



Herpes Simplex Encephalitis Occurring During Chemo-Radiotherapy in Nasopharyngeal Carcinoma – A Case Report from Saudi Arabia

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Authors' contributions

This work was carried out in collaboration between all authors. Author KR wrote the protocol, author MMF wrote the first draft of the manuscript; author MS designed and edited the manuscript, while authors MMF and AAA managed the analyses of the study. Authors MMF, MS, FK, MT and RA managed the literature search. All authors read and approved the final manuscript.

Case Study

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ABSTRACT

Aim: To see possible association between the chemotherapy, radiotherapy or both with the reactivation of Herpes simplex virus 1(HSV1) in brain which merits further dialogue in the field of current evidence based literature.

Presentation of Case: We present a case of 46 years old male patient who developed herpes simplex encephalitis (HSE) while receiving radical chemo-radiation for locally advanced nasopharyngeal carcinoma. Full informed consent was obtained for publication of this case. He was treated with protracted course of anti-virals and is currently leading a healthy life.

Study Design: The study is a case report of a rare but important side effect of a common chemoradiation procedure.

Place and Duration of Study: The study took place at Comprehensive Cancer Center, King Fahad Medical City. It was reported during June 2013.

Discussion: HSV1 causes several disseminated primary infections including herpes labialis, gingivostomatitis, and corneal infections. It is particularly notorious for causing potentially fatal encephalitis. Its reactivation is linked to several environmental factors

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including chemotherapy and radiotherapy.

Conclusion: This case report emphasizes on the possible role of chemo-radiation as causation of this life threatening condition, its early detection, prompt and aggressive treatment.

Keywords: Herpes simplex encephalitis (HSE); chemo-radiation in nasopharyngeal carcinoma; latent herpes simplex virus-1 (HSV-1).

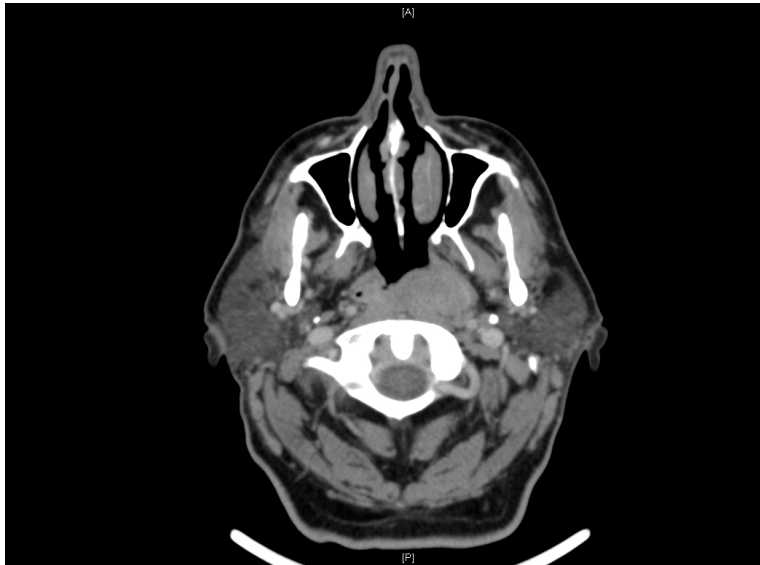
1. INTRODUCTION

Herpes simplex virus 1 (HSV-1), also known as herpes virus hominis, is a double stranded DNA virus responsible for acute disseminated primary infections such as gingivostomatitis, necrotizing encephalitis, recurrent reactivations as herpes labialis, corneal infections after a latency inside sensory ganglia with intermittent shedding of virus [1,2]. In both humans and experimental animals, HSV-1 is present in latent state in normal brain tissue. Herpes simplex encephalitis (HSE) is the most common form of fatal sporadic, non epidemic encephalitis estimated to occur at a rate of approximately 1/250,000 to 1/500,000 people each year [3]. Reactivation of HSV may occur due to a number of stimuli such as stress, ultraviolet light, hormones, hyperthermia, dental extraction and immunosuppression [4,5]. Reactivation of herpes virus may occur during radiotherapy especially for brain radiotherapy and may be a risk factor for reactivation of virus or encephalitis [6,7] although exact mechanism is not yet established.

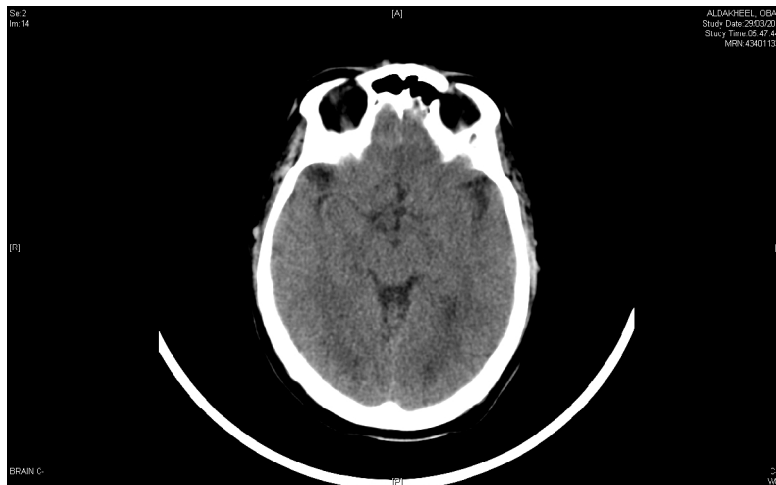
2. CASE HISTORY

This is an interesting case report of a 64 year old male who developed HSE following cranial RT and chemotherapy. Our patient initially presented with left ear tinnitus, hearing loss and left nasal obstruction over a period of 2 months. His investigations showed infiltrative soft tissue mass arising from the left fossa of Rosen Muller with bilateral retropharyngeal lymphadenopathy (Fig. 1).

The patient has had biopsy of the mass taken, which was reported as EBV positive Undifferentiated Nasopharyngeal Carcinoma. He was staged as T1N1M0 and was planned for concurrent chemo radiotherapy (70Gy of radiotherapy with Cisplatin as radiosensitizer). After 23 fractions of radiotherapy he was brought to emergency room with altered consciousness, seizures, disorientation and fever (39 degree Celsius). His initial baseline work up including complete blood count, LDH, electrolyte profile, Liver & Renal function tests, X-ray chest were all within acceptable range. Viral serology for HSV, Brucella profile, CSF for fungus, virus & bacteria and initial CT scan was unremarkable (Fig. 2).



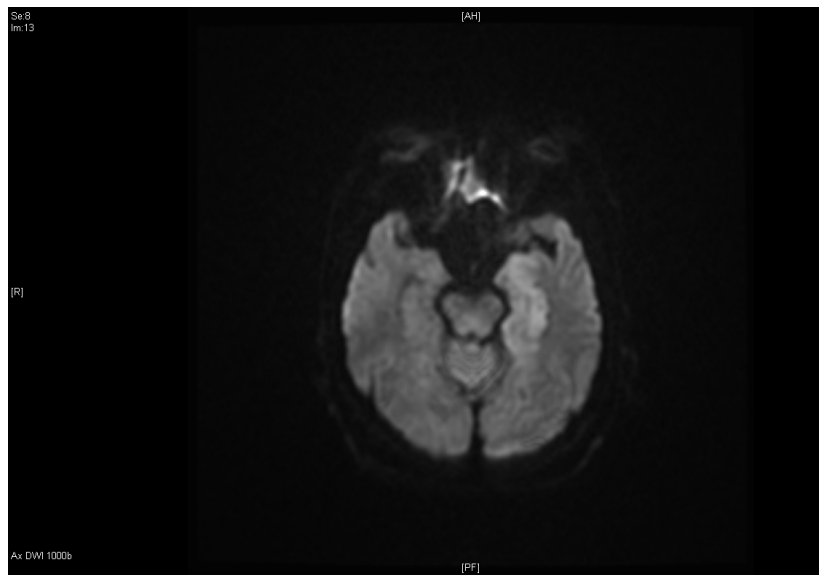
**Fig. 1. CT scan:
Infiltrative soft tissue mass arising from the left fossa of Rosen Muller with bilateral retropharyngeal lymphadenopathy**



**Fig. 2. CT scan done in ER:
Unremarkable scan, no grossly visible focus of seizures**

Immediately neurology team was consulted and he was loaded with phenytoin and once seizures settled he was maintained on Keppra and Topamax. A lumbar puncture was done and CSF results showed WBCs 9/ μ L, Neutrophils 87%, Lymphocytes 7%, RBCs 5/ μ L, Glucose 5.0 mmol/L, Protein 68 mg/dL. Provisional diagnosis of Viral Encephalitis was made. After 36 hours repeat MRI showed development of hypodensity involving medial part of the left temporal lobe including cortical and subcortical regions and extending to the ipsilateral hippocampal and parahippocampal region (Fig. 3). The 21 channel digital EEG

showed 6-7 Hz theta activity, diffuse and intermixed with slow arrhythmic 1.5 – 2 Hz Delta waves with moderate degree of slowing in generalized way, supporting possible encephalopathy process of various etiologies rather than Seizures. No Epileptic discharges were seen. Repeat CSF profile showed RBCs 24/ μ L, WBCs 14/ μ L, Neutrophils 5%, Lymphocytes 80%, Glucose 2.2 mg/dL, protein 0.82 mg/dL. All results favored viral encephalitis. HSV1 and 2 PCR was performed using HSV1 and 2 specific primers and hybridization probes for real time PCR using light cyclor instrument. An internal control was added to reaction, mixed with each clinical specimen to ensure the absence of polymerase inhibitors. HSV1 was successfully detected. So infectious diseases team was consulted and he was started on Acyclovir. He completed 4 weeks of acyclovir. His temperature along with confusion, disorientation, and seizures were settled gradually over one month period. His further chemo-radiation was stopped. The patient recovered very well from encephalitis and is currently on follow up leading a healthy life.



**Fig. 3. MRI scan after 36 hours
Hypodensity involving medial part of the left temporal lobe and extending to the
ipsilateral hippocampal and parahippocampal region**

3. DISCUSSION

Herpes simplex encephalitis (HSE) is a rare & life threatening clinical manifestation due to HSV1 infection. The co-occurrence of HSE and nasopharyngeal carcinoma is very rare, but it can occur during treatment. Both radiotherapy and chemoradiation with temozolomide can induce viral reactivation, leading to HSE relapse [8].

The incidence of HSV-1 infection during radiotherapy was estimated as being 14 of all 48 patients at risk (29.1%) [9].

There are few published case reports of herpes encephalitis after radiotherapy or chemotherapy. Development of encephalitis is from 1-8 weeks from end of treatment. Tohyama [10] reported a 5 year old male with pontine gliomas who presented with

somnolence and partial seizures 2 weeks after completing radiotherapy. Drajoge et al. [7] reported a 52 year old female who developed herpes simplex encephalitis 2 months after brain irradiation and dexamethasone administration. Molloy et al. [11] reported the case of a 25 year old female who developed bilateral temporal lobe lesions after surgical removal of a recurrent Medulloblastoma and combined chemotherapy and radiotherapy. Jacobs [12] presented the case of a 42 year old female with intracranial metastasis of breast cancer treated with steroids and radiotherapy. Two days after completion of radiotherapy she developed altered mentation and fever. PCR of CSF confirmed herpes simplex virus type 1. Okley et al. [6] described two patients with orolabial HSV reactivation during radiotherapy. One of them was case of nasopharyngeal carcinoma that was on external beam radical radiotherapy. He developed palatal, lingual and gingival ulcerations. Viral culture was positive. Second patient was 44 year old male with large cell immunoblastic lymphoma of cerebellum for which he received radiotherapy. Four days after radiotherapy he developed multiple painful oral ulcers.

Reil-Romero et al. [13] described 15 year old boy who developed herpes simplex encephalitis during radiotherapy for brain stem gliomas. It was proven with CSF PCR for HSV. G. Silvano et al. [14] presented a case of 55 year old male diagnosed as small cell lung carcinoma. He received prophylactic cranial irradiation and developed HSV-1 encephalitis 15 days after completion of radiotherapy. Peng et al. [15] reported a case of pituitary adenoma that was receiving radiotherapy for recurrence and during radiotherapy developed encephalitis. Okada M et al [8] reported a patient who was diagnosed with brain glioma and was receiving concurrent Chemo-radiotherapy and developed viral encephalitis while on treatment.

Interestingly, on other side, the role of radiation therapy in enhancing the anti-tumor activity of herpes simplex virus has been addressed in some studies. [16,17] which support the potential link between wild type HSV replication and radiotherapy. This involves the potential mechanism of enhancing replication of genetically engineered herpes simplex viruses by ionizing radiation, it may provide a new strategy for destruction of therapeutically intractable tumors.

4. CONCLUSION

Our patient and other anecdotal data suggest that radiotherapy alone or combined with chemotherapy might be a contributory factor in the occurrence of viral encephalitis in immuno-compromised host. The precise mechanism by which it occurs still remains unclear and is under investigation. Moreover the coincidence of radiotherapy & encephalitis cannot be excluded. This case suggests that radiotherapy may play a role in the activation of herpes simplex virus and emphasizes the importance of considering herpes simplex encephalitis in the differential diagnosis of acute encephalopathies during or after radiotherapy especially if steroids or chemotherapy are used concomitantly.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that the study has been performed and approved by the local ethics committee and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. This study is in public interest, and the release of information is permitted by the subject studied and the legislation.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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