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Pharmaceutical Care of a Case with Suspected Ganciclovir Resistant CMV Infection after Lung Transplantation: A Case Report

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Abstract

Aim: This study aims to provide insights into the clinical medication for suspected ganciclovir-resistant Cytomegalovirus (CMV) infection after lung transplantation.

Presentation: A 60-year-old patient with non-specific interstitial pneumonia underwent bilateral lung transplantation. About 1 month after operation, CMV nucleic acid in bronchoalveolar lavage fluid was positive and the CT value was 21.47. After 16 days of intravenous infusion of ganciclovir, CMV nucleic acid was still positive and virus replication increased. Lung CT showed obvious bilateral lung infiltration. Clinical pharmacists suggested intravenous infusion of foscarnet sodium.

Results: After 14 days, CMV nucleic acid test turned negative and the treatment was effective. However, the patient eventually developed septic shock and hemodynamic instability due to post-lung transplantation bronchial anastomotic fistula, pyothorax and the family abandoned treatment.

Conclusions: Clinical pharmacists participated in the whole process of diagnosis and treatment of this case, which reflected the professional ability and service level of clinical pharmacists and highlighted the rare but potential complexity of ganciclovir-resistant cytomegalovirus infection in patients after lung transplantation.

Keywords: Cytomegalovirus; Pneumonia; Drug resistance; Ganciclovir; Foscarnet sodium; Case report

Abbreviations: CMV: Cytomegalovirus; BALF: Bronchoalveolar Lavage Fluid; CRRT: Continuous Renal Replacement Therapy; SOT: Solid Organ Transplant; HSCT: Hematopoietic Stem Cell Transplant

Introduction

Cytomegalovirus (CMV), a type of β-herpesvirus, is a DNA virus that infects approximately 60% of adults in developed countries and over 90% in developing countries [1]. It can persist in long-lived cells of the bone marrow lineage, reactivating and exacerbating clinical conditions associated with innate and adaptive immune activation [2].

Then, Solid Organ Transplant (SOT) recipients are in an immunosuppressive state and the incidence of CMV infection after surgery is much higher than that of the normal population [3]. Moreover, CMV pneumonia is one of the most common infectious complications in transplant recipients. The incidence of CMV pneumonia in lung transplant recipients is significantly higher than that in other organ transplant recipients.

Currently, CMV can be prevented through prophylaxis or preemptive treatment [1]. Despite the decline in CMV-related mortality with the development and availability of potent antiviral drugs, there is increasing evidence that the indirect effects of CMV may be no less than its direct impact on tissue damage and infection.

CMV-induced immunosuppression may cause other opportunistic infections [4]. In addition, with the increasing use of antiviral drugs, the issue of CMV resistance has gained widespread attention.

The development of CMV infection and resistance can significantly increase the morbidity and mortality rates in lung transplant patients [5].

In general, it is extremely rare for patients to develop ganciclovir-resistant CMV infection. In the current article, we present a unique case of ganciclovir-resistant severe cytomegalovirus pneumonia after lung transplantation.

Case Presentation

Case materials

The patient is a 60-year-old male with a body weight of 75 kg. He was admitted to the Respiratory and Critical Care Medicine Department (North Zone) of China-Japan Friendship Hospital on 28 January, 2023 due to "asthma after intermittent activity for 6 years and worsened for more than 1 month." The patient developed post-activity asthma without apparent triggers 6 years ago and no attention was paid to it. Subsequently, he was diagnosed with "non-specific interstitial pneumonia" at Peking Union Medical College Hospital and was treated with pirfenidone and prednisone acetate. After the asthma symptoms were relieved, he was discharged from the hospital and was given long-term maintenance of oral steroid.

The patient experienced recurrent worsening of asthma triggered by cold exposure, physical activity or inhalation of irritating gases. Intermittent traditional Chinese medicine alleviated the symptoms. In daily life, he could ambulate independently without oxygen and receives occasional low-concentration oxygen therapy at home. At the end of 2022, the patient was diagnosed with COVID-19 and despite improvement in asthma after treatment, he could not fully recover to the pre-illness state and remained dependent on oxygen. CT scans revealed diffuse interstitial fibrosis with viral pneumonia, exacerbated in the right lung, which indicated progressive lung fibrosis.

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The patient had a history of steroid-induced diabetes due to taking previous glucocorticoid and was taking acarbose with satisfactory glycemic control. He had a 30-year smoking history with an average of 60 cigarettes per day and had quit smoking for 1 year. He denied a history of hypertension, heart disease, cerebrovascular diseases or other significant medical conditions.

The admission examination was as follows: temperature 36.3°C, pulse 94 beats/min, respiratory rate 24 breaths/min, blood pressure 114/74 mmHg. The patient was alert, oriented and in good spirits. Lung auscultation revealed slightly coarse breath sounds bilaterally with crackles in the lower lungs and no wheezing. Cardiac examination was unremarkable and abdominal examination showed soft abdomen without tenderness or rebound tenderness. There was no edema in the lower extremities. The auxiliary examination results showed that white blood cells were 11.07 × 109/L, neutrophils were 75.4%, lymphocytes were 17.9%, C-reactive protein was <2.50 mg/L and procalcitonin was <0.1 ng/mL. Chest CT results revealed diffuse interstitial fibrosis with viral pneumonia and the right lung was worse than before.

The admission diagnosis was as follows:

- Non-specific interstitial pneumonia
- Type I respiratory failure
- Chronic cor pulmonale
- Heart failure class III
- Fatty liver.
- Hyperlipidemia
- Gastroesophageal reflux disease
- Severe osteoporosis
- Gallbladder stones
- Steroid-induced diabetes due to correct medication use
- Viral pneumonia

Treatment procedure

Two days after admission, the patient's serum CMV antibody IgG was positive and IgM was negative On 4 February, 2023, the patient underwent bilateral lung transplantation. During the procedure, cytomegalovirus nucleic acid testing in Bronchoalveolar Lavage Fluid (BALF) was negative (all subsequent samples were BALF). On 7th March, CMV nucleic acid testing turned positive with a CT value of 21.47. Due to the patient undergoing Continuous Renal Replacement Therapy (CRRT), ganciclovir was administered at a dose of 75 mg qd intravenously from 9th March to 16th March. Subsequently, CT values continued to decrease, indicating that viral replication was still increasing. On 14th March, the ganciclovir through concentration was 2.00 μg/ml and in combination with the patient's condition, the ganciclovir dose was doubled to 150 mg qd intravenously, On March 16, he underwent chest CT (Computed Tomography) and the results showed that the infiltration of both lungs was obvious (Figure1) and sodium phosphonoformate chlorite injection 3 ng qd was added for combined treatment starting from 22nd March. Ganciclovir trough concentrations on 22nd March and 27th were 2.36 μg/ml and 2.00 μg/ml, respectively. On March 27th, the patient's CMV CT value increased to 26.47, which was higher than before. On April 4th, 12th and 25th, the CMV nucleic acid test was negative for three consecutive times and the treatment was effective. All anti-CMV drugs were discontinued on 17th April (Please refer to Table 1 for the CMV treatment process).

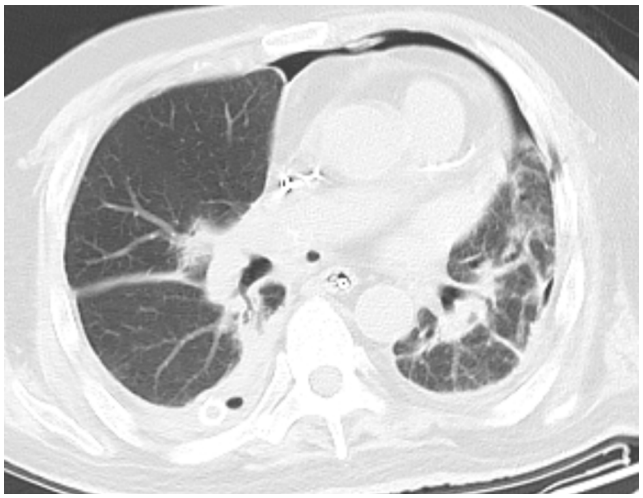

Figure 1: Chest CT scan showing significant bilateral lung infiltration.

Date	Cytomegalovirus nucleic acid testing	CT value	Anti-CMV drugs	Usage and dosage
7 March, 2023	Positive	21.47	Ganciclovir	75 mg ivgtt qd
14 March, 2023	Positive	20.41		
17 March, 2023	Positive	20.05	Ganciclovir	150 mg ivgtt qd
22 March, 2023	Positive	-		
27 March, 2023	Positive	26.47	Ganciclovir,	150 mg ivgtt qd,
4 April, 2023	Negative	-	Foscarnet sodium	3 g ivgtt qd
12 April, 2023	Negative	-		
25 April, 2023	Negative	-	All anti-CMV drugs will be discontinued on 17 April, 2019.	

Table 1: Treatment process of pulmonary CMV.

Throughout the treatment process for CMV infection, the medication regimen was actively adjusted to achieve a successful diagnosis and treatment idea of changing the CMV infection from positive to negative. This successful therapeutic approach is worth exploring. However, the patient ultimately developed bronchial anastomotic fistula and empyema after lung transplantation, leading to septic shock and hemodynamic instability. The family decided to discontinue treatment and the patient voluntarily completed the discharge procedures on 27th April.

Results and Discussion

CMV is the most common opportunistic viral infection in Solid Organ Transplant (SOT) recipients, typically occurring within 1-6 months after transplantation [6]. The most common symptoms of CMV infection include fever, pulmonary involvement and abnormal blood counts and primarily affect immunosuppressed patients. Antiviral drugs commonly used for CMV in transplant recipients include ganciclovir, valganciclovir, cidofovir, fomivirsen and sodium phosphonoformate. The 2018 international version of the SOT guidelines recommends pre-

transplantation CMV IgG serology for both donors and recipients for risk stratification, with the degree of risk being in the following order: D+/R->D+/R+>D-/R+>D-/R- (D+: CMV-positive donor, R-: CMV-negative recipient) [5]. CMV resistance is not uncommon in SOT. The incidence of resistance reported in various studies varies, but it is more common in lung transplant patients and the reported cases are basically D+/R– patients [7]. Furthermore, without antiviral prophylaxis, the majority of high-risk SOT recipients will experience CMV infection, which may lead to viremia, disease and end-organ damage [8]. A recent study evaluating prevention strategies at 224 transplant centers showed that 90% of D+/R- SOT centers used universal precautions [9]. Despite the current use of prophylactic strategies after transplantation that reduce the risk of CMV disease, CMV disease can still occur in up to 50% of high-risk SOT patients (D+/R-) and 17% of CMV-positive recipients (R+) [10]. The patient in this article is CMV IgG positive and is a CMV seropositive recipient (D-/R+). The doctor may have considered the low risk of CMV and was worried about the occurrence of bone marrow suppression, so prevention or preemptive treatment was not carried. The patient underwent bilateral lung transplantation on 4th February and CMV nucleic acid testing turned positive on 7th March, so he started ganciclovir anti-CMV treatment. Currently, there are few reports on ganciclovir CMV resistance in D-/R+ patients after lung transplantation.

Ganciclovir is the most commonly used antiviral drug at present and it is also the first-line prevention and treatment drug recommended by the guidelines for anti-CMV infection, which has a good effect on CMV infection. Intravenous ganciclovir is the primary treatment for CMV infection, while oral ganciclovir can be used for prophylaxis. Due to the low oral bioavailability of ganciclovir, it is generally not recommended for CMV prophylaxis or preemptive treatment in SOT recipients. The prophylactic dose of intravenous infusion of ganciclovir is 5 mg/kg, once a day, the therapeutic dose is 5 mg/kg twice a day and the dose needs to be adjusted according to the creatinine clearance rate. The main adverse effect is bone marrow suppression [3]. The patient's CMV nucleic acid test result was positive on 7th March and the CT value was 21.47. Since the patient was undergoing CRRT, the clinical pharmacist recommended treatment with ganciclovir injection 75 mg qd. According to guidelines, when the patient's creatinine clearance is below 30 ml/min, the initial dose of ganciclovir induction therapy should be 1.25 mg/kg once every 24 hours and the maintenance dose should be 0.625 mg/kg once every 24 hours [5]. In addition, clinical pharmacists remind clinicians that patients need to be screened regularly for complete blood counts during the use of ganciclovir to prevent the development of myelosuppression. The patient received an adequate dose of ganciclovir and continued antiviral therapy for 8 days. However, the test was still positive for CMV and the CT value was lower than before and the viral copy number was still increasing, which was considered to be an infection with ganciclovir-resistant CMV.

After ganciclovir/valganciclovir exposure, the most common mutations occur in the *UL97* gene, followed by the *UL54* DNA polymerase gene. Ganciclovir itself has no direct anti-CMV effect and must be monophosphorylated by the viral kinase *UL97* as the first activation step. Intracellular enzymes subsequently phosphorylate it into active ganciclovir-triphosphate, which can competitively inhibit the CMV-DNA polymerase encoded by the viral gene *UL54*. Therefore, mutations in the *UL97* or *UL54* genes can lead to the development of drug resistance [11]. Ganciclovir, valganciclovir and fomivirsen all block CMV replication by targeting the viral polymerase *UL54* [12]. In addition to the obvious toxic and side effects of currently commonly used anti-CMV drugs, some patients' CMV strains are resistant to drugs such as ganciclovir, valgancirol and sodium phosphate potash. Besides, prolonged use of these antiviral drugs can also induce CMV resistance [13]. Spontaneous mutations and those selected under antiviral pressure in the *UL97* and/or *UL54* genes may result in treatment failure, with most mutations conferring resistance to ganciclovir, followed by valganciclovir and fomivirsen [14]. Reports of resistance to sodium phosphonoformate are rare [15]. Sodium phosphonoformate is a first-line drug for treating ganciclovir-resistant CMV infections due to *UL97* gene mutations. However, its major drawback is significant renal toxicity [16].

Currently, the novel antiviral drug letermovir has been approved for primary prophylaxis against CMV infection in adult Hematopoietic Stem Cell Transplant (HSCT) recipients. It acts on the endonuclease complex formed by *pUL56, pUL89* and *pUL51* and inhibits the processing and packaging of DNA, thus Inhibits CMV replication. Therefore, letermovir does not exhibit cross-resistance with other drugs. It can be considered to be tried when other drugs are inaccessible or ineffective [17]. Due to technological constraints, the patient in this case did not undergo CMV gene testing, so it was not possible to determine what type of mutation this patient had. However, the patient achieved good results with high-dose ganciclovir in combination with full-dose sodium phosphonoformate treatment. It is considered that the mechanism of CMV resistance in this patient is a single mutation of the *UL97* gene.

The occurrence rate of ganciclovir resistance after treatment in Solid Organ Transplant (SOT) patients is generally low (<5%). However, some studies report higher rates, ranging from 5% to 12%, up to 18% in lung recipients and up to 31% in intestinal and multivisceral transplant recipients [18]. For asymptomatic or mildly symptomatic diseases, or low-level DNA emia, guidelines recommend using high-dose ganciclovir (5.10 mg/kg-12 mg/kg every 7 hours with normal renal function). For severe, life-threatening, or vision-threatening diseases, international guidelines recommend using foscarnet [19]. Foscarnet is a second-line treatment for CMV, but due to its significant renal toxicity, it is not recommended for routine prophylaxis and preemptive treatment. When it is used for the treatment of *UL97* mutant ganciclovir-resistant CMV disease, the dose is 60 mg/kg three times a day or 90 mg/kg twice a day as an intravenous infusion [20]. When continuous or recurrent CMV-DNAemia or disease is present during prolonged antiviral therapy, antiviral drug resistance should be suspected. For ganciclovir, prolonged treatment is generally considered with cumulative drug exposure for at least 6 weeks or longer, including at least 2 weeks of continuous full-dose treatment [18].

Given the patient's condition, the clinical pharmacist suggested doubling the ganciclovir dose to 150 mg once a day starting from 17th March. Subsequently, due to concerns about the patient's deteriorating condition and poor prognosis for lung transplantation, on 22nd March, the pharmacist recommended empirically adding intravenous ganciclovir (150 mg once daily) in combination with foscarnet sodium chloride injection (3 g once/day) for treatment and obtain effective curative effect.

As the widespread use of ganciclovir for the prevention and treatment of CMV infection after SOT, ganciclovir-resistant CMV is becoming increasingly common. Current research indicates that ganciclovir resistance is generally associated with prolonged antiviral exposure, increased immunosuppression, reduced antiviral prophylactic doses and organ transplants, particularly lung transplants [21]. The patient's viral copy number is still increasing after 8 days of ganciclovir treatment, suggesting that the patient has risk factors for

CMV resistance: High levels of CMV replication in lung transplant hosts [13].

The incidence of ganciclovir-resistant CMV has historically been low in most transplant populations [22]. However, patients who develop drug-resistant CMV infection have reduced overall survival and the peak CMV viral load and duration of CMV viremia are associated with the development of ganciclovir-resistant CMV infection [23].

Conclusion

Ganciclovir-resistant CMV infection in transplant recipients has its specificities and the diagnostic and treatment strategies differ from those of ordinary CMV infections. Currently, empirical treatments for ganciclovir resistance include increasing the dose of intravenous ganciclovir or combining it with foscarnet sodium. After suspected ganciclovir resistance, the patient was first treated with a double dose and then combined with sodium phosphonate to achieve CMV nucleic acid conversion in view of the severity of the patient's condition. In clinical practice, if there is poor response to ganciclovir treatment, clinicians should consider the possibility of ganciclovir-resistant CMV and make timely adjustments to the treatment regimen.

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Authors Contribution

Dongjie Guo and Xin Shao were involved in concept and writing. Jun You and Xianhong Jang was involved in literature search and manuscript revision. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate. The ethics of the project is approved and supervised by the Ethics Committee of Leshan People's Hospital.

Consent for Publication

Written informed consent to publish this information was obtained from the patient patients' anonymity was preserved.

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