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CASE REPORT

Next-generation sequencing technology for the diagnosis of *Pneumocystis* pneumonia in an immunocompetent female: A case report

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Abstract

BACKGROUND

Pneumocystis pneumonia (PCP) is a serious fungal infection usually seen in patients with human immunodeficiency virus, and it is more frequently found and has a high fatality rate in immunocompromised people. Surprisingly, it rarely occurs in immunocompetent patients. However, the clinical diagnosis of this pathogen is made more difficult by the difficulty of obtaining accurate microbiological evidence with routine tests. This case reports a PCP patient with normal immune function who was diagnosed through next-generation sequencing (NGS).

CASE SUMMARY

A 23-year-old female who had no special disease in the past was admitted to the hospital with a persistent fever and cough. Based on the initial examination results, the patient was diagnosed with bipulmonary pneumonia, and empirical broad-spectrum antibiotic therapy was administered. However, due to the undetermined etiology, the patient's condition continued to worsen. She was transferred to the intensive care unit because of acute respiratory failure. After the diagnosis of *Pneumocystis jirovecii* infection through NGS in bronchoalveolar lavage fluid and treatment with trimethoprim/sulfamethoxazole and caspofungin, the patient gradually recovered and had a good prognosis.

CONCLUSION

This case emphasizes that, for patients with normal immune function the possibility of PCP infection, although rare, cannot be ignored. NGS plays an important role in the diagnosis of refractory interstitial pneumonia and acute respiratory failure.

Key Words: *Pneumocystis* pneumonia; *Pneumocystis jirovecii*; Next-generation sequencing; Immunocompetent; Trimethoprim/Sulfamethoxazole; Case report

Core Tip: Although *Pneumocystis* pneumonia (PCP) in immunocompetent patients is rare, it should be considered in infected patients with sudden onset of respiratory failure. However, using routine clinical examination, it can be challenging to differentiate between colonizing bacteria and subclinical infections. Instead of traditional laboratory techniques, next-generation sequencing (NGS) was used to make the diagnosis in the current case report. Early diagnosis and fast treatment helped to avoid ineffective treatments and improve the prognosis. This case emphasized that PCP can arise in immunocompetent patients, and NGS may be an effective test method for the quick and accurate diagnosis of PCP.

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INTRODUCTION

Pneumocystis pneumonia (PCP) is an opportunistic fungal infection caused by the invasion of the single-celled fungus *Pneumocystis jirovecii*, and it is more common in patients with human immunodeficiency virus (HIV) infection[1]. According to the most recent data, there are still over 500000 instances of PCP worldwide annually, with a death rate of up to 30%, although the incidence of HIV has decreased and can now be effectively prevented due to the deployment of highly active antiretroviral therapy[2,3]. Additionally, as the use of immunosuppressants has increased in recent years, PCP is more frequently found in patients with organ transplantation, malignant tumors, autoimmune diseases, and long-term corticosteroids, leading to an increase in nonHIV PCP immunocompromised individuals and eventually surpassing that of HIV patients[4]. Nonetheless, in the clinic, PCP without immunosuppression is incredibly rare[5]. In this case, a patient with a normal immune system developed severe pneumonia and acute progressive respiratory failure. Sputum cultures were negative many times, and treatment with conventional antibiotics was ineffective. Finally, PCP infection was detected in alveolar lavage fluid using next-generation sequencing (NGS) of bronchoalveolar lavage fluid (BALF). This case suggests that the possibility of PCP infection should not be ignored and the value of NGS in the diagnosis of refractory respiratory failure in patients with normal immune function and severe pneumonia.

CASE PRESENTATION

Chief complaints

A 23-year-old woman presented with a persistent fever (up to 40.5°C) accompanied by cough and sputum for a week.

History of present illness

The symptoms began 1 wk before the onset of the disease with recurrent fever due to cold with cough and sputum.

History of past illness

No particular disease was noted for the patient history.

Personal and family history

No personal or family history of infectious disease, genetic disease, or other particular disease was noted.

Physical examination

The vital signs were as follows: Body temperature, 38.0°C; blood pressure, 96/63 mmHg; heart rate, 130

beats per min; and respiratory rate, 20 breaths per min. No other positive signs except slightly coarse breath sounds as well as moist rales in both lower lungs were observed during auscultation.

Laboratory examinations

Laboratory tests showed that the main inflammatory parameters and (1-3)-β-D-glucan test (G test) level increased significantly (Table 1). Liver and kidney function, especially the lactate dehydrogenase (LDH) levels, deteriorated (Table 2). The results of the galactomannan test (GM test), purified protein derivative test, initial screening test for HIV antigens/antibodies and tests for other common respiratory pathogens, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, parainfluenza virus, Epstein□Barr virus, and influenza A and B, were negative. Based on the positive results of the G-test, increased inflammatory indicators, and elevated LDH levels, we preliminarily considered that the patient might have fungal infection. However, we could not determine the cause of respiratory failure and the specific source of infection with routine testing. Treatment with broad-spectrum antibiotics and ventilators could not prevent disease progression. To diagnose and save the patient more quickly and accurately, we conducted bronchoscopy examination and collected BALF specimens for NGS with the PMseq pathogen high-throughput sequencing platform MGISEQ-2000 for metagenomic sequencing of RNA pathogenic microorganisms at Complete Genomics (BGI, Shenzhen, China). With a sequencing depth of 31 M, BALF-NGS identified one fungus, *Pneumocystis jirovecii* (Table 3). The number of sequences was 12152.

Imaging examinations

Chest imaging suggested inflammatory infiltration in both lungs (Figures 1 and 2).

FINAL DIAGNOSIS

According to the patient's medical history, clinical characteristics, laboratory examinations and imaging results, we determined that *Pneumocystis jirovecii* was the causative pathogenic microorganism. The final diagnoses were bilateral interstitial pneumonia (*Pneumocystis* pneumonia), acute respiratory failure and multiple organ dysfunction syndrome.

TREATMENT

Based on the initial test results, cefoperazone sulbactam (2.0 g, q12 h, intravenous drip) together with voriconazole (200 mg, q12 h, intravenous drip) were given. After being transferred to the intensive care unit (ICU), the patient was tracheally intubated and underwent prone ventilation (AC mode, FIO_2 90%, PEEP 10 cm H_2O). Broad-spectrum antibiotic therapies were administered, including meropenem (1 g, q8 h, intravenous drip), vancomycin (0.5 g, q6 h, intravenous drip), voriconazole (200 mg, q12 h, intravenous drip), and oseltamivir phosphate (75 mg, q12 h, oral administration). When the etiology was identified as *Pneumocystis jirovecii*, the antifungal therapies were adjusted to trimethoprim/sulfamethoxazole (TMP/SMX, TMP 0.8 g/SMZ 0.4 g, q6 h, oral administration) and caspofungin intravenously (50 mg, qd, intravenous drip).

OUTCOME AND FOLLOW-UP

After 14 d of standard anti-PCP and respiratory support treatments, the patient's temperature returned to normal, and her respiratory condition improved significantly (SpO_2 over 98%, PaO_2/FIO_2 452 mmHg). She was removed from the ventilator successfully. With almost all laboratory indicators returning to normal, the patient was transferred to the general ward for further treatments. Chest computed tomography indicated the basic absorption of inflammation at discharge. Follow-up indicated a good prognosis for the patient.

DISCUSSION

PCP is a serious, potentially fatal opportunistic illness that frequently applies to patients with compromised immune systems[6], and the incidence of PCP infection in non-HIV patients has increased recently. However, PCP in people with normal immune function is rare and difficult to clearly diagnose by permanent routine methods. Thus, the first startling aspect of this case is that PCP can arise in immunocompetent patients. Second, for bilateral interstitial pneumonia and acute respiratory failure, for which the etiology is difficult to determine, NGS may be an effective test method for quick and

Table 1 Main inflammatory parameters

Item	Result on admission	Results at ICU	Reference range
WBC (× 10^9)	4.31	2.64	3.5-10
RBC (× 10^{12})	2.49	2.10	3.5-5.5
HGB (g/L)	84	69	114-163
NEUT (× 10^9)	3.65	2.42	1.8-6.3
%NEUT	84.8	91.7	40-75
MONO (× 10^9)	0.04	0.04	0.1-0.6
%MONO	0.9	1.5	3-10
LYMBP (× 10^9)	0.60	0.17	1.1-3.2
%LYMBP	13.9	6.4	20-50
PLT (× 10^9)	114	69	125-350
CRP (mg/L)	7.51	37.69	0-5
ESR (mm/h)	47	120	0-20
PCT (ng/mL)	0.75	> 100	0-0.046
IL-6 (pg/mL)	6.33	33.64	< 7
G test (pg/mL)	572.42		< 60

ICU: Intensive care unit; WBC: White blood cells; RBC: Red blood cells; HGB: Hemoglobin; NEUT: Neutrophils; MONO: Monocytes; LYMBP: Lymphocytes; PLT: Platelets; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; PCT: Procalcitonin; IL-6: Interleukin-6; G test: (1-3)-β-D-glucan test.

Table 2 Liver and renal function results

Item	Result on admission	Results at ICU	Reference range
TBIL (μmol/L)	12.8	64.9	3.6-20.5
TP (g/L)	65.3	46.3	65-85
ALB (g/L)	37.3	22.2	40-55
ALT (U/L)	42	61	9-50
AST (U/L)	37	39	15-40
sCrea (μmol/L)	76	307	57-97
Urea (mmol/L)	8.53	31.25	3.1-8
UA (μmol/L)	314	629	210-420
LDH(U/L)	852		94-250

Blood was collected for liver and renal function. ICU: Intensive care unit; TBIL: Total bilirubin; TP: Total protein; ALB: Serum albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; sCrea: Serum creatinine; UA: Uric acid; LDH: Lactate dehydrogenase.

Table 3 Next-generation sequencing gene detection of bronchoalveolar lavage fluid

Genus	Number of sequences	Species	Number of sequences
Pneumocystis	12297	*Pneumocystis jirovecii*	12152

accurate diagnosis such that patients can receive appropriate treatments.

PCP is rarely found in immunocompetent patients, and the clinical manifestations of PCP in HIV and non-HIV patients are similar but different. First, most PCP patients experience fever, followed by chest tightness, shortness of breath, a dry cough, and less sputum as their chief complaints. As the disease progresses, hypoxia gradually worsens and eventually leads to progressive dyspnea; however, the

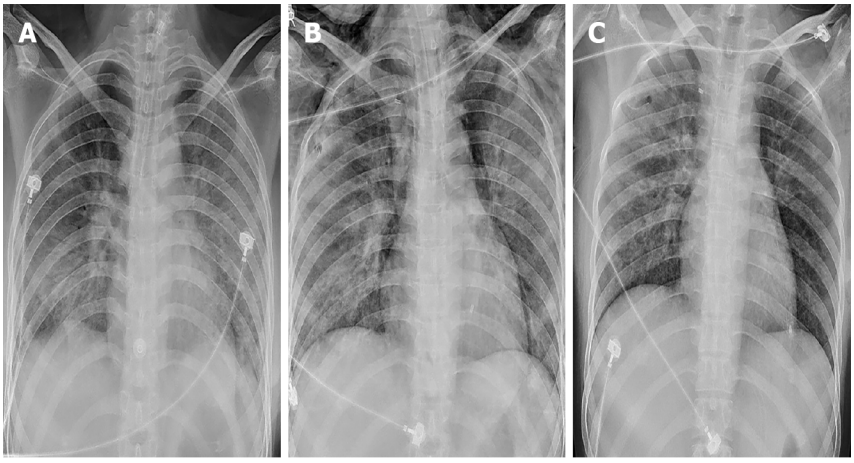

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Figure 1 Chest X-ray of patient. A: Chest X-ray findings on admission, increased texture in both lungs and hyperdense shadows in both lungs with an unclear border; B: Chest radiograph results at intensive care unit, bilateral lung exudation increased compared with the previous one, complicated by pneumothorax; C: Chest X-ray images at discharge. The exudate was partially absorbed in both lungs.

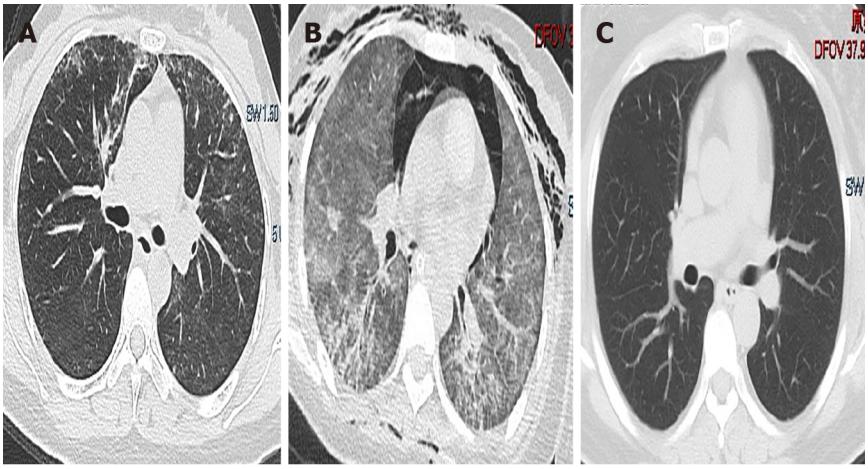

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Figure 2 Chest computed tomography scans of patient. A: Computed tomography (CT) images on admission, diffuse stripes and cords in both lungs with increased density and fuzzy edges; B: CT results in the intensive care unit, consolidation, aerothorax and ground-glass opacities in both lungs; C: CT findings at discharge, the marked resolution of ground-glass opacities and consolidation.

pulmonary signs frequently do not correspond to the severity of symptoms[7]. PCP primarily has a subacute course in HIV-positive patients, whereas in non-HIV-positive patients the symptoms quickly progress to respiratory failure[8]. In this case, a PCP patient without HIV infection also experienced high fever, cough, shortness of breath, interstitial pneumonia, and rapid progression of respiratory failure. Second, in addition to differences in clinical manifestations, the severity of the disease and the proportion of patients who even need endotracheal intubation and mechanical ventilation between HIV and non-HIV PCP patients are different. In one cohort study, approximately 41% of patients with PCP needed to be admitted to the ICU, among whom 36% needed mechanical breathing[9]. With a mortality rate of 53% in non-HIV patients compared with 15% in HIV patients, 28% in HIV patients requiring invasive mechanical ventilation, and up to 60% in non-HIV invasive mechanical ventilation patients[10, 11]. In general, HIV patients are admitted to the ICU less frequently than non-HIV patients. In addition to the rapidly progressing bilateral interstitial pneumonia, the acute exacerbation of respiratory failure was the main reason for the patient being transferred to the ICU in our case. Anti-PCP therapy and respiratory support therapy (tracheal intubation and prone ventilation) were the main effective treatments for this patient.

Except for the difference in clinical manifestations, it is challenging to make an early diagnosis of non-HIV PCP patients[12,13]. The gold standard for diagnosing PCP often uses microscopy for the detection of *Pneumocystis jirovecii* cysts or trophozoites in BALF by special staining and immunofluorescence methods. Because *Pneumocystis jirovecii* cannot be cultivated in vitro, BALF is particularly recommended clinically[14]. However, the sensitivity of special staining and immunofluorescence staining is not high,

at approximately 50%, which is lower than that of the polymerase chain reaction (PCR) method. PCR is a simple and fast method for the clinical detection of *Pneumocystis jirovecii* in BALF and sputum specimens. However, due to its high sensitivity of 98%, it cannot easily differentiate between colonization and subclinical infection, leading to a limited number of true-positive results[15]. G test, which is a part of many fungal walls, is highly sensitive for the diagnosis of HIV PCP patients, but the specificity is not high in nonHIV PCP patients. Other invasive fungal infections, such as *Candida*, *Aspergillus pneumoneum*, and *Fusarium* infection, also present G test positivity. In our case, because the patient had no history of immune deficiency, a positive G test was more likely to be considered a common fungal infection rather than PCP infection. PCP diagnosis using traditional assays is still exceedingly difficult.

With the rapid advancement of molecular detection technology in recent years, BALF-NGS has emerged as a new diagnostic technique that is used in clinical settings for its high sensitivity and specificity (97.4% and 85.12%, respectively), particularly for the detection of special pathogen infections and mixed infections in immunosuppressed and immunocompetent patients[16]. It has the important advantages of being quicker, more accurate, and safer. Additionally, NGS was demonstrated to be significantly more sensitive than immunofluorescence staining (25%) and the G test (67.4%) in a retrospective study. It is important to note that the two were consistent in detecting *Pneumocystis jirovecii* when NGS was conducted separately using BALF and blood samples from the same patient[17]. In this case, the patient developed bilateral interstitial pneumonia and rapidly aggravated respiratory failure. In addition to a positive G test, increased inflammatory indicators and elevated levels of LDH, we did not obtain more effective laboratory positive test results. The pathogen causing pulmonary infection and respiratory failure has not been found, resulting in poor effects of antibiotics and respiratory support treatments. The results identified one fungus, *Pneumocystis jirovecii*, which was confirmed to be the pathogenic microorganism. After been diagnosed of PCP and given anti-PCP treatment, the patient recovered and had a good prognosis. No pneumocystis-specific analysis was performed for our case, which might be a limitation.

The standard suggested dose of meperidine 15-20 mg/kg/d and sulfamethoxazole 75-100 mg/kg/d given in 4 separate doses for 21 d is now the first-line treatment for PCP in all populations[18]. NonHIV PCP patients still experience high mortality rates and a high frequency of adverse events, such as rash, fever, gastrointestinal discomfort, leukopenia, hepatotoxicity, and renal insufficiency[19]. To remedy these problems, various complementary and alternative therapies are urgently needed. Caspofungin has received much attention as a novel class of echinocandin antifungal medication because it inhibits the synthesis of G test, which affects the creation of *Pneumocystis jirovecii* cell wall and ultimately causes *Pneumocystis jirovecii* death[20]. Despite the lack of prospective research, certain case reports have shown caspofungin's significant efficacy when used either alone or in conjunction with other treatments, and it can be used to treat PCP[21]. In this case, although the patient had no history of HIV infection, immune deficiency, hormone use or other diseases, we immediately administered standard anti-PCP treatment after the diagnosis of PCP through BALF-NGS. The patient's renal function and urinalysis were both normal at the time of admission, but with the aggravation of the disease, the patient's organ function, especially renal function, became abnormal. Considering the abnormality of renal function, in addition to the first-line treatment (TMP/SMX), we also used caspofungin as one of the anti-PCP treatments that has little impact on organ function, as reported in the literature[22]. Diseases of the immune system are a prominent factor in PCP.

In the past, studies have suggested corticosteroids as an adjuvant medication in addition to antibiotics. Research has revealed that corticosteroids dramatically lower mortality in HIV PCP patients [23]. However, it is debatable whether to treat nonHIV PCP with corticosteroids because the majority of patients are already taking them prior to the onset of pneumonia and because prolonged use of corticosteroids can cause immune deficiency, which is a significant contributing factor to non-HIV patients' susceptibility to PCP. Currently, the recommended course of treatment is a combination of corticosteroids and immunosuppressants based on supportive therapy. However, this course of treatment will also cause varying degrees of damage to the immune system, greatly increasing the risk of infection by pathogens such as fungi and bacteria. Therefore, corticosteroids and immunosuppressants were not administered in our case. Instead, supportive care was used to slow the progression of the disease.

CONCLUSION

In conclusion, we observed nonHIV PCP in individuals evaluated for the lack of underlying risk factors, which are rare and sometimes overlooked. Early application of NGS can help to quickly identify pathogens and buy time for patients who have sudden respiratory failure or a particular, atypical suspected infection. NGS is important in the identification of clinical infectious diseases.

FOOTNOTES

Author contributions: Huang JJ and Wu J contributed to manuscript writing; Zhang SS and Liu ML contributed to collection of clinical data; Yang EY and Pan Y contributed to data analysis and production of charts; all authors have read and approved the final manuscript.

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