CASE REPORT

Proton beam therapy for malignant transformation of intracranial epidermoid cyst

Zhe Chen,[1] Masayuki Araya,[2] Hiroshi Onishi[1]

[1]Radiology, University of Yamanashi Faculty of Medicine, Chuo, Yamanashi, Japan
[2]Proton Therapy Centre, Aizawa Hospital, Matsumoto, Nagano, Japan

Correspondence to
Dr Zhe Chen,
z.chenmd@live.com

Accepted 12 June 2019

SUMMARY

We report the first clinical case on the successful use of proton beam therapy in the management of malignant transformation of intracranial epidermoid cyst. A 43-year-old man was initially diagnosed as this disease with left facial paresis, hypesthesia and hypoalgesia in the territories of the trigeminal nerve. After failure of surgical interventions, he was referred to our radiation centre. We performed a postoperative proton beam therapy for treatment. We delivered a total dose of 57 GyE in 31 fractions. He tolerated the treatment well with mild acute toxicities and remained healthy and functional by 2-year follow-up postradiotherapy. No evidence of delayed radiation-induced neurotoxicity was observed.

BACKGROUND

Malignant transformation of intracranial epidermoid cyst (IEC) is a rare disease, and few reports are available.[1–3] Management of such diseases can be problematic, especially when combined with brainstem involvement. Surgical resection plus adjuvant radiation therapy showed a prospective effect.[4 5] Stereotactic radiosurgery has been used as high-precision methods of radiation delivery.[5 6] But, none of the previous cases were treated by proton beams. We report the first clinical case treated by proton beam therapy as a postoperative treatment and discuss the capacity of proton beam therapy in the management of this unusual disease.

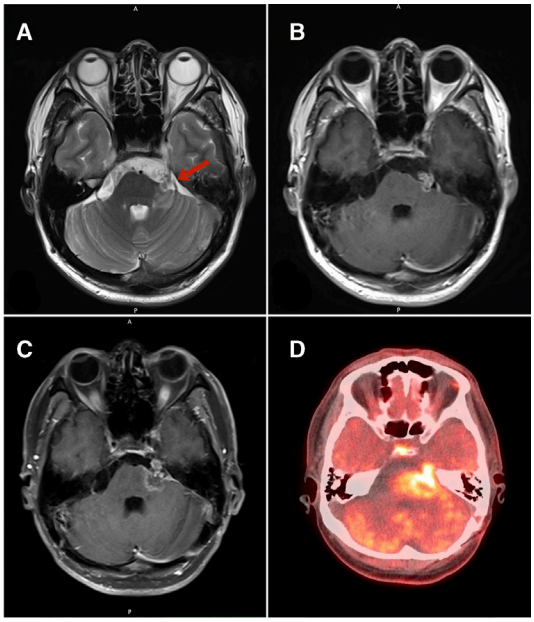

Figure 1 (A) T2-weighted MRI showed a high signal intensity, cystic, space-occupying lesion in the left cerebellopontine angle and (B) gadolinium-enhanced T1-weighted MRI showed a contrast enhancing tumour. (C) After previous surgery, enhanced MRI revealed tumour remnant, associated with an invasion of the brainstem. (D) ^{11}C-methionine positron emission tomography (MET-PET) confirmed the tumour.

CASE PRESENTATION

A 43-year-old man was initially diagnosed at another institution with left facial paresis (House-Brackmann grade III[7]), hypesthesia and hypoalgesia in the territories of the trigeminal nerve. He also complained of dimness of vision in the left eye at the same time. T2-weighted MRI showed a high signal intensity in the left cerebellopontine angle (CPA) (figure 1A, arrow). Gadolinium-enhanced T1-weighted MRI also showed the enhancing lesion (figure 1B). Diffusion-weighted image revealed a high signal intensity lesion at the same location.

A left retrosigmoid suboccipital craniotomy was performed. However, the tumour could not be totally removed due to the adherent to the brainstem and the VII/VIII cranial nerve complex. Histopathological findings showed poorly differentiated squamous epithelium elements. The squamous component comprised large epithelial cells with hyperchromatic, pleomorphic nuclei and abundant, dense eosinophilic cytoplasm. Keratinisation and intercellular bridges were present (figure 2). Immunohistochemical staining was also performed. Pan-keratin (AE1/AE3) and Ki67 were positive.

Follow-up brain MRI showed a remnant tumour. Because the completed resection was impossible, he visited our radiation centre in May 2016 to proceed with radiation therapy. Gamma knife radiosurgery (GKRS) was also considered at first. However, because of the remnant tumour was too close to the brainstem, GKRS may cause unprecedented broken to the brainstem. Finally, we decided to use the proton beam. Brain MRI was rescanned (figure 1C), ^{11}C-methionine positron emission tomography (MET-PET) confirmed the remnant tumour (figure 1D), and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) proved no distant metastasis.

TREATMENT

The patient underwent postoperative proton beam therapy in June 2016. To achieve the desired target

To cite: Chen Z, Araya M, Onishi H. *BMJ Case Rep* 2019;**12**:e229388. doi:10.1136/bcr-2019-229388

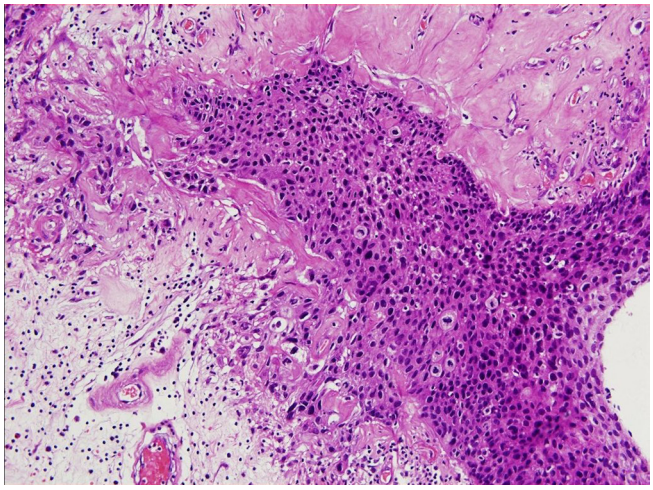

Figure 2 Solid tumour nests with an ectatic centre showing squamous differentiation. The squamous component comprised large epithelial cells with hyperchromatic, pleomorphic nuclei and abundant, dense eosinophilic cytoplasm (H&E, ×400).

coverage and normal tissue sparing, especially the brainstem, we use the pencil beam scanning technique with single-field optimisation (SFO). Radiation was delivered in three phases: 36 GyE in 20 fractions for the whole resection cavity, followed by a cone-down boost of 14.4 GyE in eight fractions and finally boost to the remnant tumour of 6.6 GyE in three fractions. The total prescription was 57 GyE in 31 fractions (figure 3A and B). Treatment plan was created in the Eclipse treatment planning system

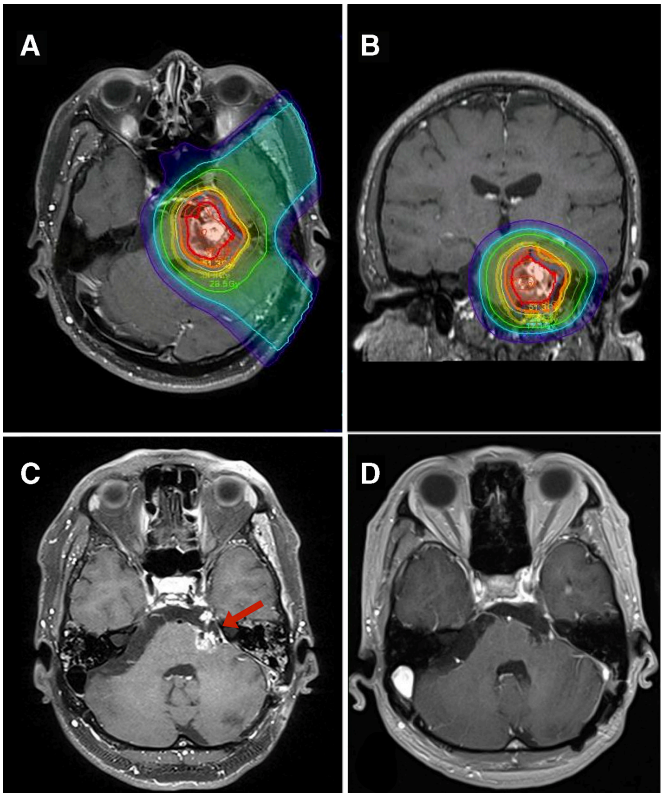

Figure 3 (A) Axial and (B) coronal colorwash isodose distribution for proton beam therapy. (C) MRI was taken in the treatment period showed a shrinkage of the tumour. (D) The tumour was disappeared at the follow-up MRI taken at 2 months after proton beam therapy.

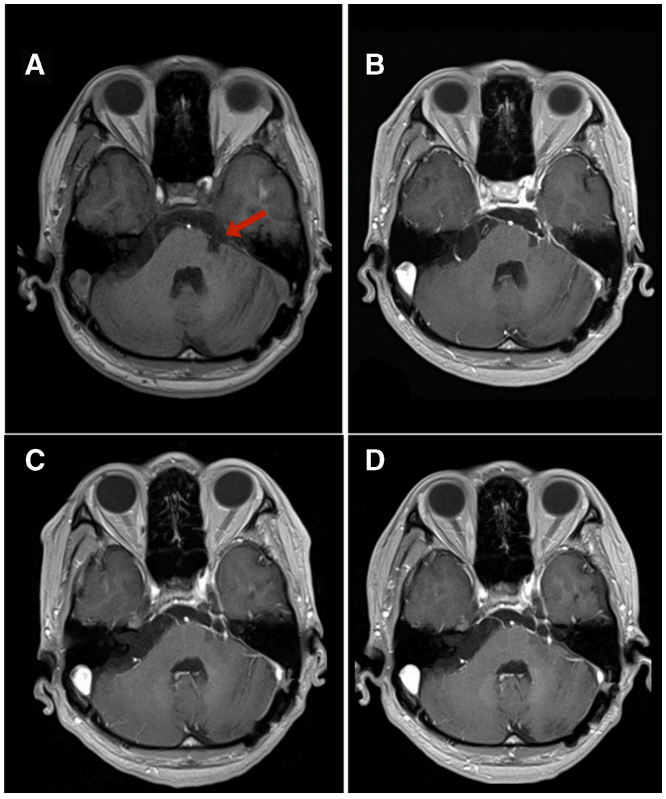

Figure 4 Post-treatment gadolinium-enhanced T1-weighted MRI showing the healing timeline of the CPA tumour. (A) 4 months after treatment. (B) 7 months after treatment. (C) 13 months after treatment. (D) 24 months after treatment. CPA, cerebellopontine angle.

V.13.7 (Varian Medical Systems, Palo Alto, California, USA). The proton beam therapy system was manufactured by Sumitomo Heavy Industries. The Common Terminology Criteria for Adverse Events V.4.0 was used to assess the acute and delayed radiation toxicities.

OUTCOME AND FOLLOW-UP

The patient tolerated the radiotherapy well without unexpected break. Grade I acute radiation dermatitis and acute otitis media were observed during the treatment. MRI taken in the treatment period showed shrinkage of the tumour (figure 3C, arrow). The gadolinium-enhanced tumour disappeared at the follow-up MRI taken at 2 months after treatment (figure 3D). MRI taken at 4, 7, 13 and 24 months after treatment showed no recurrence of the tumour (figure 4A–D). He remained healthy and functional at 2-year follow-up postradiotherapy. No evidence of delayed radiation-induced neurotoxicity was observed.

DISCUSSION

The dominant reason for intracranial squamous cell carcinoma (SCC) is metastases from distant organs.[8 9] Primary intracranial SCC is thought to originate from malignant transformation of a dermoid or epidermoid cyst.[10] Epidermoid cysts are generally benign mass and usually grow slowly representing about 0.2%–1.8% of all intracranial tumours. The CPA is the dominant region for 7% of intracranial tumours. The gender distribution had a female predominance, and the mean age was 51.4 years.[6] Garcia *et al* definite their diagnostic criteria at first,[11] and Hamlat *et al* reclassified primary intracranial SCC into five

Table 1 Cases of malignant transformation of intracranial epidermoid cyst, which was treated by radiation therapy

Author/published year	Patient's age (years)/ sex	Location	First treatment	Adjuvant RT techniques	Dose of prescription	Outcome
Davidson and Small, 1960[16]	46, M	R Frontal	OP	CRT	N/A	N/A
Dubois *et al*, 1981[17]	53, M	Fourth ventricle	OP	CRT	N/A	Dead 2 months
Garcia *et al*, 1981[11]	61, M	R CPA	OP	CRT	N/A	Dead 25 months
Goldman and Gandy, 1987[1]	57, F	Intraventricular	OP	CRT	5000 rads	Alive 36 months
Matsuno *et al*, 1987[8]	43, M	CPA	OP	CRT	N/A	Dead 28 months
Salazar *et al*, 1987[18]	49, M	Posterior fossa	OP	CRT	N/A	Alive 10 months
Knorr *et al*, 1991[19]	74, M	CPA	OP	CRT	N/A	Dead 1.5 months
Mori *et al*, 1995[20]	42, M	R CPA	OP	CRT	N/A	Dead 26 months
Nishio *et al*, 1995[21]	57, M	CPA	OP	CRT	50 Gy	Alive 30 months
	42, M	Middle fossa	OP	CRT	60 Gy	Dead 3.5 months
Fuse *et al*, 1995[22]	74, F	CPA	OP	CRT	N/A	Dead 12 months
Uchino *et al*, 1995[23]	57, M	CPA	OP	CRT	60 Gy	Alive 4 months
Murase *et al*, 1999[14]	50, F	CPA	OP	GKRS	14 Gy	Alive 60 months
Link *et al*, 2002[3]	57, M	CPA	OP	CRT+GKRS	45 Gy+15 Gy	Dead 32 months
Park and Park, 2003[24]	65, M	R CPA	OP	CRT	50 Gy	Alive 6 months
Guan *et al*, 2004[25]	42, F	Temporal	OP	CRT	6000 rads	Alive 12 months
Tamura *et al*, 2006[5]	56, F	CPA	OP	CRT+GKRS	15 Gy+12 Gy	Alive 13 months
Kim and Kim, 2008[26]	72, F	R CPA	OP	IMRT	54 Gy	Alive 12 months
Kano *et al*, 2010[27]	64, F	Parapontine	OP	CRT	50 Gy	Dead 25 months
Nakao *et al*, 2010[2]	74, F	CPA	OP	CRT	46 Gy	Alive 17 months
Lakhdar *et al*, 2011[28]	52, M	CPA	OP	CRT	50 Gy	Alive 1 month
Chon *et al*, 2012[6]	43, M	CPA	OP	GKRS	15 Gy+12 Gy	Alive 40 months
Pikis and Margolin, 2016[29]	77, M	CPA	OP	CRT	55 Gy	Dead 6 months
Roh *et al* 2017[13]	53, F	CPA	OP	IMRT	67.2 Gy	Dead 48 months
Current study, 2018	43, M	CPA	OP	PBT	57 GyE	Alive 29 months

According to the existing literature, the best treatment method of a malignant transformation of IEC is maximal surgical resection with uttermost protection of surrounding structures, subsequent with a radiation therapy.[4] Surgery alone is not efficient enough because tumour is tight adherence to surrounding structures, and total removal is generally difficult to achieve. Hamlat *et al* reported a 9-month median survival time.[12] Nagasawa *et al* also reported overall survival time as 6.6 months in surgery alone arm, and 12.7 months in those who underwent adjuvant radiation therapy following radical surgery.[4] Our case showed exceeded overall survival to the formers.

CPA, cerebellopontine angle; CRT, conventional radiation therapy; F, female; GKRS, gamma knife radiosurgery; Gy, grey; GyE, grey equivalent; IEC, intracranial epidermoid cyst; IMRT, intensity-modulated radiation therapy; M, male; N/A, not available; PBT, proton beam therapy; OP, operation; RT, radiation therapy.

groups.[12] According to Hamlat's classification, our case can be classified as an initial malignant transformation of a benign cyst.

We performed a literature review of studies published by searching in four databases: PubMed, Web of Science, Scopus and Google Scholar. We used the following keywords for search strategy: 'intracranial epidermoid cyst', 'malignant transformation of intracranial cyst', 'intracranial squamous cell carcinoma', 'radiation therapy of intracranial cyst', 'proton beam therapy' and 'proton therapy'. Up to December 2017, 44 cases of malignant transformation of IEC have been reported.[13] Our case is the 45th case, which was diagnosed primarily. We extracted the data from the relative studies, which was used the radiation therapy in the treatment course. There were 24 cases described the use of radiation therapy as an adjuvant treatment. Some of them disclosed the delivery method and dose of prescription (table 1).

However, a consensus recommendation for radiation therapy is lacking for the rarity of the disease. Tamura *et al* performed a meta-analysis for the survival of malignant transformation of IEC.[5] They suggested that a postoperative GKRS may offer better local control of intracranial SCC. By this article was written, four cases of GKRS have been described in the previous literature, with a marginal dose of 12–15 Gy.[3 5 6 14] The mean survival was 36.25 months. But, from our experience, GKRS is fatality when the tumour is adhering to the brainstem. So, we choose a more safe and efficient delivery method as proton beam therapy.

Proton beam therapy is a modern modality of radiation therapy and increasingly being used in many kinds of cancers. A stream of high-energy proton beams was produced by particle accelerator, which can be used in a medical treatment. Holliday *et al* indicated that because the proton particles do not deposit any unnecessary dose beyond the target, it has the potential to reduce the harm to adjacent normal tissues, such as the brainstem. The pencil scanning beam technique helps to confirm the dose distributions to target volumes layer by layer. SFO is another novel technique using computer algorithm, which is suitable for the unilateral target, and varies

Learning points

- Primary malignant transformation of intracranial epidermoid cyst is very rare.
- Surgery alone is not efficient enough, and subsequent radiation therapy is needed.
- This case is the first report of the successful use of proton beam therapy in the management of malignant transformation of intracranial epidermoid cyst.

of depths.[15] These new techniques enable us to approach the dangerous region without brainstem damage.

In conclusion, primary malignant transformation of IEC is a rare disease without consensus treatment. Surgery alone is not efficient enough. We report the first clinical case on the successful use of proton beam therapy in the management. Prospective trials are wanted to determine the optimal management.

Contributors MA and ZC contributed to conception and design of study. ZC contributed to acquisition of data and drafted the manuscript. HO revised the manuscript critically for important intellectual content.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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