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Case Report

Herpes Simplex Encephalitis in Medulloblastoma Patients: Case Report and Review of Literature

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1. Abstract

Encephalitis caused by Herpes Simplex Virus (HSV) and medulloblastoma are both fairly rare disorders with relatively poor prognoses. We experienced a case of HSV encephalitis (HSE) in which the patient presented 1 year after surgical resection and radiation therapy and 1 month after chemotherapy. The patient had a good initial response to a 3 weeks course of IV acyclovir; however, he presented with infection relapse 5 days after hospital discharge with major neurological manifestation and progressive gliosis. A review of the literature for similar reported cases was done and we stressed on the importance of confirming a negative HSV polymerase chain reaction (PCR) test from the cerebrospinal fluid (CSF) prior to discontinuation of therapy, especially in the immune compromised hosts.

3. Introduction

Medulloblastoma is the most common malignant solid tumor in childhood, with the highest frequency among other brain tumors accounting for 30% of pediatric brain tumors and 7% to 8% of all brain tumors. According to the World Health Organization (WHO), medulloblastoma is classified as a grade IV tumor and defined as "a malignant, invasive embryonal tumor of the cerebellum with preferential manifestation in children, predominantly neuronal differentiation and an inherent tendency to metastasize via cerebrospinal (CSF) pathways [1, 2].

Herpes simplex virus is a worldwide common viral infection that starts as a latent infection then reactivates causing genital or cutaneous herpes, conjunctivitis, encephalitis, keratitis, or eczema herpeticum. Herpes simplex virus encephalitis (HSE) is considered as a very rare disease associated with high mortality rate that reaches 70% if left untreated [3]. An estimated worldwide incidence is one case per 250,000–500,000 individuals per year in which reactivation of the infection accounts for 70% of all HSE cases [3] while moderate to severe sequelae have been reported in 35-70% of the cases [4]. Multiple factors contribute to the reactivation of HSV, such as fever or exposure to ultraviolet light. Furthermore, studies suggested that reactivation is due to a multisystem process under the influence of neuronal, immune, and viral factors rather than a single factor [5]. Radiotherapy (RT) can trigger the reactivation of oral HSV infection, with raised concerns of having brain irradiations as a risk factor for the virus reactivation and HSV encephalitis [6]. Although HSV encephalitis triggered by neurosurgical procedures is a rare occurrence, neurosurgical procedures have occasionally been reported as precipitating factors for HSE [7-11]. In neurosurgical patients, postoperative HSE may involve areas of the brain other than the temporal lobe, resulting in atypical presentations. HSE has also been described in patients with Central Nervous System (CNS) tumors, including CNS lymphoma, spinal ependymoma, astrocytomas and high-grade gliomas, in whom the diagnosis of encephalitis may be delayed due to the confounding clinical presentations [12-15]. In these cases, cranial radiation therapy was the most commonly reported risk factor for disease development [16], while other reports described temozolomide-based chemoradiation as a contributing factor [17]. Here we report a case of relapsed necrotizing HSE that occurred in a child who received chemo-radiation for medulloblastoma treatment and present a review of the current literature for similar cases of HSE occurring in medulloblastoma patients.

4. Case report

A 9-year-old Saudi male who is known to have anaplastic medulloblastoma presented to the emergency room (ER) at King Abdulaziz Medical City in Jeddah, Saudi Arabia with fever and headache for 3 days associated with behavioural changes, decreased Level of Consciousness (LOC), irritability and decreased activity for 2 days. In the ER, he developed an attack of left sided seizure, which was

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aborted with Lorazepam. The patient had a history of posterior medulloblastoma with hydrocephalus diagnosed one year prior to his presentation. The patient underwent total gross resection with Ventriculo-peritoneal (VP) shunt insertion and RT followed by chemotherapy 10 months after (1 month prior to presentation) including cisplatin, cyclophosphamide, etoposide, cis-retinoic acid and vincristine. He developed several complications following his treatment, which included febrile neutropenia, fungal sinusitis and one episode of VP shunt infection, which were all treated successfully. Additionally, he was known to have a seizure disorder for which he was receiving levetiracetam. On examination in the ER, his temperature was 38^{O}C, pulse 120 bpm, blood pressure 99/63 mmHg, respiratory rate 30 breaths/min. The patient looked dehydrated. ENT, chest, abdomen, and CVS examinations were unremarkable. Neurologically, he has a VP shunt which was working well; he was disoriented and agitated. Lab investigations were as follows: WBC 4.9 x109/L, haemoglobin 11.5 g/dL, neutrophil 3.6, platelet 127 x109/L. Electrolytes were normal with phosphate 1.6 mmol/L, calcium 2.4 mmol/L, magnesium 0.9 mmol/L.

A brain Magnetic Resonance Imaging (MRI) was performed and demonstrated abnormal diffuse increased signal intensity at T2 involving the right supramarginal gyrus, insular/subinsular regions, hippocampal and parahippocampal regions, orbital gyrus, cingulate gyrus and the right thalamus. It is also involving the left cingulate gyrus and left hippocampus. These areas were associated with scattered abnormal leptomeningeal enhancement that was highly suggestive of bilateral HSV encephalitis (Figure 1). After that, the patient was admitted with clinical suspicion of HSV encephalitis, and was started empirically on intravenous (IV) acyclovir at a dose of 10 mg/kg every 8 hours. The diagnosis of HSE was confirmed by detection of HSV in cerebrospinal fluid (CSF) molecular testing that came back 2 weeks after. IV acyclovir was discontinued afterward 3 weeks after clinical improvement.

Five days after discharge, the patient presented back to the ER, with a fever of 38^{O}C, decreased LOC and status epilepticus. He was admitted as a case of relapsed HSE and was restarted on IV acyclovir. Additionally, the patient was started on ceftriaxone, vancomycin and voriconazole. A brain CT was done and showed multiple gliosis and brain MRI showed the same picture of HSE. Several days later, the CSF results returned back positive for HSV again.

The patient's neurological condition deteriorated and developed respiratory distress with irregular breathing. A repeat MRI showed progressive gliosis (Figure 2) and a decision was made to keep the patient with limited code. Days afterwards, the patient started to improve and regain some of his consciousness. His fever had subsided; therefore, ceftriaxone was discontinued. Another CSF sample for HSV was drawn and was negative, so it was decided for him to be switched to oral acyclovir 400 mg every 6 hours for 6 weeks and was discharged home. Later on, he was seen for follow-up in the outpatient clinic and was doing fine with permanent neurological deficits in the form of left hemiplegia and pseudo-bulbar palsy that remained after 3 years of follow-up.

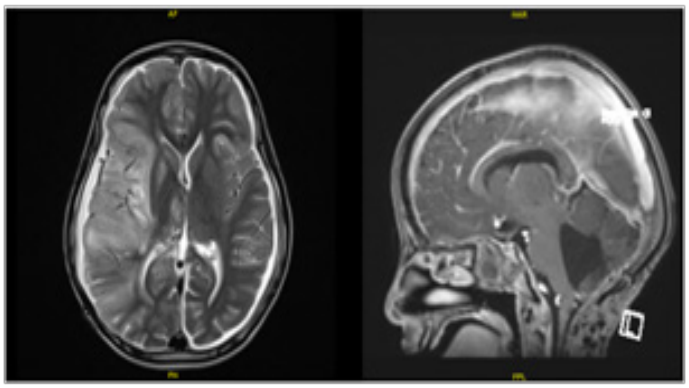

Figure 1: A brain MRI demonstrating abnormal diffuse increased signal intensity at T2 involving the right supramarginal gyrus, insular/subinsular regions, hippocampal and parahippocampal regions, orbital gyrus, cingulate gyrus the right thalamus. It is also involving the left cingulate gyrus and left hippocampus. These areas were associated with scattered abnormal leptomeningeal enhancement.

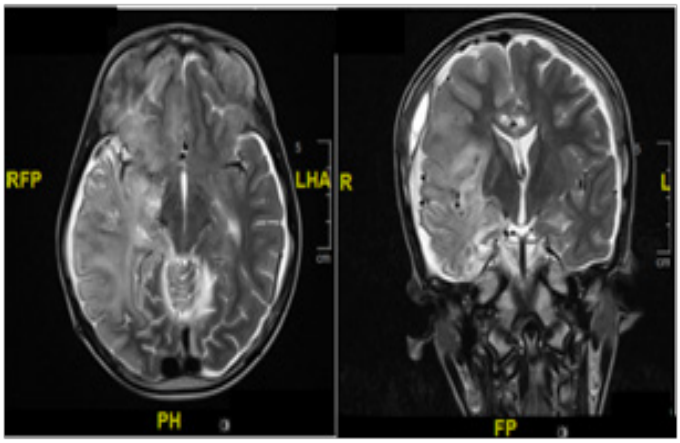

Figure 2: Brain MRI obtained upon symptom relapse demonstrating diffuse parenchymal edema involving most of the right cerebral hemisphere with new involvement mainly the cortex of the right frontal lobe, as well as the diffuse involvement of the right parietal and occipital lobes with persistent extensive involvement of the temporal lobe in the right side. Mild similar changes involve the left temporal lobe with new cortical edema and swelling with increase T2 signal intensity at the left peri insular gyrus. Also identified the interval development of abnormal high T2 signal intensity of the right caudate lentiform nucleus, as well as the right thalamus with newly identified diffusion restriction involving the right frontal parietal occipital lobes, as well as the right caudate lentiform nucleus and the right thalamus. Also new diffusion restriction changes seen at the left peri insular gyrus changesdemonstrating loss of gray white matter differentiation. Hemorrhagic changes are also noted in the hippocampal region of the right temporal lobe.

5. Discussion

Very few reports have described HSE cases in patients with medulloblastoma. (Table 1) summarizes the two reported cases in addition to our current case. In addition to these reports, HSE had been reported in other types of brain tumors [12-15].

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Table 1: A summary table of the reported cases of medulloblastoma and HSV encephalitis

Author, Year	Age	Gender	Diagnosis	Procedure	Chemotherapy	Radiotherapy	Symptoms of HSE	Time to HSE symptoms	Steroids	HSV treatment (treatment duration)	Outcome
Malloy, 2000 (6)	22	Female	Medulloblastoma	Craniotomy with complete resection	Yes, given after disease recurrence (carboplatin, and Cyclophosphamide)	Yes (postoperative radical craniospinal RT. Then received y stereotactic RT after disease recurrence)	Acute confusion	3 weeks post- RT for recurrent medulloblastoma	Yes, after disease recurrence	None As the diagnosis was made post-mortem	Death
Saran, 2008(18)	Not known	Not known		Complete resection craniospinal RT initially. Then after tumor relapse the patient underwent partial resection of the tumor	Yes, given after disease recurrence (carboplatin, and Cyclophosphamide)	Yes, SCRT	Not known	3 weeks after SCRT for recurrent medulloblastoma	Not known	None As the diagnosis was made post-mortem	Death
Present case	9	Male		Total gross resection	Cisplatin, cyclophosphamide, etoposide , cis retinoic acid, and vincristine	Yes	Status epilepticus, decreased LOC, and fever	1 year after the end of chemo-radiation	None	IV Acyclovir for 3 weeks, complicated by infection relapse 5 days after discontinuation	Relapsed HSE initially. Survived afterwards with permanent neurological sequelae

In our case, the patient underwent complete resection of the medulloblastoma followed by radiation therapy. One month after chemotherapy, he developed HSE and was treated with acyclovir for total 3 weeks with good clinical recovery; however, lumbar tap was not repeated as the test is not available in house and the decision for discontinuation was made based on clinical assessment. Unfortunately, relapse of the infection happened soon after being discharged, which resulted in significant consequences and neurological sequelae.

HSE in medulloblastoma, to our knowledge, was reported in two cases in the literature and both cases occurred after chemo-radiation [6, 18]. In the first case reported by Molloy S et al, a 22-year-old lady presented with confusion 3 weeks after receiving stereotactic RT with adjunctive chemotherapy and steroids for treatment of medulloblastoma recurrence. Her clinical condition deteriorated rapidly afterwards and died 15 days after admission. Post-mortem HSV polymerase chain reaction (PCR) tests on brain tissue revealed presence of HSV [6]. The second case was reported by Saran et al. among a series of 13 other cases of recurrent medulloblastoma treated with stereotactic conformal external beam radiotherapy (SCRT) [18]. This case developed clinical deterioration 3 weeks following SCRT and postmortem examination confirmed HSE and progressive medulloblastoma [18].

Reactivation of oral HSV during chemo-radiotherapy is a very well recognized setup of the virus given the established viral latency and opportunism [19, 20]; however, HSE encephalitis is not more common in immunocompromised compared to healthy hosts, and thus relapses of HSE is even more unusual to happen and had been very rarely reported in these patients [17, 21].

The cause of HSE relapse is not very clear; some studies attributed it to ongoing viral replication. On the other hand, Dannett et al, explained in 5 cases of relapsed HSE that the cause of relapse was not due to active viral replication and expounded it to an on-going immune-mediated and inflammatory reaction to the infection [22]. One possible explanation of relapse in our case would be the severe state of immunosuppression where immunity is unable to overcome the infection despite proper therapy. Another possible explanation would be related to inadequate dose/duration of therapy. Otherwise, this could be due to be the development of acyclovir resistance in the settings of immunosuppression. However, this explanation is not very well justified, given that our case responded clinically to acyclovir after the resumption of the same dose of therapy. Unfortunately, at that time, major neurological damage had already occurred.

The initial clinical trials on Acyclovir duration in HSV encephalitis suggested 10 days of therapy [23, 24]. However, and given the high rate of relapse rate with such duration, further recommendations advised for extending the duration to 14-21 days [25-31]. Some experts suggest confirming a negative CSF PCR result at the end of therapy especially in cases that lack appropriate clinical response, and advise for guiding the duration of antiviral therapy based on confirmed negative tests [27, 32]. This approach is even advocated by the British Neurologists and British Pediatric Allergy, Immunology and Infectious Diseases Group and adds an additional recommendation of at least 21 days of acyclovir treatment in the immunocompromised population [29].

6. Conclusion

HSE appears as a significant cause of morbidity and mortality in immunocompromised patients. These patients in particular are at considerable risk of HSE relapse, thus extended duration of IV acyclovir therapy guided by CSF examination and confirmed negative HSV PCR is advocated.

References

1. Quinlan A, Rizzolo D. Understanding medulloblastoma. J Am Acad Physician Assist. 2017; 30: 30-6.
2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathol. 2007; 114: 97–109.
3. Gnann J, Whitley R. Herpes Simplex Encephalitis: an Update. Current Infectious Disease Reports. 2017; 19: 13.
4. De Tiège X, Rozenberg F, Héron B. The spectrum of herpes simplex

encephalitis in children. Eur J Paediatr Neurol. 2008; 12: 72-81.

5. Suzich JB, Cliffe AR. Strength in diversity: Understanding the pathways to herpes simplex virus reactivation. Virology. 2018; 522: 81-91.
6. Molloy S, Allcutt D, Brennan P, Ferrell M, Perryman R, Brett F. Herpes simplex encephalitis occurring after chemotherapy, surgery, and stereotactic radiotherapy for medulloblastoma. Arch Pathol Lab Med. 2000; 124: 1809-12.
7. Jaques DA, Bagetakou S, L'Huillier AG, Bartoli A, Vargas M-I, Fluss J, et al. Herpes simplex encephalitis as a complication of neurosurgical procedures: report of 3 cases and review of the literature. Virol J. 2016; 13: 83.
8. Alonso-Vanegas MA, Quintero-López E, Martínez-Albarrán AA, Moreira-Holguín JC. Recurrent Herpes Simplex Virus Encephalitis After Neurologic Surgery. World Neurosurg. 2016; 89: 731.
9. de Almeida SM, Crippa A, Cruz C, de Paola L, de Souza LP, Noronha L, et al. Reactivation of herpes simplex virus-1 following epilepsy surgery. Epilepsy Behav Case Rep. 2015; 4: 76-8.
10. Kim SH, Lee SG, Kim SH, Kim DS, Kim HD. Relapsed Herpes Simplex Virus Encephalitis after Epilepsy Surgery. J Epilepsy Res. 2013; 3: 28-31.
11. Suzuki HI, Hangaishi A, Hosoya N, Watanabe T, Kanda Y, Motokura T, et al. Herpes simplex encephalitis and subsequent cytomegalovirus encephalitis after chemoradiotherapy for central nervous system lymphoma: a case report and literature review. Int J Hematol. 2008; 87: 538-41.
12. Raper DMS, Wong A, McCormick PC, Lewis LD. Herpes simplex encephalitis following spinal ependymoma resection: case report and literature review. J Neurooncol. 2011; 103: 771-6.
13. Berzero G, Di Stefano AL, Dehais C, Sanson M, Gaviani P, Silvani A, et al. Herpes simplex encephalitis in glioma patients: a challenging diagnosis. J Neurol Neurosurg Psychiatry. 2015; 86: 374-7.
14. Park SW, Lee GH, Cha SH, Jung DS. Anaplastic Astrocytoma Mimicking Herpes Simplex Encephalitis. J Korean Neurol Assoc. 2016; 34: 394-6.
15. Graber JJ, Rosenblum MK, DeAngelis LM. Herpes simplex encephalitis in patients with cancer. J Neurooncol. 2011; 105: 415-21.
16. Okada M, Miyake K, Shinomiya A, Kawai N, Tamiya T. Relapse of herpes encephalitis induced by temozolomide-based chemoradiation in a patient with malignant glioma. J Neurosurg. 2013; 118: 258-63.
17. Saran F, Baumert BG, Creak AL, Warrington AP, Ashley S, Traish D, et al. Hypofractionated stereotactic radiotherapy in the management of recurrent or residual medulloblastoma/PNET. Pediatr Blood Cancer. 2008; 50: 554-60.
18. Djuric M, Jankovic L, Jovanovic T, Pavlica D, Brkic S, Knezevic A, et al. Prevalence of oral herpes simplex virus reactivation in cancer patients: a comparison of different techniques of viral detection: Oral HSV reactivation in cancer patients. J Oral Pathol Med. 2008; 38: 167-73.
19. Rand K, Kramer B, Jojnson A. Cancer chemotherapy associated symptomatic stomatitis. Role of herpes simplex virus (HSV). Cancer. 1982; 50: 1262-5.
20. Nolan R. An Unusual Complication of Chemotherapy: Herpes Simplex Meningoencephalitis and Bilateral Acute Retinal Necrosis. Clin Oncol. 2004; 16: 81-2.
21. Dennett C, Klapper P, Cleator G. Polymerase chain reaction in the investigation of "relapse" following herpes simplex encephalitis. J Med Virol. 1996; 48: 129-32.
22. Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, et al. Vidarabine versus Acyclovir Therapy in Herpes Simplex Encephalitis. N Engl J Med. 1986; 314: 144-9.
23. Sköldenberg B, Alestig K, Burman L, Forkman A, Lövgren K, Norrby R, et al. ACYCLOVIR VERSUS VIDARABINE IN HERPES SIMPLEX ENCEPHALITIS. The Lancet. 1984; 324: 707-11.
24. Ito Y, Kimura H, Yabuta Y, Ando Y, Murakami T, Shiomi M, et al. Exacerbation of Herpes Simplex Encephalitis after Successful Treatment with Acyclovir. Clin Infect Dis. 2000; 30: 185-7.
25. Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, et al. Outcome of and Prognostic Factors for Herpes Simplex Encephalitis in Adult Patients: Results of a Multicenter Study. Clin Infect Dis. 2002; 35: 254-60.
26. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, et al. The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008; 47: 303-27.
27. Valencia I, Miles DK, Melvin J, Khurana D, Kothare S, Hardison H, et al. Relapse of Herpes Encephalitis after Acyclovir Therapy: Report of Two New Cases and Review of the Literature. Neuropediatrics. 2004; 35: 371-6.
28. Kneen R, Michael BD, Menson E, Mehta B, Easton A, Hemingway C, et al. Management of suspected viral encephalitis in children Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group National Guidelines. J Infect. 2012; 64: 449–77.
29. VanLandingham K, Marsteller H, Ross G, Hayden F. Relapse of herpes simplex encephalitis after conventional acyclovir therapy. JAMA. 1988; 259: 1051–3.
30. Levitz RE. Herpes simplex encephalitis: A review. Heart Lung. 1998; 27: 209-12.
31. Kennedy PGE. Herpes simplex encephalitis. J Neurol Neurosurg Psychiatry. 2002; 73: 237-8.