CASE REPORT

Viral and paraneoplastic encephalitis in a patient with liver transplant with unilateral temporoparietal lobe abnormalities: a diagnostic challenge

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SUMMARY

We report a patient who recently had a liver transplant presented with increasing confusion and intermittent hallucinations. MRI of the brain revealed diffuse left temporal and parietal lobe swelling with cortical diffusion restriction suggestive of possible infectious aetiology, although stroke was also possible given the presence of left posterior cerebral arteries with fetal origin in the anterior circulation. An EEG demonstrated subclinical seizures, for which he was placed on an antiepileptic medication. Routine laboratory testing, lumbar puncture, serum and cerebrospinal fluid testing for viral and paraneoplastic encephalitis, and brain biopsy were performed on our patient. Our clinical diagnosis was viral encephalitis, and positive N-type voltage-gated calcium channel antibody titres were suggestive of paraneoplastic limbic encephalitis. Treatment with antiviral and antiepileptic medications for subclinical seizures resulted in the improvement of his mental status, language output and motor functioning.

BACKGROUND

Viral encephalitis has been associated with states of immunosuppression and in patients with solid organ transplantation. Paraneoplastic limbic encephalitis, another diagnostic consideration, is a rare disorder which often affects the mesial temporal lobe which can be caused by neoplasms, toxic and metabolic encephalopathies, infections and side effects of cancer therapy. To our knowledge, only several case reports have reported the concurrent presentation of viral and paraneoplastic encephalitis.

In this study, we report a case of presumptive viral encephalitis associated with paraneoplastic encephalitis in a liver transplant recipient who presented with encephalopathy and new onset aphasia. This article serves to illustrate the importance of carefully considering all diagnostic possibilities in any immunosuppressed patient presenting with encephalopathy, and the importance of empirical treatment on the basis of specific epidemiological or other clinical factors. As seen in our case, the consideration of paraneoplastic limbic encephalitis, infectious aetiologies, stroke, adverse effects of medications, seizure disorders and malignancies are essential because treatment or therapies for secondary prevention are available for each entity.

CASE PRESENTATION

A 60-year-old, right-handed Hispanic man, with a history of cirrhosis from chronic hepatitis C virus

(HCV) infection, had an orthotopic liver transplant in 2011, maintained on immunosuppressant therapy, presented with subacute worsening of mentation. He had a history of prior left temporal stroke 5 years ago without known deficits and hypertension. The patient was maintained on prednisone and tacrolimus for immunosuppression, and bactrim prophylaxis. He initially presented to an outside hospital 3 months prior with jaundice, was found to be in acute rejection following results of liver biopsy and was given high-dose steroid treatment with increases made to tacrolimus. Approximately 1 month later at a follow-up appointment, he was found to have recurrent HCV infection. Significant reductions were made to prednisone and tacrolimus for probable immunosuppression-associated HCV reactivation. Two weeks prior to admission, his family noted worsening intermittent confusion along with hallucinations, but according to his family, there was an acute change 2 days prior to admission, at which point his speech stopped making sense over the phone.

He presented to our hospital with a low-grade fever, and was encephalopathic with additional examination findings of decreased fluency, psychomotor slowing, right homonymous hemianopsia, mixed aphasia and mild right upper extremity weakness. His ECG demonstrated atrial fibrillation with rapid ventricular response. Head CT was initially concerning for acute left middle cerebral artery stroke. However, a MRI brain showed diffuse swelling and mass effect of the left temporal lobe extending to the parieto-occipital junction, with diffusion restriction of the temporal lobe cortex and scattered areas of apparent diffusion coefficient (ADC) dropout suggesting a possible infectious aetiology (figure 1A,B). Stroke was still in our differential, given that our patient had a fetal origin of the left posterior cerebral artery, which could have presented with both an anterior and posterior circulation infarct (figure 1C). However, stroke was still less likely given the atypical areas of diffusion restriction limited to the cortices, and absence of neurovascular occlusion. He was not started on anticoagulation for concern of haemorrhagic conversion and large size of lesion on imaging. No patent foramen ovale, vegetations or intramural thrombi were noted on ECG to suggest a thromboembolic source.

Encephalopathy secondary to an infectious aetiology was high on our differential given his history of immunosuppression. His immunosuppressant

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Figure 1 MRI of the brain. (A) T2-fluid-attenuated inversion recovery (FLAIR) sequence on admission showing pathological intensity signal mainly in the left temporal lobe including the hippocampus and parahippocampal gyrus. (B) Diffusion-weighted image showing hyperintensity along the temporal cortex. (C) MR angiography with fetal origin of the left posterior cerebral artery (red arrow drawn for illustration). (D) FLAIR sequence approximately 1 month following initial presentation.

regimen was held, and he was started on acyclovir for possible herpes simplex virus (HSV) encephalitis and voriconazole for antifungal therapy until cultures were resulted. A video EEG showed frequent electrographic seizures, as well as unilateral periodic lateralised epileptiform discharges and frequent left posterior sharp and slow wave discharges without clear clinical correlate, at which point he was placed on keppra. Video EEG monitoring yielded gradual resolution of epileptiform activities following keppra initiation and titration.

He was subsequently transferred to the medical intensive care unit for close monitoring. A lumbar puncture was initially deferred given left brain oedema and impending uncal herniation. Acyclovir was discontinued and foscarnet was started because of improved central nervous system penetration and better coverage for possibility of infection with HSV, human herpes virus-6 (HHV-6) and varicella-zoster virus (VSV). On day 4 of admission, a lumbar puncture was performed following mannitol administration. CSF results were unremarkable (1 WBC, 9 RBCs, 39 protein and 59 glucose). The viral encephalitis panel (adenovirus, HSV-1, HSV-2, cytomegalovirus (CMV), VZV, Epstein-Barr virus (EBV), HHV-6 and enterovirus), cryptococcus antigen and fungal culture were all negative. His mental status improved somewhat with improved alertness but still continued to demonstrate a fluent aphasia.

On day 9 of admission, he was transferred to the neurology service for further management, with plans to arrange for left craniotomy for brain biopsy. Tissue obtained from biopsy was sent for analysis by PCR for a panel of viruses, including HSV, CMV, HHV-6, which were negative. HSV culture was performed on the biopsy specimen, which was also negative. Biopsy results were non-specific, revealing reactive astrocytes and minimal inflammation. Given the patient's clinical picture of encephalopathy, fever, subclinical seizures, focal neurological findings and findings on EEG and neuroimaging, the working diagnosis was viral encephalitis, and a decision was made to complete 28 days of antiviral treatment. During his hospital course, he developed acute kidney injury in the setting of foscarnet, and subsequently was switched to renally dosed gancyclovir. Following 28 days of therapy, gancyclovir was changed to oral valgancyclovir for long-term treatment. Oral voriconazole was also continued for approximately 1 month following initiation. Tacrolimus was resumed approximately 3 weeks into his admission.

Amidst clinical and radiographical improvement, a decision was made to start coumadin for stroke prevention in the setting of atrial fibrillation and a CHADS2 score of 3 (one point for hypertension and two points for prior stroke). However, because of a precipitous increase in his international normalised

ratio (INR) following initiation of anticoagulation, coumadin was discontinued. Pradaxa was also considered, but given his impaired renal function, it was deferred for future consideration as an outpatient.

Overall, the patient made moderate improvements in language output (particularly with fluency and naming), gait and vision, with subsequent MRI showing decreased spread of his previously noted T2-fluid-attenuated inversion recovery (FLAIR) hyperintense lesion (figure 1D). A serum paraneoplastic panel yielded mildly elevated anti-N-type voltage gated calcium channel (VGCC) antibody titre of 0.04 nmol/l. No other paraneoplastic antibody (including binding, ganglionic and striational acetylcholine (ACh) receptor antibodies, Purkinje cell antibodies type 1 (PCA-1 or anti-Yo), PCA-2, PCA-Tr, antineuronal nuclear antibodies type 1 (ANNA-1 or anti-Hu), ANNA-2, ANNA-3, anti-Ma, collapsing response-mediator protein-5 (CRMP-5) or voltage-gated potassium channel antibodies) were detected. An initial chest radiograph did not reveal any malignancy. Intravenous immunoglobulin (IVIg) treatment was administered once during hospitalisation for treatment of possible limbic encephalitis, but it was not continued because of further worsening of his acute renal insufficiency, and given gradual clinical improvement seen on serial neurological examinations. He was ultimately transferred to subacute rehabilitation.

DISCUSSION

A major challenge in treating patients suspected to have viral encephalitis is that despite extensive neurological evaluations, laboratory and radiographic testing, the majority of cases cannot be clearly elucidated. Paraneoplastic limbic encephalitis, stroke and even uncommon adverse effects of immunosuppressor medications such as tacrolimus share similar clinical features including mood changes, seizures, hallucinations and memory loss, which render a specific diagnosis challenging. Our patient initially presented with a clinical picture most consistent with viral encephalitis, for which we suspected to be secondary to HSV or HHV-6. After the initiation of antiviral therapy, we noticed a mild improvement in the patient's mental status within the first 36–48 h. His MRI brain demonstrated diffuse swelling and mass effect of the left temporal lobe mainly because of cortical thickening and oedema, with medial temporal lobe involvement including the hippocampus and parahippocampal gyrus, and diffusion hyperintensity of the swollen temporal lobe cortex with multiple scattered areas showing ADC deficit. MRI findings of HSV typically include significant unilateral or bilateral fronto-temporal lobe oedema with high signal intensity on a FLAIR and T2-weighted image and restricted diffusion is common due to cytotoxic oedema, both features of which our patient had. T1-weighted imaging with contrast may have demonstrated gyral enhancement, leptomeningeal enhancement or diffuse enhancement, but was deferred in our patient due to acute kidney injury. MRI findings for HHV-6 are similar and may include increased attenuation in white matter of frontoparietal lobes, to oedema of the temporal lobes and limbic system. HHV-6 encephalitis has been well described and particularly associated with immunocompromised persons and transplant recipients.^{1–3}

The diagnostic sensitivity of nucleic acid amplification tests (PCR) for HSV and HHV-6 for CSF are greater than 95%.⁴ In our case PCR testing and cultures for HSV-1 and HSV-2, CMV, VZV, EBV, HHV-6 and enteroviruses were negative from CSF.

We believe the results were obscured as the samples were obtained more than 4 days following initiation of antiviral therapy. Although methods of serological testing (for specific IgM or IgG antibody titres) and PCR have increased the ability to detect viral causes of encephalitis, a negative result cannot be used as definitive evidence to exclude the diagnosis.⁴ Particularly with transplant recipients, the clinical utility is often limited as results are not uncommonly false negative because of the inability of immunosuppressed patients to develop antibodies.⁵ Factors such as time of CSF sampling relative to onset of clinical symptoms and treatment, sensitivity of virus-specific primers, and PCR methods may contribute to overall differences in viral detection in CSF.⁶ In addition, viral cultures of CSF specimens that are of limited value in patients with encephalitis, does not necessarily distinguish latency from active growth when positive, and are not routinely recommended.^{4–6} For the above reasons, empirical therapy for viral encephalitis should be initiated when there is high clinical suspicion, and should not be delayed for laboratory results.

In the setting of iatrogenic immunosuppression, autoimmune limbic encephalitis initially appeared unlikely in our patient, as we would have expected limbic encephalitis to have responded to immunomodulatory therapy for which this patient was on after his liver transplant. Hence, we were surprised to find that our patient demonstrated positivity to N-type VGCC antibodies. One possible explanation for the unusual presentation was that our patient became more susceptible to an autoimmune phenomenon after significant reductions were made to his immunomodulatory medications following diagnoses of HCV reactivation and into treatment of presumptive viral encephalitis. A second explanation is the possible role of viral agents in the induction of autoimmune processes such as limbic encephalitis, as our patient carried a history of recent acute on chronic HCV infection. Only several studies have described paraneoplastic limbic encephalitis which presented either initially or concurrently as acute viral encephalitis.^{7–9} This association poses the problem of a possible relation between these two entities which only becomes further challenged by the diagnostic dilemma.

The diagnostic criteria for establishing the diagnoses of paraneoplastic limbic encephalitis was first proposed by Dalmau, which includes (1) a compatible clinical picture of an insidious, subacute onset of neurological and psychiatric symptoms, (2) an interval of <4 years between the development of neurological symptoms and cancer diagnosis, (3) exclusion of other neuro-oncological complications and (4) at least one of the following: CSF with inflammatory changes but negative cytology, MRI demonstrating temporal lobe abnormalities, or an EEG showing focal slowing or epileptiform activity in one or both temporal lobes.¹⁰ Our patient met all criteria except the presentation of malignancy. However, paraneoplastic syndromes can manifest before a cancer diagnosis, illustrating the importance of a rational approach to tumour screening.^{11 12} It is also worth mentioning that although our patient met the criteria for temporal lobe abnormalities on MRI, his findings are atypical given the usual predisposition towards the mesial temporal lobes. A correct diagnosis following a thorough neurological history and physical, serological testing and neuroimaging, is very important because there are effective treatments. Paraneoplastic encephalitis could demonstrate a response after antineoplastic or immunosuppressor treatment whereas a viral encephalitis may respond to antiviral therapy.

Learning points

- ▶ Paraneoplastic limbic encephalitis, although often presenting as a chronic or subacute disease, may be clinically indistinguishable from acute viral encephalitis, and both may be present at one point.
- ▶ Empirical therapy for viral encephalitis should be initiated when there is high clinical suspicion, and should not be delayed for laboratory results, which may be obscured by the timing of testing and other false-negatives.
- ▶ Consider all diagnostic possibilities in any immunosuppressed patient presenting with encephalopathy, including, but not limited to infectious aetiologies, stroke, seizure disorders, adverse effects of medications and paraneoplastic encephalitis.

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