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CASE REPORT

Radiation-induced brain injury after a conventional dose of intensity-modulated radiotherapy for nasopharyngeal carcinoma: a case report and literature review*

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Abstract

A 61-year-old female nasopharyngeal carcinoma patient was admitted to the hospital with sudden cognitive dysfunction one month after Volumetric Intensity Modulated Arc Therapy (VMAT) conventional dose radiotherapy, and the initial diagnosis was radiation-induced brain injury (RBI). After comprehensive treatment with steroid hormones, the patient's condition rapidly improved. Typically, in nasopharyngeal carcinoma patients treated with VMAT, the incidence of RBI is extremely low when the temporal lobe dose is less than 65 Gy or 1% of the volume is less than 65 Gy. When this limit is exceeded, RBI may occur in varying degrees. However, in this case, even though the temporal lobe dose was under the prescribed limit, the patient still experienced RBI. The rare observations in this case can be used as a reference, and clinicians should seriously consider the possibility of RBI in similar cases.

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Key words: radiation-induced brain injury; nasopharyngeal carcinoma; VMAT

Radiation-induced brain injury (RBI) is caused by the radiotherapy for head and neck cancer, and presents as a radiation response syndrome in the brain tissue. The incidence of RBI at the conventional dose of Volumetric Intensity Modulated Arc Therapy (VMAT) in nasopharyngeal carcinoma radiotherapy is 0.9 to 4.8% [1–3]. The clinical manifestations vary due to the range and location of different lesions. The main clinical manifestations of the temporal lobe type are memory deterioration, visual, auditory, olfactory and taste hallucinations, multilingual or mental retardation, orientation disorders, and intracranial hypertension. The clinical manifestations of the brain-stem type are dizziness, speech disorder, and walking instability [4]. In clinical practice, Magnetic Resonance Imaging (MRI) is the most commonly used method for the examination of RBI. Edema is the most common early manifestation of the injury. Late manifestations include brain atrophy, white matter necrosis, brain softening, and deposition of hemosiderin. The T1WI of the necrotic area shows a low signal and the T2WI shows a high signal [5]. Although with standardization of radiotherapy technology and dose, VMAT can significantly improve the local control rate of nasopharyngeal carcinoma with reduced exposure volume and dose for normal tissues, varying degrees of radiation brain damage are still possible. The main factors that determine the extent of RBI are radiation dose, divided dose, irradiation method and exposure volume, and individual radiotherapy sensitivity [6]. Nasopharyngeal carcinoma is different from brain tumor, for which radiation therapy is intended to be curative. The prescription dose is high, as the exposed brain tissue

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is small in size, and the exposed area is usually located at a distance from important functional areas associated with sensory processes and motor. Generally, the dose limit for the brain tissue is relaxed to meet the dose coverage of the target area in the progress [7]. In clinical practice, the method of delineation of the temporal lobe is commonly used to limit the exposure dose for the brain. The dose limit for the temporal lobe is less than 65 Gy or 1% of the volume < 65 Gy, and radiation brain damage rarely occurs under this dose limit. However, we observed a rare case wherein a nasopharyngeal carcinoma patient who was recently admitted to our hospital developed RBI after intensity-modulated radiotherapy and administration of a sputum leaf dose of Dmax < 60 Gy. We hope to reduce complications of radiation therapy in the future by analyzing the cause of RBI in this case and provide evidence for the optimization of precision radiotherapy.

Case history

A 61-year-old female patient was admitted to the Department of Radiation Oncology of the affiliated hospital of North Sichuan Medical College on August 30, 2018, one day after a diagnosis of nasopharyngeal carcinoma (T3N0M0 phase III), which required chemotherapy. The contraindications of radiotherapy were not considered after completing the relevant examinations, and radiotherapy was performed on the nasopharyngeal lesions and cervical lymphatic drainage areas on September 3, 2018.

In the first stage of treatment, the VMAT technique was used with a prescribed dose of P-GTVnx: 61.6 Gy/28Fx, P-GTVnd: 61.6 Gy/28Fx, P-CTV1: 60.2 Gy/28Fx, and P-CTV2: 50.4 Gy/28Fx. In the second stage, the dose prescribed was P-GTVnx: 11 Gy/5Fx. There was no atypical discomfort reported during the treatment, and the patient was discharged from the hospital on October 22, 2018.

On October 30, 2018, the patient was admitted to the Department of Neurology at our hospital for sudden cognitive impairment, concomitant with depression, gaze, slow reactions, physical decline, inability to calculate, confusion and memory loss, inability to recognize objects, and spatial and temporal orientation disorders among other symptoms. Physical examination showed the following: patient was conscious; the bilateral pupils were sensitive to light reflection; eyeball movement was normal; corneal reflex was present; symmetry of the bilateral frontal stria; nasolabial fold was symmetrical; no sag or drooping; tongue was centered; normal muscle tension; normal tendon reflex; mutual exercise and sensory system examination did not cooperate; and pathological signs were negative.

On October 30, 2018, the CT examination showed

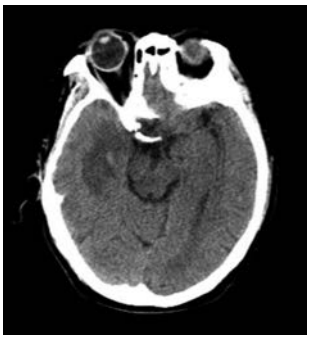

Fig. 1 Brain CT scan: Irregular slightly high-density shadow can be seen in the right temporal lobe

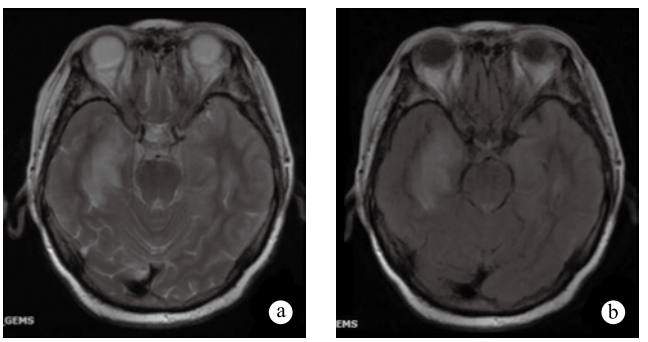

Fig. 2 MRI scan: T2WI and FLAIR show slightly higher signal, T1WI shows slightly lower signal

that the right temporal lobe presented with irregular, high-density shadows, and large patches of low-density shadows could be seen around the region (Fig. 1).

On November 1, 2018, the MRI examination showed flaky abnormal signals in the bilateral temporal lobe; the T1WI showed a slightly low signal, the T2WI and fluid attenuated inversion recovery (FLAIR) showed a slightly high signal, and the DWI of the left island insular cortex showed a slightly higher signal in the cerebral gyrus than in the surrounding areas. There was a patchy enhancement at the bottom of the right temporal lobe (Fig. 2).

On November 12, 2018, the MRI examination showed that the bilateral frontal temporal lobes presented with scattered, patchy and small abnormal signal shadows. The T1WI showed low signal, the T2WI and FLAIR showed high signal, the bilateral hippocampus and left insular lobe, temporal lobe, and occipital lobe showed patchy abnormal signal shadows. The T1WI showed an equal signal, whereas the T2WI and FLAIR showed a slightly higher signal, and the DWI showed slightly high B value. There was no widening and deepening in the brain pool and the cerebral sulcus, and no displacement of the midline structure and no abnormal signals in the cerebellum and brainstem were found. Radioactive encephalitis was considered in the bilateral hippocampus,

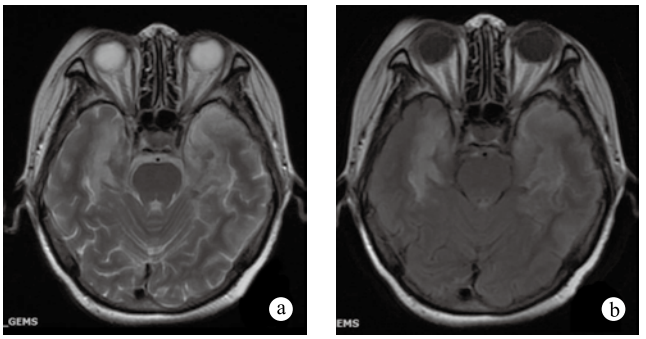

Fig. 3 MRI scan: There was no widening and deepening in the brain pool and the cerebral sulcus,and no displacement of the midline structure and no abnormal signals in the cerebellum and brainstem were found

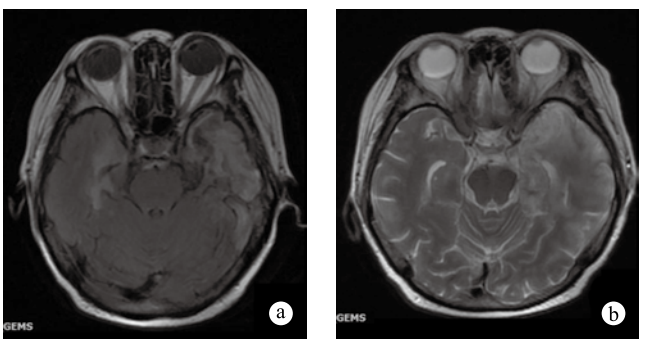

Fig. 4 MRI scan: After one-month hormone shock therapy

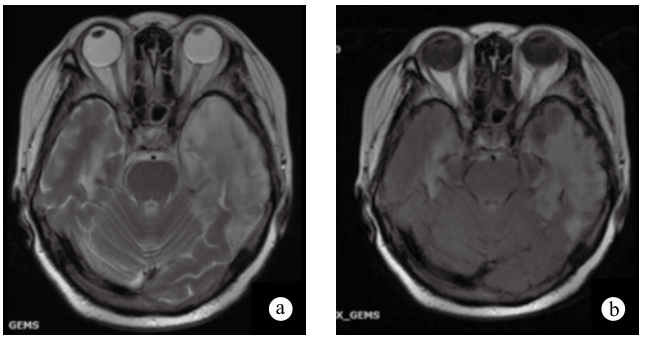

Fig. 5 Re-examination of MRI

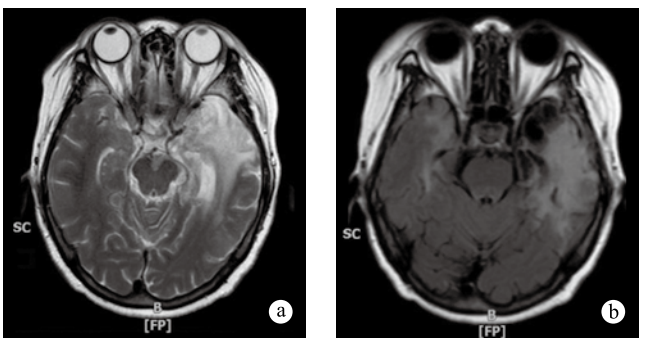

Fig. 6 Re-examination of MRI

left insular lobe, temporal lobe, and occipital lobe (Fig. 3).

At this time, the patient showed increased excitability, loss of appetite, dizziness, lethargy, memory loss, and slightly slow reactions. She could recognize familiar people, but could not recall names, whereas the symptoms of spatial and temporal disorientation were slightly improved.

On December 1, 2018, the MRI examination showed that the bilateral hippocampus, temporal lobe (sputum was extremely dominant, and left side was significantly larger than the right side), and the left-sided island leaf showed flaky abnormal signals, mainly on the left side of the lesion. The T1WI showed an equal signal compared with the dominant, whereas the right temporal lobe lesion showed a slightly higher patchy signal. The right temporal lobe and the left side of the lesion showed a slightly higher signal intensity; T2WI and T2-FLAIR also showed slightly higher signals; the DWI high B value was slightly higher; and the enhanced scan showed no obvious enhancement. The bilateral frontal and temporal lobes had scattered, spotted and patchy abnormal signals; the T1WI showed low signal, whereas the T2WI and T2-FLAIR showed high signals (Fig. 4).

The treatment plan included active dehydration with mannitol (125 mL q12h), dexamethasone (10 mg bid, lasting for four weeks), oxygen inhalation with a mask, a single dose of ginseng polyphenol (200 mg qd) for promoting blood circulation and correcting blood stasis, butylphthalide (0.2 g tid) for improving nerve function, edaravone (30 mg bid) as a free radical scavenger, and cerebroside carnosine (5 mL qd) as a nutritional nerve supplement. This treatment proved to be effective, and the patient gradually recovered cognitive functions.

After one month of hormone shock therapy, the dose was gradually reduced. On December 9, 2018, the patient was discharged from the hospital and was treated with dexamethasone (6 mg bid, taken orally), and the reduction lasted for 3–4 months. The patient was requested to visit the hospital for regular follow-up cranial MRIs.

MRI examination on January 4, 2019 showed that the bilateral hippocampus, temporal lobe (sputum is extremely dominant, and left side is significantly larger than the right side), and left lobes presented with flaky abnormal signals, mainly to the left of the lesion. The T1WI showed equal signal compared with the dominant, whereas the right temporal lobe lesion showed a slightly higher patchy signal. The right temporal lobe and the left side of the lesion showed slightly higher signal intensities; the T2WI and T2-FLAIR also showed slightly higher signals; the DWI high B value was slightly higher; and the enhanced scan showed no significant enhancement (Fig. 5).

At this time, the general condition of the patient had

improved; there was no dizziness and sleepiness, patient had recovered memory, reactions were normal, and time and space orientation was normal. The patient's dexamethasone dose was maintained at 0.75 mg qd.

On March 25, 2019, the changes in the hippocampus and temporal lobe lesions were not obvious compared with the results on January 4. However, the patient's previous symptoms improved significantly, and no special discomfort was reported (Fig. 6).

Discussion

Pathogenesis

Most researchers believe that only a single factor cannot explain the complex pathological manifestations of RBI, and it is the result of multiple factors. There are several theories that may explain the underlying mechanism:

(1) Glial cell theory: Radiation directly damages brain tissue, mainly acting on the glial cells, which can cause a disorder in myelin phospholipid formation, myelin phospholipid loosening, and reactive glial proliferation in the white matter, as well as demyelination and white matter atrophy [9].

(2) Autoimmune theory: Animal experiments have shown that oligodendrocytes and their enzyme systems produce autoantigens after radiotherapy, which induces autoimmune responses of the body, leading to demyelination of the brain glial cells, cerebral edema, and other pathological changes [5].

(3) Free radical theory: The central nervous system is extremely sensitive to oxidative damage. Ionizing radiation causes ionization of macromolecular substances in the cells, causing the cells to form a large number of oxygen free radicals. This leads to the formation of peroxides due to lipid peroxidation of the cell membranes, causing cell damage.

(4) Theory of vascular injury: Shortly after radiotherapy, the volume of vascular endothelial cells in the brain increases, and their nuclei shrink and fragment, resulting in a large reduction of endothelial cells. This in turn leads to infiltration of inflammatory cells around the blood vessels, due to which there is an increase in vascular permeability, leading to edema of surrounding tissues. Such phenomena lead to microcirculation disorders, brain ischemia, and irreversible necrosis. In the late stage after irradiation, extensive capillary atrophy results in a large number of ischemic lesions in the brain, which accelerates liquefaction necrosis of the brain [10].

Diagnosis

The case characteristics of this patient are consistent with previous literature reports in our country and abroad. There was a clear history of radiotherapy, relatively complex clinical manifestations, and lack of specificity. Plain CT scan in the acute and early-delayed response period showed extensive non-specific, low-density edema zones. MRI showed equal or low signals in the T1WI, and high signals in the T2WI and T2-FLAIR. One month after radiotherapy of the patient, the head CT showed an irregular, slightly high-density shadow in the right temporal lobe, and large patches of low-density shadow could be observed around the region. MRI showed abnormal patchy signals in the bilateral hippocampus and left insular lobe, temporal lobe, and occipital lobe; the T1WI showed equal signals, and T2WI and FLAIR showed slightly higher signals. The presence of typical symptoms (drowsiness, memory loss, irritability, and fatigue), time of onset of symptoms (1–6 months after irradiation), and effectiveness of the treatment (generally recoverable after treatment) confirmed the diagnosis of the early-delayed response period of RBI.

Treatment

RBI is usually a progressive, irreversible chronic change, but timely intervention in the acute phase, for both early and late onset RBI, has a significant therapeutic effect. The treatment protocol that was followed has been given below:

(1) Glucocorticoids as the main treatment; Feng Qing *et al* [11] used glucocorticoids for radiation encephalopathy, which can effectively relieve clinical symptoms, reduce brain tissue damage and brain edema, and effectively repair brain metabolism and nerve cell function in patients [11].

(2) Glycerol fructose or mannitol and torasemide were used to reduce brain edema and intracranial pressure [12].

(3) High pressure oxygen absorption; hyperbaric oxygen can increase tissue oxygen partial pressure, stimulate endothelial growth factor production, and stimulate cell and vascular repair mechanisms [13].

(4) Free radical scavengers; edaravone, a brain protectant, can not only scavenge free radical molecules, but also induce peroxidation reaction to alleviate the symptoms of brain edema.

(5) Warfarin and heparin can prevent and reverse vascular endothelial injury, improve microcirculation, and facilitate the repair of RBI.

(6) Simultaneously, the treatment was supplemented with vasodilators, nutrient supplements for nerves, large doses of vitamins, and blood circulation and stasis stimulus to improve brain function.

After the above treatment, the patient's symptoms improved and her cognitive function recovered significantly. However, the imaging results showed no obvious changes compared with the previous examination, and the patient required close observation and follow-up.

Unique characteristics of the case: summary and relevance

In the first stage, the prescribed dose was P-GTVnx: 61.6 Gy/28Fx, P-GTVnd: 61.6 Gy/28Fx, P-CTV1: 60.2 Gy/28Fx, and P-CTV2: 50.4 Gy/28Fx. In the second stage, the prescribed dose was P-GTVnx: 11 Gy/5Fx. The maximum dose for the left temporal lobe was 5996.8 cGy, whereas the maximum dose for the right temporal lobe was 5751.1 cGy. Su *et al* [14] found that when the Dmax dose for the temporal lobe was greater than 64 Gy or D1cc was greater than 52 Gy, the incidence of RBI increased by approximately 2.5% with every 1 Gy increase in the dose. The recommended dose limits are Dmax < 68 Gy or D1cc < 58 Gy to ensure safety. Furthermore, Su *et al* [15] found that the absolute volume of the temporal lobe V40 (aV40) and the percentage of the temporal lobe V40 (rV40) were also independent risk factors for the occurrence of RBI. The recommended limits were rV40 < 10% and aV40 < 5 cc. In this patient's case, even though the radiation dose was significantly lower than the aforementioned cutoffs, radiation brain damage still occurred. The observations of this case report can be used for reference when developing radiation therapy protocols in the future.

Conclusion

The occurrence of RBI is not only closely related to the radiation source, single dosage, total dose division, and total treatment time, but also related to other factors such as the patient's age, cancer pathology, clinical stage, individual sensitivity, cervical lymphadenopathy, neck and brain arteriosclerosis, and concurrent chemoradiotherapy. Moreover, there are no standard criteria for temporal lobe delineation, and there are numerous variations in protocols. We speculate that individual-specific factors may be the most important, as different individuals have different sensitivities to radiotherapy. Studies [16]have found that individuals with high radiosensitivity developed RBI earlier than those with low radiosensitivity. However, further studies are required to develop methods for determining an individual's sensitivity to radiotherapy before treatment.

The overall curative effect of RBI treatment is not satisfactory. Clinicians should focus on the prevention and reduction of the occurrence of RBI when performing head and neck radiotherapy. Similar to the results from the relevant body of literature, Lee *et al* [3] found that the incidence of RBI increased by 8.3% in patients with nasopharyngeal carcinoma treated with stereotactic radiotherapy compared to that in those treated with high-dose rate brachytherapy because brachytherapy did not involve an increase in the total dose of radiation to the temporal lobe. In the future, we should consider the use of close-range illumination instead of external exposure. In addition, studies have found that intensity-modulated proton radiotherapy (IMPT) can further improve the dose distribution for tumors and normal tissues and reduce the incidence of RBI. Taheri-Kadkhoda *et al* [18] compared the dose-study of Intensity-modulated radiation therapy (IMRT) and IMPT simulations in patients with nasopharyngeal carcinoma. It was found that IMPT not only significantly optimized the coverage of tumor target areas but also reduced the average exposure of the temporal lobe to approximately 40% of the exposure during IMRT. This suggests that proton radiotherapy may have potential advantages over other techniques as it minimizes damage to the central nervous system. However, specific findings need to be confirmed with large-scale clinical trials.

In summary, factors specific to patients with nasopharyngeal carcinoma should be fully considered during radiotherapy. We should accurately design the target area according to individual differences, strictly limit the temporal lobe dose, strengthen the monitoring and follow-up of patients after radiotherapy, and develop advanced radiotherapy methods to reduce the incidence of RBI.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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