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CASE REPORT

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Metagenomic next-generation sequencing for the diagnosis of *Corynebacterium striatum* meningitis: case report and literature review

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Abstract

Objective To report a case of *Corynebacterium striatum* meningitis and conduct a comprehensive literature review to determine the clinical presentation, microbiology, and treatment approaches for these patients.

Materials and methods A 75-year-old male patient presented with headache and fever; however, bacterial cultures of cerebrospinal fluid (CSF) yielded negative results. Metagenomic next-generation sequencing (mNGS) of CSF subsequently identified *Corynebacterium striatum* meningitis as the causative agent for meningitis. A systematic search was performed across various databases encompassing systematic reviews, cohort studies, case series, and case reports involving patients diagnosed with *Corynebacterium striatum* meningitis regardless of age. Clinical presentation characteristics and the most frequently employed diagnostic technologies were obtained. A narrative summary of the findings is presented.

Results *Corynebacterium striatum* meningitis patients do not exhibit any specific age or sex predisposition or distinctive symptoms or signs. In patients with *Corynebacterium striatum* meningitis, CSF tests typically reveal an increased number of white blood cells (predominantly polymorphonuclear cells), elevated protein levels, and decreased glucose levels. Notably, the prevalence of antibiotic-resistant strains of *Corynebacterium striatum* has increased in recent years, leading to a gradual rise in antibiotic treatment failure rates. It is predicted that by 2030, vancomycin may be the sole effective drug available.

Conclusion The possibility of *Corynebacterium striatum* infection should be considered during clinical diagnosis and laboratory testing procedures for bacterial meningitis. mNGS can serve as a supplementary gold standard in the diagnosis of bacterial meningitis, effectively enhancing the detection rate of rare pathogens.

Keywords *Corynebacterium striatum* meningitis, Bacterial meningitis, Metagenomic next-generation sequencing, Case report

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Introduction

Corynebacterium, a gram-positive bacillus, is characterized by its non-diphtheritic nature and inability to form spores or exhibit motility. It exhibits facultative anaerobic growth, enabling survival under both aerobic and anaerobic conditions [1]. The most recent update of the List of Prokaryotic Names Validly Published (PNVP) in June 2017 included 129 species within the Corynebacterium genus, among which 54 species have been identified as potential pathogens causing human infections [2, 3]. Among these species, *Corynebacterium striatum* is frequently encountered in clinical microbiology laboratories [4].

Corynebacterium striatum (C. striatum) has emerged as an increasingly important pathogen, particularly in immunocompromised patients, due to its multidrug resistance and ability to form biofilms and colonize medical devices. These characteristics complicate treatment and underscore the need for timely and accurate diagnosis. Although *C. striatum* is a rare cause of bacterial meningitis, it poses significant clinical concern due to the severity of infections it can cause. Typical symptoms of *C. striatum* meningitis include fever, headache, neck stiffness, and altered consciousness. While the disease often follows a monophasic course, it can lead to fatal outcomes in severe infections or in patients with compromised health conditions. The clinical significance of *C. striatum* is further heightened by its multidrug resistance, which presents substantial challenges in infection management. Therefore, timely microbiological diagnosis and appropriate antibiotic therapy are crucial for effectively addressing these infections.

Case presentation

A 75-year-old male patient had experienced an eight-day episode of fever, headache, dizziness, and unsteady gait. Six days prior to admission, he developed incoherent speech and a vacant stare, prompting a visit to a local hospital where he was diagnosed with ischemic stroke and treated with aspirin and atorvastatin(see Fig. 1). However, his condition did not improve, and he continued to experience recurrent low-grade fevers. Consequently, the patient and his family sought further evaluation at our hospital.

Upon admission, the patient presented with a temperature of 36.9 °C and presented symptoms, including dizziness, headache, vomiting, somnolence, irritability, incoherent responses, and impaired attention and orientation. The neurological examination revealed no positive meningeal signs, and other physical examinations were unremarkable. Laboratory tests upon admission revealed a blood lymphocyte percentage of 17.3%, a monocyte percentage of 11.2%, monocyte count of 0.76×10^{12}/L, white blood cell count of 6.8×10^{9}/L, neutrophil percentage of 70.3%, total protein level of 61.3 g/L, albumin level of 30.7 g/L, total cholesterol level of 2.57 g/L, and high-density lipoprotein cholesterol level of 0.70 g/L. The elevated monocyte percentage indicated possible infection, whereas the low protein level and BMI (18.1 kg/m^2) suggested mild malnutrition. To provide further

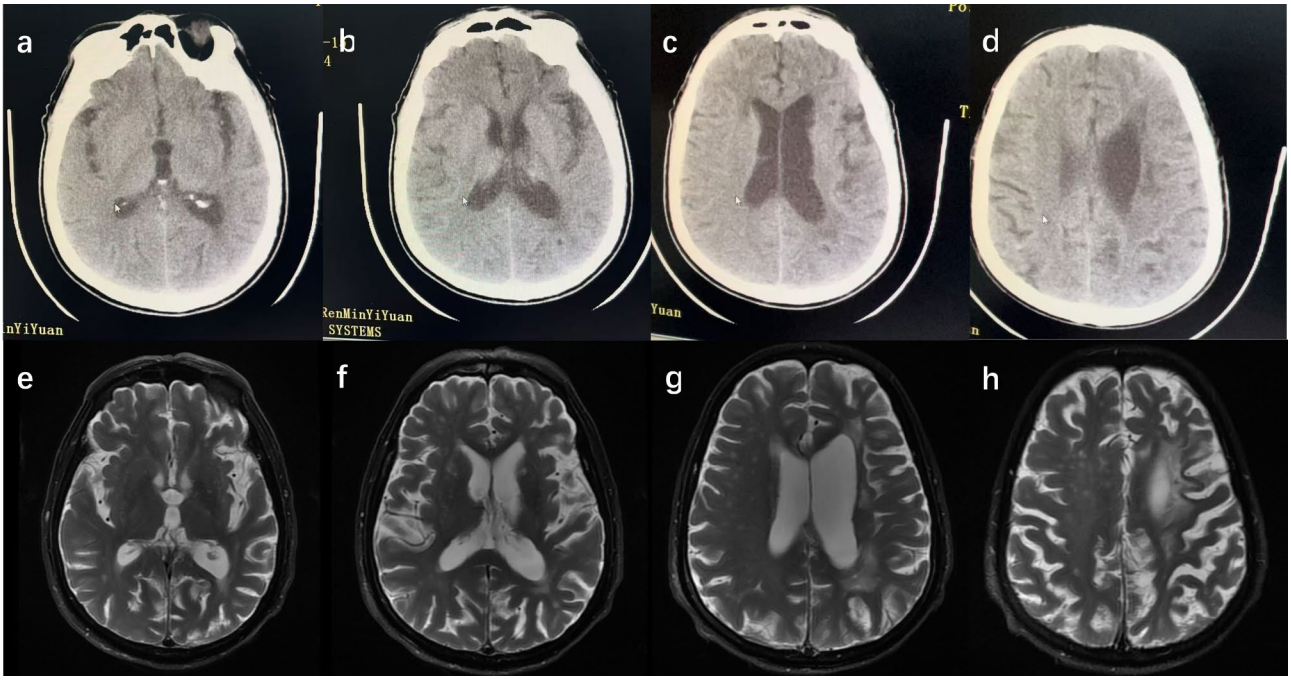

Fig. 1 Cranial CT scans from the local hospital (**a**–**d**) demonstrate multiple lacunar infarctions. Cranial MRI T2-weighted sequences upon admission (**e**–**h**) reveal multiple lacunar infarctions and encephalomalacia

clarification of the diagnosis, a lumbar puncture was performed following the exclusion of contraindications. The results revealed an intracranial pressure of 170 mmH_2O and yielded yellow, clear CSF. Laboratory analysis of the CSF revealed elevated protein levels. Specifically, the CSF contained 40×10^6/L white blood cells, 20×10^6/L mononuclear cells, 20×10^6/L polymorphonuclear cells, and 260×10^6/L red blood cells, all of which were significantly elevated. CSF chloride was 118.4 mmol/L, protein was 0.88 g/L, and CSF glucose was 2.83 mmol/L (with a blood glucose of 8.2 mmol/L). No acid-fast bacilli, Cryptococcus, or fungi were observed in the CSF smears.

On the basis of the available evidence, bacterial meningitis was considered. While awaiting pathogen identification, the patient received empirical treatment with ceftriaxone and penicillin to provide coverage against common bacterial pathogens associated with meningitis. Following this therapeutic regimen, the patient experienced improvements in symptoms such as dizziness, headache, and mental status, although intermittent low-grade fevers persisted with temperatures fluctuating between 36.8 °C and 38 °C.

On September 24th, the cerebrospinal fluid pathogen microbial genome detection results (performed by Golden Meditech Laboratory Group Co. Ltd. Zhengzhou, China) revealed *Corynebacterium striatum* with a sequence count of 65,668 and a relative abundance of 94.17%. No concurrent infections from other bacteria, fungi, viruses, or suspected background microorganisms were detected. Consequently, treatment with ceftriaxone and penicillin was discontinued and replaced with vancomycin. After 24 h of treatment, the patient's body temperature decreased to 36.5 °C, accompanied by a gradual improvement in consciousness and alleviation of headache symptoms. The patient's condition continued to improve steadily.

Laboratory tests on September 27th and 30th revealed a decrease in monocyte count and percentage to normal levels, indicating a gradual reduction in infection symptoms. On October 3rd, a repeat lumbar puncture was performed, yielding clear, colourless cerebrospinal fluid. The white blood cell count in the CSF was 5×10^6/L, the red blood cell count was 40×10^6/L, the CSF protein concentration was 0.628 g/L, and both the white blood cell count and red blood cell count in the CSF were significantly lower than those in previous findings, with normal chloride levels restored. The patient remained stable, with no recurrence of fever, clear consciousness, and good spirits, and was discharged on October 4, 2022. One-month follow-up confirmed the patient's recovery.

Literature review and discussion

We conducted a PubMed search using the terms "*Corynebacterium striatum*" AND ("Meningitis" OR "cerebrospinal fluid"), which yielded eight publications. Four of these genes were unrelated to the clinical presentation of *Corynebacterium striatum* and were excluded. The remaining four case reports of *C. striata* meningitis were thoroughly analysed, and an additional relevant case was identified through references cited in these articles, thereby increasing the total number of cases to five.

Since K. Weiss et al. first reported *C. striata* meningitis in 1996, over the past 28 years, only a small number of such infection cases have been documented (see Table 1). We found five relevant articles that, in total, covered eight patients with *C. striata* meningitis. A thorough review of the global literature indicated that C. striatum meningitis has no specific age or sex preference. It affects people across a wide age range, with the youngest patient being 13 months old and the average age of these patients being 23.59 years. Among them, four patients (50%) were male. Almost all patients had a disruption in the continuity of cerebrospinal fluid with the external environment, often linked to cutaneous injuries that could potentially lead to intracranial infections. This suggests that C. striatum is an organism that colonizes the skin. However, our patient had no obvious trauma history, recent surgical procedures, long - term antibiotic use, or diabetes. We hypothesize that in this specific case, advanced age and immunosuppression caused by malnutrition might have contributed to the occurrence of C. striatum infection. The growing incidence of C. striatum infections, especially in immunocompromised patients, emphasizes the significance of recognizing this pathogen as a potential cause of nosocomial infections. Factors like prolonged hospitalization, the use of invasive medical devices, and prior antibiotic use are associated with an elevated risk of C. striatum infections.

The symptoms of *C. striata* meningitis are nonspecific and resemble those of other forms of meningitis. All patients presented with fever and headache, accompanied by common manifestations of nausea and neuropsychiatric abnormalities (e.g., irritability, apathy). CSF analysis revealed elevated white blood cell counts (predominantly polymorphonuclear cells) and protein levels in these patients, whereas glucose levels decreased due to bacterial consumption. Previous reports identified C. striatum meningitis through conventional bacterial cultures and biochemical tests; however, the case we present marks the first instance of utilizing CSF metagenomic next-generation sequencing (mNGS). Despite the administration of one or more antibiotic treatments to all patients, three individuals (37.5%) died from infection. Traditional diagnostic methods, such as Gram staining and bacterial culture, often fail to identify *C. striatum* due to its slow

Table 1 Summary of neurological cases of *Corynebacterium striatum* infection reported in the literature

Study	Our patient	Weiss [29]	Hoy [30]	Hoy [30]	Hoy [30]	Súnbúl [31]	Súnbúl [31]	Kammoun [32]	Zhang [33]
Gender/Age	M/75Y	M/23Y	M/20 M	F/13 M	F/6Y	M/17Y	F/58Y	M/28Y	F/54Y
Symptom	Headache, nausea, vomiting, fever	Headache, chills	Fever, irritable	Fever	Lethargic, fever	Fever	Headache, nausea, vomiting, fever	Fever, coma	Headache, blurred vision, vomiting, paraphasia
Susceptible factors	MaInutrition, hypoproteinae-mia	Cerebro-meningeal fistulas	Intracranial-external drainage catheter	Intracranial-external drainage catheter	Intracranial-external drainage catheter	Intracranial-external drainage catheter	Intracranial-external drainage catheter	Acquired pneumonia, urinary tract infection, fungemia	Skin injury, brain abscess, pulmonary abscess
CSF results	WBC:400; Cl^-:118.4; Prot.: 0.88; Glu:2.83	WBC:1130; Glu:1.5; Prot.: 4.35;	NA	NA	NA	WBC:220; Glu:5.38; Prot.:2.29; Cl^-:88.8;	WBC:270; RBC:12,000; Glu:3.11; Prot.:1.50; Cl^-:111	WBC:240; Glu:0.28; Prot.:0.76	WBC:12,100; Prot.: 1.58; Glu:0.39
Principal treatment	Ceftriaxone, penicillin, vancomycin	Ceftriaxone vancomycin	Vancomycin	Chloramphenicol	Chloram-phenicol vancomycin	Ampicillin cefotaxi-me, vancomycin	Ceftriaxone vancomycin	Imipenem, Colimycin vancomycin	Vancomycin, Meropenem
Outcome	Alive	Alive	Alive	Alive	Alive	Died	Alive	Died	Died

Abbreviations: CSF, cerebrospinal fluid; Prot., protein (g/L); WBC, white blood cell (cells/mm3); Cl-, chloride(mmol/L); Glu, glucose(mmol/L) NA, not available;

growth and phenotypic similarities to other Corynebacterium species. In contrast, mNGS offers a rapid and accurate alternative, enabling the detection of rare and atypical pathogens that are often missed by conventional techniques. This case highlights the potential of mNGS to improve diagnostic accuracy and guide timely treatment, particularly in cases where traditional methods yield inconclusive results.

Corynebacterium striatum, a constituent of the human skin and nasal microbiota, has historically been regarded as a commensal organism. However, its clinical and laboratory significance is often overlooked, and it is erroneously considered inconsequential contamination [5]. Until 1980, Bowstead TT reported the first case of pulmonary infection caused by *Corynebacterium striatum* in a leukemia patient [6], leading to the recognition of its potential pathogenicity. Research conducted by Seung Ji Kang revealed that Corynebacterium strains isolated from patients with positive blood cultures presented significantly increased biofilm-forming abilities, highlighting the importance of biofilms in the virulence mechanism of this species [7]. An increasing number of reports have demonstrated the correlation between Corynebacterium species pathogens and various infections in immunocompromised patients, including those with malignancies, diabetes, renal failure, and HIV/AIDS, as well as patients who have undergone invasive surgeries and prolonged hospital stays [8–10]. Diseases associated with *Corynebacterium striatum* infections that have been reported include bacteremia, endocarditis, catheter-related bloodstream infections, osteomyelitis, pulmonary infections, pulmonary nodules, septic arthritis, skin infections, keratitis, and intracranial infections [11–16]. A study conducted at the University of Szeged Medical School reported an increase in the frequency of *Corynebacterium striatum* isolates from respiratory samples as well as blood and superficial samples between 2012 and 2021. This trend was particularly pronounced during the COVID-19 pandemic, suggesting a substantial surge in the prevalence of *Corynebacterium striatum* infections during this timeframe [17]. Given the infrequency of *Corynebacterium striatum* as a pathogen, along with its relatively slow growth rate and challenges associated with phenotypic identification in the laboratory setting, clinical diagnosis is further complicated, potentially leading to underestimation of its true incidence [18]. In addition to causing endogenous infections, the *Corynebacterium striatum* is also capable of causing nosocomial infections. In a comprehensive analysis of 34 reported cases, Prescott P. Lee reported that 56% of *Corynebacterium striatum* infections were hospital-acquired infections. Among these cases of nosocomial infections, 58% are associated with foreign body-related infections (FBRIs) and the utilization of medical devices [3, 19]. Moreover,

transmission of Corynebacterium spp. between patients can occur through contact with healthcare personnel or hospital environments, resulting in outbreaks of nosocomial infections [20, 21]. Reports emphasize the importance of healthcare personnel maintaining bare elbows and adhering to strict hand hygiene practices. Additionally, ensuring adequate disinfection and cleaning protocols for hospital environments and medical equipment at appropriate concentrations and durations is also an effective measure for preventing nosocomial infections caused by *Corynebacterium striatum* [3]. These measures have the potential to reduce patient hospitalization duration, lower mortality rates, and subsequently alleviate the burden on both hospitals and society. The increasing prevalence of multidrug-resistant *C. striatum* strains poses significant challenges in clinical management. Current treatment options are limited, with vancomycin often being the only effective antibiotic. However, the emergence of vancomycin-resistant strains highlights the urgent need for the development of novel therapeutic strategies, including the exploration of alternative antibiotics and combination therapies.

The gold standard methods for diagnosing the pathogen include bacterial culture and biochemical testing (CB test) [22]. Laboratories can perform Gram staining followed by microscopic observation to preliminarily assess the presence of bacteria in clinical samples. Subsequently, biochemical testing is conducted to identify the pathogen [23]. In cases of opportunistic infections, diagnosing *Corynebacterium striatum* through routine Gram staining and initial observation becomes even more challenging. Several systems based on biochemical testing have been developed to identify different isolates of Corynebacterium species [24]. Among them, the API Coryne system is more sensitive than the RapID CB Plus system and the BBL Crystal system. However, this system still encounters issues related to misidentification of isolates and fails to identify all Corynebacterium isolates. Given the limitations associated with bacterial culture and biochemical testing for *Corynebacterium striatum*, the integration of high-throughput sequencing with bioinformatics analysis, such as mNGS, serves as a valuable supplementary method to the gold standard [25]. Owing to its ability to directly identify pathogen sequences in clinical samples, mNGS significantly enhances diagnostic speed and accuracy, making it particularly useful for detecting novel, rare, and atypical pathogens [26]. In this case, the patient presented with nonspecific clinical manifestations and had no relevant medical history. A cerebrospinal fluid pathogen smear and bacterial culture yielded no abnormalities. However, through cerebrospinal fluid mNGS analysis, we successfully identified an infection caused by *Corynebacterium striatum* and promptly initiated appropriate antimicrobial therapy. As a result of this timely diagnosis facilitated by cerebrospinal fluid mNGS analysis, the patients experienced a favourable prognosis. In conclusion, cerebrospinal fluid mNGS played a pivotal role in facilitating the accurate diagnostic process for this patient.

The standardization of antimicrobial susceptibility testing for *Corynebacterium striatum* remains a challenge in both clinical practice and laboratory settings, impeding the implementation of effective treatment strategies. Currently, glycopeptides, linezolid, quinolones, daptomycin, and tigecycline have demonstrated efficacy against *Corynebacterium striatum* infections. Vancomycin should be the preferred antibiotic for treating infected patients with *Corynebacterium striatum* infections, either as monotherapy or in combination with piperacillin-tazobactam. Linezolid, tedizolid, or daptomycin can be considered for severe infections caused by this bacterium, whereas amoxicillin-clavulanic acid may suffice for mild infections caused by *Corynebacterium diphtheriae* [27]. However, in recent years, certain strains exhibiting high resistance to quinolones, most β-lactams, aminoglycosides, macrolides, and other antibiotics have emerged [20, 24, 27, 28]. With the identification of antibiotic-resistant strains of *Corynebacterium striatum*, the failure rate of antibiotic therapy is gradually increasing. However, projections on the basis of trends in resistance suggest that vancomycin may remain the only effective drug until 2030 [17]. Notably, achieving appropriate blood drug concentrations is closely related to the clinical efficacy of vancomycin. Therefore, monitoring vancomycin blood levels during patient treatment is necessary for dosage adjustment or prevention of renal damage.

Summary

The clinical presentation of meningitis caused by *Corynebacterium striatum* is complex due to its nonspecific symptoms, slow growth rate, and difficulties in phenotypic identification in laboratory settings [18]. Consequently, reported cases of intracranial infections caused by this pathogen are rare. Despite antibiotic treatment, the mortality rate in these cases reaches 33.33%, primarily attributed to delayed diagnosis or ineffective therapy. This underscores the fact that *Corynebacterium striatum*, though uncommon, is a potentially life-threatening pathogen, particularly for immunocompromised patients with cerebrospinal fluid exposure to the external environment. Therefore, it is critical to consider *Corynebacterium striatum* infection during clinical diagnosis and laboratory evaluations. mNGS serves as a valuable complementary tool for bacterial identification, facilitating early diagnosis and timely intervention. However, the high equipment and personnel costs associated with mNGS may limit its accessibility in resource-constrained healthcare settings. Timely pathogen identification

during the diagnostic process and the selection of appropriate antibiotics are crucial for achieving favourable outcomes. With the emergence of multidrug-resistant strains of *Corynebacterium striatum*, therapeutic options are increasingly restricted, highlighting the urgent need for the development of novel bactericidal antibiotics.

Limitations

This study has several limitations. First, the number of reported cases of *Corynebacterium striatum* meningitis is limited and lacks statistical significance, thereby limiting the generalizability of the results. Second, the case reports we identified are rare or atypical, introducing potential selection bias that could impact interpretation. These limitations imply that the presented information may not be comprehensive, the data may be insufficient, and the descriptions might be constrained. Nevertheless, we have conducted a systematic review of reports of C. striatum-related infections and performed a comprehensive analysis of the relevant literature to establish a theoretical foundation and practical reference for the diagnosis and treatment of C. striatum meningitis.

Abbreviations

CSF	Cerebrospinal fluid
mNGS	Metagenomic next-generation sequencing
C. striatum	*Corynebacterium striatum*
Prot.	Protein (g/L)
WBC	White blood cell (cells/mm3)
Cl	Chloride(mmol/L)
Glu	Glucose(mmol/L)
NA	Not available

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Author contributions

Xiaolei Liu and Zhijun Wang were responsible for managing the patients during their hospital stay. Xiaolei Liu, Xinran Zhao, and Zhijun Wang were involved in the diagnosis and treatment of the disease. Xinran Zhao collected clinical data. Xinran Zhao, Shaoli Wei, and Zelin Wu prepared the manuscript. All authors reviewed and made significant contributions to the final version.

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Data availability

The raw sequence data reported in this paper have been deposited in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2021) in National Genomics Data Center (Nucleic Acids Res 2022), China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences (GSA: CRA023743) that are publicly accessible at https://ngdc.cncb.ac.cn/gsa. The rest of the data is included in this published article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

This case report has been published with the written informed consent of the patient's son, including any relevant data and accompanying images. The patient's son was fully informed of the purpose of the publication and the possible disclosure of identifying information. He acknowledges and approves the use of such information for scientific and educational purposes.

Competing interests

The authors declare no competing interests.

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