HHV-6 encephalitis in a non-transplanted adult acute myeloid leukemia patient

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Dear Editor,

Here, we report a case of a clinically manifest human herpesvirus-6 (HHV-6) encephalitis in a neutropenic patient with acute myeloid leukemia (AML) in a non-transplant setting while on antimicrobial prophylaxis including aciclovir.

A 38-year-old female patient was admitted to the hospital with newly diagnosed AML. Following second consolidation chemotherapy containing high-dose cytarabin, the patient showed signs of forgetfulness, myoclonia in both arms, and eventually suffered from a generalized tonic-clonic seizure. Electroencephalography showed generalized slowing but no epileptiform activity. The MRI showed restricted diffusion bilateral within the frontal striatum, as well as increased contrast enhancement in the lenticulostrate arteries, indicative of inflammatory lesions (Fig. 1a). Polymerase chain reaction (PCR) analyses of the cerebrospinal fluid (CSF) and blood serum were positive for HHV-6. Intravenous antiviral therapy with ganciclovir was commenced. The patient continued to display amnesia of short-term memory, which was slowly declining within the following weeks. Repetitive MRI scans showed increased inflammatory changes 9 days later (Fig. 1b) that receded within the following 2 weeks with only residual inflammation within the basal ganglia. Twenty-five days following initiation of ganciclovir PCR for HHV-6 from blood serum was negative, and secondary prophylaxis with oral valganciclovir was started.

With regard to the AML therapy, indication for allogeneic hematopoietic stem cell transplantation (allo-HCST) from an HLA-matched sibling was met due to ongoing detection of NPM1. Before allo-HSCT PCR for HHV-6 in CSF as well as blood was negative, and MRI scan showed few residual inflammatory signs within the basal ganglia (Fig. 1c). Allo-HSCT was performed after conditioning chemotherapy with treosulfan and fludarabine, and immunosuppression with cyclosporine and methotrexate was administered as described [1]. Importantly, no signs and symptoms of virus reactivation during and following allo-HSCT were noticed as the patient continued on prophylactic valganciclovir, continuously. An MRI scan 3 months after initial diagnosis of HHV-6 encephalitis and performed allo-HSCT displayed no signs of cerebral inflammation (Fig. 1d). Sixty days after allo-HSCT bone marrow biopsy showed a complete remission. Table 1 shows a time course of the AML therapy, MRD levels, HHV-6-PCR, and MRI scans.

HHV-6 displays latency after the primary infection. End-organ disease usually occurs in an immunocompromised host and is most likely due to reactivation. HHV-6 is the most frequent cause of encephalitis in an allo-HCST setting and typically takes a subacute course with slow beginning of confusion, amnesia, and change of personality [2]. Post allo-HSCT HHV-6 reactivation is associated with higher incidences of acute graft-versus-host disease, CMV reactivation, and non-relapse mortality [3]. Outcome of HHV-6 encephalitis post allo-HSCT is poor with a mortality rate of 20 to 40% and a high proportion of patients suffering from neurological sequelae including temporal lobe epilepsy [4, 5]. Treatment options include ganciclovir, foscarnet, and cidofovir that inhibit HHV-6 replication [6]. As HHV-6 reactivation often coincides with the onset of disease, routine screening is not

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recommended [7]. In 2019 guidelines for management of HHV-6 infection in patients with hematologic malignancies were published [8].

To our knowledge, this is the first report of clinical manifest HHV-6 encephalitis in a leukemic patient prior to allo-HSCT without any predisposing factors contributing to an immunocompromised state before the diagnosis of AML was made. Since MRI scan may be negative at the beginning of the disease, close clinical and diagnostic monitoring is necessary if a patient presents with acute-onset altered mental status (encephalopathy), short-term memory loss, or seizures. This case indicates the significance of observing clinical signs and symptoms of incipient encephalopathy and rapid diagnostic and therapeutic measures to prevent residual damage.

Table 1  Time course including AML therapy, MRD, microbiologic tests, and MRI scans

| Therapy                      | Induction therapy (7+3 protocol) | 1st consolidation (HD-AraC) | 2nd consolidation (HD-AraC) | Allo-HSCT | +31 days post allo-HSCT | +63 days post allo-HSCT |
|------------------------------|----------------------------------|-----------------------------|-----------------------------|-----------|------------------------|-------------------------|
| Start date                   | 17.01.2020                       | 04.03.2020                  | 12.05.2020                  | 18.08.2020| 17.09.2020             | 19.10.2020              |
| NPM1 mutation (%)            | 2240                             | 0.6                         | 0.5                         | 0.07      | 0.03                   | 0.003                   |
| HHV-6-PCR-blood (days post chemotherapy) | Positive (+34, +50, +66) | Negative                     |                             |           |                        |                         |
| HHV-6-PCR-CSF (days post chemotherapy) | Positive (+34) | Negative                     |                             |           |                        |                         |
| Chimerism (5)                |                                  |                             |                             | 89        | 100                    |                         |
| MRI imaging (days post chemotherapy) | (Fig. 1a) +34 | (Fig. 1c) −8               | (Figure 1b) +42             |           |                        |                         |

Fig. 1 MRI T2-FLAIR imaging studies during the course of HHV-6 encephalitis. a Slight bilateral asymmetrical diffusion restricted areas in corpora striata. b Marked bilateral asymmetrical diffusion restricted areas in corpora striata. c Regression of diffusion restricted areas in corpora striata. d Normal appearance of corpora striata without evidence of diffusion restriction.
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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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