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CASE-BASED REVIEW

Benign skull and subdural lesions in patients with prior medulloblastoma therapy

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Abstract

Purpose To report on our institutional cohort of patients and review the literature of medulloblastoma patients who developed skull/subdural-based lesions following treatment.

Methods Following institutional review board (IRB) approval, we retrospectively reviewed the medical records of four children with a history of treated medulloblastoma who developed non-specific skull-based/subdural lesions incidentally found on surveillance imaging.

Results Biopsies of the lesions proved the pathology to be low grade and included inflammatory myofibroblastic tumor, cortical fibrous defect consistent with fibroma, fibrous tissue, and fibrous dysplasia. The finding of calvarial or subdural fibrous lesions in children following therapy for medulloblastoma was noted in four out of 201 (136 with available follow-up data) medulloblastoma patients seen or discussed in our institution over the past 10 years.

Conclusions These lesions can grow over time and pose a differential diagnostic challenge with metastatic disease when identified. The skull and subdural space should be scrutinized for secondary lesions on surveillance imaging of patients with medulloblastoma who have received craniospinal irradiation as knowledge of this benign occurrence will assist with management.

Keywords Pediatric brain tumor · Medulloblastoma · Skull lesion · Bone lesions · Fibrous

Introduction

Medulloblastoma is the most common pediatric malignant brain tumor accounting for approximately 20% of childhood brain tumors [3]. The standard of care for patients with medulloblastoma diagnosed 3 years of age and older includes maximum safe surgical debulking and craniospinal irradiation (CSI) with local boost radiotherapy followed by adjuvant chemotherapy [5, 11, 12]. The progression-free survival (PFS) for children with medulloblastoma diagnosed at > 3 years of age ranges from 60 to 67% for high-risk disease to 75–80% for average-risk disease at 5 years [9, 13, 18]. However, medulloblastoma survivors experience many late effects including neurocognitive sequelae, endocrine dysfunction, ototoxicity, and secondary malignancies [2, 6, 17]. There is limited data available on the incidence of skull-based lesions in patients with medulloblastoma. In this study, we provide an institutional survey of three cases of skull-based lesions and one subdural lesion concerning for recurrences in patients with history of medulloblastoma.

Historical background

Bone lesions can be a sign of disease progression in medulloblastoma patients. Bone changes in survivors of pediatric CNS tumor as a result of radiation therapy are well known as they can affect bone density and growth [4]. There are few

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Table 1 Description of the four cases. Summary of demographic data, diagnosis, prior treatment, location of secondary lesion, and histopathology. *MB* medulloblastoma, *met* metastatic, *AR* average risk, *y* year, *m* month

Case #	Gender	Primary diagnosis	Age of primary diagnosis (years)	Treatment	Time from primary diagnosis to secondary lesion	Time post-completion of therapy	Location of secondary lesion	Pathology of secondary lesion
1	M	Classic MB, met	10 y 9 m	Subtotal resection ACNS0332	3 y 1 m	2 y 3 m	Left frontoparietal skull	Cortical fibrous defect most consistent with fibroma
2	F	Anaplastic group 4 MB, met	10 y 8 m	near total resection, ACNS0332	2 y	1 y 4 m	Left frontal cranial bone skull lesion	Fibrous tissue
3	M	AR MB	5 y 11 m	near total resection, A9961	8 y 10 m	7 y 5 m	Right paramedian frontal calvarium, skull lesion	Fibrous dysplasia
4	M	Anaplastic MB, met	6 y 6 m	Subtotal resection ACNS0332	20 m	10 m	Left frontal convexity, brain, extra-axial/ subdural Subdural membrane	Inflammatory myofibroblastic tumor Dense fibroconnective tissue

studies that characterize the development of post-radiation calvarial lesions. One study reports a single case of fibrohistiocytoma with giant cells of the vertex as a long-term sequelae of medulloblastoma therapy [6]. A single-case report describes a frontal bone intravascular papillary endothelial hyperplasia (IPEH) incidentally found 3 years after radiotherapy completion in a medulloblastoma survivor [10]. A more recent study reveals a 7.3% incidence of low-grade bone lesions in survivors of medulloblastoma and CNS embryonal tumors formerly known as central primitive neuroectodermal tumors (PNETs). These lesions represent Langerhans cell histiocytosis, benign spindle cell lesion with myxoid change, and fibrous dysplasia [8]. Wallace et al. retrospectively evaluated patients undergoing neurosurgical evaluation for calvarial bone lesions that were incidentally detected on surveillance imaging post-radiation therapy [16]. Of the 17 patients that they studied, six had a primary diagnosis of medulloblastoma, and three of those six were found to have benign fibro-osseous lesions. When compared with ependymomas, medulloblastoma patients developed skull lesions at a shorter time from radiation [16]. Radiation-induced osteonecrosis, one of the known complications of radiotherapy, is caused by altered blood supply to the bone as well as dysfunction in osteoclast and osteoblast activity, and may explain the development of benign bone lesions in patients who have undergone radiotherapy [1, 14].

Clinical presentation

All four of the medulloblastoma survivors in this series presented with asymptomatic calvarial lesions detected on routine surveillance imaging. The median age of initial medulloblastoma diagnosis was 8.6 years (range 5.9–10.8 years). The median time from radiation completion to development of a skull-based or subdural lesion on imaging in our cohort was 2.7 years (range 1.8–9 years). There was a total of 201 medulloblastoma patients on record in our institution over the past 10 years. Of those, 40 received proton radiation therapy and then returned to their primary treating institution. Another 25 of the cases were only reviewed in our institution as second opinions or solely for pathology review. Thus, we do not have the long-term follow-up data on 65 of the 201 medulloblastoma patients. Out of the 136 patients that we do have follow-up data available on, four (2.9%) were incidentally found to have a benign calvarial lesion.

Diagnosis

Radiographically, benign lesions typically have well-defined borders, narrow zone of transition, and sclerotic margins, without aggressive features of associated soft tissue mass, aggressive periosteal reaction, or moth eaten/bony destruction. Magnetic

resonance imaging (MRI) optimally evaluates the bone marrow and soft tissues of the head for signs of disease involvement. CT can yield complimentary findings to further characterize any bone lesions detected by MRI. Osteolytic metastases on MRI are typically T1 hypo- to iso-intense with enhancement that is variable [7]. This MRI pattern, however, can also be observed in lesions of benign/low-grade pathology such as eosinophilic granuloma [15]. These incidental bone lesions can be a cause of anxiety for patients and their families and pose a differential diagnostic challenge from malignant lesions or recurrent disease on imaging. Thus, all four patients in this review underwent surgical resection of the lesions to aid in diagnosis.

The pathology revealed that all four skull lesions were fibrous in nature; however, one was a myofibroblastic lesion with a storiform and fascicular growth pattern intimately associated with a florid proliferation of inflammatory cells (lymphocytes, plasma cells, and eosinophils), subsequently diagnosed as inflammatory myofibroblastic tumor (IMT). Three of the benign fibrous lesions had variable histologic features on a spectrum of fibroblastic proliferation (fibrous dysplasia, fibroma, and cellular fibrous tissue).

Management

All of the lesions were surgically excised to aid in diagnosis. No further treatment was needed for these benign lesions.

Prognosis and outcomes

The long-term prognosis of medulloblastoma patients who were incidentally found to have a benign fibrous skull-based or subdural lesions is unknown. However, since these lesions

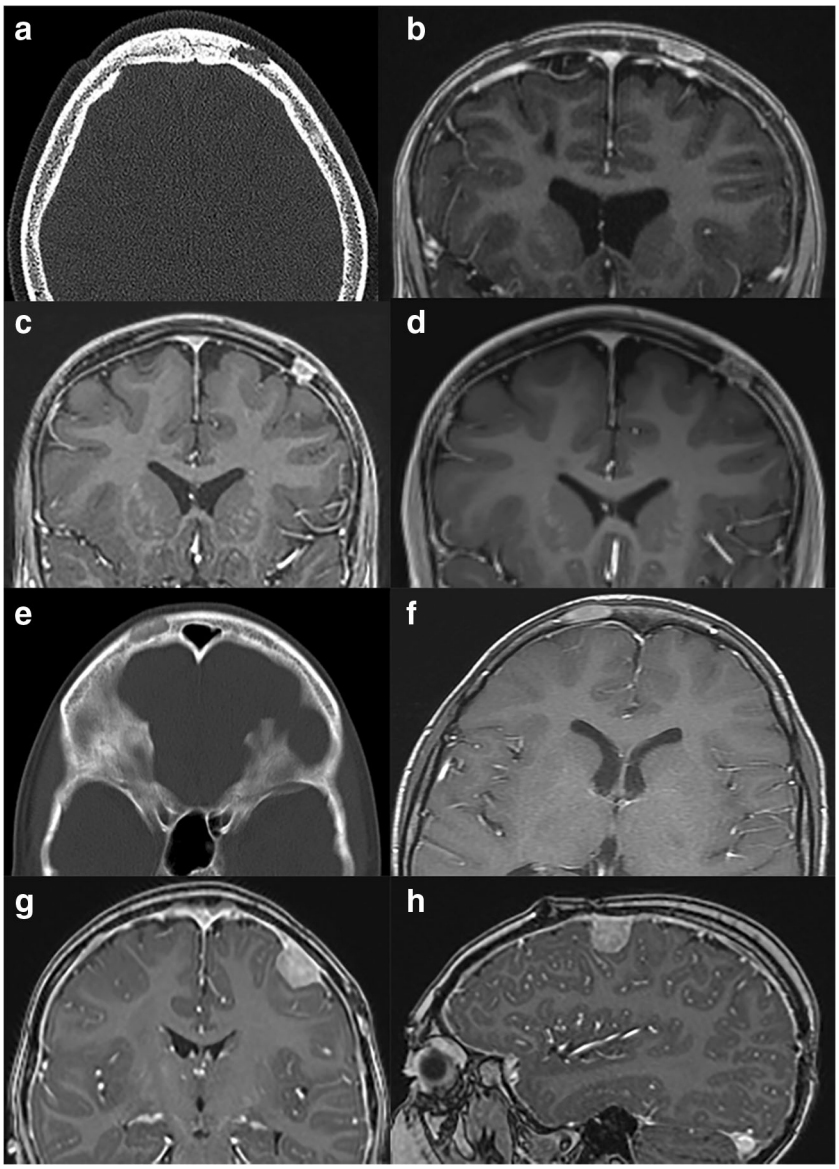

Fig. 1 **a** and **b** Case 1 – 10-year-old male with classic medulloblastoma; axial CT in bone windows showing focal lucent well-defined lesion in the left frontal bone without any associated soft tissue mass or periosteal reaction. **b** Coronal post-contrast T1-weighted MRI image shows a focal enhancing lesion in the marrow corresponding to the focal lucency. **c** and **d** Case 2 – 10-year-old female with anaplastic medulloblastoma; Two coronal post-contrast T1-weighted MRI images preformed 3 months apart show interval growth a focal enhancing lesion in the left parietal bone. **e** and **f** Case 3 – 5-year-old male with average-risk medulloblastoma; similar to case 1, **e** shows a focal well-defined lucent lesion in the right frontal bone on axial CT in bone windows and corresponding enhancement of the lesion on the post-contrast T1-weighted MRI (**f**). **g** and **h** Case 4 – 6-month-old male with metastatic anaplastic medulloblastoma; coronal (**g**) and sagittal (**h**) post-contrast
T1-weighted MRI images show a focal homogenously enhancing lesion that appears to be abutting or arising from the dura associated with mass effect on the adjacent parenchyma

are unrelated to recurrent disease, we suspect that the overall outcome for medulloblastoma survivors who develop benign fibrous lesions is solely driven by their underlying malignancy, and these lesions do not contribute to overall prognosis or outcome.

Exemplary case descriptions

The clinical course, imaging, and histopathology are presented below.

Case 1

A 10-year and 9-month-old male was diagnosed with posterior fossa classic medulloblastoma after presenting with 6 weeks of nausea (Table 1). This patient had an incomplete resection and his lumbar cerebrospinal fluid (CSF) was positive for malignant cells (Fig. 3). He was treated per the high-risk ACNS0332 protocol which included proton chemoradiation consisting of CSI (3600 cGy and a boost to 5580 cGy to the tumor site) with daily carboplatin and weekly vincristine followed by maintenance chemotherapy (cisplatin, cyclophosphamide, and vincristine). At 2 years and 3 months after completion of therapy, this patient was incidentally found to have a new focal 13-mm-enhancing lesion in the left frontoparietal calvarium on routine surveillance MRI (Fig. 1b). Follow-up CT head scan demonstrated a lucent lesion with slightly lobulated margins straddling the left coronal suture, without associated soft tissue mass, bony expansion, or periosteal reaction (Fig. 1a). On imaging, it had a benign, non-specific appearance with primary differentials to include osseous hemangioma fibrous lesion, but metastatic disease could not be confidently excluded. He underwent a left frontal craniectomy and excision of the lesion with intraoperative frameless stereotactic navigation. Pathology confirmed a cortical fibrous defect most consistent with a benign fibroma (Fig. 2a).

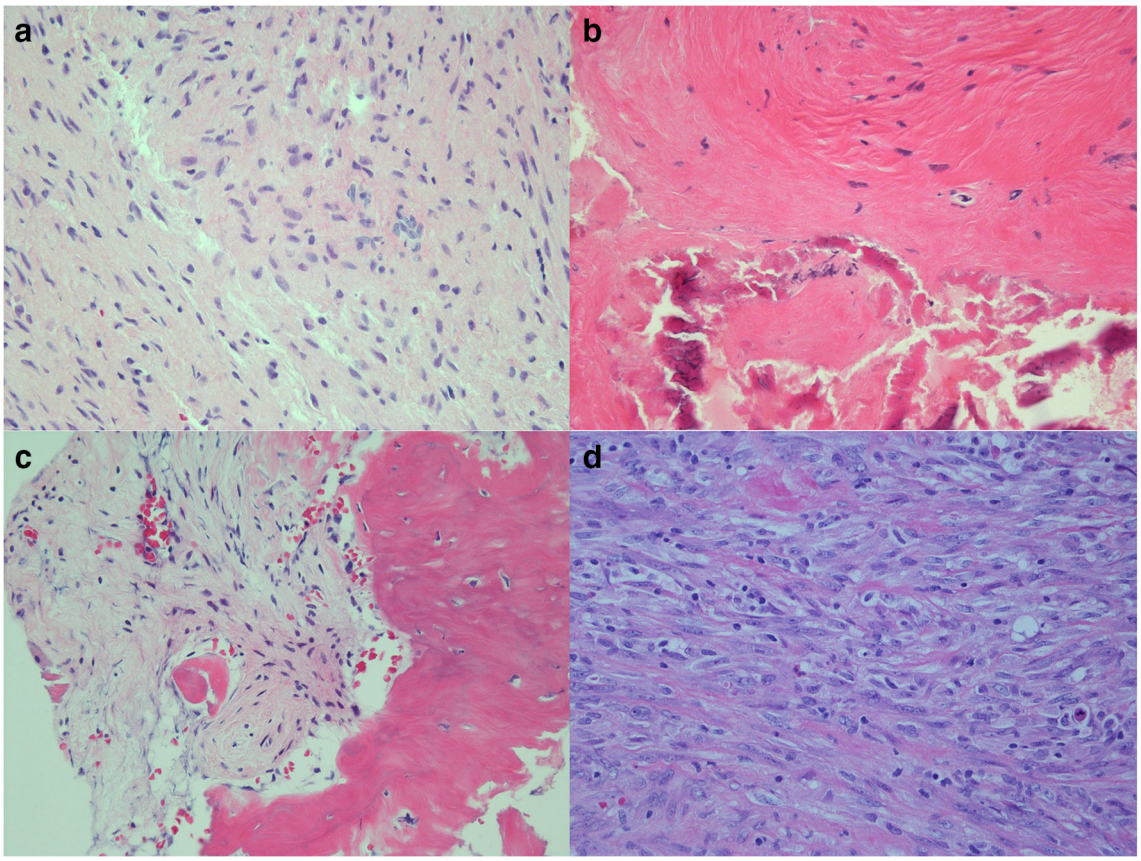

Fig. 2 **a** Case 1: Sections from this lesion show a benign fibroblastic lesion composed of spindled fibroblasts in a hypocellular stroma. Increased mitotic activity was not seen. The neoplastic cells were negative for beta catenin and STAT6 (not shown). H&E × 40 magnification. **b** Case 2: Sections from this lesion show devitalized bone and cellular benign appearing fibrous tissue. H&E × 40 magnification. **c** Case 3: Sections from this lesion show branched and anastomosing trabeculae of woven bone with no conspicuous osteoblastic rimming. The intervening fibrous stroma contained cytologically bland spindle cells and no significant mitotic activity. H&E × 40 magnification. **d** Case 4: Sections from this lesion show a mildly atypical proliferation of spindled cells forming a storiform and fascicular growth pattern. Intimately associated with the proliferation are inflammatory cells mostly consisting of lymphocytes, plasma cells, and eosinophils. Entrapped ganglion-like cells were also seen. H&E × 40 magnification

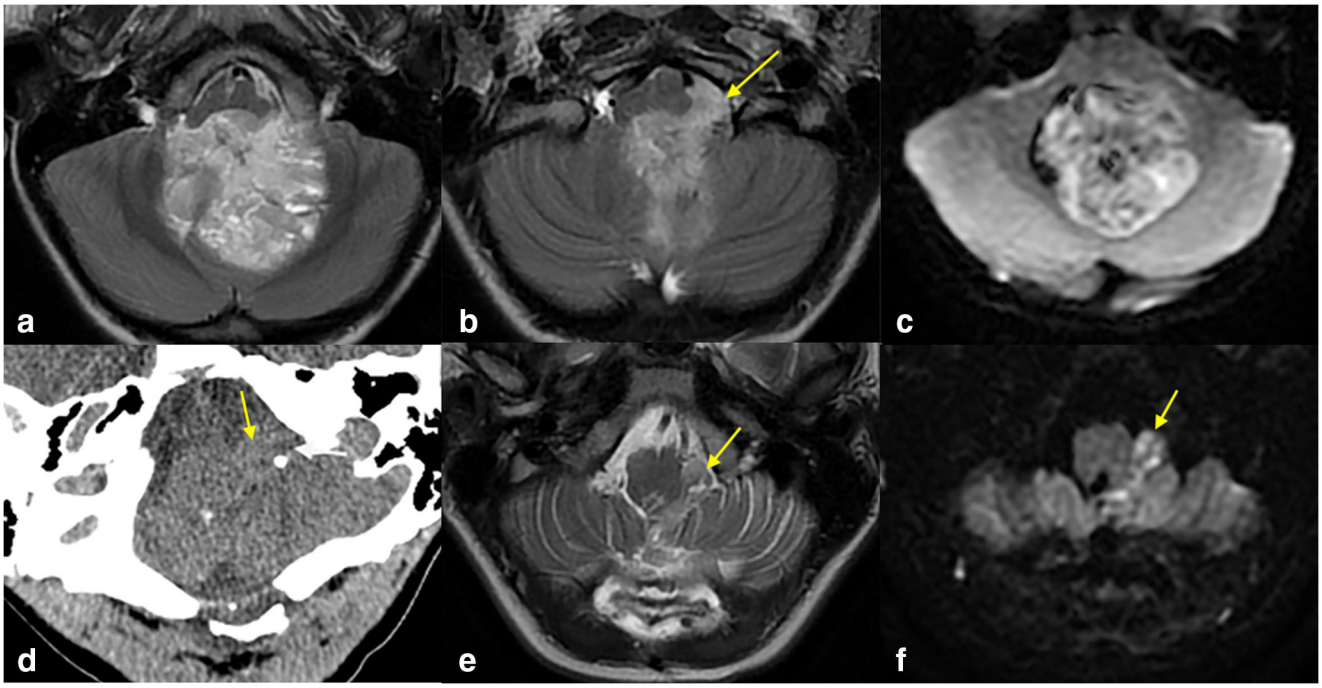

Fig. 3 Case 1. MRI; Axial T2 (**a**, **b**), and diffusion-weighted imaging (**c**) shows original tumor in the fourth ventricle extending through the foramen of Luschka on the left. Post-operative CT (**d**) and MRI (**e**, **f**); axial CT (**d**); T2 (**e**) and diffusion-weighted imaging (**f**) of residual tumor extending through the left foramen of Luschka (yellow arrows)

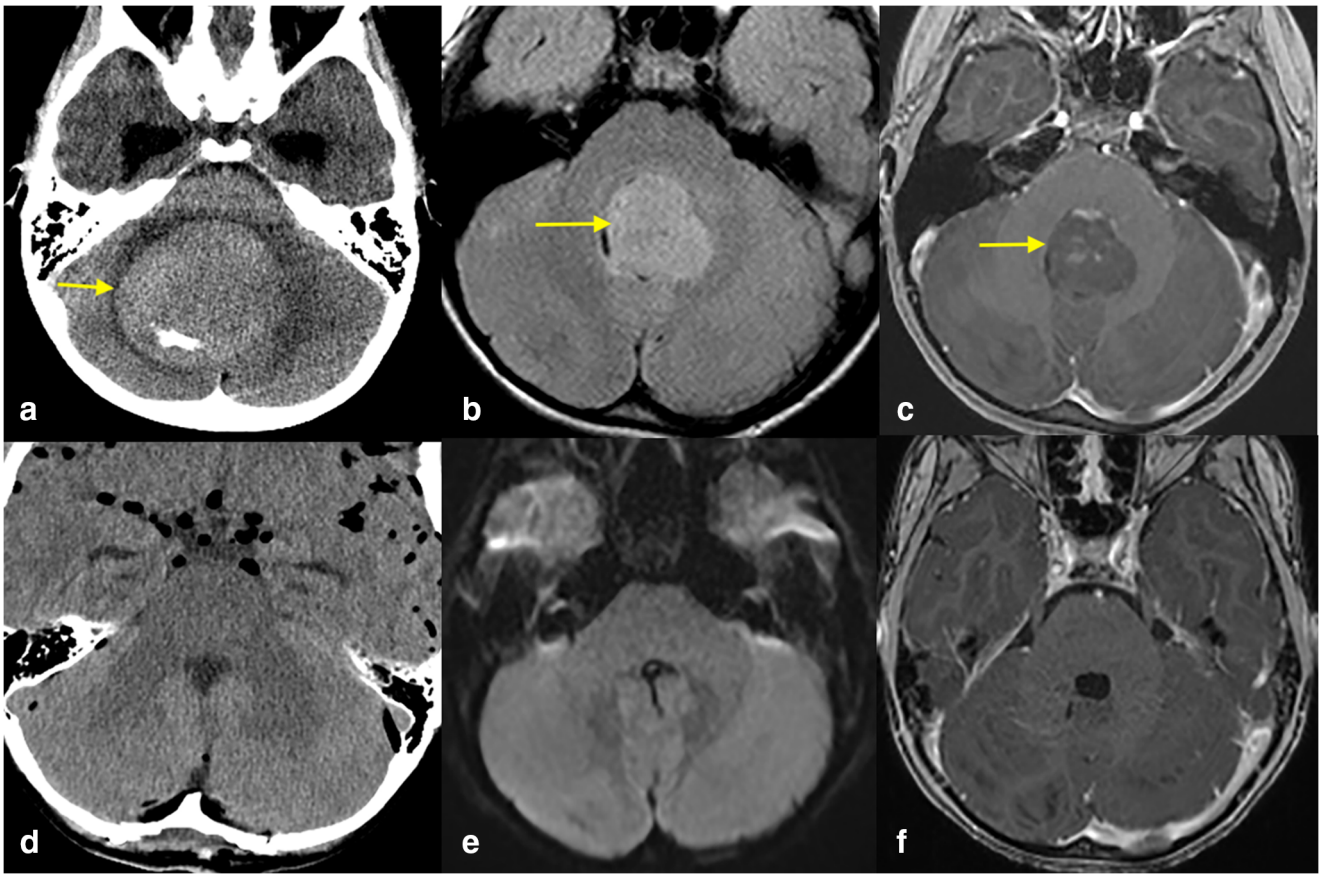

Fig. 4 Case 2. Axial CT (**a**); MRI; FLAIR (**b**), and post-contrast T1W (**c**) shows partially calcified and mildly enhancing original tumor in the fourth ventricle (yellow arrows). Post-operative CT (**d**) shows immediate post-operative findings with post-surgical pneumocephalus and MRI; diffusion-weighted imaging (**d**) and post-contrast T1W (**f**) images showing no abnormal diffusion restriction or enhancement to suggest residual tumor

Case 2

A 10-year and 8-month-old female presented with 2 weeks of morning headaches and emesis. The patient had a near total resection of a posterior fossa anaplastic group 4 medulloblastoma (Table 1, Figs. 3 and 4). On lumbar puncture, the CSF was positive for metastatic disease and treatment per the high-risk ACNS0332 protocol ensued with proton radiotherapy followed by maintenance chemotherapy (see the "Case 1" section for treatment details). Fourteen months after completion of therapy, a growing left frontal calvarial lesion was detected on surveillance imaging (Fig. 1c and d). This enlarging left frontal calvarial lesion was previously thought to be related to a burr hole from a ventricular catheter placement. Due to its increasing size, excision of the lesion was undertaken with intraoperative frameless stereotactic navigation. Brain MRI revealed concurrent findings of recurrent intraparenchymal metastatic disease. The pathology of the left frontal osseous lesion demonstrated fibrous tissue without evidence of neoplasia (Fig. 2b).

Case 3

A 5-year and 11-month-old male was diagnosed with average-risk medulloblastoma after presenting with headaches, clumsiness, and nystagmus (Table 1). The patient underwent a surgical resection followed by treatment per A9961 Regimen B which included photon radiation therapy (2340 cGy of CSI and 3240 cGy boost to the primary tumor site) and concurrent weekly vincristine followed by maintenance chemotherapy (cyclophosphamide, cisplatin, and vincristine) (Fig. 5). Post-therapy sequela included growth hormone insufficiency for which he was treated with growth hormone and letrozole. At 7 years and 5 months after completion of chemotherapy, surveillance MRI revealed an incidental finding of an enlarging ovoid enhancing lesion in the right paramedian frontal calvarium with benign imaging characteristics (Fig. 1f). On CT evaluation, the skull lesion had a ground glass appearing matrix without internal calcification or new bone formation (Fig. 1e), an appearance typically observed with fibrous dysplasia. The child underwent excision of the skull lesion and the pathology demonstrated fibrous dysplasia (Fig. 2c).

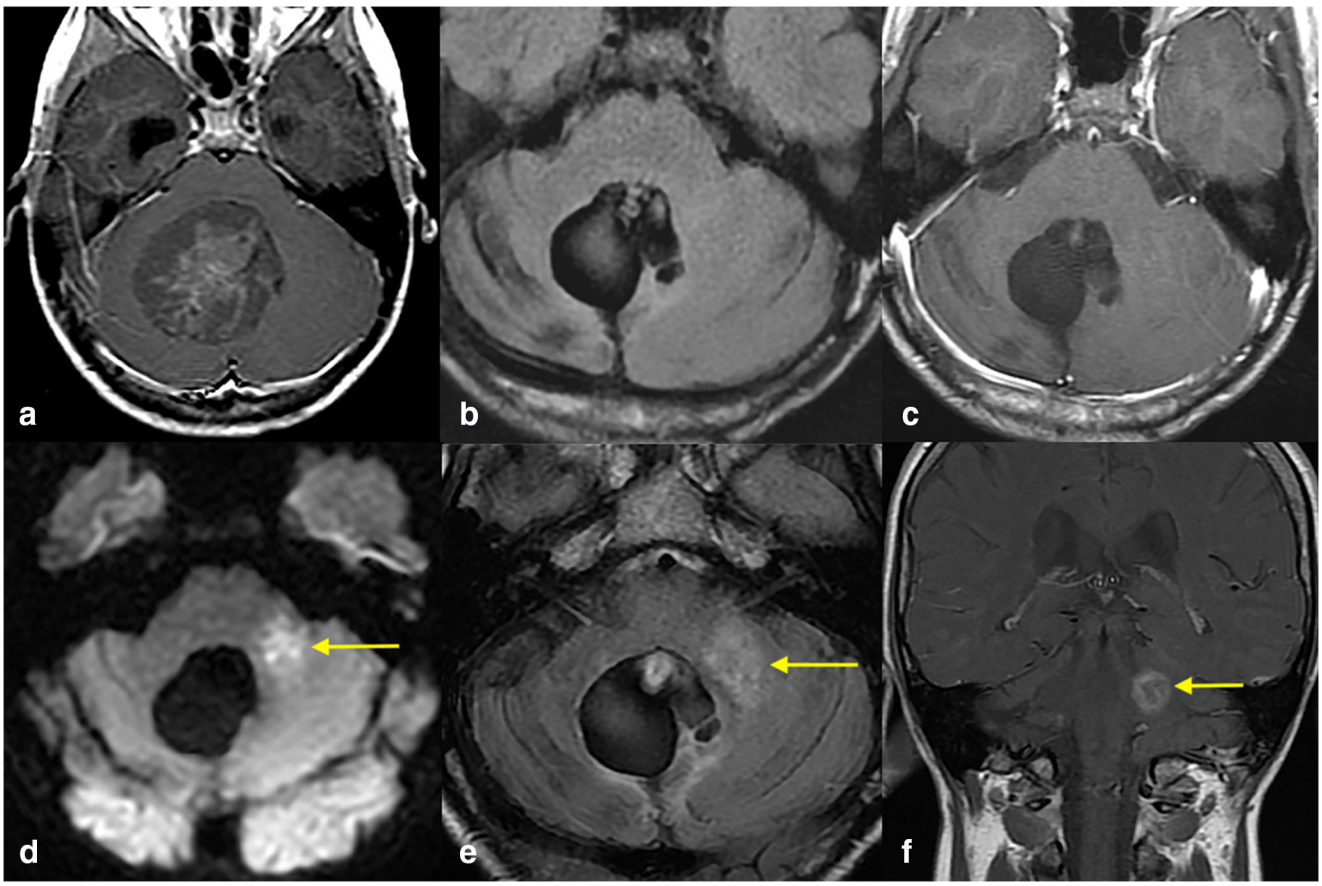

Fig. 5 Case 3. MRI images for case 3; (**a**) axial post-contrast T1W depict the heterogeneously enhancing original tumor in the fourth ventricle; (**b**) axial FLAIR and (**c**) post-contrast T1W show post-operative total resection of the tumor with post-surgical distortion of the fourth ventricle. Subsequent surveillance MRI; axial diffusion-weighted imaging (**d**); FLAIR (**e**) and post-contrast T1W showing an enhancing and diffusion-restricting lesion expanding the left brachium pontis (yellow arrows). This was a biopsy-proven low-grade glioma

Case 4

A 6-year and 6-month-old male presented with neck pain. An MRI of the brain and spine revealed a posterior fossa mass and metastatic disease to the brain and spine subsequently diagnosed as metastatic anaplastic medulloblastoma (Table 1, Fig. 6). After a subtotal resection of the tumor, the child received treatment per ACNS0332 with proton radiation therapy followed by maintenance chemotherapy (see the "Case 1" section for treatment details) (Fig. 6). A surveillance MRI 10 months post-treatment demonstrated a new extra-axial solid-enhancing nodule that appeared dural-based, overlying the posterior left frontal convexity with associated mild mass effect on subjacent parenchyma (Fig. 1g and h). There was no associated marrow signal change in the immediate adjacent calvarium. A CT head scan performed on the day prior showed no detectable associated osseous abnormality. The patient underwent surgical resection of the left posterior frontal lesion with neuronavigational assistance. The pathology revealed an inflammatory myofibroblastic tumor in the subdural space of the left frontal convexity and dense fibroconnective tissue in the subdural membrane (Fig. 2d).

Conclusions

We report four (2.9%) cases of benign fibro-osseous lesions in medulloblastoma survivors who have received prior radiation therapy out of the 136 patients that we have available follow-up data on over the past 10 years. These lesions are typically asymptomatic and are found incidentally. Their discovery can lead to differential diagnostic dilemmas as confident diagnosis cannot be made on medical imaging. Surgical resection provides a conclusive diagnosis with no further intervention needed. Alternatively, watchful waiting with routine imaging surveillance may also be appropriate in some cases. This case series demonstrates that not all skull lesions in medulloblastoma survivors are recurrent or metastatic disease. Three of the four patients in this study had undergone therapy for high-risk disease which includes higher-dose radiation therapy. It is possible that this increased radiation dose puts patients at greater risk of developing these benign skull and extra-axial or subdural lesions. Future larger studies are needed to determine if higher radiation dose puts patients at greater risk of developing these lesions. Knowledge of their occurrence will aid in appropriate management of these patients.

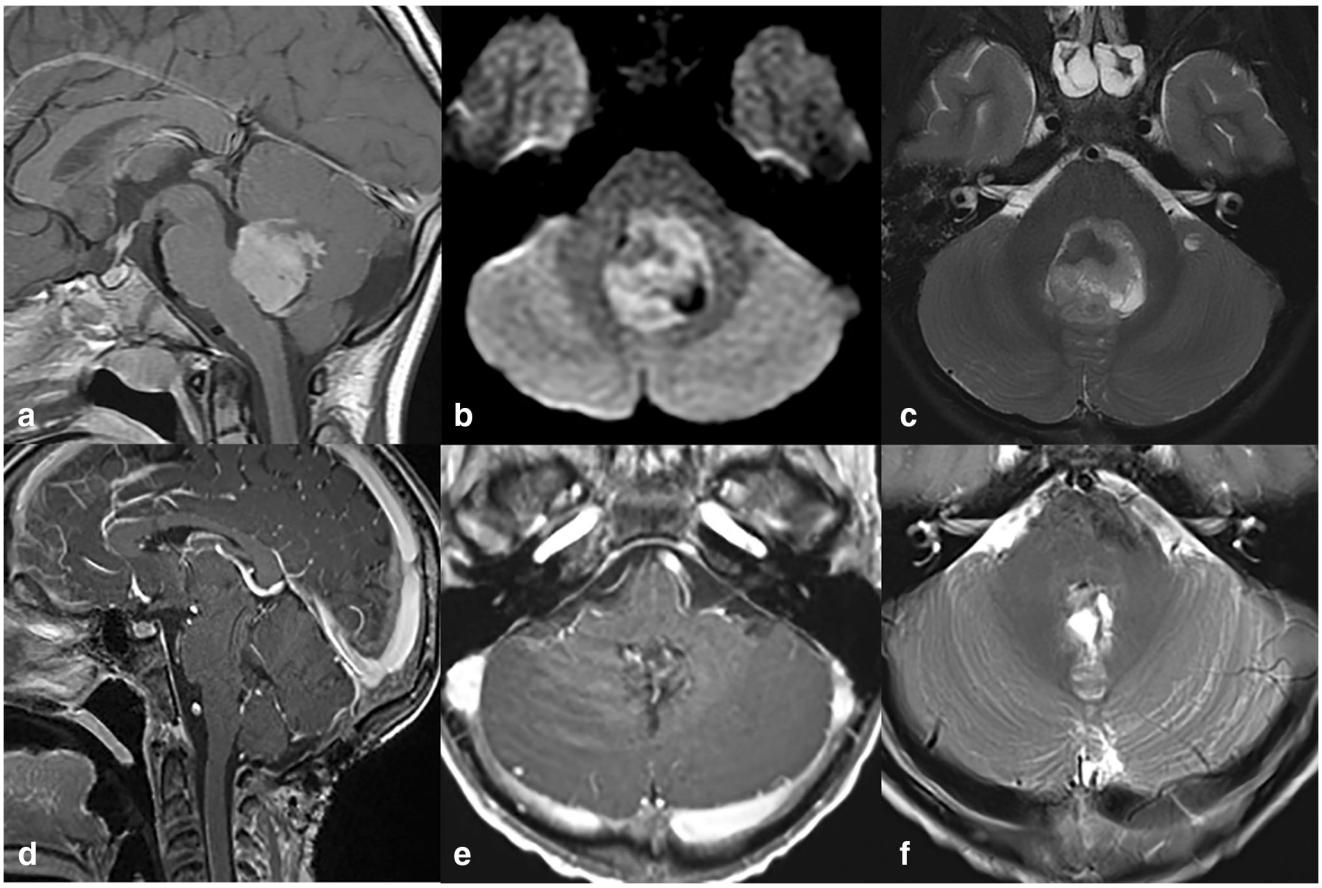

Fig. 6 Case 4. MRI images for case 4; (**a**) sagittal post-contrast T1W depicts the original tumor in the fourth ventricle; (**b**) axial diffusion-weighted image and (**c**) axial T2W show diffusion restriction consistent with high cellularity and heterogenous T2 signal. Post-operative MRI; sagittal (**d**) and axial (**e**) post-contrast T1W; axial T2W (**f**) shows complete surgical resection

Authors' contribution All authors have contributed significantly to the design, data collection, and writing of this manuscript.

Availability of data and material (data transparency) All relevant data is included.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethics approval Institutional review board approval was obtained for completion of this study.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

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