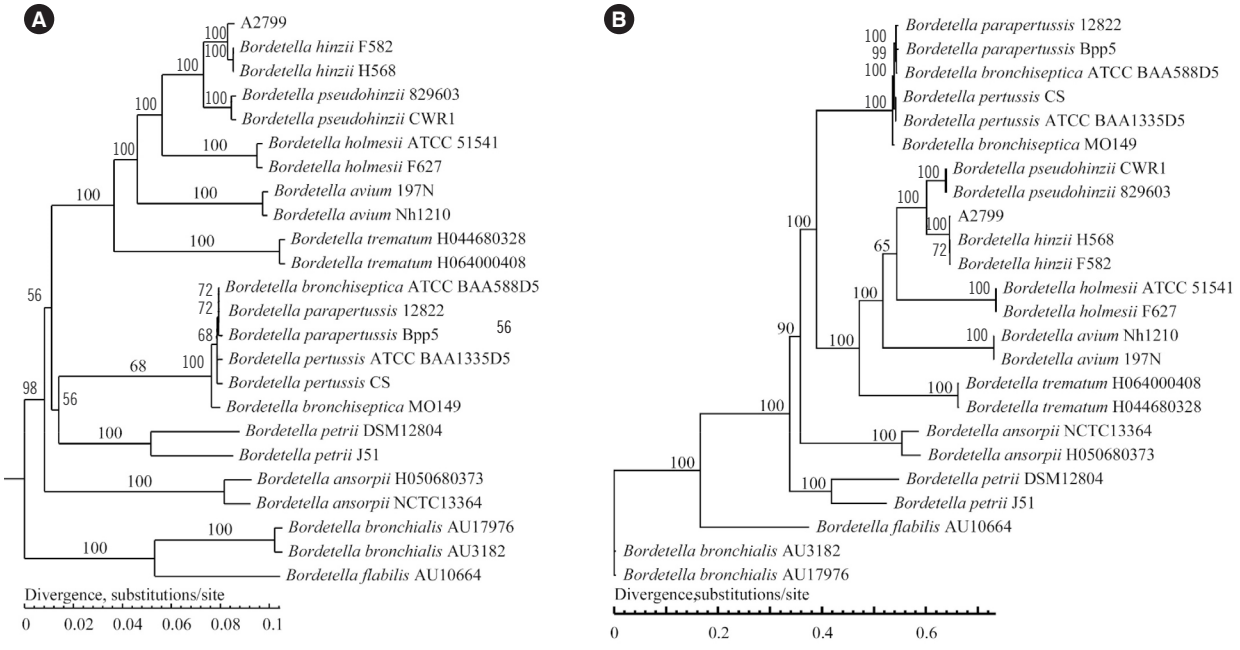

Fig. 1. Phylogenetic trees based on whole-genome sequencing and analysis. (A) Phylogenetic tree based on the gene content (pan-genome tree). (B) Phylogenetic tree based on 810 core-genome single nucleotide polymorphisms (core-genome tree).

sults in a favorable outcome.

AUTHOR CONTRIBUTIONS

Zhou H designed the study. Chen D, wang H, Lu X performed the data collection and sampling and carried out the experiments. Cui Y, Ma X, Lou J, Zhou H carried out the sequencing and data analysis. Chen D, Lou J and Zhou H wrote the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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