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CASE REPORT

Rare Co-Infection of the Lungs with EBV and Pneumocystis Carinii in a Patient with Kidney Cancer: a Case Report

Jing X. Liu, Qin Zhang, Jing S. Bai, Ai S. Fu, Rong X. Liu, Jing M. Wang, Xin Y. Zhou, Shan Gao, Qian C. Chen, Jia B. Zhang, Yan L. Ge

Department of Respiratory Medicine, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei, China

SUMMARY

Background: **Epstein-Barr virus (EBV) is the primary agent of infectious mononucleosis, lymphoma, and nasopharyngeal carcinoma, but rarely involves the lungs. Pneumocystis carinii is commonly found in patients with HIV infection and is not pathogenic when the host is healthy, but opportunistic infections can occur when the body is immunocompromised, causing pneumocystis pneumonia (PCP). It is rare for both diseases to occur in the lungs of the same patient.**
Methods: **Next-generation sequencing (NGS), laboratory examination, chest CT scan, electronic bronchoscopy, and pathogenetic examination were used in this study.**
Results: **Laboratory tests showed (1-3)-β-D-glucan of 889.47 pg/mL, negative human immunodeficiency virus (HIV) antibody, and negative Aspergillus immunological test. Chest CT showed multiple high-density shadows in both lungs, and EBV infection combined with Pneumocystis carinii pneumonia was confirmed by bronchoscopic biopsy and NGS examination.**
Conclusions: **Elevated serum (1-3)-β-D-glucan is not a specific index for infectious diseases. Bronchoscopy and the NGS has high specificity in pathogen detection of infectious diseases.**
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Correspondence:
Yan L. Ge
North China University of Science and Technology Affiliated Hospital
Tangshan, Hebei
China
Phone: +86 15932081296
Email: 495732196@qq.com

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KEYWORDS

Epstein-Barr virus, Pneumocystis carinii, bronchoscopy, NGS, renal cancer

CASE REPORT

Epstein-Barr Virus (EBV) is one of the herpes viruses that is responsible for causing infectious mononucleosis, lymphomas, and carcinomas primarily in immunocompromised individuals. EBV-induced pneumonia is a very rare disease, and in this new era of viral pneumonia, EBV-induced pneumonia should be considered in the differential diagnosis when dealing with lung infections [1]. Pneumocystis carinii is a fungus that resides on the alveolar surface of normal human lungs and is not pathogenic when the host is healthy, but opportunistic infections occur when the body is immunocompromised, causing pneumocystis pneumonia (PCP), which is commonly seen in patients with HIV infection. In re-

cent years, with the use of immunosuppressive drugs, the incidence of Pneumocystis carinii pneumonia in HIV-negative patients has been on the rise [2]. The imaging manifestations of these two diseases are diverse and do not usually overlap, making them difficult to differentiate from other diseases. The presence of both pathogenic infections in the lungs of a single patient is rare, making a definitive diagnosis more difficult.

A 47-year-old male kidney cancer patient came to the hospital mainly because of fever and dyspnea. The patient had a maximum temperature of 39℃ with no obvious symptoms of cough and sputum. He had a history of kidney cancer and had undergone left nephrectomy and postoperative radiation therapy, and was currently on targeted drug maintenance therapy. Physical examination showed coarse breath sounds in both lungs, audible dry rales, left renal agenesis, and no abnormalities in other organs. He then underwent appropriate laboratory tests. Laboratory tests showed (1-3)-β-D-glucan of 889.47 pg/mL (reference values 0 pg/mL to 60 pg/mL), calcitoninogen of 0.25 ng/mL (reference values 0 ng/mL to 0.05 ng/mL), erythrocyte sedimentation rate of 35 mm/h (reference values 0 mm/h to 15 mm/h), normal white blood cells, negative tumor series, and negative HIV antibody. A CT scan of the chest showed multiple lamellar hyperdense shadows in the right lung and nodular hyperdense shadows in the upper lobe of the left lung, which were considered to be inflammatory lesions (Figure 1A). We gave anti-inflammatory treatment, and the patient's febrile symptoms did not improve significantly, so we decided to perform bronchoscopy as well as send the lesion site for NGS examination to further clarify the presence of specific pathogenic special infection. Bronchoscopy showed grayish-black tissue covering the upper lobe of the right lung, and the rest of the bronchi were normal (Figure 1B, 1C). We performed a transmural lung biopsy in the posterior segment of the right upper lobe as well as bronchoalveolar lavage. The biopsy tissue was sent for pathological examination and the lavage fluid was sent for NGS examination. The posterior pathology results suggested nests of anisocytic cells in the lung tissue (Figure 1D, 1E) and immunohistochemical results supported clear cell renal cell carcinoma metastasis. ck(+), cd68(+), pax8(-), caix(+), vimentin(+). The NGS result of the lavage fluid suggested Pneumocystis carinii (+) with sequence number 26,291, which was a Pneumocystis pneumonia infection. So, we gave compound sulfamethoxazole tablets as antifungal treatment, as well as prednisone to suppress the inflammatory response. After treatment, a review of the chest CT showed that the nodular high-density shadow in the upper lobe of the left lung disappeared, and the blade-like high-density shadow in the right lung was smaller than before (Figure 1F). The patient's fever and dyspnea symptoms were now better and his temperature was under control. Due to the gradual improvement of the patient's symptoms, we decided to reduce the patient's hormone dosage, but during the patient's application of hormone dosage reduction, fever reappeared and the temperature was as high as 39.5℃. Due to the patient's long history of fever, we performed a systematic examination of the patient. Laboratory findings were normal white blood cells, procalcitonin was < 0.05 ng/mL (reference values are 0 ng/mL to 0.05 ng/mL), Aspergillus immunological test (-), Cryptococcus antigen (-), Mycobacterium tuberculosis-specific cellular immune response (-), syphilis spiral antibody test (-), human immunodeficiency virus antibody test (-), and the patient's pituitary CT suggested no significant abnormal changes (Figure 1G), and abdominal CT suggested a lack of the left kidney, and no obvious infectious lesions were found (Figure 1H). However, the patient always had febrile symptoms, and we wanted to perform bronchoscopy on the patient again, but the patient refused bronchoscopy due to his condition. So, we performed a respiratory pathogenic NGS test on the patient, and the results suggested human herpesvirus type 4 (+) with sequence number 13,237, which was EBV infection. So far, the diagnosis was clear, and the patient had a dual infection of EBV and Pneumocystis carinii, so we treated the patient with dual antiviral and antifungal treatment. After treatment, the patient's fever disappeared and did not recur, and the chest CT showed a significant improvement of high-density shadow (Figure 1I), and his condition was significantly improved.

DISCUSSION

Epstein-Barr virus (EBV) is a herpes virus that causes infectious mononucleosis, lymphoma, and cancer primarily in immunodeficient individuals. Pulmonary involvement in EBV infection is rare, and pulmonary manifestations associated with EBV infection are more commonly described as lymphadenopathy (usually hilar and mediastinal lymphadenopathy), pleural effusion, and interstitial pneumonia [3,4]. Pneumocystis carinii is a yeast-like fungus usually present in HIV-infected patients causing respiratory infections and the resulting opportunistic infection known as Pneumocystis carinii pneumonia (PCP), but Pneumocystis carinii infection may also occur in cancer patients on immunosuppression and this opportunistic infection can present rapidly with respiratory distress and a high morbidity and mortality rate [5-7]. These two pathogens belong to two systems, one belonging to a viral infection and the other to a fungal infection. These two pathogens are rarely present in the same patient, leading to a dual infection with different pathogens. It is clinically difficult to screen for both pathogens and is highly susceptible to misdiagnosis, making clinical diagnosis difficult. We report a new case of co-infection with two pathogens, EBV and Pneumocystis carinii, and highlight the clinical and diagnostic challenges of these treatable diseases. The clinical and imaging manifestations of both diseases are nonspecific, and the imaging manifestations may sometimes show overlapping infections, making them highly susceptible to clinical misdiagnosis [8,9].

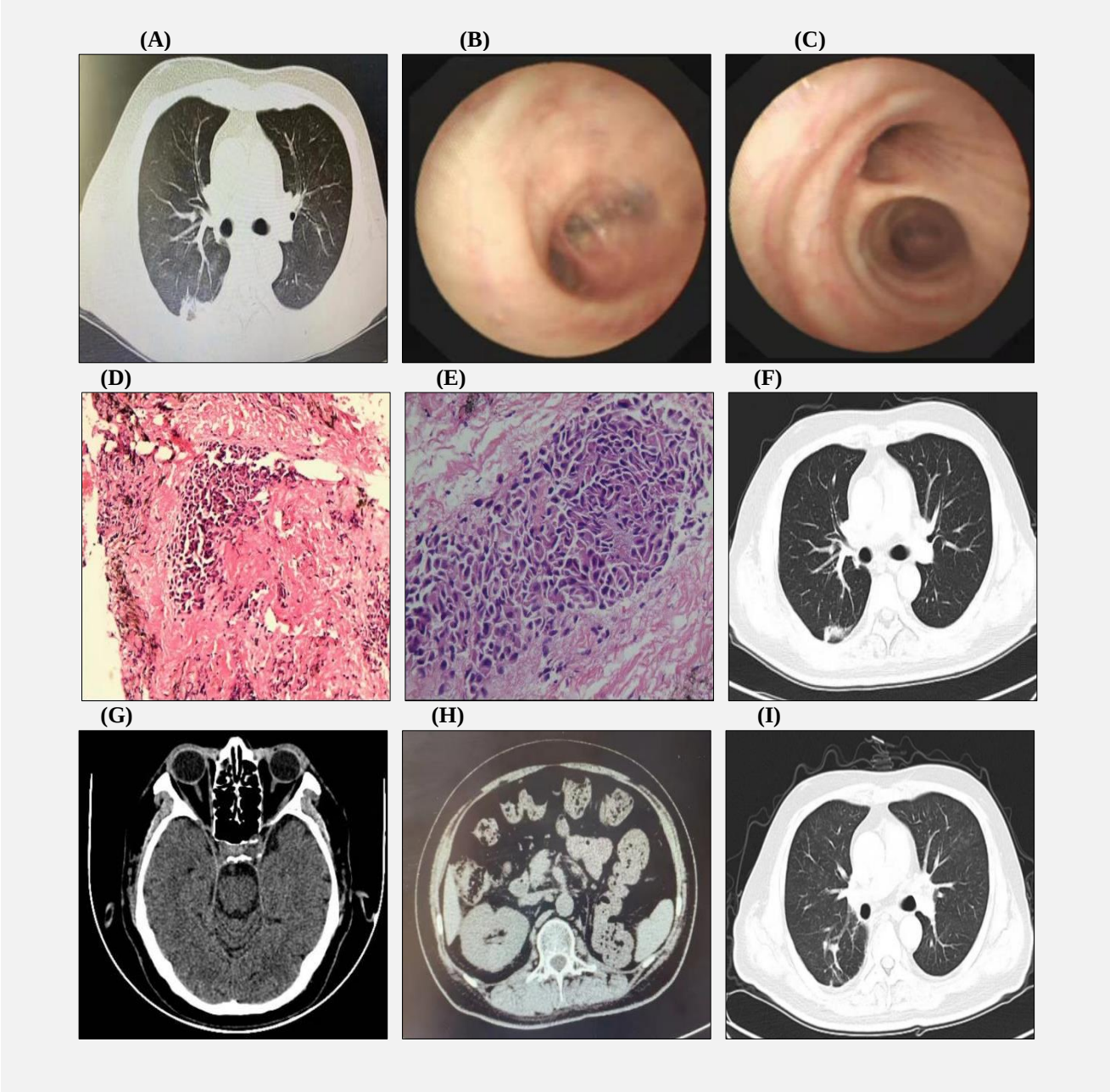

Figure 1. Patient imaging and histological results.

The chest CT scan showed multiple lamellar hyperdense shadows in the right lung and nodular hyperdense shadows in the upper lobe of the left lung (Figure 1A). Bronchoscopy showed grayish-black tissue covering the upper lobe of the right lung, and the rest of the bronchi were normal (Figure 1B, 1C). The pathology results suggested nests of anisocytic cells in the lung tissue (Figure 1D, 1E). The reexamination of chest CT indicated that the nodular high-density shadow in the upper lobe of the left lung disappeared, and the blade-like high-density shadow in the right lung was smaller than before (Figure 1F). The pituitary CT suggested no significant abnormal changes (Figure 1G). The abdominal CT suggested a lack of the left kidney, and no obvious infectious lesions were found (Figure 1H). The chest CT showed a significant improvement of high-density shadow (Figure 1I).

The initial laboratory tests and the CT scan of the chest confused us: the chest CT showed multiple lamellar hyperdense shadows in both lungs, positive for serum (1-3)-β-D-glucan and negative for HIV, and together with the patient's own history of cancer and the application of hormonal therapy, we first considered the presence of a pulmonary fungal infection. We performed a bronchoscopic biopsy and NGS pathogen testing. The pathological findings suggested that nests of anisocytic cells were seen in the lung tissue. The immunohistochemical

results supported clear cell renal cell metastatic carcinoma, but the patient was currently on targeted drug therapy, so we did not intervene on the metastatic cancerous tissue for the time being. NGS results showed Pneumocystis carinii infection. We gave the patient oral compound sulfamethoxazole tablets as antifungal treatment and prednisone to suppress the inflammatory response. After treatment, the patient's chest CT scan showed that the nodular hyperdense shadow in the upper lobe of the left lung disappeared, and the blade-like hyperdense shadow in the upper lobe of the right lung was smaller than before. We began to think that we had found the infecting agent and that the patient's symptoms were improving, so we reduced the hormone dosage. Surprisingly, the patient's fever did not completely resolve. As the hormone dosage was reduced, the fever soon returned and was higher than the previous maximum temperature. Therefore, we examined the patient for other sites, but the patient's whole-body CT scan showed no significant abnormalities. We began to question the possibility of multiple pathogenic infections in the patient's lungs and considered other diagnostic methods, such as NGS pathogen testing, which is direct evidence of detectable pathogens [10]. Since the patient refused a second bronchoscopy, we performed an NGS examination of the patient's sputum. The NGS results suggested EBV infection, so we administered antiviral treatment along with antifungal treatment. After the treatment, the patient's febrile symptoms completely disappeared and his condition improved significantly.

Recently, NGS testing has rapidly emerged as a promising single, culture-independent pathogen detection tool that can be performed directly on clinical specimens [11]. NGS targets all DNA or RNA present in the sample, allowing detection of the entire microbiome as well as the human host genome or transcriptome in patient samples [12]. Combined with current bronchoscopic interventions, the more rapid and direct extraction of lesion specimens for testing makes the results more accurate, shortens the clinician's treatment cycle significantly, and improves patient prognosis and quality of life even more. In this case, the patient was just consistently febrile, the cause of which was unknown, and a whole-body CT scan showed no obvious infectious lesions. During the treatment, the patient's febrile symptoms did not improve significantly, although the inflammation in the patient's lungs was partially absorbed. Eventually, EBV infection and Pneumocystis carinii infection were identified by NGS testing at different sites. After antiviral and antifungal treatment, the clinical outcome of the patient was satisfactory.

It is worth noting that HIV-negative patients with low immune function can be complicated with Pneumocystis carinii pneumonia, but only a very small number of cysts are detected in BALF and the number of pathogens is small, the diagnosis of PCP is very difficult [13]. In recent years, with the continuous development of experimental diagnostic techniques, the combined application of 2 or more methods such as tracheoscopic immunofluorescence staining, NGS detection, serum (1-3)-β-D-glucan, and serum lactate dehydrogenase can improve the diagnosis. In addition, early bronchoscopy and sending NGS for testing can confirm the diagnosis based on anti-PCP treatment [14]. In contrast, EBV is associated with a range of clinical conditions in immunodeficient patients. Clinical syndromes range from limited benign manifestations (e.g., EBV hepatitis) to PTLD (including true lymphoma) [15]. Diagnosis of EBV disease in this population is challenging, and while immunocompromised patients may exhibit typical EBV infection, asymptomatic infection is more common in all types of patients and can occur at any age and in a variety of different clinical situations. Even immunocompromised hosts often experience infection without clinical symptoms [16]. Therefore, the possibility of infection by pathogens of different species in the same individual must be considered in the diagnosis of immunocompromised patients with unexplained fever. The lesson learned from our patient's case is that we initially thought that the high-density CT chest shadow was due to a fungal infection and did not recognize the possibility of co-infection with different species of pathogens. Patients with prolonged fever that does not subside with treatment should undergo bronchoscopy and be tested for NGS pathogens at different sites.

CONCLUSION

Elevated serum (1-3)-β-D-glucan is not a specific index for infectious diseases. When a patient has dense shadows or nodules in different parts of the lung, these lesions may not be infected by the same pathogen. Bronchoscopy and the NGS has high specificity in pathogen detection of infectious diseases, especially when certain pathogens are extremely rare.

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Ethical Approval:
This study was approved by the ethics committee of North China University of Science and Technology Affiliated Hospital. All procedures performed in studies were in accordance with the ethical standards. Informed consent was obtained.

Declaration of Interest:
No conflicts of interest.

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