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Case Report

Surgery and dose-escalated radiotherapy for a *de novo* intracranial squamous cell carcinoma of the cerebellopontine angle

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ABSTRACT

We report an extremely rare case of *de novo* intracranial squamous cell carcinoma of the cerebellopontine angle. The patient underwent craniotomy for debulking of the lesion to relieve mass effect on the brainstem and to establish a tissue diagnosis. Cancer staging revealed no other primary cancers and no evidence of metastatic disease. Postoperatively, he received image-guided intensity-modulated radiotherapy to the tumor bed followed by fractionated radiosurgery boost to the gross residual disease for a total average dose of 7000 cGy. He had a complete response to radiation and remains 42-months' disease-free post-treatment.

1. Introduction

Most cases of intracranial squamous cell carcinoma (ICSCC) are due to metastatic diseases. Primary ICSCC is rare, accounting for 0.2–1.8% of all intracranial lesions [1]. These tumors usually arise from the malignant transformation of benign lesions such as epidermoid cysts [2]. Current management entails surgical resection followed by radiotherapy and/or chemotherapy, with variable outcomes. The literature on *de novo* ICSCC is sparse, as there is only a handful of case reports on this disease [3,4]. We present a case of *de novo* ICSCC and review the pertinent literature on its diagnosis, treatment and outcome.

2. Case report

A right-handed man in his late sixties presented with a progressive right facial weakness initially diagnosed as a Bell's palsy. Months later, he developed right facial numbness, tinnitus, conjunctivitis, dysgeusia, dysphagia, anorexia, and a 20-pound weight loss. In addition, he had a rapid onset of right-sided paresis resulting in impaired gait. Physical examination revealed a *House-Brackmann* grade IV right facial nerve palsy, absent right corneal reflex, right-sided sensorineural hearing loss and hypoglossal nerve paralysis, and right hemiparesis grade +3/5 in the lower limb and +4/5 in the upper limb. He had a 30 pack-year history of smoking, with no other significant history.

Brain MRI (Fig. 1) showed a T1-hypointense, heterogeneous, T2-hypointense, lobulated, avidly enhancing expansile extra-axial mass in the right Meckel's cave and cavernous plexus with extension into the right cerebello-pontine angle (CPA) and ambient cisterns. There was vasogenic edema in the brainstem, right cerebellar hemisphere and vermis. Abnormal gadolinium enhancement was noted in the right facial nerve and geniculate ganglion and in the right V2 and V3 trigeminal nerve segments.

The patient underwent a maximum total resection of the tumor via a right suboccipital craniotomy with stereotactic neuronavigation and cranial nerve and brainstem mapping. The tumor was densely adherent to the brainstem and the affected cranial nerves. Intraoperative frozen section identified a poorly differentiated malignancy. Residual tumor was left in the cavernous sinus and brainstem. The final pathology (Fig. 2) confirmed a poorly differentiated epithelioid cells neoplasm with large irregular nuclei and a moderate amount of eosinophilic cytoplasm. The tumor cells were randomly disposed on a markedly collagenous background showing dense lymphocytic infiltration with scattered mitotic figures. No keratin deposition was identified. Immunohistochemically, there was intense cytoplasmic reactivity for broad-spectrum cytokeratin and for CK5. There was very focal plasma membrane staining for EMA. There was light focal nuclear staining for p40 and GATA-3. The Ki67 proliferation index was high focally. The

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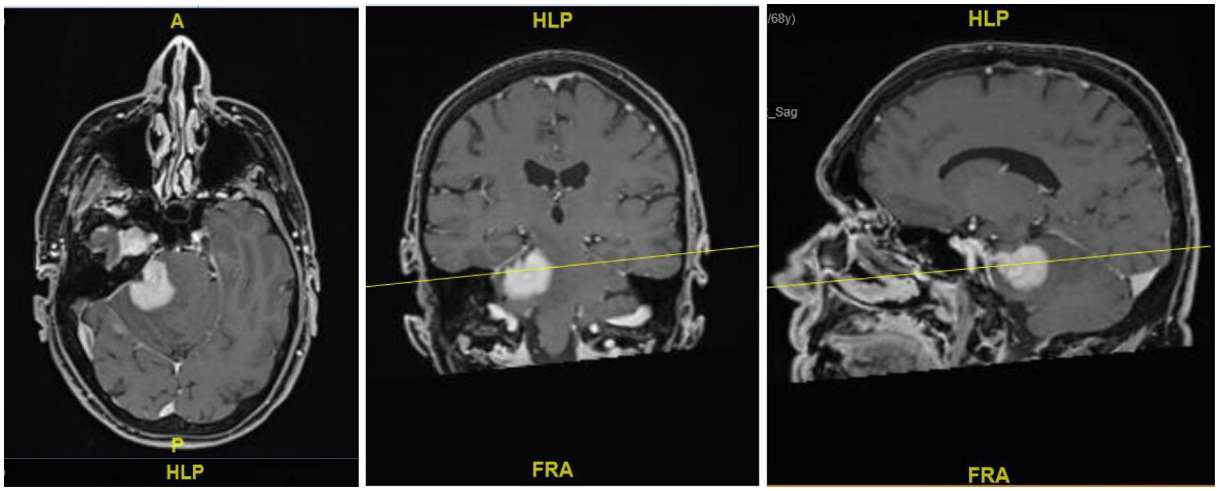

Fig. 1. Preoperative postgadolinium T1-weighted MRI (A: axial, B: coronal, and C: sagittal). Avidly enhancing lobulated mass centered in the right cavernous sinus/Meckel's cave and CPA cistern causing moderate mass effect on the brainstem.

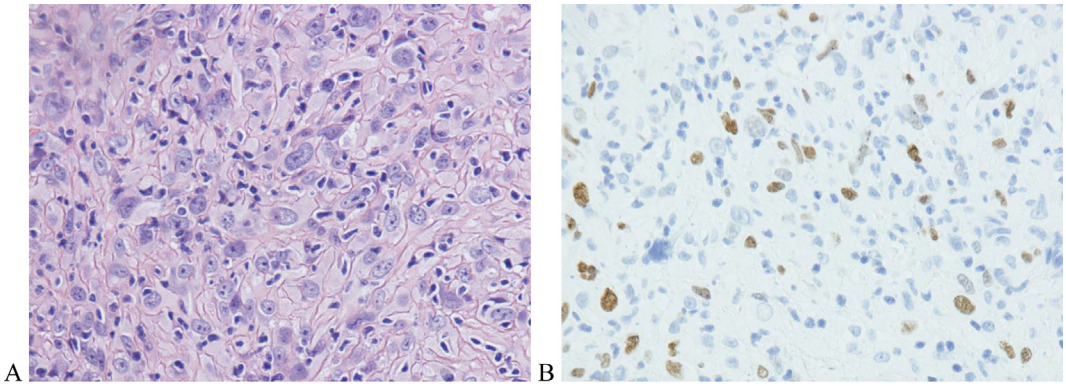

Fig. 2. A) Routinely stained sections of the tumor showed a poorly differentiated non-small cell carcinoma. Hematoxylin and eosin. Bar = 50 μm. B) Nuclear immunostaining for p40 is seen in a minority of tumor cells, consistent with squamous cell carcinoma. P40 immunostaining. Bar = 50 μm.

cells were negative for CD20, GFAP, CD3, CD15, EBER, S100, CD68, CD163, CK7, CK20, CD1a, PAX8, and SALL4. The pathology was consistent with a squamous cell carcinoma.

Immediate postoperative brain MRI showed residual tumor in right Meckel's cave and right cavernous sinus, with a persistent mass effect on the brainstem. There was a new right superior cerebellar territory infarct. The patient had persistent right hemiparesis and right-sided V, VII, VIII and XII nerves' deficits and developed new right-sided III, IV and VI cranial nerve palsies.

The patient underwent an extensive cancer screening workup. There was no malignancy in the neck. Full body PET/CT scanning did not reveal any primary or metastatic disease. The consensus recommendation by the multidisciplinary oncology team was for radical radiotherapy. The patient agreed to treatment following informed consent. The patient was made aware of the small chance of optic chiasm injury and brainstem necroses. He was treated with a combination of 5400 cGy in 27 daily fractions of Volumetric Modulated Arc Therapy (VMAT) based Intensity Modulated Radiotherapy (IMRT) with daily cone beam image guidance to Planning Target Volume 1 (PTV1) which included the entire preoperative tumor bed. The patient was treated with a boost dose of 2000 cGy in 10 daily fractions to PTV2 using fractionated stereotactic radiotherapy (FSRT or radiosurgery, SRS) to the gross residual tumor using CyberKnife (CK). The cumulative Dose Volume Histogram (DVH) showed 95% of PTV I was covered by 5570 cGy (103% of the intended 5400 cGy) and 95% of PTV II was covered by 6970 cGy (99.6% of 7000 cGy and 94.2% of 7400 cGy). The dose to 1 cc, 0.03 cc, and Dmax point for the brainstem from the 2 treatment phases were 6460, 6720 and 6983 cGy, respectively (Fig. 3). The Dmax to the optic chiasm was 5720 cGy.

The patient tolerated radiotherapy well with mild fatigue, alopecia and anorexia. The patient developed no late toxicity from the radiotherapy. In follow-up, the residual tumor has completely regressed. Incidentally, he was found to have a 2.6 cm left kidney mass on imaging after thirty months, suspicious for a renal cell carcinoma. To rule out an unlikely squamous cell histology, CT guided biopsy of the kidney was performed. Biopsy revealed a clear cell carcinoma, WHO/ISUP nuclear grade 2/4, without necrosis or lympho-vascular invasion. He was offered surgery or definitive stereotactic ablative radiotherapy (SBRT) using CK. The patient opted for CK based SBRT and was treated to a dose of 3900 cGy in 3 fractions. The patient has remained clinically and radiologically stable until his last follow up in 42 months. He has had no clinical or radiologic recurrence at the skull base, head and neck or other parts of the body. His permanent sequelae include residual deficits in right-sided III–VIII cranial nerves. The patient has shown improvement in swallowing function. He regained the weight that was lost. His hemiparesis and gait have gradually improved.

3. Discussion

We present a case of a middle-aged man with a large Meckel's cave/CPA tumor causing brainstem compression and invading the

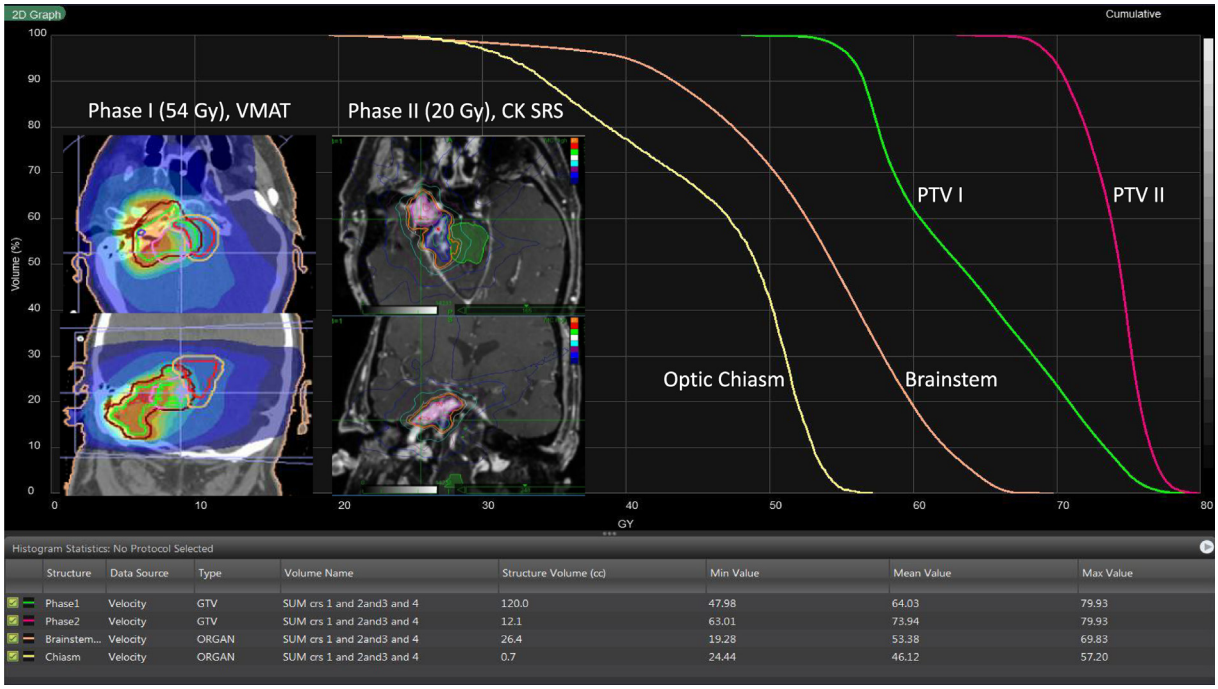

Fig. 3. Representative sections (axial and coronal) from phase I (54 Gy by VMAT) and phase II (20 Gy by CK SRS), with DVH to PTV I, PTV II, brainstem and optic chiasm, and dose statistics of these four volumes.

ipsilateral V, VII, VIII and XII cranial nerves. Craniotomy and debulking surgery were performed and the pathology was *de novo* ICSCC. He was also treated with radical dose-escalated radiotherapy using VMAT to the preoperative tumor bed followed by a radiosurgery boost, to a total dose of 7000 cGy. At 42-months, he is showing clinical improvement with a complete radiologic response to treatment.

Most of the reported cases of ICSCC have arisen from malignant transformation of epidermoid cysts and a handful were *de novo*. The mechanism of this transformation is not clear, and no valid explanation has been determined yet [4,5]. Our patient did not have a prior history of an epidermoid cyst and the histology did not show the epidermoid cyst's typical multiple lining layers of squamous epithelium nor the lamellar keratin [6]. Given its extradural extension, our case correlates with five of the six criteria for ICSCC [5,7]: (1) tumor restricted to the intracranial and intradural compartments; (2) no extension beyond the dura mater or cranial bones or through cranial orifices; (3) no communication with the middle ear, air sinuses, or sella turcica; (4) no nasopharyngeal tumor; (5) presence of benign squamous cell epithelium within the malignant tumor; and (6) exclusion of metastatic carcinoma [4].

There have been 6 cases of *de novo* ICSCC published between 1981 and 2018. Three of the tumors were located at the CPA cistern and 3 cases at non-CPA locations (Table 1). Compared to these, our case achieved the longest survival (so far, 42 months after radiotherapy last day) with complete radiologic response. All cases of *de novo* ICSCC of the CPA were adults older than 50 years of age while the 3 non-CPA cases occurred in younger patients (age range 5–35 years).

Adjuvant treatment with radiation, including radiosurgery, may play a role in improving outcomes of *de novo* ICSCC in the CPA. Nagasawa et al. [8], Liu et al. [4] and Kwon et al. [9] postulated that radiotherapy had a significant impact on the results of patients with ICSCC. It was recommended to offer the patient a dose-escalated radiotherapy course to optimize chances of local control for the residual tumor. IMRT using VMAT technique was used to treat the entire surgical bed to cover the potential microscopic residual tumor. This was followed by a CK SRS boost to the remaining gross residual disease. Dose-escalation to 7000 cGy or higher are often used to control epithelial tumors in many sites, including the head and neck region. Radiosurgery helps to minimize dose to the adjacent brainstem while escalating dose to the gross residual tumor. Due to the proximity of the residual tumor to the brainstem, conventional fractionation of 200 cGy per fraction was used in both phases (IMRT and FSRT). It remains a significant challenge to safely treat tumors adjacent to or involving the brainstem while trying to minimize the risk of brain stem necroses. The QUANTEC report concluded that there is limited evidence relating toxicity

Table 1
Published *de novo* ICSCC cases (M: Male; F: Female; S: Surgery; CTX: Chemotherapy; RT: Radiotherapy; SRS: Radiosurgery).

Year	Reference	Age (years), Sex (M/F) & location	Treatment	Outcome
CPA *de novo* ICSCC				
1981	Garcia et al. [7]	61 M (right CPA ICSCC)	S & RT	Died at 9 months
1990	Ebisudani et al. [13]	72 F (right CPA ICSCC)	S	Died at 1 month
2018	Satyanarayana et al. [3]	50 M (left CPA ICSCC)	S	Alive, but undetermined
2021	Present case	69 M (right CPA ICSCC)	S, RT/SRS	Alive at 42 months
Non-CPA *de novo* ICSCC				
2003	Jain et al. [14]	5 F (right temporal, adenosquamous)	S, CTX & RT	Alive at 15 months, progression
2012	Mallick et al. [15]	35 F (right frontal, basaloid SCC)	S & RT	Alive at 24 months
2018	Liu et al.	20 M (left lateral ventricle SCC)	S	Alive at 9 months

to small volumes receiving doses above 6000–6400 cGy using conventional fractionation and that the risk of clinically apparent complications will increase at maximum doses greater than 6400 cGy. This report in parallel to what Emami et al. reported about the brainstem necrosis and infarction with a TD50/5 of 6500 cGy [10,11]. In our case the dose to 1 cc brainstem was 6460 cGy (less than 6500 cGy) with a maximum point dose of 6983 cGy. In a recent report on chordomas by Sahgal et al. [12], IMRT was safely used and they allowed for maximum point doses to the brainstem above 6500 cGy (mean maximum point dose of 6765 cGy and range 460 cGy–7350 cGy). In their series there were no cases of late brainstem injury or necroses [12]. The patient in our report remained clinically well and developed no late toxicity from the radiotherapy. We did not offer chemotherapy in the present case due to the patient's factors including patient age and low ECOG performance status. In addition the multidisciplinary team felt that there was limited clinical evidence for the chemotherapy benefit in this category of cancers [4,8,9].

Improvement in the diagnostic tools (MRI and PET/CT era), surgical procedures (neuro-navigation and intra-operative mapping), and modern dose-escalated radiotherapy using image-guided VMAT and radiosurgery were factors that may have helped us achieve an excellent disease control in our case.

4. Conclusion

De novo ICSCC of the CPA is an extremely rare tumor and it represents a therapeutic challenge. The management of our case included maximum safe neurosurgical resection followed by dose escalated radiotherapy (total dose to gross residual tumor 7000 cGy). Due to the infiltrative nature of the tumor and the involvement of the cavernous sinus and brainstem, a combination of IMRT and SRS boost was used to cover the entire preoperative tumor bed while escalating dose to the gross residual tumor. Dose escalation helped to optimize the chance of local disease control and survival as compared to the historical cohort of reported cases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Cuoco JA, Rogers CM, Busch CM, Apfel LS, Entwistle JJ, Marvin EA. Intracranial squamous cell carcinoma arising from a cerebellopontine angle epidermoid cyst remnant four decades after partial resection. Front Oncol 2019;9:694. https://doi.org/10.3389/fonc.2019.00694.
[2] Link MJ, Cohen PL, Breneman JC, Tew JM. Malignant squamous degeneration of a cerebellopontine angle epidermoid tumor. J Neurosurg 2002;97(5):1237–43. https://doi.org/10.3171/jns.2002.97.5.1237.
[3] Satyanarayana SS, Rao GD. Primary intracranial squamous cell carcinoma denovo in the cerebello-pontine angle. Sch J Appl Med Sci. 2018;6(4):1689–92. https://doi.org/10.21276/sjams.2018.6.4.63.
[4] Liu X, Chen Z, Dong Y, He X, Pan X, Tong D. Primary intracranial squamous cell carcinoma arising de novo: a case report and review of the literature. World Neurosurg 2018;120:372–81. https://doi.org/10.1016/j.wneu.2018.08.067.
[5] Hamlat A, Hua Z-F, Saikali S, et al. Malignant transformation of intra-cranial epithelial cysts: systematic article review. J Neurooncol 2005;74(2):187–94. https://doi.org/10.1007/s11060-004-5175-4.
[6] Roh TH, Park YS, Park YG, Kim SH, Chang JH. Intracranial squamous cell carcinoma arising in a cerebellopontine angle epidermoid cyst. Medicine (Baltimore) 2017;96.
[7] Garcia CA, McGarry PA, Rodriguez F. Primary intracranial squamous cell carcinoma of the right cerebellopontine angle. J Neurosurg 1981;54(6):824–8. https://doi.org/10.3171/jns.1981.54.6.0824.
[8] Nagasawa DT, Choy W, Spasic M, et al. An analysis of intracranial epidermoid tumors with malignant transformation: treatment and outcomes. Clin Neurol Neurosurg 2013;115(7):1071–8. https://doi.org/10.1016/j.clineuro.2012.10.026.
[9] Kwon SM, Kim JH, Kim Y-H, Hong SH, Kim CJ. Treatment and survival outcomes of primary intracranial squamous cell carcinoma. World Neurosurg 2019.
[10] Mayo C, Yorke E, Merchant TE. Radiation associated brainstem injury. Int J Radiat Oncol 2010;76(3). https://doi.org/10.1016/j.ijrobp.2009.08.078.
[11] Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21(1):109–22. https://doi.org/10.1016/0360-3016(91)90171-Y.
[12] Sahgal A, Chan MW, Atenafu EG, et al. Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: preliminary outcomes. Neuro Oncol 2015;17(6). https://doi.org/10.1093/neuonc/nou347.
[13] Ebisudani D, Hamazaki F, Oka H, et al. An autopsy case of primary intracranial squamous cell carcinoma. Neurol Surg 1990;18(2):193–8.
[14] Jain R, Gujar S, McKeever P, Robertson P, Mukherji S. Imaging findings associated with childhood primary intracranial squamous cell carcinoma. Am J Neuroradiol 2003;24(1):109.
[15] Mallick S, Biswas A, Kumar N, et al. Primary intracranial basaloid squamous cell carcinoma: an enigma. Neurol Neurochir Pol 2012;46(5):489–95.