EJCRIM
European Journal
of Case Reports
in Internal Medicine

UNCOVERING THE CAUSE OF PNEUMONIA: REACTIVATION OF HHV-6B IN AN IMMUNOCOMPROMISED PATIENT

Leonor Rodrigues, Juliana Nogueira, Daniela Alves, Filipa Ferreira, João Fonseca

Internal Medicine Department, Unidade Local de Saúde da Região de Aveiro, Aveiro, Portugal

Corresponding author's e-mail: leonorrodrigues97@hotmail.com

Received: 18/08/2025
Accepted: 26/08/2025
Published: 16/09/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient for the publication of this report and accompanying images.
This article is licensed under a Commons Attribution Non-Commercial 4.0 License

How to cite this article: Rodrigues L, Nogueira J, Alves D, Ferreira F, Fonseca J. Uncovering the cause of pneumonia: reactivation of HHV-6B in an immunocompromised patient. *EJCRIM* 2025;**12**:doi:10.12890/2025_005783

ABSTRACT

Human herpesvirus 6 (HHV-6) is a ubiquitous virus that commonly infects the paediatric population and establishes latency in the host following primary infection. As in other herpesviruses, HHV-6 may reactivate when the immune system becomes severely compromised, such as after chemotherapy or haematopoietic cell transplantation. We report a case of an 83-year-old male, previously diagnosed with multiple myeloma and treated with lenalidomide plus bortezomib, who was admitted to the internal medicine department with bilateral pulmonary thromboembolism. During his stay, he developed severe respiratory dysfunction and fever. A diagnosis of nosocomial pneumonia was established based on imaging and blood tests. Despite broad-spectrum antibiotic therapy the patient remained febrile with worsening respiratory function and developed an erythematous rash on the face and trunk. The chest CT scan revealed scattered ground-glass opacities bilaterally. Investigations for opportunistic agents (serologies and DNA) were also performed, with positive IgM cytomegalovirus (CMV) antibodies, but negative CMV antigen and DNA quantification, while serum DNA was positive for HHV-6. Antibiotics were discontinued and bronchoalveolar lavage (BAL) was performed with HHV-6 polymerase chain reaction (PCR) testing positive, identifying HHV-6B. Treatment with intravenous ganciclovir led to the resolution of symptoms and hypoxaemia. The patient was discharged and completed 21 days of valganciclovir at home. After one year, the patient remains on chemotherapy without pulmonary sequelae or new HHV-6B reinfection.

KEYWORDS

Human herpesvirus 6, pneumonitis, valganciclovir, multiple myeloma

LEARNING POINTS

- Human herpesvirus 6 (HHV-6) can reactivate in immunocompromised individuals and cause severe atypical pneumonia, so it is important to recognise this entity when a patient fails to improve their clinical outcome with conventional therapy.
- In patients diagnosed with pneumonitis, DNA PCR testing can detect HHV-6 from bronchoalveolar lavage fluid making this a powerful diagnostic tool.
- Treatment options for HHV-6 pneumonitis should be considered, such as combined ganciclovir and foscarnet or, as in our case, oral valganciclovir can be a good alternative.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

INTRODUCTION

Human herpesvirus 6 (HHV-6) is a member of the Roseolovirus genus and belongs to the Betaherpesvirinae subfamily. There are two HHV-6 variants, HHV-6A and HHV-6B. They are genetically related to cytomegalovirus (CMV), the only other human beta herpesvirus[1]. It is well known that primary HHV-6 infection usually occurs in children younger than 3 years and is associated with high fever that lasts for several days, followed by exanthema subitum. It can sometimes be complicated by neurologic manifestations such as febrile seizures and encephalitis[2]. After the primary infection the virus remains latent in a broad range of cells – including bronchial glands – and most adults with chronic HHV-6 are asymptomatic. However, it can reactivate in immunocompromised patients and cause life-threatening infections including encephalitis, bone marrow suppression, graft-versus-host disease, hepatitis and pneumonitis, especially post haematopoietic stem cell transplantation (HSCT)[3,4]. This is also frequently associated with CMV reactivation and can increase mortality[1]. Here, we report a case of an immunocompromised patient undergoing chemotherapy for multiple myeloma, who had not undergone HSCT, and developed HHV-6 pneumonitis.

CASE DESCRIPTION

An 83-year-old male was admitted to the internal medicine department with the diagnosis of bilateral pulmonary embolism, intermediate to high risk of early death and a pulmonary embolism severity index score class V, although haemodynamically stable. Regarding his medical history, he was diagnosed with multiple myeloma (MM) four years before his admission and was currently treated with lenalidomide plus bortezomib.

After 48 hours, he developed fever associated with rhonchi on lung auscultation, elevated inflammatory parameters and neutropenia. His chest X-ray showed some infiltrates, and he was started on empirical antibiotic therapy with piperacillin/tazobactam, for pneumonia.

On the fifth day of antibiotic therapy, he was still febrile and severely ill, so vancomycin was added to the piperacillin/tazobactam. In this context, several microbiological and serological tests were performed: blood and urine cultures, legionella antigen and sexually transmitted diseases tests in urine, anti-streptolysin O (ASO), serologies for respiratory virus, CMV, herpes simplex virus (HSV), varicella zoster virus, toxoplasma and mycoplasma, Wright reaction and Venereal Disease Research Laboratory testing. All were negative with the exception of a positive IgM for CMV. Viral DNA quantification and CMV antigenemia were ordered.

A high-resolution lung CT was performed, showing some areas of low-density ground-glass densification, with thickening of interlobular septa *(Fig. 1)*.

Despite treatment, the patient's clinical state was worsening, with increased oxygen therapy needs. He presented with non-pruritic erythema of the neck and upper chest *(Fig. 2)*. Results of viral DNA quantification were positive for HHV-6 and negative for CMV. Empiric antibiotics were stopped, and a bronchoscopy was performed, testing bronchoalveolar lavage fluid (BALF) by PCR for opportunistic viruses such as CMV, HSV, HHV-6, *Pneumocystis jirovecii*, mycobacterial and fungal cultures. PCR testing of the BALF was positive for HHV-6B DNA and detected CMV DNA. Given the negative CMV antigenemia and serum CMV DNA, the clinical picture was attributed to HHV-6B pneumonitis, while CMV detection was likely a cross-reaction or contamination. The patient was diagnosed with HHV-6 pneumonitis and therapy with IV ganciclovir 5 mg/kg, every 12 hours was initiated. Within a couple of days, he presented with clinical improvement. Oxygen requirements progressively declined until complete discontinuation. The erythema gradually disappeared after antiviral therapy began, and inflammatory parameters also decreased to normal levels. He was switched to oral valganciclovir 900 mg every 12 hours, after 6 days of IV ganciclovir. The patient also underwent functional rehabilitation due to deconditioning from prolonged bed stay.

He was discharged home after 34 days of hospitalisation and stopped valganciclovir when he had completed 21 days. At the follow-up evaluation, 15 days after discharge, he had no dyspnoea, erythema or fever. The oxygen saturation was 99% on room air and lung auscultation was normal. He was still undergoing functional rehabilitation in our hospital and maintaining follow-up by Haematology due to MM under treatment.

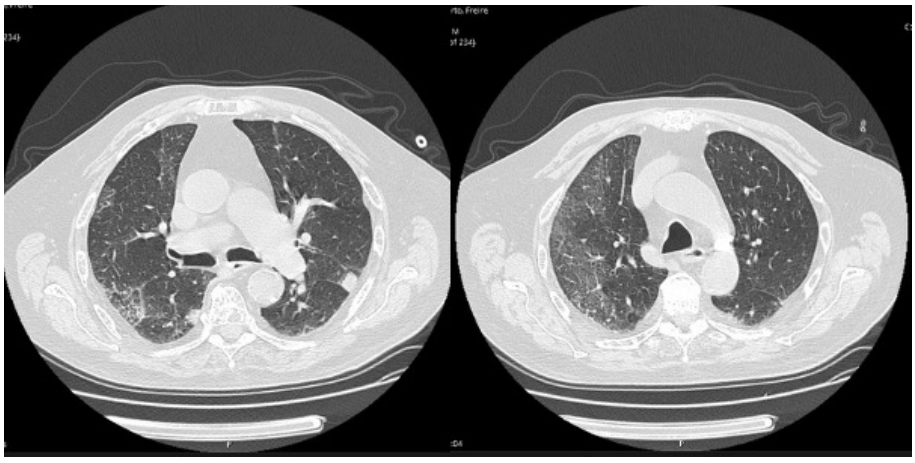


Figure 1. Chest CT images at the onset of pneumonitis with ground-glass densification and thickening of interlobular septa.



Figure 2. Erythema of the neck and upper chest.

DISCUSSION

HHV-6 reactivation is well described in immunocompromised patients after allogeneic HSCT as an opportunistic infection, but it can also occur during chemotherapy for haematological malignancies and cause interstitial pneumonitis[5]. Radiologic findings of HHV-6 associated pneumonitis appear like other herpes virus infections of the lung (HSV and CMV), making the differential diagnosis difficult. High-resolution lung CT plays a central role, but findings are non-specific, such as reticulation, ground-glass opacity, crazy-paving pattern infiltrations in central areas of the lung, consolidation and pleural effusions[5].

The diagnosis relies on the presence of HHV-6 DNA in peripheral blood or detection of HHV-6 DNA in clinical specimens such as respiratory secretions after BALF, as reported in this clinical case, that supports viral pneumonitis. Previous studies in allogeneic HSCT and solid organ recipients with acute respiratory failure and HHV-6B detected in BALF showed that these patients had an increased risk for overall mortality and death compared with those without HHV-6B detection in BALF. So, active HHV-6B replication in BALF could be an appropriate trigger for anti-HHV-6 treatment[6,7].

In vitro, foscarnet, ganciclovir and cidofovir can inhibit HHV-6B replication. In the absence of clear guidelines, these treatments may reasonably be proposed to immunocompromised patients with severe clinical presentation for three weeks, as proposed by some experts[1,8].

We decided to treat the patient with IV ganciclovir, then switched to valganciclovir, an oral prodrug approved for the treatment and prevention of CMV disease in both HIV and non-HIV infected patients.

It is important to note that the term HHV-6 reactivation, in clinical practice, is applied to the reactivation of a latent virus (endogenous) and reinfection (exogenous), because these entities are difficult to distinguish from each other.

In conclusion, recognition of HHV-6B as a pulmonary pathogen is challenging, but early detection will lead to treatment and improve outcomes in immunocompromised patients.

REFERENCES

1. Agut H, Bonnafous P, Gautheret-Dejean A. Update on infections with human herpesviruses 6A, 6B, and 7. *Med Mal Infect* 2017;**47**:83–91. doi: 10.1016/j.medmal.2016.09.004
2. Tesini BL, Epstein LG, Caserta MT. Clinical impact of primary infection with roseoloviruses. *Curr Opin Virol* 2014;**9**:91–96. doi: 10.1016/j.coviro.2014.09.013
3. Nakayama T, Okada F, Ando Y, Honda K, Ogata M, Goto K, et al. A case of pneumonitis and encephalitis associated with human herpesvirus 6 (HHV-6) infection after bone marrow transplantation. *Br J Radiol* 2010;**83**:e255–258. doi: 10.1259/bjr/19375793
4. Azzi JM, Park D, Abdul-Hay M, Cole K, Cirrone F, Kreditor M, et al. Human herpes virus-6 encephalitis following autologous blood and marrow transplant. *Clin Hematol Int* 2020;**2**:32–34. doi: 10.2991/chi.d.191123.001
5. Kuwahara-Ota S, Chinen Y, Mizuno Y, Takimoto-Shimomura T, Matsumura-Kimoto Y, Tanba K, et al. Human herpesvirus-6 pneumonitis in a patient with follicular lymphoma following immunochemotherapy with rituximab. *Infect Drug Resist* 2018;**11**:701–705. doi: 10.2147/IDR.S163686
6. Hill JA, Vande Vusse LK, Xie H, Chung EL, Yeung CCS, Seo S, et al. Human herpesvirus 6B and lower respiratory tract disease after hematopoietic cell transplantation. *J Clin Oncol* 2019;**37**:2670–2681. doi: 10.1200/JCO.19.00908
7. Mariotte E, Schnell D, Scieux C, Agbalika F, Legoff J, Ribaud P, et al. Significance of herpesvirus 6 in BAL fluid of hematology patients with acute respiratory failure. *Infection* 2011;**39**:225–230. doi: 10.1007/s15010-011-0114-8
8. Ward KN, Hill JA, Hubacek P, de la Camara R, Crocchiolo R, Einsele H, et al. 2017 European Conference on Infections in Leukaemia (ECIL). Guidelines from the 2017 European Conference on Infections in Leukaemia for management of HHV-6 infection in patients with hematologic malignancies and after hematopoietic stem cell transplantation. *Haematologica* 2019;**104**:2155–2163. doi: 10.3324/haematol.2019.223073