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Coinfection of *Streptococcus suis* and *Nocardia asiatica* in the human central nervous system: A case report

Chen YY *et al.* Mixed infection of brain

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Abstract

BACKGROUND

Streptococcus suis (*S. suis*) is an anthroponozoonotic pathogen that shows clinical manifestations of meningitis, septicemia, and arthritis in infected humans. *Nocardia* is another type of anthroponozoonotic bacteria, with clinical manifestations of skin, lung, and brain abscesses in infected humans. Few intracranial infections caused by *S. suis* or *Nocardia* have been reported. To the best of our knowledge, no study has reported a patient with simultaneous intracranial infection by *S. suis* and *Nocardia*.

CASE SUMMARY

A 66-year-old male presented at Liaocheng People's Hospital (Liaocheng, Shandong Province, China) reporting dizziness with nausea and vomiting. Metagenomic next-generation sequencing (mNGS) was performed on cerebrospinal fluid for examination, and the patient was diagnosed with suppurative meningitis caused by *S. suis* infection. He received anti-infection treatment with penicillin sodium and ceftriaxone. The patient's condition initially improved but then deteriorated. Further mNGS of cerebrospinal fluid revealed both *S. suis* and *Nocardia*. Imaging examination revealed a brain abscess. Furthermore, a mixed infection of *S. suis* and *Nocardia* was detected in the patient's central nervous system. The patient was treated with antibiotics and sulfamethoxazole. He was discharged after his condition improved.

CONCLUSION

This case shows that the disease can be recurrent in patients with intracranial infection of a rare pathogen. The possibility of mixed infection should also be considered, especially in patients treated with immunosuppressive agents. mNGS of cerebrospinal fluid is a supplement to conventional microbial pathogen identification methods. Patients with unknown pathogen diagnosis, early extensive use of antibiotics and infection with rare pathogens can be diagnosed by the combination of conventional methods and mNGS of cerebrospinal fluid.

Key Words: *Streptococcus suis*; *Nocardia*; Meningitis; Brain abscess; Case report

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Core Tip: *Streptococcus suis* (*S. suis*) meningitis is rare in the neurology department. *S. suis* combined with *Nocardia* is also rare, and intracranial infection of atypical pathogens is difficult to identify. *Streptococcus* cultivation requires high nutrition. In addition, the difficulty of cultivating *S. suis* makes the clinical identification more challenging and usually prolongs therapies. mNGS can be utilized to determine pathogens in the early phase of illness.

INTRODUCTION

Streptococcus suis (*S. suis*) is a facultative anaerobic gram-positive bacterium located in the nasal cavity, tonsils, upper respiration tract and gastrointestinal tract of pigs. This microbe can be transmitted through contact, the respiratory tract and the digestive tract^[1]. It enters the human body, spreads through the blood to the epithelial cells of the choroid plexus in the brain and crosses the blood-brain barrier, resulting in intracranial infection. The common complications of *S. suis* infection are hearing loss and vestibular dysfunction^[2]. Since the first case in Denmark in 1968, over 1600 mankind *S. suis* infections have been documented in 30 nations across the globe, especially in Southeastern Asian countries^[3]. *S. suis* is divided into 35 serotypes (Types 1-34 and Type 1/2), as per the different antigenicity of the capsular polysaccharide; the common serotypes with strong pathogenicity to pigs are Type 1, Type 2, Type 1/2, Type 7 and Type 9^[4].

Nocardia is a gram-positive aerobic bacterium and an opportunistic pathogen. It is widely distributed in soil and water and mainly invades the human body through respiratory tract inhalation and damaged skin. Infection by *Nocardia* leads to abscesses

of the respiratory system, skin and central nervous system as well as systemic disseminated infection. At least 100 species of *Nocardia* have been identified; the medically relevant strains include *Nocardia asteroides*, *Nocardia brasiliensis*, *Nocardia farcinica*, etc.

Few cases of simultaneous infection with *S. suis* and *Nocardia* have been reported. The current case was an elderly male patient who had *S. suis* meningitis with a *Nocardia* brain abscess, and metagenomic next-generation sequencing (mNGS) of cerebrospinal fluid confirmed the coinfection of *S. suis* and *Nocardia*. The present research was accepted by the Ethical Board of Liaocheng People's Hospital, and the publication of clinical data was approved by the patient's family^[5,6].

CASE PRESENTATION

Chief complaints

A 66-year-old hospitalized male who complained of dizziness.

History of present illness

The patient developed dizziness, nausea, and vomiting 4 d prior. The vomit was non-brown-colored stomach contents, accompanied by confusion, headache, and hearing loss in both ears. One day prior, his dizziness aggravated, and he presented to the hospital.

History of past illness

The man was healthy, with no specific diseases.

Personal and family history

N/A.

Physical examination

Body temperature 38.5 °C, heart rate 66 bpm, and blood pressure 210/110 mmHg. The patient reported blurred consciousness, binaural hearing loss, signs of meningeal irritation displayed by neck rigidity, positive Kernig's and Lesage's signs, normal muscular strength and limb muscle tension, and negative pathologic signs.

Laboratory examinations

On admission, the patient's examination results were completely normal, including leukocyte count, hypersensitive C-reactive protein, procalcitonin, electrolytes, liver and kidney function tests and coagulation function tests. On the second day of hospitalization, cerebrospinal fluid examination showed 62.9×10^3 white blood cells (WBCs)/ μL , with a protein level of 8036 mg/L, glucose level of 3.8 mmol/L and chloride ion concentration of 139 mmol/L. The cerebrospinal fluid pressure was 270 mm H₂O; in routine examination of the cerebrospinal fluid, the appearance was light yellow and slightly muddy; the Pandy test was positive, with 2.4×10^8 /L karyocytes, 51% neutrophils, and 69% lymphocytes. Biochemical examination of cerebrospinal fluid revealed a total protein content > 1.07 g/L (normal, approximately 0.15-0.40 g/L), dextrose level of 1.87 mmol/L (normal, approximately 2.5-4.4 mmol/L), chloride level of 114.60 mmol/L (normal, approximately 120-132 mmol/L), body temperature of 38.5 °C, heart rate of 66 bpm, and blood pressure of 210/110 mmHg. The patient reported blurred consciousness and binaural hearing loss. He had signs of meningeal irritation in the form of neck stiffness and positive Kernig's and Lesage's signs.

After 5 d, cerebrospinal fluid was extracted by lumbar puncture and subjected to mNGS. The result revealed *S. suis* (with 1884 detected sequences), and the relative abundance was 93.27%. No pathogens were found by routine methods such as cerebrospinal fluid culture or blood culture.

We then performed lumbar puncture every week to extract cerebrospinal fluid and examined inflammatory indices, with cerebrospinal fluid culture and blood culture performed.

After 37 d, the patient's condition worsened. We repeated mNGS of cerebrospinal fluid, and the results revealed *S. suis* (the number of detected sequences was 130) and *Nocardia asiatica* (the number of detected sequences was 31598). The results of the seven cerebrospinal fluid examinations are shown in Table 1, and the etiological examination of the cerebrospinal fluid is shown in Table 2.

Imaging examinations

N/A.

FINAL DIAGNOSIS

The initial diagnosis on admission was intracranial infection. Coinfection of *S. suis* and *Nocardia* infection was the final diagnosis.

TREATMENT

The sufferer was hospitalized and finished routine examination, and he received lumbar puncture on the second day after admission. The routine culture, staining and bacterial examinations of cerebrospinal fluid were negative. According to the biochemical results of cerebrospinal fluid, we considered bacterial meningitis and empirically gave the patient ceftriaxone 2 g once a day. After 5 d of treatment, the patient's condition did not improve significantly, and he still had dizziness, nausea and vomiting. Physical examination revealed a clear mind, poor spirit, positive meningeal stimulation sign, normal muscular strength and limb muscle tension, and negative pathologic signs on both sides. The outcomes showed that the *S. suis* sequence was detected; the number of sequences identified was 1884, and the relative abundance was 93.27%. The patient was diagnosed with suppurative meningoencephalitis caused by *S. suis* infection. The treatment plan was adjusted as follows: ceftriaxone 2 g q12h plus penicillin sodium 4 million units q6h intravenous drip, combined with the hormone dexamethasone 10 mg qd and *Ginkgo biloba* extract 70 mg bid to improve the patient's hearing. The patient's temperature gradually returned to normal, and the patient had

no symptoms other than binaural hearing loss. After 37 d of treatment, the patient had a fever again, the body temperature reached 38.8 °C, and severe headache occurred. Laboratory examination showed that the WBC count registered $7.8 \times 10^9/\text{L}$ (referential range: $4\text{--}10 \times 10^9/\text{L}$), and the neutrophil percentage registered 73.5% (referential range: 40%–75%). Subsequently, considering that the patient had drug resistance or that the patient's condition was repeated, we continued to apply the antibiotics ceftriaxone 2 g q12h and penicillin sodium 4 million units q6h. Nevertheless, his body temperature increased persistently, and our team discovered that he displayed neck stiffness again. Therefore, our team finished lumbar puncture. Cerebrospinal fluid test revealed a WBC content of $34 \times 10^6 \text{ WBC}/\mu\text{L}$, a protein content of 4470 mg/L, a GLU content of 2.48 mmol/L, and a chloride ion level of 124.40 mmol/L. *Nocardia* was identified in the cerebrospinal fluid *via* mNGS on day 2. At the time, our team thought that *Nocardia* meningitis was rare, that the probability of *Nocardia* endocranial infection was low, and that the probability of contamination was high. Therefore, our team didn't modify the therapeutic regimen. Subsequently, his body temperature still presented a fluctuation between 38 °C and 39 °C. Just when we were overwhelmed, we discussed with neurologists, infectious disease specialists and hematologists, considering that the patient's central nervous system was reinfected with *Nocardia*, and developed a treatment plan: ceftriaxone, penicillin sodium, and compound sulfamethoxazole tablets combined with anti-infective therapy. His body temperature restored to normal on the 2nd day posterior to the modification of the therapeutic regimen. After 65 d, his clinical symptoms improved. The patient was discharged from the hospital. After returning home, he continued to take compound sulfamethoxazole tablets trimethoprim-sulfamethoxazole (TMP-SMX), with TMP 80 mg and SMX 400 mg 2 tablets/time, 2 times/d for a total of 12 mo until the 1-year follow-up.

OUTCOME AND FOLLOW-UP

At the 1-year follow-up, the patient had left hearing loss in both ears and could work normally.

DISCUSSION

The current patient frequently consumed pork and was infected with *S. suis* after eating contaminated pork. His drinking history and diabetes history are risk factors for *S.suis* infection^[7]. *Nocardia* infection can occur in patients taking immunosuppressant hormones and by *S. suis*, which destroys the blood-brain barrier. Brain computed tomography scan of the brain of the patient led to the diagnosis of *Nocardia* infection of the central nervous system. During infection, the pathogen enters the brain tissue through the lumbar puncture wound, resulting in brain abscess^[8].

There was no improvement in binaural hearing impairment at the 1-year follow-up. Animal studies have shown that hearing impairment is related to suppurative labyrinthitis caused by the invasion of *S. suis* in the subarachnoid space to the external lymph through the cochlear aqueduct, which leads to the disturbance of inner ear microcirculation and the direct invasion of the cochlear nerve by *S. suis*^[9]. Hearing impairment affects the daily life of patients, and questions regarding how to predict, prevent and treat hearing impairment are urgent problems that remain to be solved.

The patient's condition initially improved after the initial treatment for *S. suis* and then deteriorated. We speculated that the patient was not sensitive to the current treatment and that there might be drug-resistant strains of *S. suis*. Therefore, we repeated mNGS and found that the counts of *S. suis* deoxyribonucleic acid (DNA) decreased (from 1884 to 130), which confirmed that our treatment was effective. We also identified 31598 *Nocardia* sequences by mNGS. Therefore, we concluded that the deterioration of the patient's condition was caused by intracranial infection with *Nocardia*, and the patient was diagnosed with coinfection of *S. suis* and *Nocardia*. After the treatment plan was adjusted to penicillin sodium combined with ceftriaxone and sulfamethoxazole, the patient's systemic and nervous system symptoms improved within a few weeks. The number of leukocytes decreased gradually, and the proportion of multiple nuclei cells decreased significantly, as observed in the re-examination of

cerebrospinal fluid. The patient's condition improved, and the mNGS results obtained at the time were consistent with the clinical situation.

mNGS is a multi-faceted technique which can determine pathogenic agents more quickly and accurately in contrast to conventional approaches and can even offer novel enlightenment regarding illness propagation, virulence, and antibiotic tolerance. In contrast to conventional identification approaches which can merely identify some target pathogenic agents, mNGS is a shotgun sequence identification approach of ribonucleic acids (RNAs) and DNAs from clinic specimens, in which the entire DNAs or RNAs of the specimen to be examined are blended and subjected to sequencing, and the data are afterwards contrasted with the pathogenic agent data base to acquire pathogen categorization data. Such approach can identify substantial pathogenic agents in a run in 48 h. The pathogenic agent profiles involve nearly every virus, bacterium, fungus, and parasite which is capable of infecting sufferers. The detailed description of the materials and approaches for mNGS were presented by supplemental material.

There were no pathogenic bacteria found in the multiple evaluations of blood culture, cerebrospinal fluid culture and smears, which may be related to the extensive use of cephalosporins in the early stage of treatment. mNGS quickly and accurately diagnoses pathogens without the influence of antibiotic treatment^[10]. mNGS detects pathogenic pathogens, including rare pathogens, more appropriately than traditional detection methods. mNGS also determines all DNA/RNA genome information in a sample in a single run and allows for the identification and typing of all pathogens without specific primers, which can play an important role in the diagnosis and treatment of complex and mixed infectious diseases with repeated negative clinical routine examinations. Rapid detection and identification offer the opportunity for treatment at early stages of disease, which helps control the condition, shorten recovery time, improve the prognosis and shorten the hospital stay duration. Therefore, mNGS can provide reliable and effective evidence for the diagnosis and treatment of CNS infectious diseases, with certain clinical application value^[7].

CONCLUSION

In the case of intracranial infection with rare pathogens, if the disease continues during treatment, clinicians should also consider coinfection more than the possibility of drug resistance. mNGS of cerebrospinal fluid can accurately and quickly diagnose pathogen infection in the nervous system in rare cases of infections of multiple pathogens. Based on the number of reads and relative abundance, mNGS could be used for semiquantitative detection, which can evaluate the therapeutic effect to a certain extent in addition to its important diagnostic value.

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