A case of Castleman disease with hemophagocytic syndrome derived from HHV8 infection

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Background: For a patient presenting with fever, multiple lymphadenopathy and splenomegaly, pathogen infection should be preferentially considered, followed by lymphoid malignancies. When traditional laboratory and pathological detection cannot find the pathogenic microorganism, metagenomic sequencing (MGS) which targets the person’s genome for exceptional genetic disorders may detect a rare pathogen.

Case presentation: Here, we introduced the diagnostic clue of a case of multicentric Castleman disease (MCD) with hemophagocytic syndrome which was elicited from the detection of human herpesvirus-8 in the blood of a HIV-1 infected person by MGS technology during pathogen inspection. This case highlights the need to increase the awareness of MCD among clinicians and pathologists.

Conclusions: MGS technology may play a pivotal role in providing diagnostic clues during pathogen inspection, especially when pathogens are not detectable by conventional methods.

Keywords: Human herpes virus-8, Multicentric Castleman disease, Hemophagocytic syndrome, Metagenomic sequencing technology
Case presentation

A 49-year-old man with confirmed HIV-1 infection 14 days before treated with lamivudine, tenofovir and efavirenz was admitted with a 3-month history of fatigue, weight loss and fever. He smokes occasionally but denies any alcohol or illicit drug use. He also reported unprotected sex. He has splenomegaly and generalized lymphadenopathy occurred in the neck, axilla, mediastinum and celiac on physical examination and computed tomography scan. A detailed clinical work-up for infection, immune and malignant diseases were performed. His CD4 count was 48 cells/μl and HIV viral load was 8596 copies/ml. Laboratory tests showed pancytopenia, elevated erythrocyte sedimentation rate and C-reactive protein, polyclonal hypergammaglobulinemia and hypoalbuminemia. Serological testing for cryptococcus, Epstein Barr virus, cytomegalovirus was unrevealing (Table 1). Furthermore, peripheral blood cultures

Fig. 1  a Hemophagocytosis image in bone marrow. b Mapping of 5621 human herpesvirus-8 (HHV8) reads derived from the patient’s peripheral blood sample. c The distribution of viral sequences identified in the patient’s peripheral blood. d Phylogenetic analysis showed sequences from representative serovars, strains, and species of HHV8. The scale bar denoted the number of nucleotide substitutions per site.

Fig. 2  a Hematoxylin and eosin staining of lymph node showed plentiful plasma cell infiltration in peri follicular and mantle zone. The follicle had an atrophic germinal center. b Positive HHV8 expression in plasma cells localized in peri follicular and mantle zone by immunohistochemical staining (original magnification ×200).
incubated for 5 days were also negative. Hemophagocytosis could be seen on bone marrow smears (Fig. 1a), complied with fever, splenomegaly, three-line cytopenia, high level of serum ferritin and soluble CD25, supporting the diagnosis of HPS. A lymph node biopsy with the highest standardized uptake value (SUV = 6.0) provided by a positron emission tomography–computed tomography (PET–CT) scan revealed nonspecific lymphocyte proliferation. Pathological imaging of lymph node biopsy showed nonspecific lymphocyte proliferation and excluded malignancy.

To find the cause of HPS, a MGS assay of plasma was performed and the result revealed a HHV8 viremia of 5621 unique reads with coverage of identified viral genes 94.93% (Fig. 1b–d). HHV8-associated diseases were further considered. No Kaposi’s sarcoma evidence was found on the skin, oral and gastrointestinal mucosa by endoscopy. Then the evidence of HHV8 viral load test positive demonstration of in situ hybridization and histopathology evaluation on the lymph node tissue confirmed HHV8-associated multicentric Castleman disease (HHV8-MCD). It was characterized by the presence of sheets of plasma cell in the interfollicular zone. Prominent high endothelial venules could be observed in the interfollicular region. Moreover, the lymphoid follicles were dissolved, with atrophic germinal centers (Fig. 2a, b). Treatment with 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone and combined with ganciclovir for anti-HHV8 treatment in the context of HIV infection, improved the patient’s condition. Nevertheless, the Charlson Comorbidity Index was 8, which suggests poor prognosis.

### Discussion and conclusions

HHV8 infection is found to correlate with Kaposi’s sarcoma (KS) and hematologic diseases, including primary effusion lymphoma and MCD [4]. Here, we have documented a case of HHV8-MCD which was diagnosed based on the detection of HHV8 in the plasma of a HIV-1 infected person by MGS technology and histopathological findings. It was difficult to diagnosis without HHV8 stains because its histological features can be similar to other diseases such as HIV lymphadenitis.

For a case of fever unknown origin, pathogenic microorganism inspection commonly does not include HHV8 detection. But specific HHV8 detection is suggested for a HIV-1 infected patient with fever and lymphatic hyperplasia, because immunodeficiency increases the risk of HHV8 infection. MGS assay may provide a valuable diagnostic support for HHV8 infection [5]. Further, for a HIV/AIDS patient with HHV8 co-infection, KS and Castleman disease (CD) should be considered [6]. HPS is a reactive disorder of the reticuloendothelial system, and occasionally be found in HIV/AIDS patients with malignancies, severe opportunistic infections or autoimmune diseases [7]. CD with HPS is extremely rare and it is difficult to differentiate HPS and CD due to their similar presentations [8]. Thus, HHV8 finding may provide a diagnostic clue for CD with HPS.

To our knowledge, previously documented case of HHV8-associated MCD was mainly diagnosed by the histologic confirmation of lymph node [9, 10]. However, the diagnostic clues and process remain unclear. Here, we presented the diagnostic procedure of the infectious disease, which may provide reference for the diagnosis of unusual pathogens.

### Table 1  Laboratory test results on admission

| Test item                          | Test value | Normal range  |
|------------------------------------|------------|---------------|
| White blood cell counts (10⁹/L)    | 2.85       | 3.5–9.5       |
| Neutrophil counts (10⁹/L)          | 1.26       | 2.0–7.5       |
| Neutrophils percentage (%)         | 59.6       | 40–75         |
| Lymphocyte percentage (%)          | 30.9       | 20–50         |
| Hemoglobin (g/L)                   | 82         | 130–175       |
| Platelets (10⁹/L)                  | 67         | 125–350       |
| Blood urea (mmol/L)                | 6.68       | 2.9–8.2       |
| Creatinine (μmol/L)                | 74         | 57–97         |
| Alanine transaminase (U/L)         | 21         | 9–50          |
| Glutamic–oxaloacetic transaminase (U/L) | 27       | 15–40        |
| Total bilirubin (μmol/L)           | 15.2       | 5–21          |
| Direct bilirubin (μmol/L)          | 6.8        | <7            |
| Albumin (g/L)                      | 27.9       | 40–55         |
| Triglycerides(mmol/L)              | 2.94       | 0.45–1.69     |
| Lactate dehydrogenase (U/L)        | 242        | 120–250       |
| CD4 cell counts (cells/μL)         | 48         | 600–800       |
| Erythrocyte sedimentation rate (mm/hr) | 70     | 0–15          |
| High-sensitivity C-reactive protein (mg/L) | 167.3    | 0–3           |
| Procalcitonin (ng/mL)              | 298        | <0.1          |
| Plasma (1,3) beta-o-glucan (pg/mL) | 28.3       | <60           |
| Serum galactomannan antigen         | Negative   | Negative      |
| Cryptococcus antigen               | Negative   | Negative      |
| Anti-EBV/EA immunoglobulin M antibody | Negative | Negative      |
| Anti-EBV-VCA immunoglobulin M antibody | Negative | Negative      |
| Anti-CMV immunoglobulin M antibody | Negative   | Negative      |
| Anti-Mycoplasma immunoglobulin M antibody | Negative | Negative      |
| Anti-Chlamydia immunoglobulin M antibody | Negative | Negative      |
| EBV DNA (copies/mL)                | <500       | <500          |
| CMV DNA (copies/mL)                | <500       | <500          |
| HIV RNA loads(copies/mL)           | 8596       | <500          |
| Soluble CD25(ng/mL)                | 952.4      | 13.1–43.7     |
| Serum Ferritin(μg/L)               | 2902       | 15–200        |

EBV: Epstein Barr virus, CMV: cytomegalovirus, EA: early antigen, VCA: viral capsid antigen, HIV: Human Immunodeficiency Virus
In conclusion, physicians should be expanding the knowledge for diseases presenting with fever and lymphadenopathy and be aware about the possibility of MCD in patients with immunodeficiency. The diagnosis might be difficult, but the etiology should be repeatedly sought. MGS may provide a diagnostic clue for infection-associated diseases.

Abbreviations
MGS: Metagenomic sequencing; MCD: Multicentric Castleman disease; HHV8: Human herpes virus-8; HPS: Hemophagocytic syndrome; PET–CT: Positron emission tomography–computed tomography; HHV8-MCD: HHV8-associated multicentric Castleman disease; KS: Kaposi’s sarcoma; CD: Castleman disease.

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Authors' contributions
XC and YW collected clinical data and drafted the manuscript; LJ interpreted the data and critical revised the manuscript; JC performed the pathological diagnosis; CL performed the lymph node biopsy; CG, TZ and YM revised the manuscript for important intellectual content; YZ obtained funding and performed study supervision. All authors read and approved the final manuscript.

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Declarations
Ethics approval and consent to participate
This study was performed in line with regulations issued by the National Health Commission of China and was approved by the local Commission of Ethics (reference number LL 2019-053-K). Informed consent was obtained from the participant included in the study.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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