Adult medulloblastoma following fractionated proton therapy for acoustic neuroma

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Abstract

Introduction: Radiation-induced medulloblastoma is exceedingly rare. Four cases of adult medulloblastoma were previously reported to have occurred following whole brain or craniospinal irradiation. Development of systemic malignancies secondary to proton beam therapy is extremely uncommon, with a lifetime risk lower than 1 %.

Methods and Results: A 39-year-old woman presented with gait instability and a right cerebellar mass following an 8-year latency period post-fractionated proton therapy for an acoustic neuroma. To date, no cases of new onset medulloblastoma have been reported following proton beam therapy. The differential diagnosis by imaging studies includes brain radiation necrosis. **Conclusion:** The current report highlights the possible, although rare, risks and complications associated with proton beam radiation. Further studies are needed to address issues related to the management and treatment of radiation-induced medulloblastomas.

Keywords Proton beam radiotherapy · Vestibular schwannoma · Radiation-induced neoplasms · Medulloblastoma · Brain radiation necrosis

Introduction

Medulloblastomas occur infrequently in adults and account for approximately 1 % of adult central nervous system tumors. Adult medulloblastomas are believed to behave clinically similar to childhood tumors with an approximately equal 5-year overall survival rate of 70 % comparable to similar survival rates in childhood medulloblastomas [1, 2]. However, longer follow-up periods have revealed a decreased 20-year overall survival rate for adult (38 %) versus pediatric medulloblastomas (51 %) [3].

Recognition of radiation-induced medulloblastoma is essential, due to their aggressive clinical behavior. Furthermore, the expected benefit from an additional full course of radiation therapy is minimal because of the high and fatal complication risks. Successful therapy of medulloblastoma requires a multidisciplinary approach involving surgery, radiation therapy, and chemotherapy with a consequent risk of secondary complications.

Four cases of radiation-induced medulloblastoma following whole-brain irradiation have been previously reported [4–6]. The most prevalent secondary brain tumors reported post-radiotherapy are high-grade gliomas following gamma-knife radiosurgery [7–9]. Generally, the development of malignancies secondary to proton beam therapy is rare (<1 % lifetime risk); the most commonly induced cancers include lung and thyroid cancers, leukemias and urothelial carcinoma [10, 11]. No cases of medulloblastomas were reported to have occurred following a course of proton beam therapy. Herein, the first case of adult medulloblastoma following proton beam therapy for an “acoustic neuroma” is described. Radiation necrosis, an

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integral differential diagnosis in the current clinical scenario, is to be excluded radiologically and if clinically indicated, histopathologically.

Case report

The patient is a 39-year-old female presenting with new onset headache and gait instability. Previous medical history includes a radiological diagnosis of a right acoustic neuroma treated 8 years earlier with 54 Gy of fractionated proton beam radiotherapy in 30 sessions at Loma Linda University, California, USA. The patient is not known to have neurofibromatosis type-2 (NF2), schwannomatosis or Carney complex. There is no history of familial brain tumors. Brain magnetic resonance imaging (MRI) performed on admission revealed a residual right cerebellopontine angle small extra-axial lesion, radiologically defined as a vestibular schwannoma. An ill-defined T2 hyperintense right lateral cerebellar lesion was also noted, with contrast enhancement and significant surrounding edema extending to the contralateral side (Fig. 1). The patient developed progressive symptoms of increased intracranial pressure. A decompressive suboccipital craniotomy was performed. Microscopy revealed dense sheets of large anaplastic cells with focal formation of centrally necrotic rosette-like structures

Fig. 1 MRI images: axial FLAIR (a), axial T2 (b), sagittal (c), and axial (d) enhanced T1-weighted images of the brain showing the right-sided residual vestibular schwannoma and a new onset right cerebellar lesion. The vestibular schwannoma is heterogenous with high signal intensity on T2 and strong enhancement after contrast administration (c and d). There is evidence of mass effect on the right cerebellum. In addition, the right cerebellar lesion demonstrates high signal intensity on T2 (b) and FLAIR (a) with heterogeneous enhancement post-gadolinium administration (c and d). There is associated surrounding vasogenic edema and a mass effect on the fourth ventricle

(Fig. 2). The anaplastic cells exhibited increased nuclear to cytoplasmic ratio and prominent nucleoli. Scattered areas of perivascular pseudorosettes were also identified. Sheets of anaplastic cells involved the cerebellar molecular layer, invading, at multiple locations, cerebellar white matter, and leptomeninges. The anaplastic cells were positive for synaptophysin, focally stained for glial fibrillary acidic protein (GFAP), and expressed p53 (up to 30 % of cells; Fig. 3). Proliferative index (Ki-67) was elevated, approximately 40 %. A diagnosis of anaplastic/large cell medulloblastoma was established, supported by the cellular morphology and immunohistochemical profile. The patient opted to receive further treatment at an outside hospital. Follow-up information from the treating physician outlined increased neurological deficit 5 months post-operatively. The patient subsequently was lost to follow-up.

Discussion

The lifetime risk of brain malignancy due to scattered external neutrinos from proton beam therapy is reported to be 0.05 % for males and 0.10 % for females [12]. The highest reported lifetime risk for lung carcinoma treatment is 3.55 % for females and 1.53 % for males. These studies are purely based on extrapolations of the amount of neutrinos emitted from proton beam therapy. Tumors treated with proton beam therapy include ocular (uveal) melanoma, sarcomas of the skull base and spine, paranasal sinus, nasal and nasopharyngeal tumors, benign meningioma, carcinoma of the prostate and pediatric malignancies such as neuroblastoma, central nervous system primitive neuroectodermal tumor, and medulloblastoma [13]. Analogous to conventional photon radiation therapy, the mechanism of proton beam therapy effect on tumor cells leads to the production of free radicals, followed by DNA damage and activation of p53, caspase-9 and caspase-3 pathways with eventual tumor cell death and apoptosis [14]. The late effects and complications of radiation on normal tissues can also trigger capillary regeneration in response to significant hypoxia and cellular stress [15–17].

Widely accepted principles of radiation oncogenesis published by Cahan et al. [18] state the following: (1) a latency period is required between radiation delivery and tumor development; (2) The newly diagnosed tumor should occur within the irradiated field; (3) The new tumor must be histologically unique in comparison to the original tumor; (4) Radiological imaging should confirm the absence of the new tumor at the time of original tumor diagnosis; and (5) the patient should not be genetically predisposed to develop a new tumor. The radiation dose used in all reported cases ranged from 24 to 55 Gy with a latency period of 8–33 years (Table 1). In the current report, the radiation field covered part of the posterior fossa, the new tumor histopathologic subtype was different from the originally treated vestibular schwannoma and there was an 8-

Fig. 2 Photomicrographs of hematoxylin and eosin sections demonstrating sheets of malignant cells with rosette-like arrangement of cells surrounding necrotic foci (**a** and **b**) and areas of Homer–Wright pseudorosette formation (**c**). The anaplastic cells invade the cerebellar cortex and involve the subarachnoid space (**d**). Note the anaplastic/large cell cytology with prominent nucleoli (**b**)

year latency period before the occurrence of a new-onset tumor. Although the risk of developing malignancy secondary to proton beam radiotherapy exceeds the incidence of malignancy in a healthy cohort population, one cannot exclude the possibility of a *de novo* tumor unrelated to radiation exposure. However, there was no evidence of predisposing risk factors, including genetic, for the development of malignant neural tumors in this patient and no known clinical or family history of nervous system tumors or NF2. Although the diagnosis of NF2 increases the incidence of secondary malignancy by 0.5 %, the additional factor of radiotherapy for acoustic neuroma increases the risk of secondary malignancies by 12-fold up to a 6 % incidence [19]. Similar to retinoblastoma patients with post-radiotherapy development of secondary malignancies, the mechanism of increased post-radiotherapy malignancy in NF2 is believed to be due to allelic inactivation of NF2 and p53 genes [20]. However, one report found no evidence of

secondary malignancies post-radiotherapy for acoustic neuromas in NF2 patients with a median follow-up period of 53 months [21].

One of the main clinicoradiologic differential diagnoses is delayed cerebellar radiation-induced necrosis. This is an uncommon side effect of cranial irradiation, originally described in irradiated extracranial lesions [22]. The development of radionecrosis is inversely related to fraction number and directly proportional to the total dose and dose per fraction [23]. The concept of receiving a full radiation course with a conventional fraction size should practically have a lower risk of secondary malignancies and complications. A mean interval of 1 year is reported between radiation and the time of radiation-induced necrosis for patients receiving more than 50 Gy; however, there are reports of radionecrosis occurring as early as 3 months or as late as 19 years post-radiotherapy [23]. Clinically, the presentation

Fig. 3 The malignant cells are diffusely positive for synaptophysin (**a**), stain focally for GFAP in a stellate appearance reminiscent of entrapped astrocytes (**b**). The tumor cells express p53 in up to 30 % of cells (**c**)

Table 1 Summary of the reported cases of radiation-induced medulloblastoma

Case/series	Age/gender	Diagnosis	Margin dose	Overall survival	Latency interval	Location	New tumor
Chan et al. [6]	44/F	Craniopharyngioma	55 Gy, RT	1 month (DOD)	33 years	Left cerebral peduncles, cerebellum and pons	Anaplastic medulloblastoma
	46/F	Pilocytic astrocytoma	24 Gy, RT	1 month (DOD)	38 years	Left posterior fossa	Anaplastic medulloblastoma
Howes et al. [5]	61/F	Low-grade astrocytoma (left posterior temporal lobe)	50 Gy, cranial irradiation	NA, diffuse craniospinal spread	15 years	Right cerebellar hemisphere	Anaplastic medulloblastoma
Padma et al. [4]	29/M	Pineal gland tumor	45 Gy, cranial (wide-field) RT	4 month (DOD)	8 years	Left posterior fossa	Anaplastic medulloblastoma
Present case	39/F	Vestibular schwannoma	54 Gy, fractionated proton beam radiotherapy, 30 sessions	5 month (AWD)	8 years	Right cerebellum	Anaplastic medulloblastoma

RT radiation therapy, DOD died of disease, AWD alive with disease, NA not available

is variable including headache, seizures, personality changes, and neurologic deficits. Delayed cerebral radionecrosis on imaging may appear as an aggressive lesion due to breakdown of the blood–brain barrier. Large lesions may appear as enhancing foci, surrounded by non-enhancing necrotic areas. Perfusion MRI may aid in differentiating radionecrosis from tumor [24]. MR spectroscopy distinguishes tumors from radiation necrosis based on an increased tumoral choline peak [25], while positron emission tomography with F-18 fluorodeoxyglucose measures changes in glucose uptake. The nonspecific MRI images of a diffusely contrast-enhancing lesion with surrounding edema, combined with the history of previous radiotherapy, expanded the radiological differential diagnosis to include radiation necrosis. The pathology of radiation necrosis is characterized by fibrinoid necrosis and hyalinization of the blood vessels with surrounding parenchymal necrosis and gliosis. Therefore, since both lesions may appear radiologically similar, histopathology remains the preferred diagnostic tool.

Comparison of intensity-modulated radiotherapy or photon therapy with intensity-modulated proton therapy for childhood medulloblastomas yields an estimated secondary cancer lifetime risk of 54–71 versus 9 %, respectively, following a radiation dose of 36 Gy [26]. This implies that proton radiotherapy is relatively safer with respect to overall secondary complications in comparison to photon radiotherapy. The estimated 3-year risk of secondary malignancy ranges from 0.43 to 0.76 % for photon radiotherapy and 0.05 % for proton radiotherapy [27]. The incidence of adult medulloblastoma is reported to be 0.5 per million per year [28] rendering proton beam radiotherapy-induced medulloblastoma more probable than a de novo tumorigenic event.

The prognosis of radiation-induced medulloblastoma is unfortunately dismal. The current case showed evidence of

focal glial differentiation, a finding presumed to impart a worse prognosis [29]. The prognostic value of GFAP expression in medulloblastomas is controversial with discrepant findings reporting either a negative [30] or a positive prognostic impact [31]. GFAP expression has also been attributed merely to entrapped astrocytes [32]. Despite the correlation of high-risk metastatic disease in pediatric medulloblastomas with increased p53 expression [33], the prognostic value remains controversial [34]. Furthermore, a decreased radiation response is detected in p53-inactivated medulloblastoma cell lines [35]. The treatment of radiation-induced medulloblastoma varied from resection to chemotherapy with lomustine and vincristine [36]. One report advocates additional radiotherapy to complement the treatment regimen [6], provided the patient had an adequate interval to recover from the first radiation dose [37–39].

In conclusion, a unique case of proton beam radiotherapy-induced medulloblastoma is described. The relative safety of focused proton beam radiotherapy forms the basis for the management of a well-defined category of vestibular schwannomas. The radiologic differential diagnosis of radiation necrosis is considered; although, in the proper clinical setting, greater than 1-year post-radiotherapy latency time intervals may necessitate a biopsy to exclude a new-onset neoplastic process.

Conflict of interest None

References

1. Brandes AA, Franceschi E, Tosoni A, Blatt V, Ermani M (2007) Long-term results of a prospective study on the treatment of

- medulloblastoma in adults. *Cancer* 110(9):2035–2041. doi:[10.1002/cncr.23003](https://doi.org/10.1002/cncr.23003)
2. Sirachainan N, Nuchprayon I, Thanarattanakorn P, Pakakasama S, Lusawat A, Visudibhan A, Dhanachai M, Larbcharoensub N, Amornfa J, Shotelersuk K, Katanyuwong K, Tangkaratt S, Hongeng S (2011) Outcome of medulloblastoma in children treated with reduced-dose radiation therapy plus adjuvant chemotherapy. *J Clin Neurosci* 18(4):515–519. doi:[10.1016/j.jocn.2010.08.012](https://doi.org/10.1016/j.jocn.2010.08.012)
 3. Smoll NR (2011) Relative survival of childhood and adult medulloblastomas and primitive neuroectodermal tumors (PNETs). *Cancer* 118(5):1313–1322. doi:[10.1002/cncr.26387](https://doi.org/10.1002/cncr.26387)
 4. Padma MV, Jacobs M, Kraus G, McDowell P, Satter M, Adineh M, Mantil J (2004) Radiation-induced medulloblastoma in an adult: a functional imaging study. *Neurol India* 52(1):91–93
 5. Howes TL, Buatti JM, Kirby PA, Carlisle TL, Ryken TC (2006) Radiation induced adult medulloblastoma: a case report. *J Neurooncol* 80(2):191–194. doi:[10.1007/s11060-006-9175-4](https://doi.org/10.1007/s11060-006-9175-4)
 6. Chan MD, Attia A, Tatter SB, Lesser G, Zapadka ME, Mott RT, Carter A, McMullen KP, Shaw EG, Ellis TE (2011) Radiation-induced adult medulloblastoma: a two-case report and review of the literature. *J Neurooncol* 103(3):745–749. doi:[10.1007/s11060-010-0426-z](https://doi.org/10.1007/s11060-010-0426-z)
 7. McIver JI, Pollock BE (2004) Radiation-induced tumor after stereotactic radiosurgery and whole brain radiotherapy: case report and literature review. *J Neurooncol* 66(3):301–305
 8. Niranjan A, Kondziolka D, Lunsford LD (2009) Neoplastic transformation after radiosurgery or radiotherapy: risk and realities. *Otolaryngol Clin North Am* 42(4):717–729. doi:[10.1016/j.otc.2009.04.005](https://doi.org/10.1016/j.otc.2009.04.005)
 9. Shamisa A, Bance M, Nag S, Tator C, Wong S, Noren G, Guha A (2001) Glioblastoma multiforme occurring in a patient treated with gamma knife surgery. Case report and review of the literature. *J Neurosurg* 94(5):816–821. doi:[10.3171/jns.2001.94.5.0816](https://doi.org/10.3171/jns.2001.94.5.0816)
 10. Zacharatou-Jarlskog C, Paganetti H (2008) Risk of developing second cancer from neutron dose in proton therapy as function of field characteristics, organ, and patient age. *Int J Radiat Oncol Biol Phys* 72(1):228–235. doi:[10.1016/j.ijrobp.2008.04.069](https://doi.org/10.1016/j.ijrobp.2008.04.069)
 11. Shah SK, Lui PD, Baldwin DD, Ruckle HC (2006) Urothelial carcinoma after external beam radiation therapy for prostate cancer. *J Urol* 175(6):2063–2066. doi:[10.1016/S0022-5347\(06\)00324-7](https://doi.org/10.1016/S0022-5347(06)00324-7)
 12. Brenner DJ, Hall EJ (2008) Secondary neutrons in clinical proton radiotherapy: a charged issue. *Radiother Oncol* 86(2):165–170. doi:[10.1016/j.radonc.2007.12.003](https://doi.org/10.1016/j.radonc.2007.12.003)
 13. Levin WP, Kooy H, Loeffler JS, DeLaney TF (2005) Proton beam therapy. *Br J Cancer* 93(8):849–854. doi:[10.1038/sj.bjc.6602754](https://doi.org/10.1038/sj.bjc.6602754)
 14. Lee KB, Kim KR, Huh TL, Lee YM (2008) Proton induces apoptosis of hypoxic tumor cells by the p53-dependent and p38/JNK MAPK signaling pathways. *Int J Oncol* 33(6):1247–1256
 15. Oh BC, Pagnini PG, Wang MY, Liu CY, Kim PE, Yu C, Apuzzo ML (2007) Stereotactic radiosurgery: adjacent tissue injury and response after high-dose single fraction radiation: Part I—histology, imaging, and molecular events. *Neurosurgery* 60(1):31–44. doi:[10.1227/01.NEU.0000249191.23162.D2](https://doi.org/10.1227/01.NEU.0000249191.23162.D2), discussion 44–35
 16. Kargiotis O, Geka A, Rao JS, Kyritsis AP (2010) Effects of irradiation on tumor cell survival, invasion and angiogenesis. *J Neurooncol* 100(3):323–338. doi:[10.1007/s11060-010-0199-4](https://doi.org/10.1007/s11060-010-0199-4)
 17. Lin W, Lin Y, Li J, Harding HP, Ron D, Jamison S (2011) A deregulated integrated stress response promotes interferon-gamma-induced medulloblastoma. *J Neurosci Res* 89(10):1586–1595. doi:[10.1002/jnr.22693](https://doi.org/10.1002/jnr.22693)
 18. Cahan WG, Woodard HQ et al (1948) Sarcoma arising in irradiated bone; report of 11 cases. *Cancer* 1(1):3–29
 19. Baser ME, Evans DG, Jackler RK, Sujansky E, Rubenstein A (2000) Neurofibromatosis 2, radiosurgery and malignant nervous system tumours. *Br J Cancer* 82(4):998. doi:[10.1054/bjoc.1999.1030](https://doi.org/10.1054/bjoc.1999.1030)
 20. Plowman PN, Evans DG (2000) Stereotactic radiosurgery XI. Acoustic neuroma therapy and radiation oncogenesis. *Br J Neurosurg* 14(2):93–95
 21. Mathieu D, Kondziolka D, Flickinger JC, Niranjan A, Williamson R, Martin JJ, Lunsford LD (2007) Stereotactic radiosurgery for vestibular schwannomas in patients with neurofibromatosis type 2: an analysis of tumor control, complications, and hearing preservation rates. *Neurosurgery* 60(3):460–468. doi:[10.1227/01.NEU.0000255340.26027.53](https://doi.org/10.1227/01.NEU.0000255340.26027.53), discussion 468–470
 22. Glass JP, Hwang TL, Leavens ME, Libshitz HI (1984) Cerebral radiation necrosis following treatment of extracranial malignancies. *Cancer* 54(9):1966–1972
 23. Marks JE, Wong J (1985) The risk of cerebral radionecrosis in relation to dose, time and fractionation. A follow-up study. *Prog Exp Tumor Res* 29:210–218
 24. Hazle JD, Jackson EF, Schomer DF, Leeds NE (1997) Dynamic imaging of intracranial lesions using fast spin-echo imaging: differentiation of brain tumors and treatment effects. *J Magn Reson Imaging* 7(6):1084–1093
 25. Fulham MJ, Bizzi A, Dietz MJ, Shih HH, Raman R, Sobering GS, Frank JA, Dwyer AJ, Alger JR, Di Chiro G (1992) Mapping of brain tumor metabolites with proton MR spectroscopic imaging: clinical relevance. *Radiology* 185(3):675–686
 26. Brodin NP, Munck af Rosenschold PM, Aznar MC, Kiil-Berthelsen AK, Vogelius IR, Nilsson P, Lannering B, Björk-Eriksson T (2011) Radiobiological risk estimates of adverse events and secondary cancer for proton and photon radiation therapy of pediatric medulloblastoma. *Acta Oncol* 50(6):806–816. doi:[10.3109/0284186X.2011.582514](https://doi.org/10.3109/0284186X.2011.582514)
 27. Miralbell R, Lomax A, Cella L, Schneider U (2002) Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. *Int J Radiat Oncol Biol Phys* 54(3):824–829
 28. Giordana MT, Schiffer P, Lanotte M, Girardi P, Chio A (1999) Epidemiology of adult medulloblastoma. *Int J Cancer* 80(5):689–692. doi:[10.1002/\(SICI\)1097-0215](https://doi.org/10.1002/(SICI)1097-0215)
 29. Schuller U, Heine VM, Mao J, Kho AT, Dillon AK, Han YG, Huillard E, Sun T, Ligon AH, Qian Y, Ma Q, Alvarez-Buylla A, McMahon AP, Rowitch DH, Ligon KL (2008) Acquisition of granule neuron precursor identity is a critical determinant of progenitor cell competence to form Shh-induced medulloblastoma. *Cancer Cell* 14(2):123–134. doi:[10.1016/j.ccr.2008.07.005](https://doi.org/10.1016/j.ccr.2008.07.005)
 30. Janss AJ, Yachnis AT, Silber JH, Trojanowski JQ, Lee VM, Sutton LN, Perilongo G, Rorke LB, Phillips PC (1996) Glial differentiation predicts poor clinical outcome in primitive neuroectodermal brain tumors. *Ann Neurol* 39(4):481–489. doi:[10.1002/ana.410390410](https://doi.org/10.1002/ana.410390410)
 31. Goldberg-Stern H, Gadot N, Stern S, Cohen JJ, Zaizov R, Sandbank U (1991) The prognostic significance of glial fibrillary acidic protein staining in medulloblastoma. *Cancer* 68(3):568–573
 32. Coffin CM, Mukai K, Dehner LP (1983) Glial differentiation in medulloblastomas. Histogenetic insight, glial reaction, or invasion of brain? *Am J Surg Pathol* 7(6):555–565
 33. Gessi M, von Bueren AO, Rutkowski S, Pietsch T (2012) p53 expression predicts dismal outcome for medulloblastoma patients with metastatic disease. *J Neurooncol* 106(1):135–141. doi:[10.1007/s11060-011-0648-8](https://doi.org/10.1007/s11060-011-0648-8)
 34. Ertan Y, Sezak M, Demirag B, Kantar M, Cetingul N, Turhan T, Ersahin Y, Mutluer S, Anacak Y, Akalin T (2009) Medulloblastoma: clinicopathologic evaluation of 42 pediatric cases. *Childs Nerv Syst* 25(3):353–356. doi:[10.1007/s00381-008-0784-4](https://doi.org/10.1007/s00381-008-0784-4)
 35. Dee S, Haas-Kogan DA, Israel MA (1995) Inactivation of p53 is associated with decreased levels of radiation-induced apoptosis in medulloblastoma cell lines. *Cell Death Differ* 2(4):267–275
 36. Hader WJ, Drovini-Zis K, Maguire JA (2003) Primitive neuroectodermal tumors in the central nervous system following cranial

- irradiation: a report of four cases. *Cancer* 97(4):1072–1076. doi:[10.1002/cncr.11121](https://doi.org/10.1002/cncr.11121)
37. Merchant TE, Boop FA, Kun LE, Sanford RA (2008) A retrospective study of surgery and reirradiation for recurrent ependymoma. *Int J Radiat Oncol Biol Phys* 71(1):87–97. doi:[10.1016/j.ijrobp.2007.09.037](https://doi.org/10.1016/j.ijrobp.2007.09.037)
38. Bauman GS, Sneed PK, Wara WM, Stalpers LJ, Chang SM, McDermott MW, Gutin PH, Larson DA (1996) Reirradiation of primary CNS tumors. *Int J Radiat Oncol Biol Phys* 36(2):433–441
39. Nieder C, Milas L, Ang KK (2000) Tissue tolerance to reirradiation. *Semin Radiat Oncol* 10(3):200–209