Case Report

Case report: Herpes simplex encephalitis in cancer patients

Christina F. Yen[1], Madhukar S. Patel[1], Peiguo Chu[2], Yun Yen[1,*], Weber Chen[3]

[1] *Department of Clinical and Molecular Pharmacology, City of Hope National Medical Center, Duarte, CA, USA;*
[2] *Dvision of Pathology, City of Hope National Medical Center, Duarte, CA, USA;*
[3] *San Gabriel Valley Medical Center, San Gabriel, CA, USA.*

Summary **The manifestation of herpes simplex encephalitis in patients can often be interpreted as a possible brain tumor. In order to make a definite diagnosis, subsequent invasive testing is frequently required. In addition to other routine diagnostic measures, particular symptoms, especially those indicating that a patient is immunocompromised, should be considered as possible evidence indicating presence of this central nervous system (CNS) viral infection.**

Keywords: Herpes simplex virus, Encephalitis, Brain tumor, Immunocompromised, MRI

1. Case report

A 72 year-old Vietnamese man was presented with a severe headache and fever of 103 degrees. Neurological examination revealed that the patient had minimal left side weakness and mental status changes. Subsequent computer tomography (CT) scan of the head showed a mass effect that extended inferiorly from the sylvian fissure to involve the right temporal lobe with contrast enhancement. Such results were thus interpreted as a possible tumor; hence, the patient was initially treated with antibiotics and steroids. However, the patient showed no response, and to further exacerbate his previous condition, his neurological status began to deteriorate. A follow-up magnetic resonance image (MRI) of the brain, pre and post contrast, showed diffuse involvement of the right temporal lobe with multiple areas of enhancement confined to the region (Figure 1). Additionally, the MRI showed edema and displacement of the uncus into the temporal hiatus. These results led to the consideration of the presence of either encephalitis or brain tumor.

The patient thus underwent a craniotomy with right temporal lobe biopsy and right temporal lobectomy to confirm the diagnoses. Biopsy tissue revealed necrotizing meningoencephalitis as well as lymphocytic infiltration of the meningeal surface and in the brain parenchyma with perivascular distribution (Figure 2A). While there is no evidence of a neoplasm cell, the brain tissue showed further diffuse collections of foamy histiocytes and reactive gliosis indicative of necrosis (Figure 2B). The immunoperoxidase stains further confirmed the Herpes simplex virus I and II with focally positive nuclear staining (Figure 2C). Thus, the histologic and immunohistochemical features are consistent with herpes simplex encephalitis. Post-operatively, the patient developed gastrointestinal bleeding due to the presence of a locally advanced

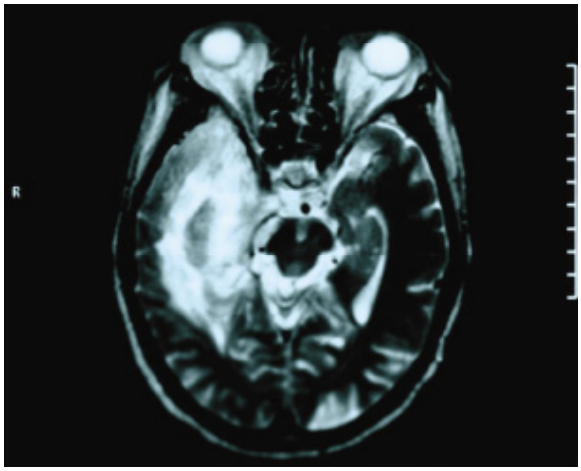

Figure 1. MRI demonstrated right temporal lobe signal enhancement.

**To whom correspondence should be addressed:*
Dr. Yun Yen, Department of Clinical and Molecular Pharmacology, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010, USA;
e-mail: yyen@coh.org.

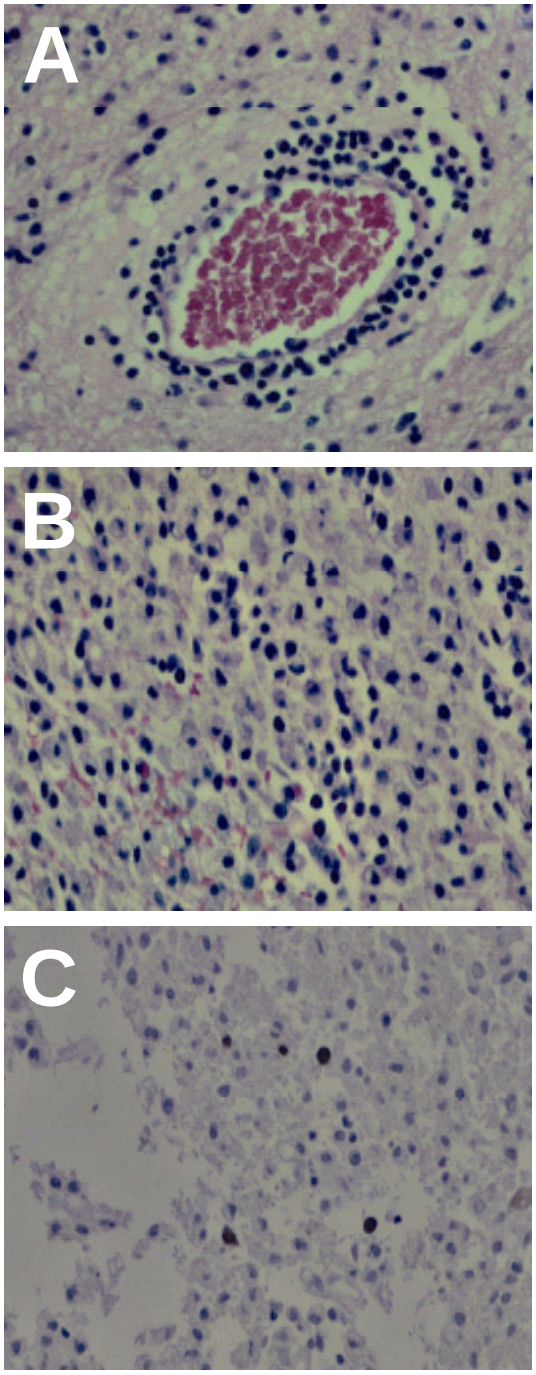

Figure 2. Pathology study of brain biopsy. (A) Biopsy tissue shows necrotizing meningoencephalitis and lymphocytic infiltration on meningeal surface and in brain parenchyma with perivascular distribution. (B) Brain biopsy tissue shows histiocytes and reactive gliosis. (C) Immunoperoxidase stain confirms Herpes Simplex Virus Type I and II with positive nuclear staining.

carcinoma of the sigmoid colon with liver metastasis, confirmed via intraoperative findings. Endoscopic examination further corroborated the presence of a sigmoid colon carcinoma.

2. Discussion

Because this case involves the coexistence of advanced carcinoma with a CNS viral infection, it exemplifies the difficulty of differentiating herpes simplex encephalitis from a brain tumor. Thus, routine tests such as a CT scan or MRI, which are important in delineating the extent of the disease, do not necessarily yield pathognomic findings and are often not enough to confirm either condition (*1*). Laboratory tests such as polymerase chain reaction of the viral genome in cerebrospinal fluid and serum herpes simplex virus antibody measurements are also not definite methods of diagnosing herpes simplex encephalitis; ultimately, a biopsy was necessary to make the diagnosis (*2*,*3*). Worse, polymerase chain reaction results can be confounded with false positive results (*4*). The lack of results and the potential of inaccurate ones only further complicates the diagnosis of encephalitis, cancer, or both.

Herpes simplex virus type 1 encephalitis must also be duly noted in cases with immune-suppressed or compromised patients due to the increased danger and presence of the disease in this demographic. The presence of herpes simplex encephalitis is similar to that of a brain tumor and should be considered in the differential diagnosis, especially in immunocompromised patients with extremely elevated temperatures. Studies have correlated an increased presence of herpes simplex encephalitis in immunocompromised patients (*5*). Furthermore, even in studies with only herpes simplex-susceptible, not immunocompromised, mice, immune response in mere days to fatal herpes simplex virus type 1 revealed brain stem lesions and CNS pathology, which led to fatal encephalitis (*6*). Taken together, it is obvious that the differential of herpes simplex encephalitis be considered early in the treatment of immunosuppressed or compromised patients who have undergone other pertinent diagnostic tests that indicate the possibility of the herpes simplex type 1 virus.

Given the nature of herpes simplex encephalitis, it is absolutely necessary to prioritize its diagnosis if there are any suspicions. Early detection and prompt treatment with an antiviral agent is essential due to high mortality rates (*7*). However, this is encumbered by lengthy and invasive tests and its similarity to brain tumors. Even in non-viral limbic encephalitis devoid of a connection to cancer, it is a challenge to detect CNS antibodies to confirm a diagnosis of encephalitis (*8*). Thus, invasive testing measures are absolutely necessary, not only to confirm potential viral infection but also to ensure the presence or nonexistence of cancer, which may have similar symptoms but different diagnostic results. Thus, thorough invasive testing is the only means of substantially confirming the presence of both conditions.

References

1. Neumann NU, von Albert HH. Hemorrhagic herpes encephalitis. A difficult differential diagnosis with computerized tomography. Fortschr Med. 1982;

100:183-186.
2. Akhan SC, Coskunkan F, Mutlu B, Gündes S, Vahaboglu H, Willke A. A probable case of herpes simplex encephalitis despite negative PCR findings. Infection. 2001; 29:359-361.
3. Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. Herpes. 2004; 11 (suppl 2):57A-64A.
4. Landry ML. False-positive polymerase chain reaction results in the diagnosis of herpes simplex encephalitis. J Infect Dis. 1995; 172:1641-1643.
5. Schiff D, Rosenblum MK. Herpes simplex encephalitis (HSE) and the immunocompromised: a clinical and autopsy study of HSE in the settings of cancer and human immunodeficiency virus-type 1 infection. Hum Pathol. 1998; 29:215-222.
6. Lundberg P, Ramakrishna C, Brown J, Tyszka JM, Hamamura M, Hinton DR, Kovats S, Nalcioglu O, Weinberg K, Openshaw H, Cantin EM. The immune response to herpes simplex virus type 1 infection in susceptible mice is a major cause of central nervous system pathology resulting in fatal encephalitis. J Virol. 2008; 82:7078-7088.
7. Schroth G, Gawehn J, Thron A, Vallbracht A, Voigt K. Early diagnosis of herpes simplex encephalitis by MRI. Neurology. 1987; 37:179-183.
8. Bataller L, Kleopa KA, Wu GF, Rossi JE, Rosenfeld MR, Dalmau J. Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. J Neurol Neurosurg Psychiatry. 2007; 78:381-385.

(*Received January 3, 2009; Revised January 8, 2009; Accepted January 8, 2009*)