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ABOUT COVER

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CASE REPORT

Pneumocystis jirovecii diagnosed by next-generation sequencing of bronchoscopic alveolar lavage fluid: A case report and review of literature

Qing-Wei Cheng, Hong-Li Shen, Zhi-Hui Dong, Qian-Qian Zhang, Ya-Fen Wang, Jin Yan, Yu-Sheng Wang, Ning-Gang Zhang

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Abstract

BACKGROUND

The advent of molecular targeted agents and immune checkpoint inhibitors has greatly improved the treatment of advanced renal cell carcinoma (RCC), thus significantly improving patient survival. The incidence of rare drug-related adverse events has gained increased attention.

CASE SUMMARY

We report a patient with advanced RCC treated with multiple lines of molecular targeted agents and immune checkpoint inhibitors, who developed a pulmonary infection after treatment with everolimus in combination with lenvatinib. Determining the pathogenic organism was difficult, but it was eventually identified as *Pneumocystis jirovecii* by next-generation sequencing (NGS) of bronchoscopic alveolar lavage fluid (BALF) and successfully treated with trimethoprim-sulfamethoxazole.

CONCLUSION

Rare pulmonary infections caused by molecular targeted agents are not uncommon in clinical practice, but their diagnosis is difficult. Evaluating BALF with NGS is a good method for rapid diagnosis of such infections.

Key Words: Renal cell carcinoma; Everolimus; Pneumocystis jirovecii pneumonia; Next-generation sequencing; Bronchoscopic alveolar lavage fluid; Case report

Core Tip: The application of molecular targeted agents and immune checkpoint inhibitors have greatly improved the prognosis of advanced renal cell carcinoma (RCC). We report a patient with advanced RCC treated with multiple lines of molecular targeted agents, who developed a *Pneumocystis jirovecii* pneumonia after treatment with everolimus in combination with lenvatinib. The pathogenic organism was identified by next-generation sequencing (NGS) of bronchoscopic alveolar lavage fluid (BALF) and successfully treated with trimethoprim-sulfamethoxazole. Evaluating BALF with NGS technology might be used to detect pathogens and determine the correct treatment plan for patients with rare infections caused by the use of molecular targeted agents.

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INTRODUCTION

Renal cell carcinoma (RCC) is a malignant tumor originating from the renal tubular epithelium and accounts for 80% to 90% of renal malignancies[1]. According to GLOBOCAN 2020 global cancer statistics, RCC was the 14th most prevalent and the 15th most deadly malignancy[2]. Radical surgical resection is the mainstay treatment for localized renal cancer, while a combination of systemic drugs is preferred for advanced renal cancer. Sorafenib was first approved for the treatment of metastatic renal cancer in 2005[3], followed by the approval of targeted drugs such as pegaptanib, sunitinib, axitinib, sorafenib, and everolimus[4-7]; while immune checkpoint inhibitors such as navulizumab, pablizumab, and ipilimumab have also been licensed for use[8-10]. The combination of various molecular targeted drugs and immune checkpoint inhibitors has resulted in a rise in rare adverse effects.

Herein, we report a case of RCC that progressed after multiple lines of therapy and improved with the mammalian target of rapamycin (mTOR) inhibitor, everolimus in combination with lenvatinib; however, the patient complained of a dry cough that developed into a lung infection. Due to difficulty in identifying the infection, empirical anti-bacterial treatment was initially administered, with unsatisfactory results. Eventually, this rare case of *Pneumocystis jirovecii* infection was confirmed using next-generation sequencing (NGS) of bronchoscopic alveolar lavage fluid (BALF), and the infection improved after appropriate treatment.

CASE PRESENTATION

Chief complaints

A 61-year-old man diagnosed with RCC for nearly 3 years presented to our department because of a dry cough with occasional expectoration on February 22, 2022.

History of present illness

The patient was admitted to our hospital with "hematuria for 7 d" on August 5, 2019. A computed tomography (CT) scan on admission revealed right kidney and right renal pelvis occupancy, suggestive of malignancy. In addition, multiple nodules in both lungs were seen, and metastasis was suspected. A timeline of the episode of treatment is shown in Figure 1. After consultation and discussion, the patient agreed to undergo a laparoscopic radical right nephrectomy. Postoperative pathology revealed clear cell RCC of the right kidney. Following surgery, he was treated with oral sunitinib. A follow-up CT scan after 9 mo revealed metastases in the right adrenal gland, and axitinib was given to the patient. Three months later, CT imaging found that the metastases in the right adrenal gland and both lungs were significantly larger than before. He was thus treated with nine cycles of the immune checkpoint inhibitor sintilimab. However, a subsequent CT scan showed that the right adrenal metastasis was slightly enlarged, with multiple metastases appearing in the abdominal cavity, while the size of the lung

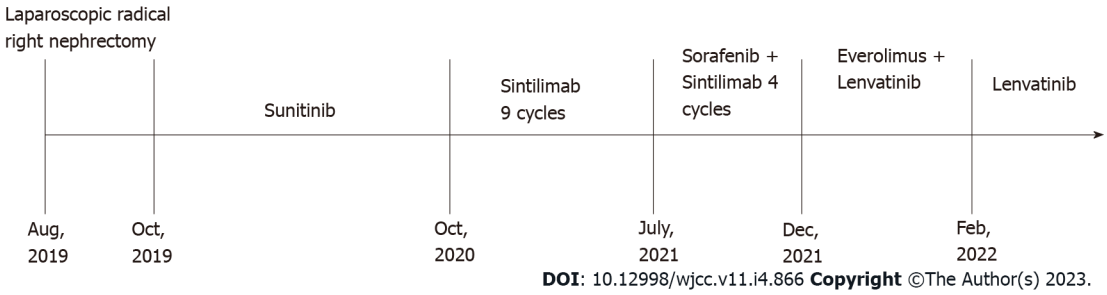

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Figure 1 Patient treatment timeline.

metastases was unchanged. On July 19, 2021, four cycles of sorafenib in combination with sintilimab were administered. CT scanning revealed that the lung and abdominal cavity metastases were slightly larger than before, and new subcapsular metastases were detected on the right lobe of the liver. On December 14, 2021, he was switched to everolimus 10 mg once daily in combination with lenvatinib 8 mg once daily. However, on February 22, 2022, the patient developed a dry cough with occasional and little sputum, accompanied by mild dyspnea after activity. No fever or other discomfort was observed.

History of past illness

The patient had no past illness.

Personal and family history

The patient had no specific personal and family history.

Physical examination

On physical examination, the patient's basic vital signs were within normal limits, and his respiratory sounds were rough on both lungs, without dry or wet rales.

Laboratory examinations

The initial blood investigations revealed the following: Leukocytes 5.17 × 10^9/L (reference range: 4.0-11.0), hemoglobin 121.0 g/L, platelet count 400 × 10^9/L, lymphocytes 15.9%, monocytes 6.8%, neutrophils 76.3%, eosinophils 0.6%, basophils 0.4%, high sensitivity C-reactive protein 37.0 mg/L (reference range: 0-5 mg/L), and procalcitonin 0.07 ng/mL (normal value < 0.052 ng/mL). Liver and kidney functions were normal, and sputum culture revealed normal oral flora.

Imaging examinations

CT scan on February 23, 2022 (Figure 2A) identified multiple patches and ground glass shadows in both lungs and scattered soft tissue nodules of different sizes in both lungs, suggestive of a pulmonary infection. The lung and peritoneal metastases were slightly smaller in size. The infection was treated with cefuroxime sodium, piperacillin sulbactam, and moxifloxacin injections, but the patient's condition did not improve, and he still had a persistent dry cough. Another CT scan on the March 21, 2022 (Figure 2B) showed little to no resolution of the lung infection.

FINAL DIAGNOSIS

A bronchoscopy lavage fluid NGS test was performed on March 25, 2022. The patient underwent bronchoscopy, and the fiberoptic bronchoscope reached the trachea and bronchi of both lungs. Irrigation with sterile saline was performed repeatedly in the left lower lobe bronchus and right lower lobe bronchus. The collected samples were then sent to the laboratory for NGS testing and analysis, which revealed *Pneumocystis jirovecii* infection.

TREATMENT

Two cotrimoxazole tablets (sulfamethoxazole 0.4 g, trimethoprim 80 mg/tablet) were given every 6 h and 40 mg methylprednisolone succinate was given twice a day for 5 d, followed by 40 mg once daily for 5 d.

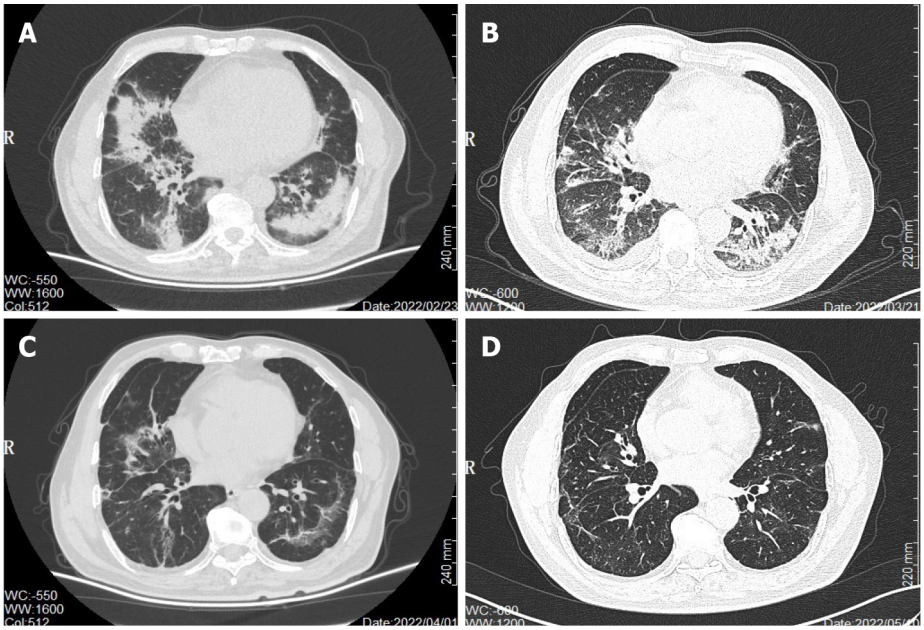

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Figure 2 Chronological computed tomography of the chest demonstrating changes in the lungs. A: Multiple patches and ground glass shadows in both lungs and scattered soft tissue nodules of different sizes in both lungs in February 2022; B: There was no significant change in pulmonary inflammation after empirical anti-infective treatment in March 2022; C: Pulmonary infection was significantly improved and resolved in both lungs in April 2022; D: Pulmonary infection almost completely disappeared in May 2022.

OUTCOME AND FOLLOW-UP

Following treatment, the patient's cough disappeared. Cotrimoxazole tablets were continued for 3 wk, and the repeat CT on April 1, 2022 (Figure 2C) and May 10, 2022 (Figure 2D) showed significant improvement and resolution in both lungs. There were no treatment-related adverse effects. At present, the patient is well and has not complained of symptoms such as cough and dyspnea.

DISCUSSION

Kidney cancer is the third most prevalent urogenital tumor in China, accounting for 2%-3% of adult malignant tumors, and its incidence is increasing annually[11]. Targeted therapy is the primary treatment strategy for advanced renal cancer. According to their targets, these drugs can be divided into two main categories: Vascular endothelial growth factor (VEGF)/VEGF receptor inhibitors and mTOR inhibitors. VEGF, a major factor in the angiogenesis process in RCC, is a primary target of anti-angiogenic treatments[12,13]. Additionally, mTOR, which is positioned downstream of phosphoinositide 3-kinase and protein kinase B and is regulated by phosphatase and tensin homolog, is heavily involved in RCC development[14]. Inhibition of the mTOR pathway can inhibit both angiogenesis and tumor cell proliferation. Everolimus, an mTOR inhibitor, has been found to improve survival in metastatic RCC patients after TKI-targeted drug therapy failure[15,16].

Everolimus is not only approved for use in advanced RCC but also for the treatment of advanced breast cancer[17], pancreatic neuroendocrine tumor[18], subependymal giant cell astrocytoma associated with tuberous sclerosis[19], and other tumors. It can also prevent immunological rejection after kidney, liver, or heart transplantation[20]. The adverse reactions of everolimus mainly affect the digestive system, respiratory system, endocrine system, and skin mucosa[21,22], with interstitial lung disease (ILD) being the most common pulmonary associated toxicity[23-25]. The incidence of non-infectious pneumonia of metastatic RCC treated with everolimus can reach up to 14%[16]. Following everolimus administration, our patient developed a dry cough, with the CT scan revealing a pulmonary infection. Repeated sputum culture and sputum smear showed no clear evidence of microbial infection. After empirical anti-bacterial treatment, the therapeutic outcome was poor. We thus suspected an uncommon bacterial or fungal infection, but identifying the pathogen was challenging. Therefore, we resorted to BALF NGS testing and revealed that *Pneumocystis jirovecii* was the cause of the infection. Prior to the lung infection, the patient had been treated with many lines of targeted treatments and immune checkpoint inhibitors, and his immune function was compromised. Following treatment with everolimus in combination with lenvatinib, he acquired a rare *Pneumocystis jirovecii* infection. Given that lenvatinib is a multi-targeted anti-angiogenic agent, its common adverse effects include hypertension,

fatigue, diarrhea, palmoplantar erythroderma syndrome, proteinuria and hemorrhagic events, while everolimus is immune-suppressive, making patients susceptible to opportunistic pulmonary infections [26]. Loron *et al*[27] found that the use of everolimus in patients with advanced RCC can lead to rare pathogenic infections, including *Pneumocystis jirovecii* infections. As a result, we speculate that the *Pneumocystis jirovecii* infection in this patient was associated with the use of everolimus.

Pneumocystis jirovecii can accumulate on the surface of the respiratory tract of healthy humans and can proliferate when the immune system is weakened, leading to opportunistic infections[28]. In the 1980s, with the emergence of the human immunodeficiency virus (HIV), *Pneumocystis jirovecii* pneumonia (PJP) became more prevalent in HIV patients[29]. With the increased use of immunosuppressive drugs, the incidence of PJP has gradually increased in non-HIV-infected patients, especially in those with malignant tumors who are treated with immunosuppressants[30,31]. The early stage of infection in non-HIV-infected patients is characterized by a repeated low-grade fever and dry cough without characteristic symptoms, and the disease can advance rapidly to fever and respiratory failure. The mortality rate of non-HIV patients with PJP is 30% to 50%, higher than that of HIV patients[32].

The clinical features of PJP are not specific, and the diagnosis mainly depends on the detection of pathogens. Normal or reduced white blood cells are often seen while serum lactate dehydrogenase and blood fungal (1-3)-β-d-glucan are elevated, and the G test is positive; however, these markers have limited specificity and clinical translational value[33]. X-ray and CT chest examinations lack specificity in the early stage of infection, while after disease progression, CT imaging usually shows diffuse, bilateral pulmonary "ground glass" interstitial infiltrates, which may also appear as pulmonary nodules. Nonetheless, these imaging changes are not specific, especially as they are identical to the presentation of ILD in everolimus-induced interstitial pneumonia, which can easily lead to misdiagnosis [34]. Unlike bacterial and other fungal infections, most non-HIV individuals have a low PJP load, and standard smear microscopy has a low sensitivity; thus, early PJP diagnosis is difficult. Microscopic inspection is commonly utilized to confirm PJP, and clinical specimens typically employed include induced sputum, bronchoalveolar lavage fluid, and lung tissue biopsy, but induced sputum culture has a low positive rate, and lung tissue biopsy is traumatic and difficult to carry out clinically. The BALF technique allows targeted sampling of the lower respiratory tract with a diagnostic positivity rate of 90% to 99% compared to sputum analysis[35]. Polymerase chain reaction (PCR) of alveolar lavage fluid samples is a reliable method for diagnosing PJP, with some studies indicating that PCR has a sensitivity of ≥ 97% and a negative predictive value of ≥ 99%[36]. If the BALF PCR test is negative, PJP can be ruled out, while a positive PCR makes distinguishing between colonization and active infection difficult[37].

Traditional diagnostic methods, such as smear microscopy and induced sputum culture, have a low positive rate for the diagnosis of *Pneumocystis jirovecii* infection. Lung tissue biopsy is a traumatic examination. BALF test has a higher positive rate. As a new detection method independent of microbial culture, NGS is a second-generation gene sequencing technology with the advantages of high throughput, wide coverage and high accuracy[38,39]. NGS can directly detect the nucleic acid sequence of pathogenic bacteria in the samples and determine their type and proportion[40]. It can be used for the detection of not only a variety of pathogens, such as bacteria, fungi, viruses, and parasites, but also a variety of specimens, such as sputum, blood, cerebrospinal fluid, alveolar lavage fluid, and tissue. Compared with the traditional culture method, NGS has higher detection rate and higher negative predictive value. At present, NGS has been successfully used to diagnose and treat difficult and critical infectious diseases, identify unknown pathogens, monitor drug-resistant genes, carry out epidemiological follow-up investigations, *etc*[41,42]. While identifying rare pathogens (*e.g.*, *Legionella pneumophila*, *Corynebacterium striatum*, *Listeria spp.*, *Pneumocystis jirovecii*, *cryptococcus*, *Chlamydia pinioticus*) is challenging clinically, NGS detection of alveolar lavage fluid can offer a rapid diagnosis and determine a correct anti-infection treatment. Notably, NGS of BALF is more sensitive and specific than the traditional approaches in diagnosing HIV-negative PJP[43]. However, NGS still faces many problems with a widespread application. Diagnosis by NGS testing needs to be combined with host factors, and chest CT findings. NGS pathogen test can only identify the pathogen, but cannot detect antimicrobial susceptibility. In addition, the current research on NGS testing of atypical respiratory pathogens is mostly in the form of case reports and clinical studies with a small sample size. Further clinical studies with a larger sample size are required to compare its sensitivity and specificity with traditional detection methods.

Trimethoprim-sulfamethoxazole (TMP/SMZ) is the preferred drug for the treatment of PJP, and it is emphasized that early and adequate dosage yields the best outcome[44], and the standard course to treat PJP is 3 wk[45]. The main side effects of TMP/SMZ include skin rash, drug fever, leukopenia, renal dysfunction, electrolyte disorder, and hepatotoxicity. Patients with renal insufficiency should lower their TMP dosage according to the creatinine clearance rate. For some patients with ineffective TMP/SMZ treatment or intolerable side effects, in recent years, caspofungin combined with low-dose TMP/SMZ has been used in patients with PJP infection following organ transplant. These two drugs have a synergistic effect, achieving satisfactory efficacy and a low incidence of adverse reactions[44,46].

CONCLUSION

With the widespread use of anti-tumor immunosuppressants, the risks of lung infection with atypical bacteria or fungi in cancer patients have increased, and existing traditional diagnostic procedures make such infections difficult to diagnose. Therefore, in the event that tumor patients experience lung infection after anti-tumor treatment and the effect of conventional diagnosis and treatment are unsatisfactory, evaluating BALF with NGS technology can be used to detect pathogens and determine the correct treatment plan for such patients. Collectively, we believe that this approach is promising in the early diagnosis of such infections and deserves more clinical attention.

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FOOTNOTES

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