

CASE REPORT

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Early diagnosis of Legionnaires' pneumonia in an immunocompromised neuroblastoma patient using metagenomic next-generation sequencing: A case report

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ABSTRACT

Introduction: *Legionella pneumophila* (*L. pneumophila*) is an aerobic, Gram-negative intracellular pathogen commonly responsible for community-acquired pneumonia and a significant causative agent in hospital-acquired pneumonia. Immunocompromised individuals, such as those undergoing organ transplantation, chemotherapy, or corticosteroid therapy, are particularly vulnerable to *L. pneumophila* infections. These infections often lead to Legionnaires' pneumonia, which is challenging to differentiate from other respiratory pathogen infections based solely on clinical presentation. Moreover, traditional pathogen detection methods have low sensitivity for *Legionella*, further complicating the diagnosis of Legionnaires' pneumonia.

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Received: 28 July 2024

Accepted: 25 September 2024

Published: 28 October 2024

Case Report: This case report presents a 6-year-and-9-month-old boy who developed persistent high fever during chemotherapy following the surgical resection of a retroperitoneal neuroblastoma. Imaging studies revealed significant pneumonia manifestations. Metagenomic next-generation sequencing (mNGS) of nasopharyngeal swabs and bronchoalveolar lavage fluid confirmed the diagnosis of Legionnaires' pneumonia.

Conclusion: This case highlights the challenges and critical importance of early and accurate diagnosis of *Legionella* infections, particularly in immunocompromised patients such as those undergoing chemotherapy. The use of advanced diagnostic techniques like metagenomic next-generation sequencing (mNGS) is essential for the prompt identification and treatment of Legionnaires' pneumonia in this vulnerable population, improving patient outcomes. This report emphasizes the need for heightened awareness and advanced diagnostic techniques in managing atypical pneumonia pathogens in vulnerable populations.

Keywords: Immunocompromised patient, *Legionella pneumophila*, Legionnaires pneumonia, Metagenomic next-generation sequencing

How to cite this article

Xiao M, Banu A, Zeng X, Shi S, Chen S, Ge N, Tang C, Huang Y, Wang G, Hu X, Cui X, Yin F, Peng R, Chang M. Early diagnosis of Legionnaires' pneumonia in an immunocompromised neuroblastoma patient using metagenomic next-generation sequencing: A case report. Int J Case Rep Images 2024;15(2):89–95.

Article ID: 101478Z01MX2024

doi: 10.5348/101478Z01MX2024CR

INTRODUCTION

Legionella pneumophila (*L. pneumophila*), an intracellular bacterium prevalent in various environments, is classified as an opportunistic pathogen [1–3]. This Gram-negative, aerobic organism was named following an outbreak of an unexplained respiratory illness identified in Philadelphia, USA, in 1976 [4]. Its genome is comprised of a circular chromosome roughly 3.3 Mb in size [5]. *Legionella pneumophila* is a significant cause of both community-acquired and nosocomial pneumonia, particularly in immunocompromised individuals [6]. Reports indicate that at least 150 outbreaks of legionellosis attributable to *L. pneumophila* have occurred worldwide, with immunocompromised populations being at heightened risk [7]. *Legionella pneumophila* infections account for up to 10% of all bacterial pneumonias, with mortality rates significantly higher in immunocompromised patients, including those undergoing chemotherapy [8]. Legionnaires' disease (LD) is classified as an atypical pneumonia, with clinical manifestations that often include extrapulmonary symptoms such as gastrointestinal and neurological issues, which can complicate early diagnosis compared to typical bacterial pneumonias [9].

Legionella pneumophila is extensively found in natural water systems, including freshwater reservoirs and waterways, as well as in artificial water systems such as landscape fountains, plumbing systems, air conditioning units, and shower installations [10–12]. *Legionella pneumophila* thrives in warm water environments, with optimal growth occurring between 20 and 42°C. This characteristic enables the bacterium to persist in artificial water systems such as air conditioning units, plumbing, and other warm water sources [9]. The ability of *L. pneumophila* to proliferate within biofilms offers it protection against environmental stresses like disinfection [13]. Human infection ensues following the inhalation or aspiration of aerosols harboring the pathogen [14]. Upon infection, *L. pneumophila* invades and replicates within alveolar macrophages, mirroring its infection of protozoan hosts in the environment [15]. The bacterium's virulence is attributed to factors such as flagella, fimbriae, type II and type IV secretion systems, and iron-acquisition strategies [16]. Among the more than 15 identified serogroups, *L. pneumophila* serogroup 1 is the primary causative agent of legionellosis [7].

As a significant respiratory pathogen, *L. pneumophila* infections can vary from mild symptoms such as fever, muscle aches, and nausea, to severe manifestations such as respiratory distress, respiratory failure, multi-organ failure, and potentially death [17]. Immunocompromised individuals, such as those undergoing chemotherapy, are at higher risk for severe *L. pneumophila* infections. These infections can progress rapidly, leading to severe pneumonia, multi-organ failure, and septic shock [18]. Extrapulmonary manifestations such as neurological or gastrointestinal symptoms may also occur, often leading

to early misdiagnosis. Additionally, the bacterium requires a specialized medium for culturing, complicating the diagnostic process in the absence of positive microbiological tests. Previous reports of *L. pneumophila* infections have typically been confirmed using polymerase chain reaction (PCR) targeting specific microorganisms rather than through next-generation sequencing (NGS) [19–21]. Next-generation sequencing offers a broader, unbiased diagnostic approach, particularly useful in immunocompromised patients presenting with atypical pneumonia symptoms.

Immunocompromised individuals, including cancer patients undergoing chemotherapy, are at increased risk of severe infections [22]. Neuroblastoma, a malignant tumor arising from neural crest cells, often necessitates intensive chemotherapy, resulting in prolonged immunosuppression [23]. This report outlines the clinical progression, diagnostic challenges, and management of a pediatric neuroblastoma patient who developed LD during chemotherapy-induced bone marrow suppression. The case highlights the critical need to address *L. pneumophila* infections in immunocompromised individuals, where traditional diagnostic methods may be inadequate. Advanced diagnostic techniques, such as mNGS, play a pivotal role in the early detection of these infections, allowing for timely intervention and better control of lower respiratory tract infections in this vulnerable population.

CASE REPORT

A 6-year-and-9-month-old boy was admitted on August 6, 2023, for subsequent chemotherapy due to bilateral lower limb pain and fever persisting for three days. This occurred six months post-operation for a malignant retroperitoneal tumor. The patient was diagnosed with stage IV retroperitoneal neuroblastoma (INSS IV) in July 2022. Following surgery on December 30, 2022, the patient underwent multiple cycles of chemotherapy and radiotherapy, with the most recent chemotherapy session administered on July 12, 2023.

Upon admission, physical examination revealed a temperature of 38.4°C, pulse rate of 120 beats per minute, respiratory rate of 24 breaths per minute, and blood pressure of 98/55 mmHg. The patient measured 111 cm in height and weighed 16 kg. There were no rashes or palpable lymphadenopathy, and respiratory examination showed clear lung sounds bilaterally. Abdominal examination noted a 30 cm surgical scar in the upper abdomen, with normal bowel sounds. Neurological examination was unremarkable, and peripheral circulation was intact. The clinical parameters observed during the patient's hospitalization are presented in Figure 1.

Initial laboratory investigations showed a white blood cell count of $7.3 \times 10^9/L$ with 83.5% neutrophils, hemoglobin level of 79 g/L, platelet count of $51 \times 10^9/L$, C-reactive protein (CRP) level of 124.83 mg/L, and serum

amyloid A >320 mg/L. On the same day (August 6, 2023), imaging (DR examination) revealed that both lungs exhibited prominent markings, and soft tissue shadow in the lower mediastinum comparable to previous findings. The patient was treated with cefoperazone-sulbactam for suspected bacterial infection. Despite treatment, the patient continued to experience pain and recurrent fevers over the next two days. Given the possibility of tumor-induced fever, on August 8, 2023, the patient resumed a high-risk neuroblastoma chemotherapy regimen, which included cyclophosphamide, doxorubicin, and vincristine.

Subsequent laboratory tests on August 11, 2023, showed worsening bone marrow suppression with a white blood cell count of $1.7 \times 10^9/L$, hemoglobin level of 68 g/L, platelet count of $36 \times 10^9/L$, and CRP level of 213.90 mg/L. The patient received granulocyte colony-stimulating factor (G-CSF) and red blood cell transfusions.

Despite initial improvement, the patient developed high-grade fevers and worsening respiratory symptoms on August 21, 2023. Repeat chest imaging on August 22, 2023, identified new lung nodules and consolidation, suggesting secondary infection. Blood cultures grew *Streptococcus mitis/oralis*, prompting a switch to imipenem-cilastatin therapy. Metagenomic next-generation sequencing of respiratory samples confirmed *L. pneumophila* infection.

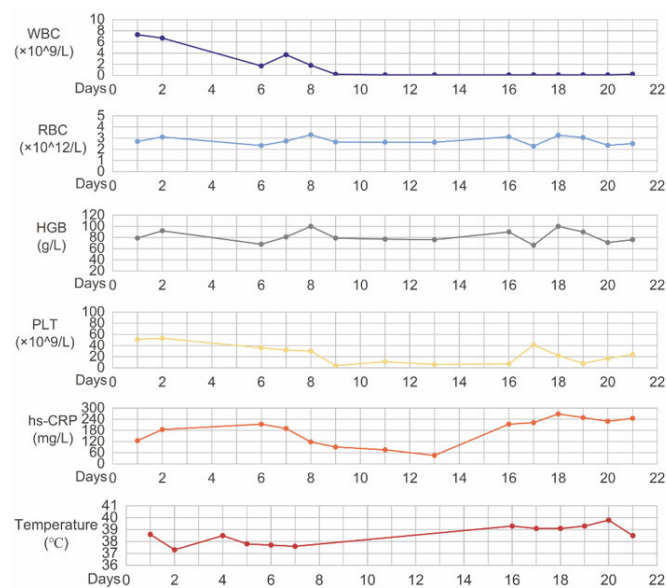


Figure 1: The clinical parameters observed during the patient’s hospitalization. Day 1 corresponds to August 6, 2023, and Day 21 corresponds to August 26, 2023, with a total hospital stay of 20 days. The body temperature reflects the highest value recorded each day, with a normal range of 36–37.2°C. The reference ranges for various clinical parameters in pediatric patients vary slightly with age. For this patient, the reference ranges in our laboratory are as follows: white blood cell count (WBC): $4.3\text{--}11.3 \times 10^9/L$, red blood cell count (RBC): $4.2\text{--}5.7 \times 10^{12}/L$, hemoglobin concentration (Hgb): 118–156 g/L, platelet count (PLT): $167\text{--}453 \times 10^9/L$, high-sensitivity C-reactive protein (hs-CRP): 0–10 mg/L.

Detailed progression and management

Day 1 (on August 6, 2023): Initial imaging studies included a chest X-ray which showed increased lung markings but no clear consolidation or pleural effusion. Laboratory findings revealed elevated inflammatory markers and a neutrophilic predominance. On the same day, the patient was empirically started on cefoperazone-sulbactam, considering his immunocompromised state and the risk of bacterial infection.

Day 3: The patient’s condition did not improve with initial antibiotic therapy. Given the possibility of tumor-related fever, chemotherapy was resumed on Day 3, following the high-risk neuroblastoma protocol. The regimen included cyclophosphamide (1380 mg, days 0–1), doxorubicin (16.5 mg, days 0–2), and vincristine (0.44 mg, days 0–2). Despite chemotherapy, the patient continued to exhibit high fevers and worsening clinical status.

Day 6: Repeat blood tests indicated significant bone marrow suppression with a white blood cell count of $1.7 \times 10^9/L$, hemoglobin level of 68 g/L, and platelet count of $36 \times 10^9/L$. The elevated CRP level (213.90 mg/L) suggested ongoing systemic inflammation. Given the patient’s critical state, G-CSF was administered to stimulate white blood cell production, and red blood cell transfusions were given to manage anemia. This sequence follows chemotherapy-related events.

Day 16: The patient experienced recurrent fevers with temperatures reaching 39.3°C. Given the failure to respond to initial antibiotic therapy and the persistent fever, the clinical team considered a broader differential diagnosis, including atypical pathogens. On Day 17, chest computed tomography (CT) revealed new pulmonary nodules and areas of consolidation suggestive of secondary infection (Figure 2).

Further microbiological investigations, including blood cultures, identified *Streptococcus mitis/oralis*. Antibiotic therapy was escalated to imipenem-cilastatin, given the identification of this organism and its potential for causing significant infections in immunocompromised hosts. Despite aggressive antibiotic therapy, the patient’s condition continued to deteriorate. The persistent fever and progressive respiratory symptoms necessitated the use of advanced diagnostic techniques. On Day 18, mNGS of nasopharyngeal swabs and bronchoalveolar lavage fluid was performed, revealing the presence of *L. pneumophila* DNA.

Upon identification of *L. pneumophila*, antibiotic therapy was adjusted to include vancomycin and levofloxacin. The decision to use levofloxacin was based on its effectiveness against *Legionella* spp. Additionally, trimethoprim-sulfamethoxazole was added to broaden the coverage against possible co-infections.

Day 19: The patient exhibited signs of severe respiratory distress, including tachypnea, retractions, and hypoxemia. Non-invasive mechanical ventilation was initiated, but the patient’s respiratory status continued to worsen, necessitating intubation and mechanical

ventilation. Supportive care included the administration of midazolam and fentanyl for sedation and pain management.

Despite maximal supportive care, the patient's condition continued to decline. On Day 20, repeat chest X-ray indicated worsening bilateral pulmonary infiltrates and right-sided pleural effusion. Laboratory tests showed persistent leukopenia (white blood cell count of $0.1 \times 10^9/L$), severe anemia (hemoglobin level of 71 g/L), and thrombocytopenia (platelet count of $17 \times 10^9/L$). C-reactive protein remained markedly elevated at 229.49 mg/L.

Given the ongoing critical illness and poor response to therapy, the patient was diagnosed with sepsis and septic shock. Intensive care management included the use of norepinephrine to maintain blood pressure, albumin infusion to manage hypoalbuminemia, and continuous monitoring for signs of organ dysfunction.

Day 21: Despite aggressive interventions, the patient's condition remained critical. His family was informed of the grave prognosis and the likely outcome. After thorough discussions and considering the patient's critical state, the family opted to withdraw life-sustaining treatments and the patient was discharged home with hospice care.

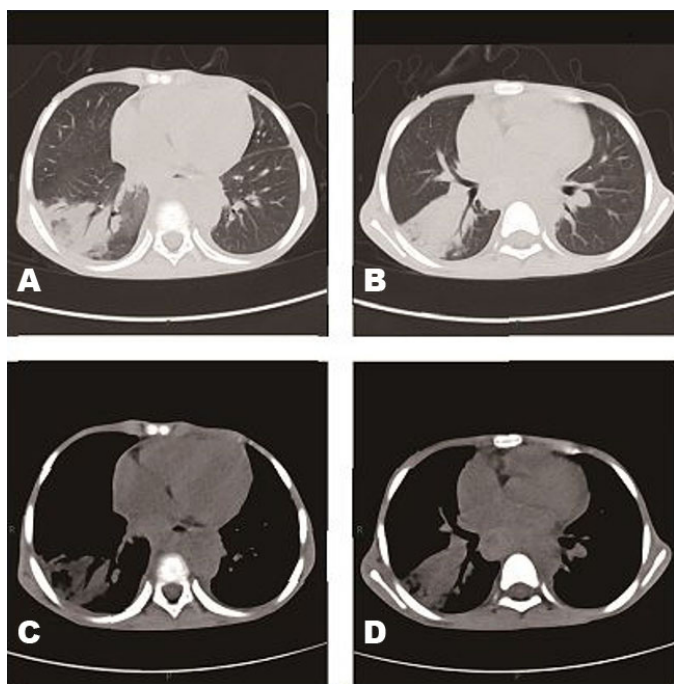


Figure 2: Computed tomography images of the patient from August 22, 2023. Images (A) and (B) represent lung windows, while (C) and (D) correspond to mediastinal windows. A newly identified nodule is observed in the left upper lobe, and a newly detected large area of consolidation is present in the right lower lobe. The chest CT of the patient indicates the presence of a severe pulmonary infection.

DISCUSSION

This case highlights the critical role of advanced diagnostic techniques, particularly mNGS [24], in

managing severe infections in immunocompromised pediatric patients. *Legionella pneumophila*, while rare, can lead to severe respiratory infections in this vulnerable population, as evidenced by the patient's presentation and clinical course. The rapid progression of the disease in this case underscores the challenges in managing infections in immunocompromised patients, where symptoms may overlap with other conditions, making diagnosis and treatment more complex.

While the severity of the disease and the extent of inflammation linked to *Legionella* are yet to be fully established, this case illustrates the importance of recognizing co-infections in immunosuppressed individuals [25]. Broader awareness of atypical pathogens, including *L. pneumophila*, is essential for clinicians treating patients with compromised immune systems, such as those undergoing chemotherapy. In this case, *L. pneumophila* infection was complicated by the patient's prolonged immunosuppression due to intensive chemotherapy for neuroblastoma.

Neuroblastoma and its aggressive treatment regimen, including chemotherapy and radiotherapy, often result in profound immunosuppression, which significantly increases the risk of severe infections [26]. Complications of neuroblastoma, such as bone marrow suppression, can exacerbate the vulnerability of pediatric patients to opportunistic pathogens like *L. pneumophila*. Chemotherapy-induced neutropenia, thrombocytopenia, and mucosal barrier disruption further complicate the management of infections, as they limit the body's ability to mount an effective immune response. In this case, the patient's immune system was heavily compromised, likely contributing to the progression and severity of the infection [27].

With advancements in technology, mNGS plays a pivotal role in identifying pathogens that may not be easily detected using traditional methods. While mNGS was critical in this case for identifying the atypical pathogen, timely clinical decision-making and the prompt initiation of appropriate therapy are equally important [28]. This case emphasizes that mNGS is a powerful tool, but it is most effective when used in conjunction with other diagnostic and therapeutic interventions.

In terms of treatment, the decision to use levofloxacin was based on its known efficacy against *Legionella* spp., but the patient's severely compromised immune system likely hindered the effective clearance of the pathogen, despite early identification. This reflects the broader issue in managing infections in pediatric oncology patients, where both the underlying malignancy and the aggressive treatment regimens contribute to an increased risk of severe infections [29].

Additionally, this case demonstrates the challenges clinicians face when families opt to withdraw life-sustaining treatment, despite the potential for recovery. In this instance, the child's family decided to discharge the patient on the second day of targeted therapy, following discussions about the grave prognosis.

The management of infections in immunocompromised patients is challenging due to the broad differential diagnoses and the need for timely, accurate diagnosis. While traditional diagnostic methods, such as culture and serology, may be useful, they often take longer and may not yield results in patients who have already received antibiotics. The combination of clinical vigilance and rapid diagnostics, such as mNGS, allows for a more tailored approach to treatment.

In this case, it underscores the necessity of an integrated approach to managing severe infections in immunocompromised patients. It highlights the importance of advanced diagnostics, but also the need for clinical judgment, patient management, and the role of timely therapeutic interventions to improve outcomes.

CONCLUSION

In conclusion, this case report highlights the pivotal role of mNGS in diagnosing LD in immunocompromised pediatric patients, such as those undergoing chemotherapy for neuroblastoma. The patient, who presented with severe infection and persistent symptoms despite conventional treatment, was accurately diagnosed with *L. pneumophila* infection through mNGS, underscoring the limitations of traditional diagnostic methods in such complex cases. The rapid identification of the pathogen facilitated timely and appropriate antimicrobial therapy, demonstrating the clinical utility of mNGS in managing atypical infections in vulnerable populations. This case underscores the necessity for advanced diagnostic tools and vigilant pathogen surveillance to improve outcomes in immunosuppressed patients, advocating for their integration into routine clinical practice to enhance the detection and management of severe infections.

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Author Contributions

Meifang Xiao – Conception of the work, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Afreen Banu – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Xiangyue Zeng – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Yi Huang – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Gaoyu Wang – Design of the work, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Ruoyan Peng – Conception of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Meng Chang – Conception of the work, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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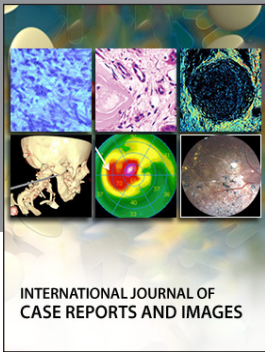
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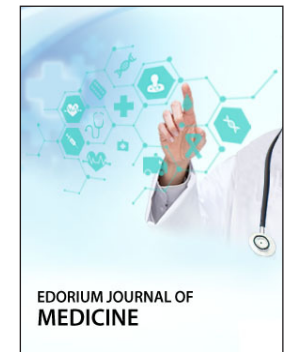
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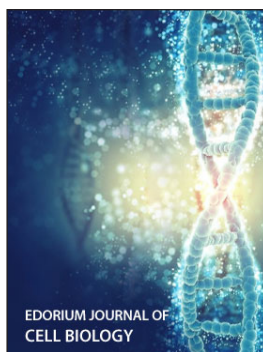
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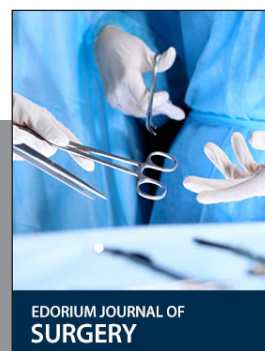
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