HHV-6 Encephalitis following Chimeric Antigen Receptor T-cell Therapy: Report of 2 Cases

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BACKGROUND

- Human herpesvirus 6 (HHV-6) is the most common cause of infectious encephalitis following hematopoietic stem cell transplant.[1]
- Chimeric antigen receptor T-cell (CAR-T) therapy is a novel cancer-directed immunotherapy
- chemotherapy conditioning for CAR-T results in prolonged, severe immunosuppression.
- HHV-6 encephalitis has not been reported in patients after CAR-T therapy.

CASES

Case 1: A 69 year old man underwent CAR-T therapy after fludarabine/cyclophosphamide (Flu/Cy) conditioning for relapsed diffuse large B cell lymphoma (DLBCL). His course was complicated by cytokine release syndrome (CRS) requiring tocilizumab and neurotoxicity requiring high dose dexamethasone. On day 29 he was febrile to 39.3℃, confused, and had difficulty speaking. Mental status (MS) worsened, so LP and MRI of the brain were performed. HHV-6 CSF PCR was positive, and ganciclovir (GCV) was started. He improved gradually over 10 days. At follow up, he reported mild short term memory difficulty but no focal deficits.

Case 2: A 57 year old man underwent CAR-T therapy after Flu/Cy conditioning for refractory DLBCL. His course was complicated by CRS requiring tocilizumab. On day 6, he had difficulty concentrating, slowed thinking, stuttering and repetitive speech. MS continued to worsen, and dexamethasone and siltuximab were given for CAR-T neurotoxicity. After 1 week he was following commands. By week 3 he remained intermittently confused and agitated, so MRI and LP were performed. HHV-6 PCR was positive in the CSF. He was started on GCV and improved gradually over the next 2 weeks but remained dysarthric with slowed speech. On day 55, HHV-6 remained detectable in CSF but not quantifiable and GCV was discontinued despite persistent cognitive deficits.

DISCUSSION

Diagnosing HHV-6 encephalitis can be challenging after CAR-T therapy because altered mental status is often attributed to CAR-T associated neurotoxicity. It is important to maintain a high index of suspicion for infectious causes of AMS after CAR-T therapy, including HHV-6 encephalitis, especially in patients treated with further immunosuppression for CRS and CAR-T related neurotoxicity.

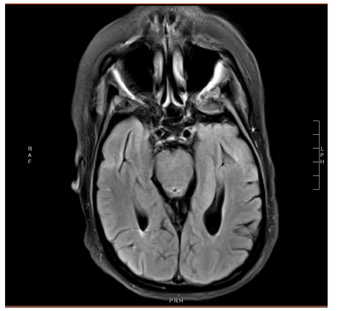
TABLE

Table 1: Demographics and clinical characteristics

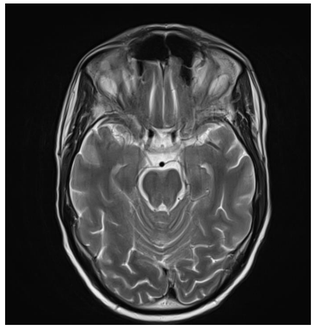
Case	1	2
Age (years)	69	57
Sex	Male	Male
Cancer	Relapsed DLBCL	Refractory DLBCL transformed from follicular lymphoma
Conditioning regimen	fludarabine/cyclophosphamide	fludarabine/cyclophosphamide
CAR-T neurotoxicity (day)	Present (4)	Present (2)
Immunosuppressants (days)	Tocilizumab 560 mg (4, 5) dexamethasone 10 mg q6h (9-11)	Tocilizumab 560 mg (2, 3) solumedrol 1 g, (8-10, 26-28) siltuximab 800 mg (8)
Onset of symptoms after CAR-T (days)	29	6
Presenting signs/symptoms	Fever, altered mental status	Difficulty concentrating, slowed thought process, stuttering, repetitive speech
LP (day)	31	33
CSF WBC (cells/mcL)	50 (53% lymphs, 32% monos, 1% polys, 1% basos)	2 (89% lymphs, 10% monos, 1% polys)
CSF RBC (cells/mcL)	570	0
CSF protein (mg/dL)	222	167
CSF glucose (mg/dL)	43	34
HHV-6B DNA in CSF (copies/mL)	1460	2910
HHV-6B in PB	Not detected	Detected, not quantified
MRI findings	Mild bilateral areas of T2/FLAIR increased signal and mild restricted diffusion within bilateral hippocampi	Mild diffuse FLAIR hyperintensity in the periventricular white matter and brainstem
EEG results	Mild to moderate generalized slowing, no clear interictal epileptiform discharges	Rare generalized discharges with triphasic morphology, no seizures
Treatment (drug, dose, duration)	Ganciclovir 5mg/kg q12 hours for 7 days, valganciclovir 900 q12 hours for 27 days	Ganciclovir 1.25 mg/kg daily (renally dosed) for 26 days
Outcome (days)	Mild short term memory difficulty. No focal deficits. (50)	Persistent cognitive deficits. (55)

IMAGES

Patient 1 MRI T2 FLAIR



Patient 2 MRI T2 weight



REFERENCES

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