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Late diagnosis of X-linked hyper-IgM syndrome presenting as community-acquired pseudomonas aeruginosa pneumonia-related septic shock

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Abstract

Pseudomonas aeruginosa (P. aeruginosa) is a gram-negative aerobic bacterium, which is rarely seen in community-acquired infection. Attention should be paid to its high mortality and invasive progress. X-linked hyper-IgM syndrome (XHIGM; HIGM1; OMIM:308230) is one type of primary immunodeficiency disease (PIDs), characterized by markedly decreased serum IgG, IgA, and IgE levels and normal or elevated serum IgM levels. We report a patient who developed a particularly severe community-acquired P. aeruginosa pneumonia-related septic shock, and a delayed diagnosis of X-linked hyper IgM syndrome was made by genome sequencing. Fatal community-acquired P. aeruginosa infections in children, including previously healthy children, should be considered to search for underlying PIDs by exome/genome sequencing.

Title page

Late diagnosis of X-linked hyper-IgM syndrome presenting as community-acquired pseudomonas aeruginosa pneumonia-related septic shock

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Conflict of interests

The authors declare that there is no conflicts of interest.

Author contributions

Lin Yang: data collection; writing original draft; writing review and editing. Lina Chen and Liang Xie: data collection and manuscript revision. Ying Xiong and Hanmin Liu: study concept and design, interpretation of results, manuscript, revision, and final approval. All authors contributed to the article and approved the submitted version.

Running head:

Late diagnosis of X-linked hyper-IgM syndrome by exome/genome sequencing

Keywords: Pseudomonas aeruginosa, community-acquired infection, X-linked hyper-IgM syndrome, PIDs, exome/genome sequencing

Abstract

Pseudomonas aeruginosa (P. aeruginosa) is a gram-negative aerobic bacterium, which is rarely seen in community-acquired infection. Attention should be paid to its high mortality and invasive progress. X-linked hyper-IgM syndrome (XHIGM; HIGM1; OMIM:308230) is one type of primary immunodeficiency disease (PIDs), characterized by markedly decreased serum IgG, IgA, and IgE levels and normal or elevated serum IgM levels. We report a patient who developed a particularly severe community-acquired P. aeruginosa pneumonia-related septic shock, and a delayed diagnosis of X-linked hyper IgM syndrome was made by genome sequencing. Fatal community-acquired P. aeruginosa infections in children, including previously healthy children, should be considered to search for underlying PIDs by exome/genome sequencing.

Introduction

Pseudomonas aeruginosa (P. aeruginosa) is a gram-negative aerobic bacterium, one of the major pathogenic bacteria in hospital-acquired infection. It is rarely seen in community-acquired infections[1]. According to some cases [2,3], community-acquired *P. aeruginosa* may cause severe aggressive infections in healthy children. 25% of fatal cases were found to carry novel pathogenic variants in PID genes by exome/genome sequencing in previously healthy children [4]. X-linked hyper-IgM syndrome (XHIGM; HIGM1; OMIM:308230) is one type of primary immunodeficiency disease(PIDs), resulting from defects in the CD40 ligand/CD40 signaling pathways leading to impairment of immunoglobulin isotype switching in B cells. It was characterized by

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recurrent infections in association with markedly decreased serum IgG, IgA, and IgE levels but normal or elevated serum IgM levels [5]. We report a patient who developed a particularly severe community-acquired *P. aeruginosa* pneumonia-related septic shock, and late diagnosis of X-linked hyper IgM syndrome was made by genome sequencing. Pediatricians should evaluate immune status in aggressive cases of community-acquired *P. aeruginosa* infection.

Case presentation

A 15-year-old male patient with a 5-day history of fever and cough was admitted to the pediatric intensive care unit (PICU) due to worsening dyspnea and mental status over four hours. The patient had a positive history of recurrent respiratory tract infections, 1-2 times per year, while his siblings did not. The patient had never received prior immunosuppressive drugs and had no previous history of malignancy. He had no skin rashes and no tobacco or alcohol use. Parents were nonconsanguineous and healthy without a history of contagious disease or sick contacts. Five days before admission, the patient started having fever and cough self-treated by unknown oral medications without improvement. One day before admission, he felt chest pain and shortness of breath. Intravenous antibiotics medications were given. Four hours before admission, the patient deteriorated rapidly with chest tightness, dyspnea, and cyanosis. The patient sent to a local healthcare facility. The physical exam revealed the following: T 38.0 °C, BP 90/58 mmHg, HR 158 bpm, R 56 bpm, SpO2 89% with peripheral cyanosis and dyspnea. Chest computed tomography (CT) showed an infection site in the right lung. Facemask oxygen and fluid resuscitation were given, then the patient transferred to our PICU with drowsiness, hypotension, and dyspnea.

Physical exam on PICU admission was as follows: BP 90/35mmHg with intravenous infusion of norepinephrine of 0.2μg/kg/min, HR 160 bpm, RR 60 bpm, temperature 38.9°C, SpO2 89% with facemask oxygen. The Glasgow coma scale was 10/15. Normal habitus, unconsciousness, breathlessness, mottled skin without petechiae or necrosis, bilateral rough breath sounds without rales or rhonchi, flat abdomen with mildly increased tension, poor circulation with prolonged capillary filling time. Initial blood investigations revealed a decrease in white cell count of 0.4×10^9/l, neutropenia of 0.07×10^9/l, and elevated C-reactive protein levels (299.6mg/l). PCT was 21.75ng/ml. Arterial blood gas showed pH 7.28, PaCO2 4 mmHg, PaO2 87mmHg, lactate 7.1mmol/Land BE – 9.4mmol/L. Serum creatinine 106mmol/l (N 35.9-83.1mmol/l), serum urea12mmol/L (N 3-8), serum bilirubin26.2 mmol/l (N <17), serum aspartate aminotransferase 102IU/L (N <40), serum alanine aminotransferase 59 IU/L(N <49). The HIV test was normal. Cardiac ultrasound showed that the left ventricular ejection fraction (LVEF) was 55% and normal cardiac structure. Chest CT showed multiple nodular, patchy shadows and bronchiectasis in the bilateral lung, while abdominal and pelvic CT scans were unremarkable.

He was intubated immediately and mechanical ventilation started. According to early goal-directed therapy (EGDT), adequate fluid resuscitation and norepinephrine were given. Blood and sputum samples were collected at first and sent for microbiology tests. Second-generation sequencing of blood and sputum samples were sent at the same time. Then empiric antibiotics treatment with imipenem and linezolid initiated. Continuous renal replacement therapy (CRRT) started due to AKI state 2 and high lactate level. Based on hemodynamic monitoring, vasoactive agents and fluid resuscitation with volume and rate were adjusted. The patient was worsening rapidly with persistent hypotension. Numerous aggressive hemodynamic resuscitation attempts and symptomatic treatment could not stop the rapidly fatal pathological process. The patient died due to septic shock 11 hours after admission. Both blood and sputum cultures indicated growth of *P. aeruginosa*two days after admission (Table 1). Second-generation sequencing of blood and sputum samples also showed quantities of *P. aeruginosa*duplication (Table 2). The patient in our study started with cough companying with chest pain, chest tightness, dyspnea and fatigue. Chest CT showed multiple nodular, patchy shadows and bronchiectasis. Community-acquired Pseudomonas aeruginosa pneumonia-related septic shock confirmed. The rare invasive progress and the history of recurrent bronchitis since 6 months raised our suspicion of underlying immunodeficiencies. Genome sequencing was made and later identified a c.512A>C (p.q174R) mutation in the CD40LG gene, and the diagnosis of XHIGM ultimately confirmed. The parents' genetic tests were not done for economic reasons. Written informed consent was obtained to publish this

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case report and any accompanying images.

Discussion

Pseudomonas aeruginosa, (P. aeruginosa) is an aerobic Gram-negative bacterium commonly found in the environment and has strong virulence, producing various toxins, including exotoxins and enzymes[5]. This opportunistic pathogen is an important cause of nosocomial infections and community-acquired infections in immunocompromised patients and patients with structural lung disease, such as bronchiectasis and cystic fibrosis [1]. The typical patient presenting with nosocomial *P. aeruginosa*infection is mechanically ventilated, has slowly progressive lung infiltrates, and has been colonized for days [6]. Community-acquired *P. aeruginosa* infections are rare but have an acute onset, rapid progression, and lead to the development of short-term shock [7,8]. The patient in our study diagnosed severe community-acquired pneumonia (CAP) due to *P. aeruginosa* and also progressed to septic shock quickly.

In CAP, *P. aeruginosa* is rarely identified as the pathogenic agent, accounting for only 0.4–6.9% in reported cases of CAP requiring hospitalization and 1.8–8.3% of CAP requiring ICU admission[1]. In severe *P. aeruginosa* CAP (PCAP), mortality of those who developed progressive septic shock and MODS can reach as high as 50–100% [9,10]. The common manifestations of PCAP are fever, cough and chest pain, usually involving the right upper lobe. Ecthyma gangrenosum is also a known cutaneous manifestation. Compared to typical CAP, PCAPs are inclined to have respiratory failure and septic shock [11] and require different antibiotic therapy [12]. The 2007 American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA) guidelines recommended empirical treatment against P. aeruginosa in community-acquired pneumonia (CAP) patients with the following specific risk factors: 1) structural lung disease, like bronchi, 2) recurrent exacerbations of COPD requiring corticosteroid/antibiotic treatment, 3) antibiotic use before admission,4)immunocompromised status. Besides, *P. aeruginosa* infection should be considered in patients with severe rapidly progressive pneumonia [6].

The resistance of community-acquired *P. aeruginosa* isolates to many commonly used anti-pseudomonal antibiotics remains extremely low, unlike the extended resistance patterns often seen in nosocomial[13,14]. In most clinical situations, the treatment of choice for a β-lactam susceptible *P. aeruginosa* infection is β-lactam monotherapy except in the following cases: 1) during the first 72 hours if the infection presents criteria of severe sepsis or septic shock [1], 2) in the neutropenic patient[15], and 3) in central nervous system (meningitis, abscess) or endovascular (endocarditis) infections [16]. Combination therapy with appropriate anti-Pseudomonas agents must be instituted immediately on presentation (within one hour) to prevent the emergence of resistance and improve the prognosis of fulminant *P. aeruginosa* pneumonia [17-19]. For critically ill patients admitted to the ICU, guidelines recommend an antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus an antipseudomonal fluoroquinolone; or the above β-lactam plus an aminoglycoside and azithromycin; or the above β-lactam plus an aminoglycoside and a fluoroquinolone. Once *P. aeruginosa* is suspected or confirmed to be the pathogenic agent, the antibiotic regimen should be adjusted to be more targeted. An antipseudomonal β-lactam plus an aminoglycoside or a fluoroquinolone, with the alternative being an aminoglycoside plus a fluoroquinolone was recommended [20]. Carbapenems have been administered as a second-line empirical antibiotic agent for patients with persistent fever despite the first-line empirical antibiotic therapy until neutropenia recovery [15]. Despite severe pneumonia with shock, bronchiectasis and severe neutropenia, we ignored the possibility of *P. aeruginosa* infection.

Community-acquired *P. aeruginosa* may cause severe aggressive infections in healthy children. 25% of fatal cases found novel pathogenic variants in PID genes by exome/genome sequencing in previously healthy children[5]. PIDs refer to a heterogeneous group of over 130 disorders that result from defects in immune system development and/or function. It is characterized by diverse clinical manifestations, such as recurrent or prolonged serious infections, autoimmune/inflammatory disease, allergy, or malignancy. Community-acquired *P. aeruginosa* pneumonia-related septic shock was unusual in our patient's age group and later raised the suspicion of immunodeficiencies. The diagnosis of XHIGM was ultimately confirmed genetically for a c.512A>C (p.q174R) mutation in the CD40LG gene. Hyper-IgM (HIGM) syndrome (24.1%) is one

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of the main PIDs in China [21]. CD40L and CD40 mutations have been classified into combined T and B immunodeficiency. Patients with XHIGM usually develop symptoms by the first or second year of life. Only 20% of patients with XHIGM survive beyond 25 years of age[22]. Therapy for HIGM is monthly infusions of IVIG that reduce the frequency and severity of infections. However, IVIG did not prevent the development of sclerosing cholangitis or bronchiectasis[23]. In a previous report, 68% of XHIGM patients had neutropenia and 45% were chronic. If neutropenia is severe, it may respond to G-CSF [24]. The use of trimethoprim-sulfamethoxazole for prophylaxis of PJP may also be beneficial [25]. Bone marrow transplantation performed early in life may cure XHIGM [22]. Congenital disorders, such as immunodeficiencies and ciliary defects, were included[26].

Despite typical clinical manifestations or features, underlying PIDs may still be ignored. Late diagnoses or misdiagnosis are common. Reaching definitive pathogeny is vital for better management of any clinical case. Failure to diagnose underlying PIDs in a child may result in potentially devastating consequences for survivors, undiagnosed siblings, and their families. Genome sequencing, in particular high-throughput or exome sequencing, successfully diagnosed monogenic conditions in the pediatric population [5]. As the cost of genome sequencing is reduced, molecular diagnosis can be made earlier to offer definitive management [27].

In conclusion, *P. aeruginosa* is an uncommon but fatal causative pathogen for community-acquired infections. Empirical antibiotics treatment should cover *P. aeruginosa* in patients with rapidly progressive disorders. Fatal community-acquired *P. aeruginosa*infections in children, including previously healthy children, should be considered to search for underlying PIDs by exome/genome sequencing.

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