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Case Report

Herpes simplex virus-1 encephalitis secondary to whole brain radiation therapy for metastatic renal cell carcinoma [☆]

Andrew Waack, BS^{a,*}, Sarah Jaggernauth, BS^a, James Iordanou, DO^b, Venkatramana Vattipally, MD^c

^a University of Toledo College of Medicine and Life Sciences, 3000 Arlington Ave, Toledo, OH 43614, USA

^b University of Toledo Medical Center, Department of Radiology, 3000 Arlington Ave, Toledo, OH 43614, USA

^c Advanced Radiology Services, P.C., 3264 North Evergreen Drive, Grand Rapids, MI 49525, USA

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ABSTRACT

Herpes simplex virus-1 (HSV-1) infection is the most common cause of encephalitis. This virus commonly lays dormant in neural ganglia, specifically the trigeminal ganglia, following retrograde axonal transport from the site of infection. States of immunosuppression can activate the virus to cause active infection. There are several causes of immunosuppression that can cause viral reactivation. Sporadic case reports have demonstrated HSV-1 encephalitis following brain radiotherapy, although no clear relationship between this treatment and HSV-1 encephalitis has been elucidated. HSV1 encephalitis that arises during immunocompromized states has an atypical presentation for encephalitis, potentially obfuscating the diagnosis and delaying subsequent treatment. The main diagnostic criteria, including CSF analysis, brain imaging, and clinical presentation, all commonly present atypically during states of immunosuppression. For these reasons, it is imperative for physicians to be aware of this rare sequelae in appropriate populations, such as patients undergoing brain radiotherapy. We present a case of an atypical presentation of HSV-1 encephalitis in a patient who recently completed radiotherapy for brain metastases secondary to renal cell carcinoma.

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Introduction

Encephalitis is brain inflammation with an associated impairment of neurological function [1]. Encephalitis can result from infectious, autoimmune or idiopathic etiologies [2]. Infection

by Herpes simplex virus-1 (HSV-1) is the most common cause of encephalitis, with an annual incidence of 2-4 cases per million people [3]. HSV-1 is a double-stranded DNA virus that has a particular tropism for the central nervous system (CNS), particularly the mesiotemporal lobe, orbitofrontal lobe and insular cortex [4]. HSV-1 routes to the CNS via hematogenous

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* Corresponding author.

E-mail address: awaack98@gmail.com (A. Waack).

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dissemination or retrograde axonal transport [5]. Being an opportunistic virus, HSV-1 can cause primary infection or become latent and later emerge during states of compromised immunity, resulting in an inflammatory response within the brain [5].

The diagnosis of HSV-1 encephalitis (HSE) relies on radiological imaging, cerebrospinal fluid (CSF) analysis and clinical presentation [6]. Magnetic resonance imaging (MRI) is the preferred imaging modality for diagnosing HSE, which typically demonstrates T2 signal hyperintensities in the temporal lobe, frontal lobe and/or insular cortex [7]. HSE CSF findings are often variable; however, polymerase chain reaction (PCR) amplification of HSV-1 DNA from CSF is considered the “gold standard” for diagnosing HSE [1]. The clinical presentation reflects the underlying brain inflammation, with fever, focal neurological deficits, memory problems, seizures, and decreased consciousness being common manifestations [1,6].

Diagnosed HSE must be treated immediately. Untreated HSE has a mortality rate of 70%, while treated HSE has a mortality rate of 10-20% [1]. Acyclovir is the drug of choice for managing HSE.

There have been several reported cases and case series of HSE secondary to whole-brain radiotherapy (WBRT) to treat brain metastases [3,4,6,8,9,10]. Furthermore, Graber et al. [3] have demonstrated an HSE incidence of 0.4% in patients after undergoing WBRT, much higher than the generally accepted incidence of 2-4 cases per million people. These findings suggest that WBRT is likely a contributing factor that predisposes cancer patients to infections by opportunistic pathogens such as HSV-1. However, no clearly defined relationship between WBRT and HSE has been established [6].

We present a case of a patient developing HSE secondary to WBRT to treat brain metastases from a primary renal cell carcinoma.

Case presentation

A 67-year-old female who recently completed WBRT for brain metastases secondary to renal cell carcinoma (RCC) presented to the Emergency Department (ED) with complaints of fever, nausea, vomiting, and weakness.

The patient's prior medical history was significant for hypothyroidism, hypertension, GERD, hiatal hernia with upper GI bleeding and metastatic RCC. The patient underwent unilateral nephrectomy, radiation therapy and cabozantinib to treat her RCC (Fig. 1). She was subsequently diagnosed with CNS metastases and was treated with WBRT, after which she developed leptomeningeal carcinomatosis and was started on tivozanib. Her hypothyroidism, hypertension and GERD were treated in accordance with the current standard of care. Lastly, she was recently admitted and treated for upper GI bleeding due to a gastric ulcer. Social history revealed a 45 pack-year smoking history and marijuana use.

On review of systems, the patient reported recent changes in activity and appetite, fatigue, nausea and vomiting. Physical exam revealed a BP of 114/53, heart rate of 48, temperature of 101°F, dry mucous membranes and a generally poor appearance; all other findings were within normal limits. Com-



Fig. 1 – Axial post contrast CT abdomen status post right nephrectomy.

plete blood count (CBC) demonstrated a hemoglobin of 11.3 (L), hematocrit of 35.4 (L), red cell distribution width of 15.7 (H) and absolute monocyte level of 1.35 K/ul (H); comprehensive metabolic panel (CMP) demonstrated a sodium level of 123 (L) and chloride of 91 (L); all other findings on CBC and CMP were within normal limits. Urinalysis revealed trace ketones, negative urine esterase, 0-5 WBCs and few bacteria. The patient was subsequently admitted.

An initial head CT on admission demonstrated no acute intracranial abnormalities and redemonstrated brain lesions for which she underwent prior MRI evaluation. Chest radiography revealed soft tissue fullness of the right hilum correlating with lymphadenopathy and a moderate size hiatal hernia.

The next day the patient demonstrated progressive neurological decline, including stupor, right gaze deviation, intermittent chewing movements that raised concern for non-convulsive status epilepticus. MR imaging was performed to evaluate these new symptoms. MR imaging revealed bilateral foci of restricted diffusion in the anterior mesiotemporal lobes, including the hippocampus and amygdala (Figs. 2–4). Later MR imaging revealed an interval decrease in the enhancing lesions in the left temporal lobe, posterior limb of the internal capsule and bilateral parietal lobes. Abnormal T2 signaling was also demonstrated in the left cerebral peduncle and pons, most likely secondary to Wallerian Degeneration. A subsequent MRI demonstrated interval development of nodular leptomeningeal enhancement in cerebellar folia, suggesting leptomeningeal carcinomatosis (Fig. 5). CSF analysis was recommended by the dictating radiologist.

HSV encephalitis was diagnosed following detection of HSV-1 DNA in a CSF PCR, and acyclovir therapy was promptly initiated.

A telehealth neurology consult was conducted to address the patient's neurological condition and corroborate imaging findings. No improvement was noted with low dose lorazepam. The patient's somnolence precluded a more aggressive approach to managing epilepsy, and the patient's family decided against electroencephalographic monitor-

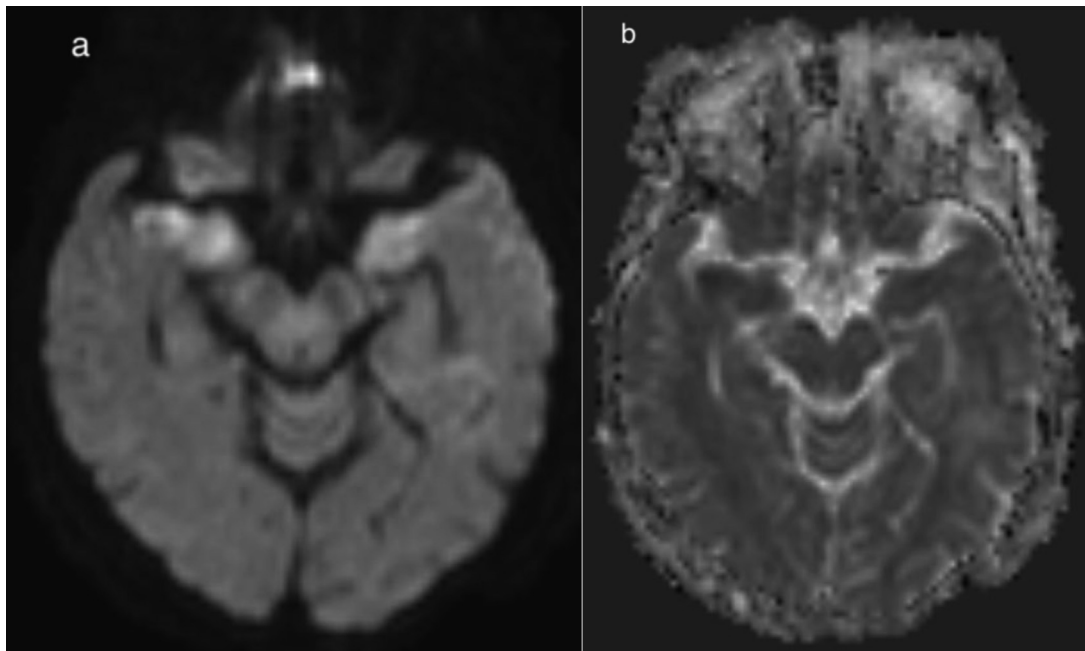


Fig. 2 – (A) Diffusion weighted image demonstrating increased signal intensity of the medial temporal lobe bilaterally, representing restricted diffusion. **(B)** Corresponding dADC map demonstrating decreased signal, indicating restricted diffusion coefficient. Superior slices to [Fig. 3](#).

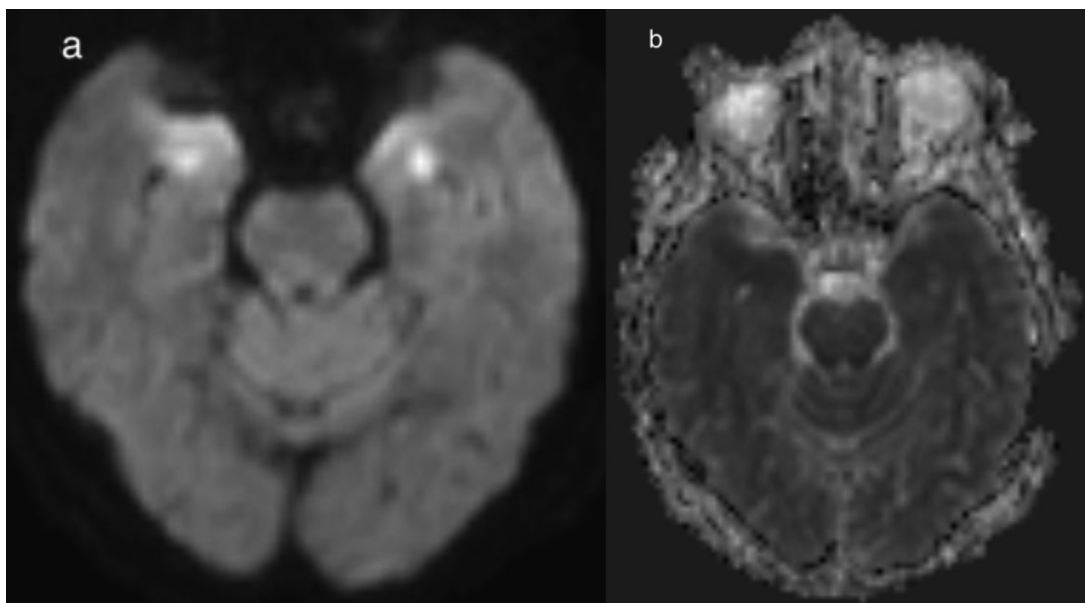


Fig. 3 – (A) Diffusion weighted image demonstrating increased signal intensity of the medial temporal lobe bilaterally, representing restricted diffusion. **(B)** Corresponding dADC map demonstrating decreased signal, indicating restricted diffusion coefficient. Inferior slices to [Fig. 2](#).

ing. Therefore, neurology recommended against prophylactic antiepileptic therapy, as the occurrence of subclinical seizures was not able to be made; however, they endorsed lorazepam and levetiracetam therapy if a clinical seizure were to occur.

Acyclovir was continued and the patient's condition was closely monitored.

Discussion

HSV-1 is a very common opportunistic infection. 57.9% of Americans between the ages of 14-49 demonstrated HSV-1 seropositivity between 1999-2004, and 53.9% between 2005 and 2010 [11]. Baringer demonstrated HSV-1 seropositivity

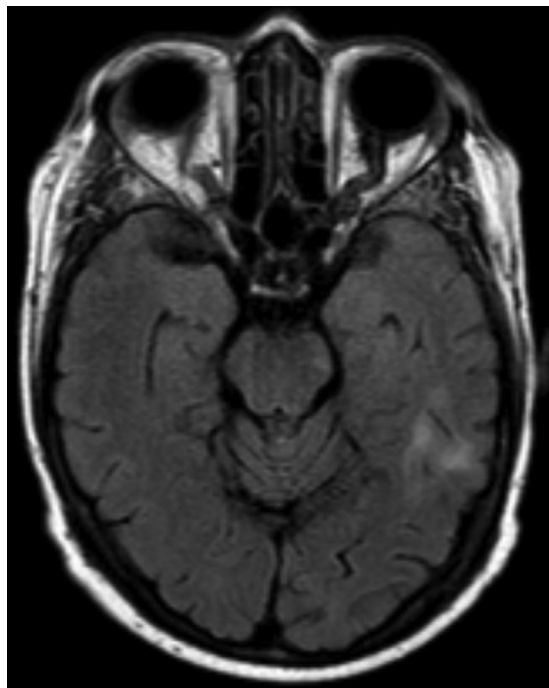


Fig. 4 – FLAIR image demonstrating increased signal intensity of the medial temporal lobes, indicating parenchymal edema.

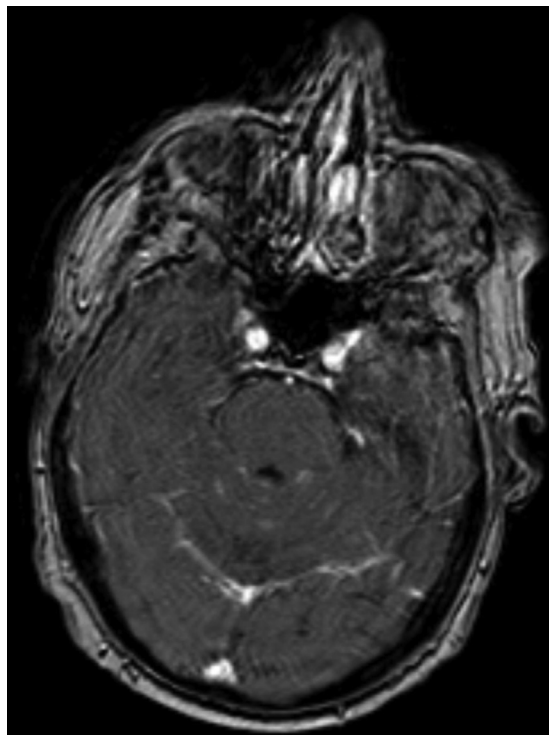


Fig. 5 – Contrast-enhanced T1 weighted MR image demonstrating enhancement of the cerebellar folia, representing leptomeningeal carcinomatosis.

in about 90% of randomly conducted autopsies [12]. HSV-1 stereotypically remains latent within infected cells and reactivates into HSE under certain conditions, including cancer, chemotherapy, stress, trauma, corticosteroids, and surgery [6,10], although HSE can occur as a result of primary infection as well [5]. WBRT is also capable of causing HSE [8,10]. Thus, immunocompromised patients are at an elevated risk of developing HSE. Furthermore, HSE associated with immunocompromised states leads to worse outcomes than typical HSE. A retrospective case-control study demonstrates a 6-fold increase in mortality in immunosuppressed patients compared to immunocompetent patients [13]. Additionally, over half of treated patients are still left with lasting neurological sequelae [14]. Thus, because latent HSV-1 infection is so common and it results in suboptimal outcomes, physicians should consider HSE as a potential diagnosis, especially in the context of immunosuppression, including WBRT, during cancer treatment. However, this may be difficult due to the presentation of HSE: HSE associated with immunosuppression has an atypical appearance and closely resembles various differentials.

The diagnosis of HSE is based on CSF analysis, radiological imaging, and clinical findings. HSE associated with immunosuppression has a unique constellation of findings that often confound the diagnosis of HSE.

HSE CSF analysis often yields variable results [5]; however, typical CSF findings in HSE include a lymphocyte-predominant pleocytosis, erythrocyte presence, elevated protein levels and normal glucose levels [5]. However, HSE in immunocompromised states consistently presents with absent CSF pleocytosis [4,6,9,13] or, if leukocytes are present, there is a polymorphonuclear predominance, with overall lower leukocyte levels compared to immunocompetent HSE patients [13]. PCR detection of HSV-1 DNA is considered the “gold standard” for diagnosing HSE; however, PCR results may be negative in the first 24-48 hours of disease, potentially leading to false negative results [15]. Therefore, if a final diagnosis cannot be made in the first few days, a subsequent PCR may need to be repeated [1]. The definitive diagnosis of HSE was made in the presented case by a positive HSV-1 PCR sample.

Radiological imaging is especially useful for the diagnosis of HSE. MR imaging is considered the gold standard imaging modality for HSE diagnosis. The optimal MRI sequences depend on the time course of disease [7]. Diffusion weighted imaging (DWI) detects cytotoxic edema in the early stages of disease; Misru et al. [7] demonstrate that DWI is the optimal sequence for detecting HSE in the early stages of disease (within the first day). Later, T2 weighted images demonstrate hyperintense lesions, which represent underlying edema [7]. FLAIR sequences have demonstrated superior sensitivity compared to traditional T2 weighted sequences for HSE because FLAIR sequencing provides superior visualization of gray matter lesions by suppressing CSF flow artifact [7]. CT imaging is often employed during the early workup of encephalitis, although its sensitivity is low compared to MRI [5]. CT can, however, provide some utility by demonstrating hemorrhages and midline shift associated with HSE, as well as potentially demonstrating lobar hypointensities [16]. In addition to the differential appearances seen on the various imaging modalities, anatomical distribution must also be considered. HSE is classically defined as following a bilateral, asymmetric distri-

bution within the mesiotemporal lobes, orbital frontal lobes and insular cortex; however, in actuality, HSE is more commonly unilaterally distributed [5]. Sporadic HSE is typically confined to the limbic areas, but HSE in immunocompromized individuals often spreads beyond the temporal lobes [7] because the immune response is too weak to contain the virus [13]. Tan et al. [13] demonstrated patients with spreading into the brainstem, cerebellum and diffusely throughout the cortex. CT findings in our presented case did not reveal any intracranial abnormalities; however, subsequent MR imaging did reveal asymmetric hyperintensities in the temporal lobes, with unilateral extensions into the cerebellum, internal capsule and cerebral peduncle. These imaging findings are consistent with the aforementioned literature: non-sensitive CT findings in HSE, with extra-temporal involvement in immunocompromized HSE demonstrated on MRI.

The typical clinical presentation of HSE includes fever, seizures, headache, confusion, focal neurological deficits, lowered consciousness and behavioral abnormalities, often preceded by a prodromal syndrome [5]. HSE associated with immunocompromized states often presents without focal neurological deficits or prodromal symptoms [13]. Our patient demonstrated decreased consciousness and probable seizures, which were not able to be confirmed due to the family's wishes not to undergo electroencephalographic examination. Our findings were consistent with immunocompromized HSE in that no focal neurological deficits were demonstrated; however, her neurological symptoms were preceded by a prodromal phase, which was found to only occur in 28.6% of immunocompromized HSE cases [13].

There are several diseases that present similarly to HSE. Autoimmune limbic encephalitis (ALE) shares several clinical and radiological features with HSE. ALE is comprised of both paraneoplastic and non-paraneoplastic etiologies [17,18]. Paraneoplastic ALE occurs as a result of antibody cross reactivity against intracellular neural tissue antigens during malignancy [17–21]. Paraneoplastic ALE typically exhibits lesions extending beyond the temporal lobes, whereas HSE is typically confined to the temporal lobes [17,18]. However, this imaging presentation may mimic the atypical HSE associated with immunocompromized states described earlier. Indeed, in the presented case, radiological differentiation between paraneoplastic ALE and HSE secondary to whole brain radiation therapy was not possible. Although rare, paraneoplastic ALE secondary to renal cell carcinoma has been reported [19–21]. The diagnosis of HSE in the presented case was made by CSF PCR detection of HSV-1. Paraneoplastic ALE can be diagnosed by the detection of auto-antibodies in the serum or CSF [17]. Additionally, ALE can occur independently of malignancy; these lesions tend to remain localized to the temporal lobes and can thus obfuscate the radiological diagnosis of sporadic HSE, which also remains localized to the temporal lobes [7]. Another major differential for HSE is gliomatosis cerebri (GC), a diffuse glioma that extends into at least 3 cerebral lobes [22]. Typical radiological findings include white matter T2 hyperintensities that do not enhance; additionally, corpus callosum involvement is common, and lesions are often bilateral [22]. MRS findings for GC demonstrate increased myoinositol and decreased N-acetylaspartate levels [23]. GC presents clinically with headaches, seizures, lethargy, and vision changes [24].

HSE often demonstrates these same clinical signs, except for vision changes; however, fever and prodromal symptoms are often demonstrated in HSE, which may help to distinguish it from GC [5]. Biopsy can be used to diagnose GC if clinical, CSF/serological, and radiological modalities have failed to reach a diagnosis [24]. It is imperative to successfully navigate the differential diagnosis and arrive at a proper diagnosis, as each of these conditions require distinct treatments.

Appropriately treating HSE decreases the mortality rate by over 50% [1]. Tan et al. [13] demonstrate an inverse correlation between Karnofsky Performance Status Scale and time until acyclovir initiation, so treatment must be administered as quickly as possible. Acyclovir should be initiated empirically upon suspicion of HSE, and it is also recommended to concurrently administer cefepime and vancomycin for prophylactic treatment of potential bacterial meningoencephalitis [5]. Intravenous acyclovir treatment should be maintained for 2-3 weeks [5]. Corticosteroid use is controversial: it can be helpful in controlling edema and preventing mass effect, although its immunosuppressive actions may impair the antiviral immune response [5]. There are 3 potential sequelae of immunocompromized HSE treatment. First, acyclovir resistance is 28 times more common in immunosuppressed HSE than sporadic HSE, resulting in an inability to clear the infection medically [25]. Next, HSV relapse following reactivation often occurs in immunocompromized HSE patients [4]; acyclovir acts to inhibit replication and relies on the immune system to clear the virus, which is impaired by corticosteroid administration, allowing the virus to remain. Lastly, autoimmune limbic encephalitis may also occur as sequelae of HSE [4]. HSE generally leads to poor outcomes, although acyclovir is an established standard of care therapy; however, immunocompromized HSE treatment is especially difficult and leads to even worse outcomes.

Patient consent

Informed consent was obtained from the family.

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