CASE REPORT

Evidence for cytomegalovirus-induced haemophagocytic syndrome in a young patient with AIDS

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SUMMARY

A 29-year-old man with HIV infection was referred to our department because of a 1-month history of low-grade fever and fatigue. Bone marrow aspiration and biopsy showed findings consistent with haemophagocytic syndrome (HPS), and immunohistochemical assessment showed cytomegalovirus (CMV) infection. HIV-associated HPS can occur at any stages of HIV disease and requires diverse differential diagnosis. CMV-associated HPS (CMV-HPS) in patients with HIV infection is relatively rare, but the present case showed that the clinicians should consider the possibility of CMV-HPS as a clinical feature of CMV infection.

BACKGROUND

HIV can cause diverse opportunistic infections and secondary haemophagocytic syndrome (HPS). HIV itself may be a trigger for HPS, but the clinical course associated with cytomegalovirus (CMV)-induced HPS in patients with HIV has not been well characterised. This report describes the clinical course of a rare case of CMV-induced HPS with HIV infection.

CASE PRESENTATION

A 29-year-old man presented to our department with a 1-month history of low-grade fever and fatigue. He had been in good health for the preceding 4 months. However, he developed transient diarrhoea and was incidentally diagnosed with HIV infection with a CD4 T-lymphocyte count of 156 cells/mm³ and a viral load of 2.9×10^5 copies/mL. Laboratory assessment at his regular outpatient follow-up, conducted 5 days prior to presentation at our department, showed CMV antigenemia (C10/C11 monoclonal antibodies) of 100/222 (per 150 000 white cell count (WCC)). About 3 days after initiation of oral treatment for CMV infection with valganciclovir (1800 mg/day), he was admitted to our department for further evaluation and treatment of a low-grade fever and CMV infection. On admission (day 1), his vital signs were normal except for a high fever of 39°C. Physical examination showed mild conjunctival anaemia, and the liver edge was palpated at two fingers breadths below the costal margin, suggesting mild hepatomegaly. Serum laboratory examination showed bicytopenia (haemoglobin (Hb) 10.1 g/dL and platelets $4.9 \times 10^3/\mu\text{L}$) and mild hypertriglyceridaemia (230 mg/dL) as well as marked elevation of glutamate oxaloacetate transaminase (GOT; 658 IU/L),

glutamic pyruvic transaminase (GPT; 314 IU/L), lactate dehydrogenase (1637 IU/L) and ferritin (19251 ng/mL). Serum CD4 T-lymphocyte count was 120 cells/mm³, and the viral load was 2×10^5 copies/mL. Chest X-ray taken on day 1 was normal, but non-enhanced abdominal CT at that time demonstrated mild hepatosplenomegaly.

INVESTIGATIONS

Based on a tentative diagnosis of HPS due to HIV infection or other unknown causes, bone marrow aspiration with biopsies was performed on day 3. On May-Giemsa stain, bone marrow smear showed blue staining foamy macrophages engulfed platelets (figure 1A) or myelocytes (figure 1B). Bone marrow biopsied specimens showed a hypercellular bone marrow and no definite evidence of malignancy, but engulfment of erythroblasts by macrophages was noted (figure 1C). Five out of eight diagnostic criteria were therefore satisfied for HPS (fever $\geq 38.5^\circ\text{C}$; any two of the following: Hb < 90 g/L, platelets $< 100 \times 10^9/\text{L}$, neutrophils $< 1.0 \times 10^9/\text{L}$; ferritin level ≥ 500 $\mu\text{g/L}$; spleen palpable greater than 3 cm below the costal margin; and the presence of haemophagocytosis without malignancy). Importantly, immunohistological identification was only positive for CMV (figure 1D) and not for herpes simplex virus (HSV) I, HSV II, Epstein-Barr virus (EBV), or *Toxoplasma gondii*. Based on these data, a diagnosis of CMV-induced HPS was made.

TREATMENT

The patient was treated with intravenous foscarnet (60 mg/kg twice a day) instead of oral valganciclovir. On day 15, owing to mild renal insufficiency, foscarnet was changed to intravenous ganciclovir (5 mg/kg twice a day).

On day 16, the *thrombocytopenia*, the elevation of liver enzymes, and the degree of CMV antigenemia had improved (platelet, $11.2 \times 10^4/\mu\text{L}$; GOT, 134 IU/L; GPT, 108 IU/L; C10, 3 (cells) per 150 000 WCC; C11, 6 (cells) per 150 000 WCC; figure 2). At that time, defervescence was noted, and fatigue resolved, but the anaemia was progressed to 6.5 g/dL. On day 21, it improved to 8.0 g/dL with an only treatment for CMV infection, and antiretroviral therapy (ART) with Epzicom (abacavir and lamivudine) and raltegravir potassium was initiated.

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Figure 1 On May-Giemsa stain, bone marrow aspiration performed on day 3 showed blue staining foamy macrophages engulfed platelets (A) or myelocytes (B). Bone marrow biopsy specimens revealed macrophages engulfing erythroblasts (C) and cytomegalovirus positive cells (D) were seen on immunohistochemical stain.

OUTCOME AND FOLLOW-UP

After initiation of ART, the WCC was recovered to the level seen at admission, and he was discharged uneventfully on day 34.

DISCUSSION

HPS is rare disorder characterised by high fever, hepatosplenomegaly, lymphadenopathy, cytopenias and hyperferritinaemia. Diverse viruses, such as EBV, CMV, HSV and herpes zoster virus,

are the most common cause of viral-associated HPS.^{1 2} Other than EBV, the most common herpesviruses associated with HPS are CMV and human herpesvirus-8.³ CMV-associated HPS (CMV-HPS) has been reported both in non-immunocompromised⁴ and immunocompromised patients, such as patients with inflammatory bowel disease,⁵ rheumatological diseases,⁶ cancer⁷ and transplant patients.⁸ To the best of our knowledge, only nine cases of CMV-HPS in Japan have been

Figure 2 Clinical course of the present case.

described, and those cases consisted of patients with rheumatological diseases (n=5),^{9–10} haematological malignancies (n=2),¹¹ diabetes mellitus (n=3, 2 of 3 had rheumatological diseases) and chronic kidney disease (n=1), suggesting a low morbidity rate. However, immunohistochemical analysis clearly depicted CMV-positive cells in biopsied specimens, and treatments directed against CMV infection led to resolution of various manifestations, including bicytopenia, elevated liver enzymes and subjective symptoms. These observations suggest that CMV infection was the main cause of HPS in this case.

HPS can occur at any stage of HIV disease, and Niedt and Schinella¹² reported that 20% of 56 autopsy cases with HIV infection had haemophagocytosis and that, antemortem clinical diagnosis was rare. Grateau *et al*¹³ reported that the incidence of HPS was 0.6%, but also stated that the role of the HIV in HPS remains to be defined. Furthermore, not all patients fulfil the criteria for HPS, and one or more of the criteria may present at a later stage in the disease, which might lead to the lack of data in large series of HIV-HPS, both pre-ART and in the ART era. HIV-HPS is often fulminant, and Bhatia *et al*¹⁴ reported that the recovery rate from HPS was significantly worse in patients with HIV (28%) when compared with patients without HIV (60–70%).¹⁵

Several reports have described the CMV-HPS in patients with HIV. Fardet *et al*¹⁶ reported that CMV-HPS among 58 patients with HIV was noted in 5% (n=2) or 20% (n=3) among 43 definite and 15 possible HPS cases, respectively. Thus, CMV infection is likely a cause of HPS in patients with HIV.

In patients with HIV, clinical manifestations of HPS require a wide differential diagnosis, and HIV itself or its associated opportunistic infections may be the underlying trigger. Therefore, diagnosis of HPS in the setting of HIV can be difficult. A study from Texas¹⁷ found that a ferritin level above 10 000 µg/L was 90% sensitive and 96% specific for HPS. A high level of awareness of the clinical and diagnostic features of HPS is important, and clinicians should be aware of the variable presentation of this disease.

Learning points

- ▶ HIV itself can cause haemophagocytic syndrome (HPS), and antemortem clinical diagnosis of HPS is often difficult.
- ▶ Among herpesviruses, Epstein-Barr virus, human herpesvirus-8 and cytomegalovirus (CMV) can cause HPS.
- ▶ CMV infection can cause HPS, even in patients with HIV.

Contributors KO and TS wrote the manuscript, and have also along with other authors, managed the patient in inpatient or outpatient settings.

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