Fatal Herpes Encephalitis in a Patient with Small Cell Lung Cancer Following Prophylactic Cranial Radiation - A Case Report with Review of Literature

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Abstract. *Herpes simplex virus 1 (HSV-1) is the principal cause of viral necrotizing encephalitis in developed countries. Small cell carcinoma of the lung accounts for about 15% of all lung cancer. HSV induced encephalitis (HSE) following prophylactic cranial irradiation (PCI) in SCLC is rare. Here, we describe the case of a 58-year-old woman with limited stage SCLC, multiple sclerosis (MS) and cutaneous lupus who developed fatal HSE following PCI. We review the literature to investigate the inter-relationships between these diseases and management of HSE.*

The herpes simplex virus 1 (HSV-1) is the chief cause of viral necrotizing encephalitis in developed countries with a reported mortality of about 70%. It is estimated that about 15-20% of patients with HSV-induced encephalitis (HSE) die despite treatment and about 60% of survivors have long-term neurological sequelae (9). Older age, lymphocytic pleocytosis, delay in performing lumbar puncture, presence of red blood cells (RBCs) in the cerebrospinal fluid (CSF), and a delay in starting acyclovir are associated with increased morbidity with HSE (1, 9). It is believed that HSE results from reactivation of latent HSV-1 residing in the trigeminal ganglion of adults. The virus migrates there by retrograde axonal transport following a primary infection of the lip or buccal mucosa. In immunosuppressed individuals, the exact trigger for reactivation and the mechanism of rapid spread are not clearly known.

Small cell lung cancer (SCLC) accounts for about 15% of all lung cancers. Chemotherapy with cisplatin and etoposide has remained first line of treatment for SCLC since the 1960s. In addition, radiation therapy (RT) is recommended for patients with limited stage disease while prophylactic cranial irradiation (PCI) is offered to all patients after completion of first line therapy. The development of HSE following PCI is a rare occurrence and is usually associated with high mortality. We report the case of a patient with SCLC, multiple sclerosis (MS) and cutaneous lupus in remission after successful chemoradiation therapy who developed HSE seven days after completing PCI and died despite aggressive antiviral therapy and supportive management. This is the third case of HSE associated with PCI for SCLC reported in the literature. We discuss the possible association between SCLC, HSE, MS and cutaneous lupus and the management of HSE.

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Case Report

A 58-year-old Caucasian female was brought to the emergency room (ER) by her daughter with a one day history of worsening confusion. The daughter reported that previous day, the patient had been confused and was having trouble speaking. In the ER, the patient complained only of an occipital headache but denied any fever. She had recently recovered from an attack of gastroenteritis and while diarrhea had subsided, she had continued to have intermittent vomiting for the previous two weeks. The daughter also reported that her mother had a 10 lb weight loss in those two weeks. Her daughter reported that on the morning of the admission to the hospital, the patient had a 15 second episode of witnessed generalized seizure at home.

The patient's past medical history was significant for subacute cutaneous lupus treated with hydroxychloroquine, SCLC (T2N2M0) diagnosed eight months ago for which she was being treated with chemoradiation, and multiple sclerosis (MS) which had never been treated. She had completed her course of treatment for SCLC with six cycles of cisplatin and etoposide and was declared cancer-free about

five months earlier. She also received RT to her chest concomitant with chemotherapy (total of 51.4 Gy in 26 fractions). She was then started on prophylactic cranial radiation and had completed a 17-day course of PCI about three days earlier (total of 25 Gy in 10 fractions). She had a history of hyponatremia from the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and hypomagnesemia presumably secondary to SCLC and cisplatin toxicity, respectively. A review of systems was only positive for left upper quadrant abdominal pain. In the ER, the patient had a witnessed generalized seizure which responded promptly to intravenous lorazepam.

Upon initial examination, her temperature was 37.3˚C, blood pressure 151/88 mm Hg, heart rate of 96/minute, respirations 20/minute and she was saturating 100% on 2 liter oxygen *via* nasal cannula. She was noted to be ashen gray in color. She had lost hair during her radiation therapy. She was noted to be obtunded with no significant response to noxious stimuli. Her Babinski reflex was extensor bilaterally. Initial laboratory examination was significant for hyponatremia (124 mEq/l), hypocalcaemia (7.1 mg/dl), hypomagnesemia (1.7 mg/dl), hypoalbuminemia (3.3 g/dl), anemia (hemoglobin 11.2 g/dl) and thrombocytopenia (133,000/mm^3). A non contrast computerized tomorgraphy (CT) of the head revealed stable changes of MS. A chest X-ray was normal. A urine spot sodium was 140, serum osmolality 252, and urine osmolality 670 consistent with SIADH. Free T4 was 1.11 and TSH 0.29. Urine analysis revealed pyuria [13 white blood cells/high powered field (hpf)], microscopic hematuria (22 RBCs/hpf), and positivity for leucocyte esterase. She was started on empirical piperacillin-tazobactam for presumptive urinary tract infection (UTI) and transferred to the intensive care unit (ICU).

In the ICU, she became progressively more obtunded but never required intubation. Two days after admission, she underwent a lumbar puncture. Analysis of the CSF revealed clear appearing fluid with 10 WBC/μl, 27 RBCs/μl and 36% neutrophils. Further analysis revealed elevated level of myelin basic protein (12.1 ng/ml, reference 0-1.1 ng/ml), normal IgG (in comparison total serum IgG level was low at 581 mg/dl, reference 768-1632 mg/dl), normal CSF albumin (22 mg/dl, reference 0-35 mg/dl). Although the initial CT scan showed no acute abnormality, subsequent magnetic resonance imaging (MRI) revealed T2 hyperintense lesions in the medial aspect of the right temporal lobe highly suspicious for HSE (Figure 1). Based on the results of the MRI, she was started empirically on intravenous acyclovir (10 mg/kg) every eight hours on the third day of admission. On day 4, the polymerase chain reaction (PCR) was positive for HSV-1 DNA. Further CSF analysis was significant for the absence of paraneoplastic antibodies and monoclonal proteins. An electroencephalogram (EEG) performed while the patient was comatose revealed background activity consisting of burst suppression pattern with slow waves and interceding delta activity. Urine culture was positive for *Klebsiella pneumoniae* and *Candida albicans* for which the patient was treated with appropriate antibiotics (levofloxacin and fluconazole). She, however, showed no significant neurological improvement. A repeat CT scan 19 days after admission revealed new lesions in the right parietal, bilateral frontal and left temporal lobes suggestive of progression of HSE. Due to lack of neurological improvement, and progressive hypoxia requiring oxygen, the family opted for comfort measures and acyclovir was stopped after 17 days. The patient subsequently died of cardiorespiratory failure, 22 days after she was admitted.

Discussion

The annual incidence of HSE in the general population is estimated to be about 2.2 per million. In contrast, among patients with cancer undergoing whole-brain radiation therapy (WBRT), the incidence is estimated to be about 4 per 1,000 (roughly 2000 times higher than the general population) (3;5). Compared to a mortality rate of between 15-30% in the general population, in one study, five patients with cancer (age range=45-73 years) post-WBRT and HSE all died. All five presented with impaired consciousness at presentation and were on dexamethasone. In three patients, HSE occurred during RT (cumulative radiation dose of between 8-48 Gy) and in the other two between 10-30 days post WBRT (5).

Clinical features of HSE include encephalopathy (>90% cases), fever (80%), seizure (50-70%) and focal deficit (30-70%). On imaging, unilateral involvement of the temporal region is more common (60-70%) than bilateral lesions (about 20%). HSE can present atypically in immunocompromised patients who often lack prodromal symptoms (29% *vs*. 80% in immunocompetent), or focal deficits (29% *vs*. 73%) and who have a significantly higher mortality [36% *vs*. 7% in one study (13)] compared to those with an intact immune system. In a study of 14 immunocompromised and 15 immunocompetent patients with HSE, there was no significant difference in CSF findings or neuroimaging abnormalities between the two groups (13). On histopathology however, the brain of immunocompromised patients showed significantly less inflammation and necrosis. Immunocompromised patients often have atypical CSF findings at presentation. In the study by Jacob *et al*. reviewing five patients with cancer who underwent WBRT, all patients had lymphocytic pleocytosis but with low CSF WBC count (1-7/μl). Furthermore, one had normal CSF protein levels at presentation, and one had a negative HSV PCR (different patients). In their article, Jacob and colleagues mention that 28 cases of HSE in conjunction with chemoradiation have been reported in the literature, including eight cases in patients who received only RT (5).

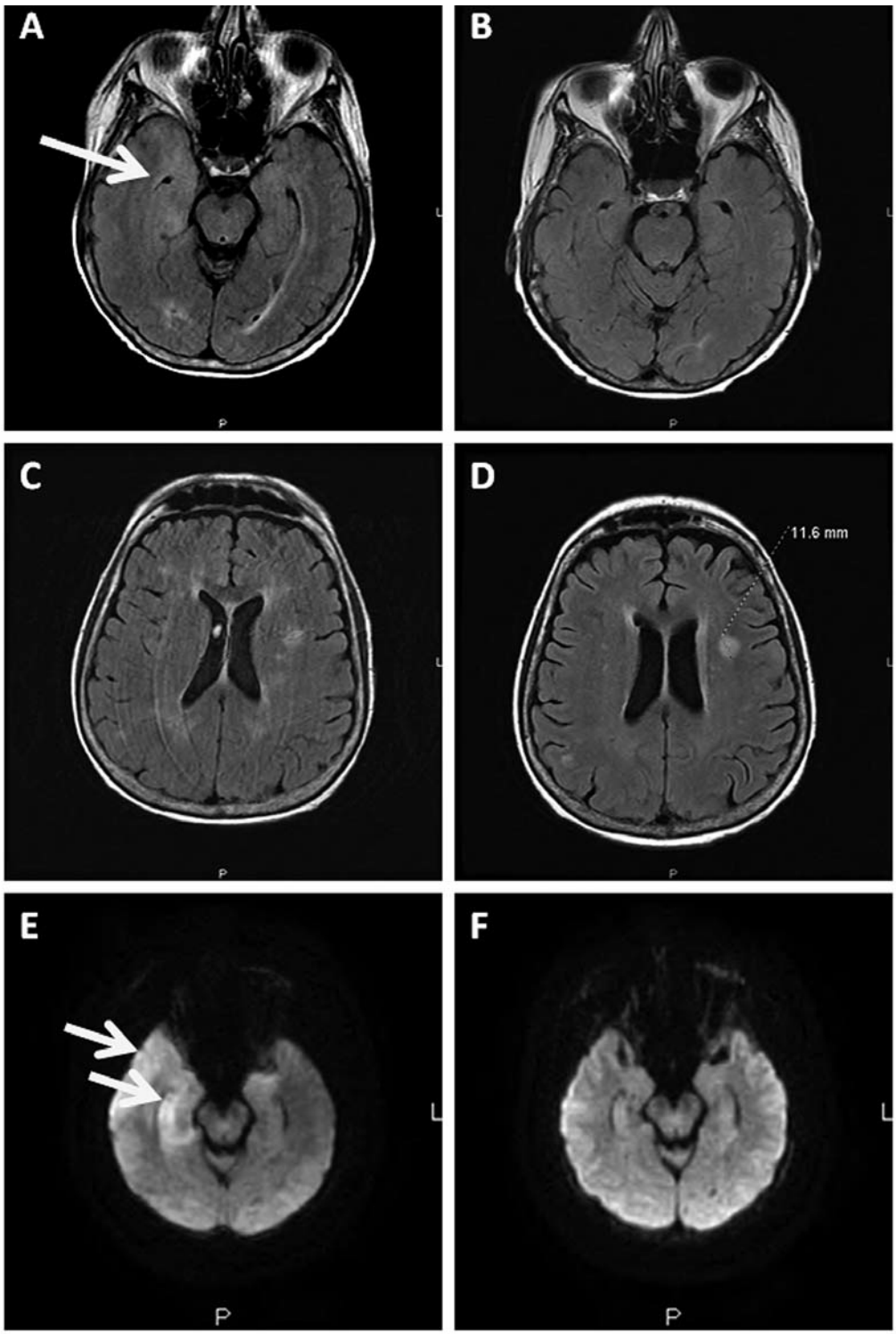

Figure 1. *Magnetic resonance imaging (MRI) of the brain reveals changes of herpes encephalitis (HSE) and multiple sclerosis. A: T2 fluid attenuated inversion recovery (FLAIR) MRI of the brain showing areas of hyperintensity in the medial part of the right temporal lobe highly suspicious for herpes encephalitis. B: MRI taken one month prior to presentation reveals no evidence of enhancement on T2 FLAIR processed images in the temporal lobe. C: Hyperintense areas on T2 FLAIR MRI at presentation represent areas of demyelination suggestive of multiple sclerosis. D: MRI of the brain taken one month earlier shows the same lesions that remained unchanged during hospitalization for HSE. E: Diffusion-weighted axial images of the brain at presentation showing prominent enhancement of the right temporal region with a milder enhancement of the left medial temporal lobe. F: Diffusion-weighted axial images one month prior to diagnosis of HSE reveal no evidence of hyperintensity in the temporal lobes.*

Current guidelines recommend treatment of HSE with intravenous acyclovir 10mg/kg given every 8 hours for 2-3 weeks (14). If in doubt whether HSV is still present after completing treatment, CSF should be checked for HSV DNA by PCR. If the PCR is positive, then a further one or two weeks of additional therapy is recommended. Immunocompromised patients who receive prophylactic acyclovir can develop resistance to it due to acquisition of a thymidine kinase gene by the virus. The estimated incidence of resistant variants of HSV-1 in immunosuppressed patients is between 5-25%. In these patients, foscarnet or cidofovir are recommended. Cidofovir is nephrotoxic but has the advantage of once weekly dosing. The use of corticosteroids is restricted to patients with severe vasogenic edema and a midline shift on CT or MRI. Although a trial is underway to evaluate the efficacy of adding dexamethasone to acyclovir [GACHE trial (8)], there is currently no evidence to recommend its routine use (12).

Given the rarity of this HSE in patients undergoing PCI, we searched published literature to investigate other cases where HSE occurred in patients with SCLC. We also searched for any reported association between MS, cutaneous lupus and SCLC and their relationship to HSE. This was based on the hypothesis that a patient with prior autoimmune disease and cancer treated with chemotherapy and RT might be more susceptible to developing HSE. The PubMed database was searched with the terms "cutaneous lupus and multiple sclerosis", "multiple sclerosis and HSV encephalitis", "multiple sclerosis and small cell lung cancer", "small cell lung cancer and HSV encephalitis" and "cutaneous lupus and small cell lung cancer". We retrieved only two other cases of HSE reported in association with SCLC. One was in a 75-year-old man who presented with loss of consciousness followed by partial seizures, fever and abnormal behavior. He was subsequently diagnosed with SCLC three weeks after admission to the hospital. On MRI, there was involvement of bilateral hippocampal regions. Interestingly, his CSF was analyzed and found to be negative for paraneoplastic antibodies (anti-Ma and anti-Hu) but several years later investigators noted that the sera reacted with Purkinje cells and with cells in the molecular layer of mouse cerebellum. Western blotting of mouse cerebellar extract with patient serum identified a 29-kDa band. The identity of that protein was however not investigated further (4). The second was of a 55-year-old man with limited-stage SCLC who presented with symptoms of cold and temperature of 39˚C ten days after the start of PCI. Over the next five days he became confused, had marked cognitive impairment, fever with shaking chills and then became progressively more somnolent and finally comatose. While CT scan at admission revealed only mild parenchymal atrophy, an MRI scan nineteen days post-admission revealed hemorrhagic spots in the white matter, and edema of the left uncus and parahippocampal convolution suggestive of acute encephalitis. A lumbar puncture at this point was positive for HSV-1 DNA and the patient was started on acyclovir. However, the patient failed to improve and died 55 days after completion of his PCI therapy (10). We found another report of HSE associated with PCI for breast cancer. This was a 55-year-old female with breast cancer who presented about 13 years after her initial diagnosis with generalized seizures and was found to have brain metastases. She was started on RT, levitiracetam and dexamethasone. After 16 fractions of RT she presented with cognitive impairment without any other systemic symptoms. This was followed by partial seizures, meningitis-like symptoms and progressive deterioration of her clinical status. She was found to be hyponatremic, with mild leucocytosis and lymphopenia. After HSV was identified in the CSF, the patient was started on iv acyclovir which was continued for four weeks. She, however, remained comatose and died 59 days after her last dose of RT. Her MRI showed diffuse bilateral frontal, temporal and parietal lesions and the EEG revealed delta and triphasic wave pattern with burst suppression (6). These reports suggest that HSE following PCI is generally fatal despite appropriate treatment.

We also found two case reports of MS associated with HSE. In one case, a 49-year-old woman presenting with unilateral headache and numbness was diagnosed with chronic lymphocytic leukemia (CLL) and HSV-1 encephalitis and treated successfully with acyclovir. A month later, she presented with new focal deficits and was diagnosed with MS that responded to high-dose parenteral steroids (11). In another report, a 36-year-old woman with MS developed acute-onset generalized seizure nine days after completing her sixth infusion of natalizumab. She demonstrated aphasia and acute impairment of memory. MRI of the brain revealed T2 hyperintense lesions in the left temporal, insular, cortical and subcortical white matter and CSF showed pleocytosis and HSV-1 positivity. EEG showed theta and delta activity in the left temporal region. After treatment with acyclovir for 21 days, the patient had persistent severe episodic memory deficit, anosognosia and aphasia five months after discharge (7). In both cases, the patients survived but were left with neurological deficits.

Finally, we searched the literature for any association between MS and cutaneous lupus. This revealed only a single case report of a female patient with long-standing MS who developed cutaneous and systemic lupus (1). There was no report of MS occurring in association with SCLC. Whether the presence of lupus and MS modulated our patient's chances of developing SCLC and subsequently of HSE remain unanswered.

A key question which begs an answer is- Is the HSV infection in patients with HSE a primary nervous system infection or merely reactivation of a latent virus?

Furthermore, it is important to ascertain what mechanisms underlie the aggressive nature of HSV-1 infection in patients with cancer or those treated with WBRT. A review of the literature suggests that like the pieces of a large puzzle, the answer is a work in progress. A few observations are worthy of mention. It is generally clear that immunosuppression promotes HSE (5). In a mouse model, Adler and co-workers demonstrated that lack of both natural killer (NK) cells and T-cells, but not T-cells alone, led to higher (100%) mortality from HSE following intranasal inoculation of HSV-1. The mode of viral infection in this model is initial pneumonitis followed by viral migration to the brain causing either overt encephalitis or latent infection in the trigeminal ganglion (15). Androstenediol (AED), a metabolic product of dehydroepiandrosteronedione, an adrenal steroid, is known to have immunomodulatory properties. When mice were injected with AED four hours prior to infection with HSV-1, they had significantly lower mortality compared to control mice (no AED). Furthermore, six days post-injection, the AED-injected mice had a significant increase in the levels of the cytokines interferon gamma (IFNG) and interleukin-2 (IL-2) in their trigeminal ganglion and an increase in NK cell activity in the spleen. Interestingly, there was no difference in viral load in the trigeminal ganglion of the treatment compared to the control mice even at six days after infection (2). Studies in patients with inherited deficiency of toll like receptor 3 (TLR3) revealed that in these patients, the neuronal cells failed to produce high levels of IFNG when infected with HSV-1 *in vitro*. However, peripheral mononuclear cells from the same patient produced adequate amounts of IFNG when infected in the same manner. These studies suggest that a deficiency of TLR3 impairs the ability of neuronal cells to produce IFNG in response to HSV1 infection, thereby promoting aggressive viral replication and infection (2). It is noteworthy that high levels of IFNG are well known to cause apoptosis of oligodendrocytes while having no effect on neurons. Thus high circulating IFNG can worsen symptoms of MS. The hypothesis that HSE is a primary nervous system infection comes from observations that patients with recurrent herpes labialis (thought to be caused by reactivation of HSV-1 residing in the trigeminal ganglion) rarely get HSE. Furthermore, the strains causing herpes labialis differ from those causing HSE. In the most commonly accepted hypothesis however, it is believed that the individual acquires HSV-1 infection in their first-or second decade of life. The virus then remains latent in the dorsal root ganglion and the trigeminal ganglion. When activated, viruses spread to the temporal and frontal lobes along the axons of the trigeminal nerve and cause necrotizing encephalitis. Some studies suggest that inhibition of autophagy in host cells may be used as a mechanism by the virus to ensure its survival and spread [HSV encephalitis has been reviewed in depth in (12)].

Conclusion

In conclusion, HSE in immunocompromised patients such as patients with SCLC following PCI may present with subtle symptoms. The most important prognostic factor in these patients appears to be early institution of antiviral therapy. Acyclovir is the first line therapy but if the patient fails to respond promptly, the possibility of resistance should be kept in mind and alternative drugs such as foscarnet or cidofovir should be considered. The overall prognosis in immunosuppressed patients with HSE is poor. Mechanisms underlying the co-occurrence of SCLC, MS and cutaneous lupus in our patient are unknown and could have contributed to her death. Further research in this field is urgently needed.

Conflicts of Interest

The Authors declare no conflicts of interest related to this publication.

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