Peribronchial Connective Tissue Infection Caused by *Bifidobacterium longum* and *Veillonella* Species Mimicking Lung Cancer

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**Abstract:**
An 86-year-old woman was admitted for the investigation of atelectasis of the upper lobe of her right lung with a mass shadow in the hilum (Golden S sign). Chest computed tomography revealed swollen connective tissue around the right bronchus, and needle aspirate grew *Bifidobacterium longum* and *Veillonella* species. She was diagnosed with peribronchial connective tissue infection, and her condition improved with antibiotics. Although this sign is strongly suggestive of malignant disease, benign disease should be considered in the differential diagnosis. Pulmonary infection caused by *Bifidobacterium longum* is extremely rare; however, clinicians should consider it as a possible cause of pulmonary infections.

**Key words:** peribronchial connective tissue infection, *Bifidobacterium longum*, *Veillonella*, Golden S sign

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**Introduction**
Atelectasis of the right upper lobe of the lung with mass shadow in the right hilum on chest radiograph is known as the Golden S sign (inverted S sign), and typically associated with right upper lobe atelectasis due to lung cancer (1-4).

*Bifidobacteriaceae* are non-motile obligate anaerobic Gram-positive rods, found among mouth commensals and flora of the gastrointestinal and female genital tracts. Although *Bifidobacteriaceae* have long been considered non-pathogenic and advocated as a probiotic, they occasionally cause opportunistic infections (5-7).

We herein report a case of peribronchial connective tissue infection caused by *Bifidobacterium longum* (*B. longum*) and *Veillonella* species in an immunocompetent patient with positive Golden S sign who was suspected of having lung cancer.

**Case Report**
An 86-year-old woman visited her primary care doctor with wheeze and general malaise as her chief complaints. Chest radiography revealed atelectasis of the upper lobe of her lung with a mass shadow in the right hilum (the Golden S sign). These findings suggested a diagnosis of lung cancer, and she was admitted to our hospital for a further investigation.

She had a history of hypertension and hyperlipidemia, and was receiving telmisartan 40 mg, amlodipine 5 mg, pitavastatin 1 mg. She was a non-smoker with no history of alcohol abuse or using probiotics containing *Bifidobacteriaceae*.

A physical examination revealed a body temperature of 38.4°C, blood pressure of 120/85 mmHg, heart rate of 92 beats per minute, respiratory rate of 30 breaths per minute, and percutaneous oxygen saturation of 91% while breathing room air. Her heart sounds were normal, but an expiratory wheeze was audible over the right middle lung field. Other systemic examinations were normal.

Blood tests revealed the following: white blood cell count, 5,590/μL (Neutrophil: 78.2%); red blood cell count, 442×10⁴/μL; hemoglobin level, 13.2 g/dL; hematocrit, 38.3%; platelet count, 17.8×10⁴/μL; and C-reactive protein, 20.5 mg/
caused by was diagnosed with peribronchial connective tissue infection (Veillonella tobetsuensis type strain (CP001820)) and patients with lymph node enlargement due to tuberculosis (1, 2), this is the first report of a Golden S sign being caused by Bifidobacterium longum and Veillonella species.

In the present case, B. longum and Veillonella species were cultured from the transbronchial needle aspirate, and the patient was diagnosed with peribronchial connective tissue infection. Therefore, this anaerobic infection produced the Golden S sign. Cases of benign diseases presenting with a Golden S signs are rare. Although the Golden S sign has been reported in patients with pulmonary fungal infection and patients with lymph node enlargement due to tuberculosis (1, 2), this is the first report of a Golden S sign being caused by Bifidobacterium longum and Veillonella species.

Although the Golden S sign should serve to alert the clinicians to the high possibility of malignant disease (3, 4), benign diseases should be considered in the differential diagnosis of patients with the Golden S sign.

Although Bifidobacterium species consists of more than 50 species, only 10 species are found in humans, and B. longum is the representative organism. Some Bifidobacter-
Figure 3. A, B: Chest contrast-enhanced CT on day 7 showing enhanced swollen connective tissues around the right bronchus.

Figure 4. A, B: Chest contrast-enhanced CT on day 73 showing that the swollen connective tissue around the right bronchus had disappeared.

| Age/ Sex | Underlying disease | Diagnosis | Isolated organism | Treatment | Outcome | Reference |
|----------|--------------------|-----------|-------------------|-----------|---------|-----------|
| 33/M     | -                  | Pneumonia | Bifidobacterium dentium | penicillin, ampicillin | Improved | [20]      |
| 52/M     | Alcoholism         | Necrotizing pneumonia | Bifidobacterium dentium | penicillin G, kanamycin, gentamicin | Dead | [21]      |
| 47/M     | Tuberculosis       | Empyema   | Bifidobacterium sp. | clindamycin, cefozopran | Improved | [22]      |
| 67/M     | Diabetes mellitus  | Lung abscess | Bifidobacterium sp. | not reported | Improved | [13]      |
| 86/F     | -                  | Peribronchial connective tissue infection | Bifidobacterium longum | amoxicillin/sulbactam, amoxicillin/clavulanate | Improved | Present case |

Table. Characteristics of Patients with Bifidobacterium Pulmonary Infections.

Bifidobacterium species are used as probiotics to promote health of the gastrointestinal tract (5-8). Bifidobacterium species other than Bifidobacterium dentium, which causes dental caries and related diseases, rarely cause invasive human infections (9). Several cases of human infections caused by Bifidobacterium species, such as bacteremia (5, 6, 8, 10), meningitis (11), peritonsillar abscess (12), pulmonary infection (6, 13), peritonitis (7), necrotizing pancreatitis (14, 15), epidural abscess (6), urinary tract infection (16-18), and shunt infection (19) have been reported. Most previous reports of Bifidobacteriaceae infections have been opportunistic infections in immunocompromised patients (7); however, our patient was not immunocompromised. A literature search revealed only four case reports of patients with Bifidobacterium pulmonary infections (Table) (13, 20-22).

Veillonella species, an anaerobic Gram-negative coccus, is part of the normal flora of the oral cavity, upper respiratory tract, gastrointestinal tract, and female genital tract. There
have been case reports of meningitis, pulmonary infections (23), head and neck infections, skin and soft tissue infections, and peritonitis caused by this organism. Veillonella species are usually recovered together with other organisms as co-infections. In this case, Veillonella species were isolated with B. longum. Although little is known about the virulence and clinical significance of B. longum, we suspect that these two organisms caused polymicrobial infection in our patient. However, the route of infection is unknown. There were no findings suggesting laryngitis or mediastinitis, so we speculate that the route was through the respiratory tract by aspiration.

Tena et al. (7) suggested that infections caused by Bifidobacteriaceae may be overlooked or underreported, since this family of bacteria is considered part of the normal microbiota. In addition, these organisms may not be recovered, as they are difficult to identify due to their fastidious growth requirements and the difficulty in distinguishing the organisms from other Gram-positive anaerobic bacilli using conventional tests.

In conclusion, although the Golden S sign is strongly suggestive of malignant disease, benign disease should be considered in the differential diagnosis of patients with this sign. Although pulmonary infections caused by Bifidobacterium species are extremely rare, especially in immunocompetent individuals, clinicians should be aware that this organism can cause pulmonary infections, and should provide appropriate treatment if this organism is identified.

The authors state that they have no Conflict of Interest (COI).

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