Diagnostic Pathology

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Human pegivirus detected in patient with reversible severe encephalitis and axillary lymphadenopathy: a case report

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Abstract

Human pegivirus (HPgV) has been postulated as a potential etiological factor in encephalomyelitis and exhibits lymphotropic characteristics. However, the co-occurrence of encephalitis and lymphadenopathy with HPgV detected has never been reported. Herein, we report a case of a 48-year-old woman admitted with fever followed by sudden loss of consciousness. Radiological imaging demonstrated encephalitis and lymphadenopathy. Initial analysis of blood and cerebrospinal fluid (CSF) failed to reveal specific etiology. The only pathogen found in CSF was later determined to be HPgV using metagenomic next-generation sequencing (mNGS). After receiving treatment with acyclovir, meropenem, and ceftriaxone sodium, the patient fully recovered. This case contributes additional evidence in support of the hypothesis regarding the pathogenic potential of HPgV and highlights the diagnostic utility of mNGS in detecting rare pathogens.

Keywords Human pegivirus, Encephalitis, Lymphadenopathy, Metagenomic next-generation sequencing

Introduction

Human pegivirus (HPgV), a member of the *Pegivirus* genus within the *Flaviviridae* family, was first discovered in 1996 [1]. Its global prevalence is substantial, with an estimated one-sixth of the global population being seropositive and around 750 million people having viremia [2]. Notably, HPgV does not exhibit any established associations with clinical pathologies. Conversely, HPgV frequently co-infects with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), and often shows beneficial clinical effects in these patients by reducing immune activation [3–5].

However, a recent meta-analysis has identified a correlation between persistent HPgV infection and increased risk of lymphoma [6]. Furthermore, there have been reports of cases of encephalomyelitis in which HPgV was the sole pathogen detected, raising questions about its nonpathogenic role in humans [7–11]. Here, we present a case with reversible severe encephalitis and axillary lymphadenopathy in which HPgV was the only pathogen identified.

Case presentation

A 48-year-old woman without known medical history presented with a 2-day history of fever, peaking at 39.0 ℃, followed by a sudden loss of consciousness. Emergency non-contrast-enhanced CT of the head, chest, abdomen, and pelvis revealed normal results, except for lymphadenopathy in the left axillary region (Figure 1). Upon admission, her initial vital signs were as follows: blood pressure 144/83 mm Hg, heart rate 122 beats/

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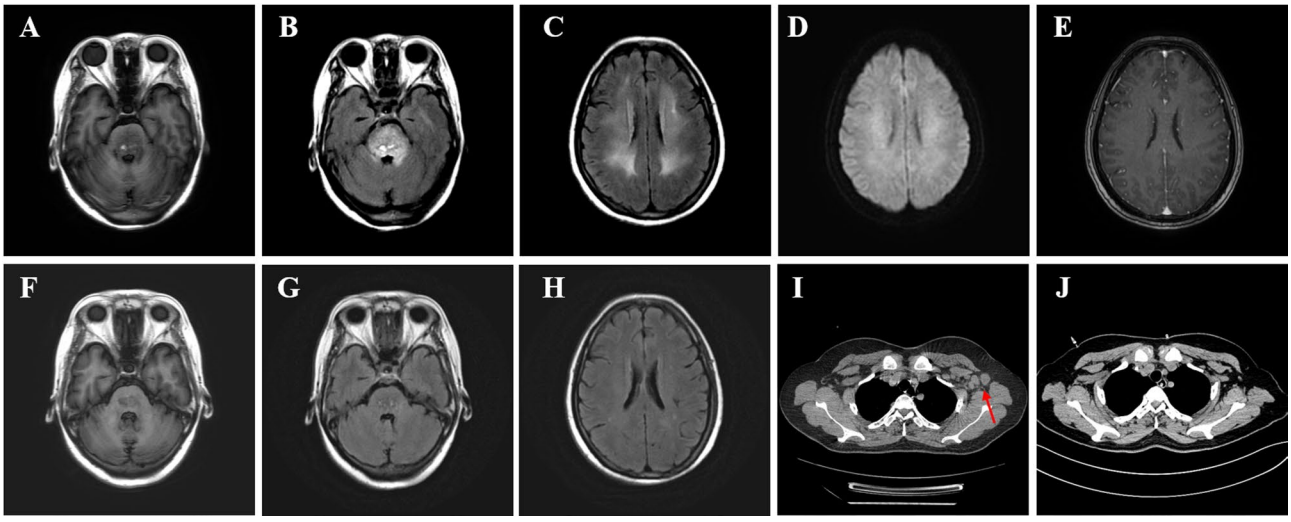

Fig. 1 (**A-E**) Initial MRI of the brain shows the lesion in the pontine region and bilateral periventricular areas. Imaging on T1WI (**A**), T2-FLAIR (**B-C**), DWI (**D**), and contrast (**E**) is shown, respectively. (**I**) Initial CT of the chest reveals lymphadenopathy in the left axillary region (red arrow). (**F-H, J**) Follow up imaging after treatment reveals nearly complete resolution of all the lesions

min, respiratory rate 44/min, temperature 38.2 ∘C, and blood oxygen saturation 94%. Laboratory investigations showed a white blood cell count of 8.78×10^9/L with lymphocytopenia, neutrophilia, and an elevated C-reactive protein level of 30.53 mg/L. The Antinuclear Antibodies test was negative. Analysis of CSF indicated the presence of 3×10^6/L white blood cells, with 23% being monocytes. The CSF protein level was 1592.0 mg/L, with glucose and chloride levels were 3.93 mmol/L and 126.2 mmol/L, respectively. Culturing and staining of the CSF for mycobacterial, cryptococcal, and bacterial pathogens produced negative findings. Further testing for antibodies against viruses, including herpes simplex virus type 1 and 2, cytomegalovirus, rubella virus, toxoplasmosis, and autoantibodies including NMDAR, AMPA1, AMPA2, LGI1, CASPR2, and GABAB in the CSF were also negative. Based on the patient's clinical presentation and laboratory findings, encephalitis was considered the most likely diagnosis. Empirically treatment with acyclovir (0.5 g three times daily) and meropenem (2.0 g three times daily) was initiated.

To further investigate the etiology, a second CSF puncture was conducted two days later, followed by mNGS analysis. This revealed HPgV as the only positive finding, with a sequence read count of 1 and a relative abundance of 3.86%. The existing treatment regimen was maintained. Two days later, after additional therapy, the patient regained consciousness and subsequently underwent a brain MRI examination. Neuroimaging revealed multiple lesions in the pontine, periventricular, and centrum semiovale regions, with punctate hemorrhages noted in the pontine lesions (Figure A-C). Diffusion weighted imaging (DWI) revealed showed no significant restriction (Figure D), and there was no enhancement observed in contrast imaging (Figure E).

Given the positive response to treatment, the regimen was extended for an additional three days. Acyclovir and meropenem were then replaced with ceftriaxone sodium. To confirm the mNGS findings, a third CSF puncture and mNGS analysis were performed. This again identified HPgV as the sole causative agent, with a sequence read count of 1 and a relative abundance of 3.4%. These results strongly suggest that HPgV may be the causative agent. After five days of treatment, the patient achieved full recovery, with significant resolution of cerebral lesions and axillary lymphadenopathy (Figures F-H, J).

Discussion

Encephalomyelitis with HPgV detection is a seldom encountered condition, with only 11 documented cases in the literature [7–11]. Furthermore, the simultaneous presentation of encephalitis and lymphadenopathy in conjunction with HPgV detection has not been previously reported.

Previous reports have shown that detection of HPgV in CSF or brain often has associated infection [7–11]. Our case is consistent with this general observation. In addition, detection of HPgV in CSF of encephalitis of uncertain etiology has occurred [7, 9, 12], whereas HPgV has failed to be detected in cases of encephalitis of known etiology [7, 9]. Furthermore, autopsy of HPgV-related fatal encephalitis demonstrated lymphocytic infiltration and gliosis in brain tissue, indicating neurotropism [8]. In vitro central nervous system (CNS) model of HPgV infection confirmed HPgV can infect astrocytes and microglia, suppressing antiviral responses and potentially causing

neurological disorders [13]. These are all in favor of the pathogenicity of CNS infection caused by HPgV.

There have been limited documented cases of HPgV-associated encephalitis with imaging findings. Balcom et al. detailed two cases showing predominant lesions in the brainstem and paraventricular regions, with potential enhancement as the disease progressed [8]. Our case also demonstrated a similar disease localization, but with the additional feature of a minor hemorrhagic component within the brainstem lesion. Additionally, our observations did not show any significant restriction in all lesions. HPgV selectively targets astrocytes and microglia in the human brain [13], leading to lesions primarily situated in the white matter during HPgV-associated CNS infections. Moreover, the infection of astrocytes may lead to modifications in the blood-brain barrier, potentially resulting in vasogenic edema and hemorrhage. These changes may represent the underlying mechanism responsible for the imaging findings observed in our case. In contrast, two other case reports described HPgV-associated encephalitis presenting as meningoencephalitis and similar to cerebral infarction (no radiological images), respectively [7, 10]. According to the information above, HPgV CNS infections can present a variety of imaging manifestations, necessitating further instances for comprehensive characterization.

In the context of HPgV-related CNS infection, the is no standardized treatment protocols at present. Notably, our case study, along with other five cases involving individuals lacking immunodeficiency, exhibited a favorable clinical course [7, 9, 10], in contrast to instances where poor outcomes, including death and impaired physical function, were observed [8, 11]. This observation implies that immunodeficiency may serve as a contributing factor to the unfavorable prognosis associated with HPgV infections.

HPgV exhibits lymphotropic characteristics and persistent infection is positively associated with lymphoma risk [2]. Hence, lymphadenopathy could potentially signify an acute HPgV infection. Despite the high prevalence of HPgV seropositivity [2], the lack of historical reports on lymphadenopathy may be attributed to the absence of significant clinical symptoms, such as pain, and the limited pathogenicity of HPgV under specific conditions.

We are aware that our case report may have some limitations. Firstly, the presence of HPgV in CSF using mNGS was not validated with alternative methods like polymerase chain reaction (PCR). Nevertheless, the consistency of results from two CSF mNGS assays enhances the credibility of our findings. Secondly, we did not perform blood mNGS analysis to detect HPgV. Thirdly, we did not perform a lymph node biopsy, which could have provided more definitive diagnostic evidence.

Conclusion

In summary, this case provides additional evidence in support of the hypothesis of HPgV CNS infection and underscores the value of utilizing mNGS of CSF in patients with unknown etiology. Further identification of cases is imperative to definitively establish the pathogenicity of HPgV.

Abbreviations

HPgV	Human pegivirus
CSF	Cerebrospinal fluid
mNGS	metagenomic Next-generation sequencing
HIV	Human immunodeficiency virus
HCV	Hepatitis C virus
DWI	Diffusion weighted imaging
CNS	Central nervous system

Author contributions

All authors contributed to the conception and design of this study. Chen Niu contributed to the clinical management of the patient. Jianfeng He and Linwei Yang performed material preparation, data collection, and analysis. Jianfeng He wrote the initial draft. Linwei Yang and Chen Niu revised the text. All the authors have read and approved the final version of the manuscript.

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Data availability

The data analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This case report study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Guihang 300 Hospital Affiliated to Zunyi Medical University.

Consent for publication

Informed consent was obtained from the patient to publish the case report.

Competing interests

The authors declare no competing interests.

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References

1. Linnen J, Wages J Jr., Zhang-Keck ZY, Fry KE, Krawczynski KZ, Alter H, et al. Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissible agent. Science. 1996;271(5248):505–8. https://doi.org/10.1126/science.271.5248.505.
2. Yu Y, Wan Z, Wang JH, Yang X, Zhang C. Review of human pegivirus: prevalence, transmission, pathogenesis, and clinical implication. Virulence. 2022;13(1):324–41. https://doi.org/10.1080/21505594.2022.2029328.
3. Bhattarai N, Stapleton JT. GB virus C: the good Boy virus? Trends Microbiol. 2012;20(3):124–30. https://doi.org/10.1016/j.tim.2012.01.004.
4. Giret MT, Kallas EG. GBV-C: state of the Art and future prospects. Curr HIV/AIDS Rep. 2012;9(1):26–33. https://doi.org/10.1007/s11904-011-0109-1.
5. Schwarze-Zander C, Blackard JT, Rockstroh JK. Role of GB virus C in modulating HIV disease. Expert Rev Anti Infect Ther. 2012;10(5):563–72. https://doi.org/10.1586/eri.12.37.
6. Fama A, Larson MC, Link BK, Habermann TM, Feldman AL, Call TG, et al. Human pegivirus infection and lymphoma risk: A systematic review and Meta-analysis. Clin Infect Dis. 2020;71(5):1221–8. https://doi.org/10.1093/cid/ciz940.

7. Fridholm H, Ostergaard Sorensen L, Rosenstierne MW, Nielsen H, Sellebjerg F, Bengard Andersen A, et al. Human pegivirus detected in a patient with severe encephalitis using a metagenomic pan-virus array. J Clin Virol. 2016;77:5–8. https://doi.org/10.1016/j.jcv.2016.01.013.
8. Balcom EF, Doan MAL, Branton WG, Jovel J, Blevins G, Edguer B, et al. Human pegivirus-1 associated leukoencephalitis: clinical and molecular features. Ann Neurol. 2018;84(5):781–7. https://doi.org/10.1002/ana.25343.
9. Bukowska-Osko I, Perlejewski K, Pawelczyk A, Rydzanicz M, Pollak A, Popiel M, et al. Human pegivirus in patients with encephalitis of unclear etiology, Poland. Emerg Infect Dis. 2018;24(10):1785–94. https://doi.org/10.3201/eid2410.180161.
10. Tuddenham R, Eden JS, Gilbey T, Dwyer DE, Jennings Z, Holmes EC, et al. Human pegivirus in brain tissue of a patient with encephalitis. Diagn Microbiol Infect Dis. 2020;96(2):114898. https://doi.org/10.1016/j.diagmicrobio.2019.114898.
11. Valyraki N, Maillart E, Pourcher V, Shor N, Tran S, Boudot de la Motte M, et al. Human pegivirus identified in severe myelitis and optic neuritis in immunocompromised patients: A pathogenic role for a forgotten virus? Rev Neurol (Paris). 2023;179(4):361–7. https://doi.org/10.1016/j.neurol.2022.06.011.
12. Carmona RCC, Cilli A, da Costa AC, Reis FC, Leal E, Dos Santos FCP, et al. Pegivirus detection in cerebrospinal fluid from patients with central nervous system infections of unknown etiology in Brazil by viral metagenomics. Microorganisms. 2023;12(1). https://doi.org/10.3390/microorganisms12010019.
13. Doan MAL, Roczkowsky A, Smith M, Blevins G, van Landeghem FKH, Gelman BB, et al. Infection of glia by human pegivirus suppresses peroxisomal and antiviral signaling pathways. J Virol. 2021;95(23):e0107421. https://doi.org/10.1128/JVI.01074-21.

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