J Neurooncol (2011) 105:415–421
DOI 10.1007/s11060-011-0609-2

CLINICAL STUDY – PATIENT STUDY

Herpes simplex encephalitis in patients with cancer

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Received: 9 March 2011 / Accepted: 22 May 2011 / Published online: 3 June 2011

Abstract Case reports and animal models suggest that chemotherapy, corticosteroids and radiotherapy (RT) may increase the risk of herpes simplex encephalitis (HSE). We retrospectively examined cases of HSE at an academic hospital devoted to cancer care. Patients were identified by positive herpes simplex virus (HSV) polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) or by brain pathology. There were seven patients with HSE over a 12 year period, four of whom had received cranial RT. During this time, a total of 997 patients were treated with cranial RT, suggesting a greater incidence than the expected risk of two to four cases per million people per year in the general population. Five patients had recently received chemotherapy and three were on dexamethasone. MRI findings were typical; four patients had bilateral anterior temporal lesions and three had unilateral-temporal lesions. Four patients had a normal CSF white blood cell count, three of whom had prior RT and dexamethasone. Four patients were positive for HSV-1, and two for HSV-2. One patient had a negative CSF PCR for HSV, but autopsy confirmed active HSE. Though still rare, the risk of HSE may be increased in patients with cancer, especially in those receiving cranial RT. MRI findings were typical, but CSF white blood cell count was normal in four patients and one had negative CSF testing, suggesting that CSF results may be misleading in this population.

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Keywords Herpes encephalitis · Radiation · Chemotherapy · Corticosteroids · Neoplasm

Introduction

Herpes simplex encephalitis (HSE) is the most common identifiable cause of viral encephalitis, occurring in two to four patients per million people annually in the general population as consistently reported from multiple studies [1–3]. It is unclear whether immunosuppression is a risk factor for HSE, and immunosuppressive chemotherapies and corticosteroids are used in many cancer patients. HSE has been reported previously in individual patients with cancer, with a majority of reported episodes occurring shortly after radiotherapy (RT) to the brain [4–8]. One autopsy study of 78 bone marrow transplant recipients identified two with HSE [7]. However, estimates of the incidence of HSE in people with cancer compared to the general population are not available. Thus, we performed a review of patients diagnosed with HSE at Memorial Sloan-Kettering Cancer Center (MSKCC).

Methods

We conducted an Internal Review Board approved retrospective study using an institutional database of all CSF test results for herpes simplex virus (HSV) by polymerase chain reaction (PCR) from the period between January 1, 1998 and October 31, 2009. The medical records of patients with CSF results positive for HSV were reviewed and data collected for clinical details. One additional case found at autopsy during this time period was also included.

Results

We identified seven patients with HSE, five of whom were women (Table 1). Their ages ranged from 45 to 76 (median 55) years old. Two patients had breast cancer and one patient each had primary CNS lymphoma (PCNSL), non-small-cell lung cancer, melanoma, renal and thyroid cancer. Five patients had received chemotherapy within 3 months of their HSE. Three patients were taking dexamethasone at the time of their HSE. Four patients had brain metastases and received whole brain RT within 3 months of their HSE; one patient had oral ulcers possibly due to mucosal HSV at the end of RT 3 weeks prior to the development of HSE. The patient with PCNSL had not received cranial RT. In all patients, MRI findings typical of temporal lobe encephalitis prompted CSF studies and acyclovir therapy. On MRI FLAIR sequences, four patients had bilateral anterior temporal lesions and three had unilateral temporal lesions. No lesion was enhancing, and these abnormalities could be distinguished clearly from intracranial tumor. All seven patients underwent lumbar puncture; CSF WBC ranged from 1 to 349 Cells/mcL (median 6), and four patients had a normal CSF white blood cell count, three of whom had prior RT and dexamethasone. Systemic white blood cell counts (median 6,400 Cells/mcL, range 4,500–10,900 Cells/mcL) and absolute neutrophil counts (median 5,700 Cells/mcL, range 3,300–9,900 Cells/mcL) were normal on admission. Absolute lymphocyte counts were in the normal range for the majority of patients, even those on chemotherapy (median 500 Cells/mcL, range 400–1,500 Cells/mcL, normal range is 500–5,300 Cells/mcL). Six of seven had an elevated CSF protein concentration. Four patients had CSF positive for HSV-1, two had CSF positive for HSV-2. One patient had negative CSF PCR for HSV, but typical MRI findings and autopsy confirmed active HSE. In the autopsy material there was a paucity of inflammation but viral inclusions staining for HSV were found, in accordance with previous reported autopsy findings in immunocompromised patients with HSE [4].

The duration of patient symptoms prior to acyclovir therapy ranged from 1 to 3 days (mean 2.4 days). One patient (case 6) with HSV-2 encephalitis also had multiple subcortical infarcts and beading of cerebral blood vessels on imaging, suggesting cerebral vasculitis from HSV in addition to HSE. Case 6 also had simultaneous left C6/7 dermatomal vesicular skin lesions that tested positive for HSV. Five patients died without significant improvement a median of 59 days from presentation (range 7–74). One patient recovered with mild residual deficits, but died of her breast cancer 430 days later. One patient was sent to hospice due to declining condition 59 days later, and no further information was available.

During the same 12 year period, 997 patients received RT to the brain at MSKCC, four of whom developed HSE, giving a risk of approximately 1 in 250 patients treated with cranial irradiation. This apparent risk is significantly greater than the expected annual incidence of two to four patients with HSE per million people annually or the 1.3–3.1 cases of encephalitis of any cause per 1,00,000 people annually between 2000 and 2008 in New York City [1, 9]. A firm denominator for our overall cancer population in this time period is not available, since many patients are seen for single consultations or receive only partial but not ongoing care at our institution.

Discussion

This retrospective study suggests an increased incidence of HSE in patients with cancer, particularly those receiving RT to the brain. Functional immunosuppression from chemotherapy or corticosteroids may also be contributing factors, but steroids could have affected only three of our seven patients. The 0.4% incidence we observed among patients receiving cranial irradiation far exceeds the expected incidence reported from large, population-based studies [1]. We found 34 cases of HSE in people with cancer reported in the literature. Information on brain radiation was provided in 23 of these patients and 15 had received cranial RT within 3 months of their HSE (summarized in Table 2), lending support to our observation that RT may increase susceptibility to HSE. The immunosuppressant effects of dexamethasone or other therapies used together with or in proximity to brain RT or RT itself may induce local effects on immune control of latent HSV in the CNS or impaired defense against reinfection. However, CNS RT alone does not explain all the increased vulnerability to HSE in our population as three of our patients did not receive cranial irradiation; however, all three had received chemotherapy or dexamethasone within 3 months of HSE, either of which may be sufficient to disrupt host immunity.

MRI abnormalities were typical of HSE in our patients; imaging provided the key to diagnosis, as some other features of their HSE were atypical. However, the MRI findings triggered the search for HSE, so patients with atypical neuroimaging features and HSE may not have been identified. CSF pleocytosis was absent in more than half our patients as has been observed previously in this population, and did not correlate with current dexamethasone use [5]. A number of features of HSE were atypical in our cohort as well as cases reported in the literature, including absence of CSF pleocytosis and a possibly higher incidence of HSV-2 as the causative agent. Six of twelve cancer patients with HSE and CSF results reported in the literature also had a

Table 1 Summary of HSE cases

	Age/sex	Cancer	Chemotherapy/dexamethasone	WBRT	Symptoms	Fever	MRI FLAIR	CSF, WBC (Cells/mcL)	CSF protein (mg/dL)	HSV type	Outcome
1	67/F	PCNSL	RMVP/none	No	AMS × 3 days	No	Bilateral temporal	4	59	1	Dead 52 days later
2	48/F	NSCLC + brain mets	Pemetrexed/Dex 6 mg	Yes, 15 days prior	Aphasia, AMS × 1 days	Yes	Bilateral temporal with hemorrhage	24	35	2	Severely impaired, lost to f/u 59 days later
3	55/M	Melanoma + brain mets	None/Dex 12 mg	Yes, 21 days prior	AMS, aphasia × 3 days	No	Bilateral temporal	6	156	1	Dead 59 days later
4	54/F	Breast + brain mets	Gemcitabine, trastuzumab/unknown	Yes, 2.5 months prior	AMS, seizures × 2 days	No	Left temporal	4	55	1	Dead 63 days later
5	76/F	Breast	Capecitabine/none	No	AMS × 3 days	Yes	Left temporal	46	64	1	Mild deficits, dead 430 days later
6	45/F	Thyroid	None/Dex 8 mg	No	AMS, aphasia 3 days after drainage of cervical epidural abscess	Yes	Bilateral temporal with vasculitis and infarcts	349	139	2	Dead 74 days later
7	69/M	Renal cell + brain mets	Sunitinib + gefitinib/unknown	Yes, 4 days prior	AMS, seizure × 2 days	No	Bilateral temporal	1	56	Unknown	Dead 7 days later

AMS altered mental status, *PCNSL* primary CNS lymphoma, *RMVP* rituximab, methotrexate, vincristine, procarbazine, *NSCLC* non-small-cell lung cancer, *Mets* metastases, *Dex* dexamethasone, *mg* total milligrams per day

Table 2 Summary of HSE cases in cancer patients reported in the literature

Case	Age/ sex	Cancer	Prior chemotherapy	RT	Symptoms	MRI FLAIR	CSF WBC cells/mm^3	CSF protein mg/dl	HSV	Outcome	Ref
1	55/M	Small-cell lung	Cisplatin, etoposide	Yes, WBRT, 15 d prior	AMS, fever	Temporal + hemorrhage	"absent"	NR	1	Dead 40 d later	[20]
2	61/M	Pituitary adenoma	No	Yes, WBRT, ongoing	Seizure during RT	Temporal	62	45	NR	Recovered	[21]
3	62/F	Lung	Yes, NR	Yes, WBRT 2 mo prior	Seizure	NR	NR	NR	2	Dead 9 d later	[22]
4	35/F	PCNSL	No, but suspected HIV	Yes, WBRT	Coma	NR	19	21	1	Dead 2 wk later	[4]
5	24/F	Glioma	Carmustine + 5-FU	Yes, WBRT, 3 mo prior	AMS, fever	NR	9	28	1	Dead 17 d later	[4]
6	75/F	DLBCL and CNS mets	RCHOP, methotrexate, procarbazine	Yes, WBRT 10 d prior	AMS	Temporal	2	63	1	Dead 2 mo later	[23]
7	5/M	Brainstem glioma	Lomustine	Yes, 2 wk prior	Fever and seizures	Temporal	NR	NR	NR	NR	[24]
8	22/F	Medulloblastoma	Carboplatin, cyclophosphamide	Yes, SRS 3 wk prior	AMS	Temporal	NR	NR	1 and 2	Dead 15 d later	[25]
9	15/M	Brainstem glioma	Temozolomide	Yes, WBRT ongoing	AMS	Normal initially, later temporal	30	58	1	NR	[26]
10	13/M	Brainstem glioma	No	Yes, ongoing	Fever, seizures	Temporal	0	57	1	Dead 8 mo later	[6]
11	42/F	Breast + CNS mets	No	Yes, WBRT 2 d prior	Coma	Temporal	3	42	1	NR	[5]
12	55/F	Breast + CNS mets	None recently	Yes, ongoing	AMS, seizure	Temporal and diffuse	26	50	NR	Dead 59 d later	[27]
13	52/F	CNS mets	NR	Yes, 2 mo prior	NR	NR	NR	NR	NR	NR	[28]
14	NR	Medulloblastoma	Carboplatin, cyclophosphamide	Yes, 3 wk prior	NR	NR	NR	NR	NR	Dead	[29]
15	57/F	Breast	Epirubicin	No	AMS	Temporal	175	1,765	1	Recovered	[30]
16	45/M	Pineal	Bleomycin, etoposide, cisplatin	No	AMS	NR	NR	'raised'	2	Recurred with retinal necrosis	[31]
17	73/M	Monoclonal gammopathy	None	No	AMS, seizures	Temporal	7	66	1	Recovered	[32]
18	63/M	Acute myeloid leukemia, in remission	Stem cell transplant 2.5 years prior, off all immunosuppressants for 5 mo	Total body irradiation 2.5 years prior	AMS	Temporal	55	57	NR	Recovered	[33]

Table 2 continued

Case	Age/ sex	Cancer	Prior chemotherapy	RT	Symptoms	MRI FLAIR	CSF WBC cells/mm^3	CSF protein mg/dl	HSV	Outcome	Ref
19	45/M	Glioblastoma	None	No	Seizure	Mass	1	51	NR	False positive	[34]
20	63/M	Glioblastoma	None	No	Seizure	Mass	2	45	NR	False positive	[34]
21	NR	PCNSL	Methotrexate	No	NR	NR	NR	NR	NR	Dead	[35]
22	NR	Glioma	Temozolomide	No	NR	NR	NR	NR	NR	Dead	[8]
23	NR	Glioma	Temozolomide	Yes, WBRT	NR	NR	NR	NR	NR	Dead	[8]
24	NR	Multiple Myeloma	Thalidomide	NR	NR	NR	NR	NR	NR	Dead	[36]
25	NR	Plasmacytoma	NR	NR	NR	NR	NR	NR	NR	Dead	[37]
26	NR	Multiple Myeloma	NR	NR	NR	NR	NR	NR	NR	Dead	[38]
27	NR	NR	BMT	NR	AMS, fever	Normal	NR	NR	NR	Recovered	[39]
28	NR	NR	BMT	NR	AMS	Bitemporal	NR	NR	NR	Dead	[39]
29	NR	NR	BMT	NR	AMS, fever, seizure	Normal	NR	NR	NR	Dead	[39]
30	NR	NR	BMT	NR	AMS	Normal	NR	NR	NR	Recovered	[39]
31	NR	NR	BMT	NR	Headache	Normal	NR	NR	NR	Recovered	[39]
32	NR	NR	BMT	NR	AMS, seizure	Normal	NR	NR	NR	Recovered	[39]
33	NR	NR	BMT	NR	NR	NR	NR	NR	NR	Dead	[7]
34	NR	NR	BMT	NR	NR	NR	NR	NR	NR	Dead	[7]

Mo months, *wk* weeks, *d* days, *PCNSL* primary CNS lymphoma, *DLBCL* diffuse large B-cell lymphoma, *AMS* altered mental status, *BMT* bone marrow transplant, *WBRT* whole brain radiotherapy, *NR* not reported, *Mets* metastases, *RCHOP* rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine (oncovin), prednisolone

normal CSF cell count (Table 2). CSF PCR for HSV was negative in one of our patients and inflammatory infiltrates were absent at autopsy in this patient. Furthermore, HSV-2 normally causes only 6% of HSE, but was seen in two of our seven patients and three of the twelve cases reported in the literature that described HSV type [1].

Systemic administration of cyclophosphamide and dexamethasone to rabbits latently infected with HSV produced active CNS HSV infection in the temporal lobes, suggesting that immunosuppression without RT may increase risk of HSE [10]. In a prospective study of infectious encephalitis due to any cause, co-existing cancer was a significant predictor of fatal outcome [2]. Oral HSV lesions can develop during RT to the head and neck, and may have occurred in one of our patients, although the viral etiology of that patient's oral ulcers was not confirmed [11]. HSE has also been reported rarely following craniotomy; however, it occurred within days of neurosurgery in all reported cases and peri-operative dexamethasone use may have contributed [12]. Although five of our patients had intracranial neoplasms (four brain metastases), none had a recent craniotomy. Toll-like receptor activation of the innate immune system is important in the CNS immune response to HSV as proven by increased susceptibility to HSE in people with genetic defects in toll-like receptor-3 pathways, and is potently impaired by corticosteroids [13–15]. Animal models suggest that radiation does not significantly alter toll-like receptor signaling and may in fact activate the innate immune system [16, 17]. Three of our patients were known to be taking glucocorticoids at the time of HSE. There are conflicting data from animal models suggesting that dexamethasone and corticosterone may be beneficial or harmful in HSE depending on the timing of administration, and a large trial using dexamethasone together with acyclovir for acute HSE is currently underway [10, 13, 18].

The retrospective nature of our study and small number of patients are major limitations. However, the similarity between our observations and individual cases reported in the literature supports our hypothesis. Our study may be an underestimate of HSE, as it only included patients diagnosed with HSE at our institution. Patients treated at our institution, but who may have been hospitalized elsewhere for HSE, would not have been included in our report. We would have also missed patients who did not undergo CSF testing or pathologic examination for HSV.

The atypical clinical features we observed suggest that patients with cancer who develop altered mental status or seizures with or without fever and have new temporal lobe abnormalities on FLAIR MRI should undergo lumbar puncture for HSV PCR and be started on acyclovir until testing is definitive, even if CSF pleocytosis is absent. In patients with typical clinical and radiographic features, treatment may be continued even if the CSF PCR result is negative as a false negative result was observed in one of our patients. While most of our patients died within 2 months of their HSE despite treatment, one patient (who had no intracranial tumor, never received cranial RT and was not taking glucocorticoids) survived more than a year with modest residual neurologic dysfunction, succumbing finally to her systemic cancer, suggesting that treatment of HSE may still be effective in this population. Acyclovir-resistant HSV may also be a consideration in these patients as acyclovir resistance is more common in immunosuppressed and bone marrow transplant patients (14% in one study) [19]. Vigilance for this diagnosis and early institution of therapy may help improve outcome.

Acknowledgments The authors would like to thank Galina Yusim for her able assistance with data collection for this project, Dr. Peter Mead for his helpful advice and Judith Lampron for her tireless editorial expertise.

Conflicts of interest None.

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