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Novel Insights from Clinical Practice

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Posttreatment Maturation of Medulloblastoma into Gangliocytoma: Report of 2 Cases

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Established Facts

- Medulloblastoma is the most common malignant brain tumor among children with an overall poor prognosis and the standard of care includes surgical resection, chemotherapy, and radiation.
- Posttreatment maturation of medulloblastoma is a very rare phenomenon with very few reported cases in the literature.

Novel Insights

- Posttreatment maturation of medulloblastoma has been seen in the literature very few times; here we present 2 cases which show maturation into gangliocytoma without heterogeneity.
- Although rare, reporting these cases and attempting to understand the genetics and treatment algorithms that lead to this maturation will offer valuable insight into advancing treatment.

Keywords
Maturation · Medulloblastoma · Gangliocytoma

Abstract

Introduction: We report 2 cases of medulloblastoma maturing into gangliocytoma after receiving multimodal therapy. Here we present 2 cases of diagnosed medulloblastoma which on re-resection were noted to be gangliocytoma without heterogeneity, which is an extremely rare occurrence. ***Case Presentation:*** The first patient, an 11-year-old boy diagnosed with high-risk (non-WNT, non-SHH) medulloblastoma, was treated with near-total surgical resection followed by craniospinal radiation therapy with weekly vincristine. He then received maintenance chemotherapy with vincristine, cyclophosphamide, and cisplatin. On surveillance MR imaging studies residual tumor in the lateral aspect of the tumor bed was noted to be slowly growing, eliciting gross-total re-

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section of the residual tumor. Histopathology showed benign gangliocytoma without residual medulloblastoma. The second patient, a 3-year-old girl, was diagnosed with medulloblastoma, desmoplastic nodular variant. She was initially treated with gross total resection and chemotherapy with etoposide, carboplatin, and high-dose methotrexate. At 4 months off therapy, she was noted to have local recurrence along the resection cavity. Second-line therapy was started with irinotecan and temozolomide, but MRI assessment during treatment showed further disease progression. She then received craniospinal radiation. Eleven months off therapy, further radiographic progression was noted, and the patient underwent second-look surgery, with pathology showing gangliocytoma and treatment-related gliosis. ***Discussion/Conclusion:*** The maturation of medulloblastoma into a ganglion cell-rich lesion is very rare, with few well-characterized previous reports. Given the rare nature of this entity, it would be of great value to understand the process of posttreatment maturation and the genetic and treatment factors which contribute to this phenomenon.

Introduction

Medulloblastoma is the most common malignant brain tumor in children and has high proclivity to metastasize within the central nervous system [1]. Historically, medulloblastoma has been separated into four histologically defined subtypes: classic, desmoplastic/nodular, extensive nodularity, and large cell/anaplastic. More recently, four genetically defined subgroups have been identified (Wnt, SHH, group 3, and group 4), with each subgroup conferring a distinctive prognosis and treatment pathway implications [2]. Treatment of medulloblastoma typically consists of surgical resection followed by radiation therapy and chemotherapy. When surgery is performed for treatment-refractory radiographic progression, pathological analysis virtually always demonstrates recurrent medulloblastoma.

Here we discuss 2 cases of World Health Organization (WHO) grade IV medulloblastoma with posttreatment maturation into gangliocytoma, a WHO grade I neoplasm. The phenomenon of posttreatment maturation of

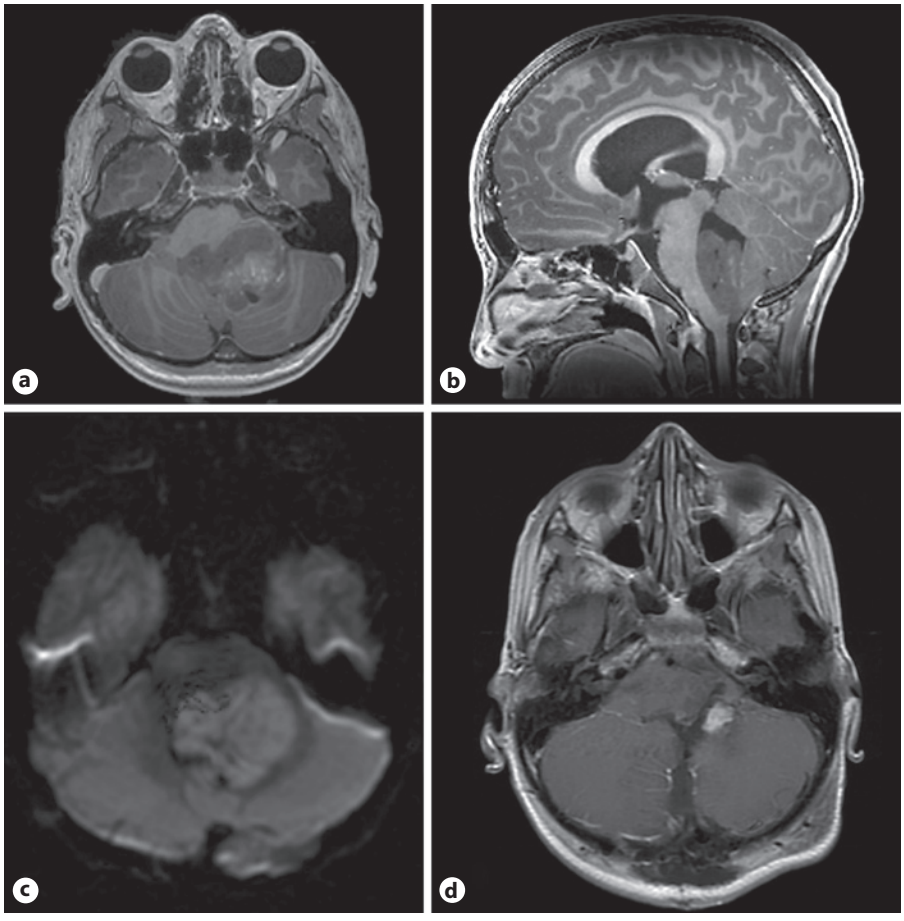

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Fig. 1. a–c MRI at the time of presentation for case 1. A large neoplasm is noted in the left lateral aspect of the 4th ventricle with compression on the brainstem with resultant hydrocephalus. The lesion demonstrates both heterogeneous contrast enhancement (**a**, **b**) and diffusion restriction (**c**). **d** The immediate postoperative MRI shows a small amount of residual tumor. **e**, **f** The pathology for initial surgical resection in case 1 demonstrating medulloblastoma with syncytial architecture, blue cells with frequent mitoses, and apoptotic bodies. Cells show diffuse staining for synaptophysin (**g**) and are GFAP negative, with background staining (**h**). Beta-catenin stain shows only cytoplasmic and membranous staining, without aberrant nuclear localization (**i**), and the Ki67 index is 70–80% (**j**).

(Figure continued on next page.)

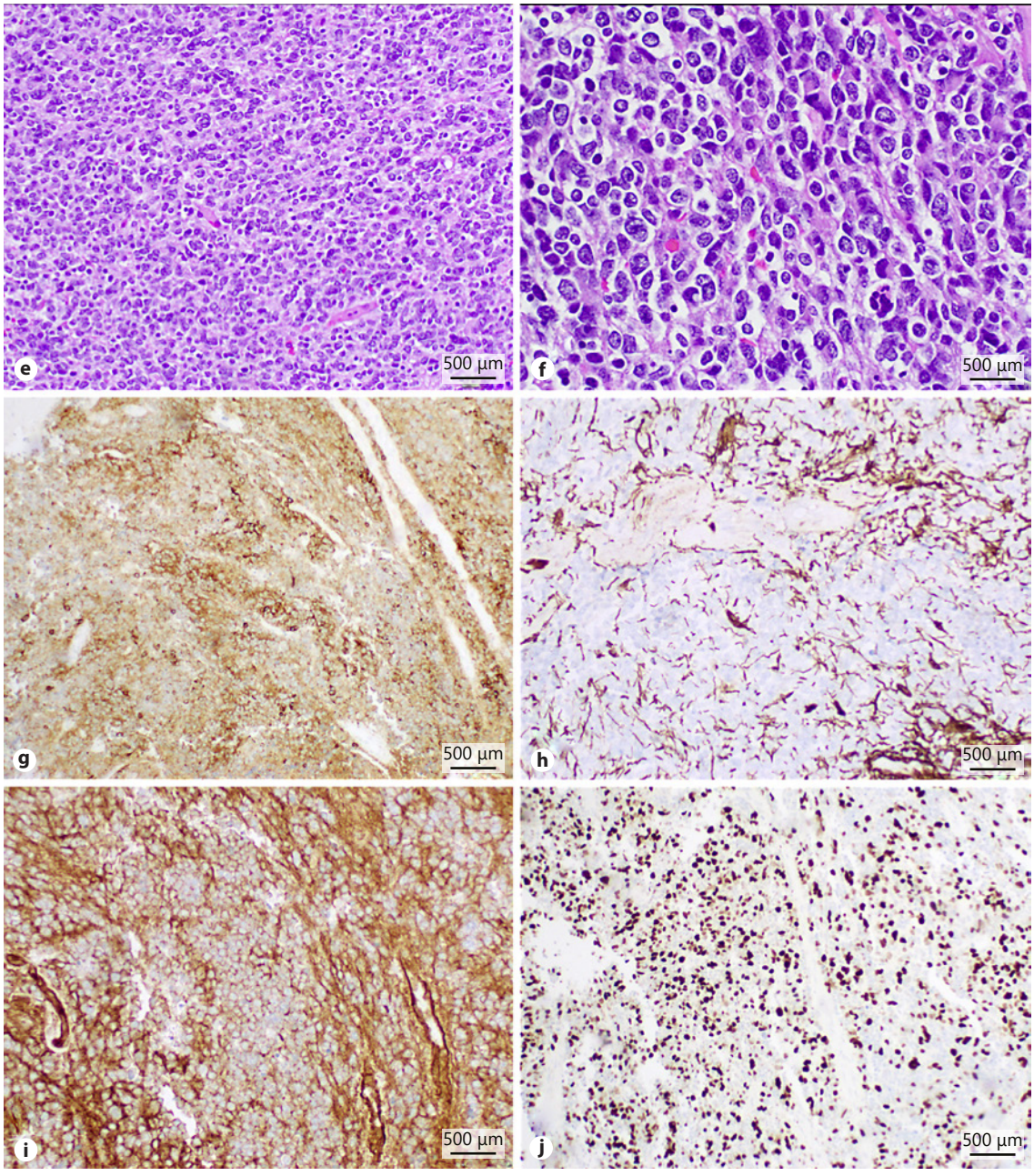
medulloblastoma is rare and poorly characterized, having been reported in the literature in only a few instances [3–8].

Case Report

Case 1

A previously healthy 11-year-old boy presented with an 8-month history of intermittent headaches accompanied by nausea and emesis. On physical examination he had a left sixth nerve palsy, horizontal nystagmus, and bilateral dysmetria. Imaging studies revealed a 4.2 × 4.7 × 4.6-cm tumor centered within the 4th ventricle extending into the left foramen of Luschka and foramen of Magendie, with associated hydrocephalus (Fig. 1a–d). Medulloblastoma was favored as the tumor showed restricted diffusion along with iso- to hypointensity on the T2-weighted sequence.

The patient underwent a posterior fossa craniotomy and C1 laminectomy for tumor resection. Postoperative imaging showed residual tumor in the left foramen of Luschka (12 mm AP × 14 mm TV). Pathological analysis confirmed the diagnosis of medulloblastoma, WHO grade IV (classic variant without anaplasia, p53 wild-type pattern, non-WNT/non-SHH molecular subgroup, neg-



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ative for *MYC*/*MYCN* amplification, Ki67 proliferation index 70–80% in the highest labeled regions; Fig. 1e–j).

Subsequently, the patient underwent craniospinal irradiation with 36 Gy administered to the craniospinal axis followed by a boost to the posterior fossa to a total of 55.8 Gy. He received concomitant weekly vincristine during radiation followed by maintenance chemotherapy with vincristine, cyclophosphamide, and cisplatin for 6 cycles. Therapy was completed 8 months after the initial diagnosis. Subsequent MR imaging performed at 20 months off therapy (28 months from diagnosis) showed a slow but progressive growth of residual tumor in the lateral aspect of the 4th ventricle (Fig. 2a, b), eliciting repeat posterior fossa craniotomy. Multiple intraoperative frozen sections showed a ganglion cell-rich lesion consistent with gangliocytoma. Gross total tumor resection was obtained (Fig. 2c). The final pathological analysis confirmed the diagnosis of gangliocytoma, WHO grade I (BRAF V600E negative, Ki67 proliferative index <1%; Fig. 2d–i), with no residual medulloblastoma. No evidence of heterogeneity was noted among the gangliocytoma. No further treatment has been administered and there is no evidence of disease with 11 months of follow-up.

Case 2

A previously healthy 3-year-old girl presented with progressive gait disturbance. Brain MRI showed a posterior fossa tumor. Gross total resection was performed (Fig. 3a, b), with pathology showing desmoplastic/nodular medulloblastoma, WHO grade IV (Fig. 3e–g). A spine MRI and CSF were negative. Adjuvant chemotherapy included etoposide, carboplatin, and high-dose methotrexate. Local recurrence along the resection cavity was identified during surveillance MR imaging at 4 months off therapy (Fig. 3c, d). At that time, interrogation of the primary tumor by next-generation sequencing revealed an *FBXW7* mutation (1436 G>A p.R479Q). Second-line therapy was provided with irinotecan and temozolomide, but MRI during treatment showed further disease progression after 4 months of this therapy. The patient then received craniospinal axis proton beam radiation for 6 weeks to 36 Gy followed by a boost to the primary site to a total of 54 Gy. MR imaging after completion of radiation therapy showed a residual nodule at the surgical cavity (Fig. 4a, b).

Further radiographic progression of the residual nodule was noted in the left superior quadrant of the fourth ventricle adjacent to the cerebellum and close to the brainstem at 11 months off therapy (Fig. 4c, d), eliciting second-look posterior fossa craniotomy. Postoperative MRI showed a subtotal tumor resection (Fig. 4g). Pathological analysis showed neuronal aggregates consistent with gangliocytoma (Fig. 4e, f), with no residual medulloblastoma identified. No heterogeneity of the gangliocytoma was noted. No further treatment has been given to the patient to date, and she has remained clinically stable with no radiographic evidence of disease for the past 3 years since repeat craniotomy.

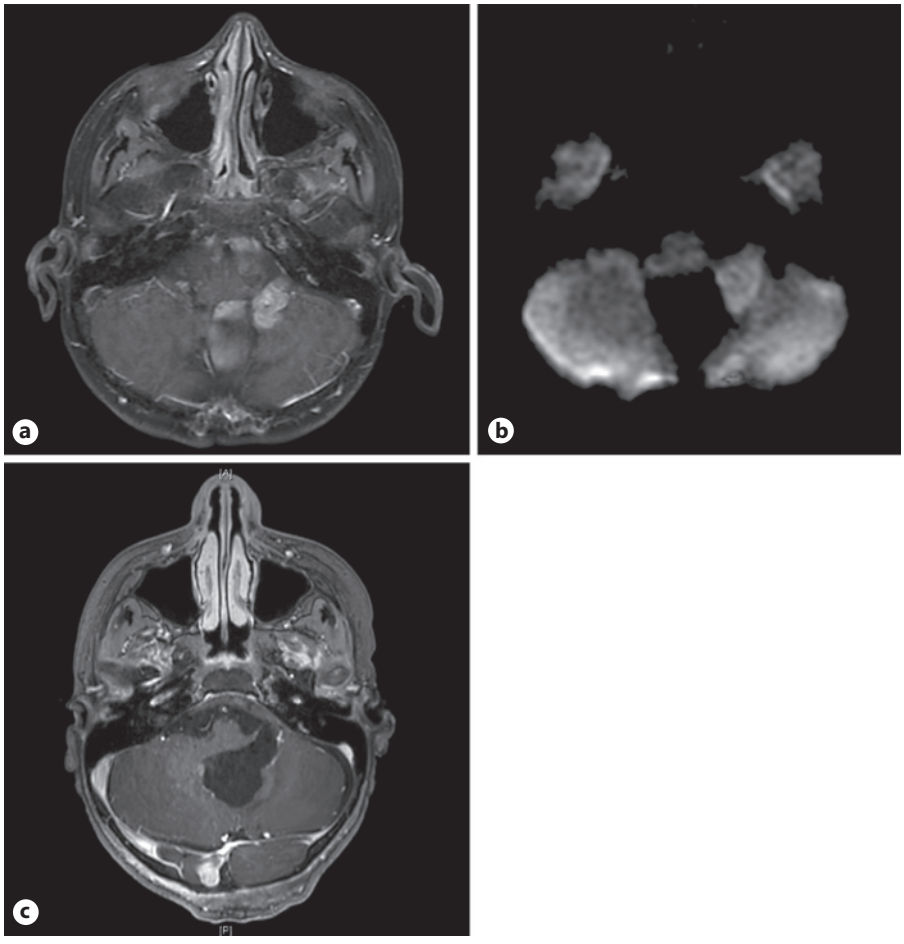

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Fig. 2. MRI at the time of tumor recurrence in case 1, with final pathology of gangliocytoma. Contrast-enhancing tumor is noted at the left foramen of Luschka (**a**) and is noted to have restricted diffusion (**b**). **c** Gross total resection was obtained without evidence of tumor on postoperative MRI. **d–i** The pathology at the time of recurrence in case 1 showing gangliocytoma. Gangliocytoma cells are mature ganglion cells with coarse Nissl substance and binucleation (**d**, **e**); GFAP-staining glial processes are present (**f**), and the Ki67 index is <1% (**g**). There is also staining for neurofilament proteins, which is positive in axons and occasional cell bodies (**h**) and synaptophysin, which is positive in ganglion cells and their processes (**i**).

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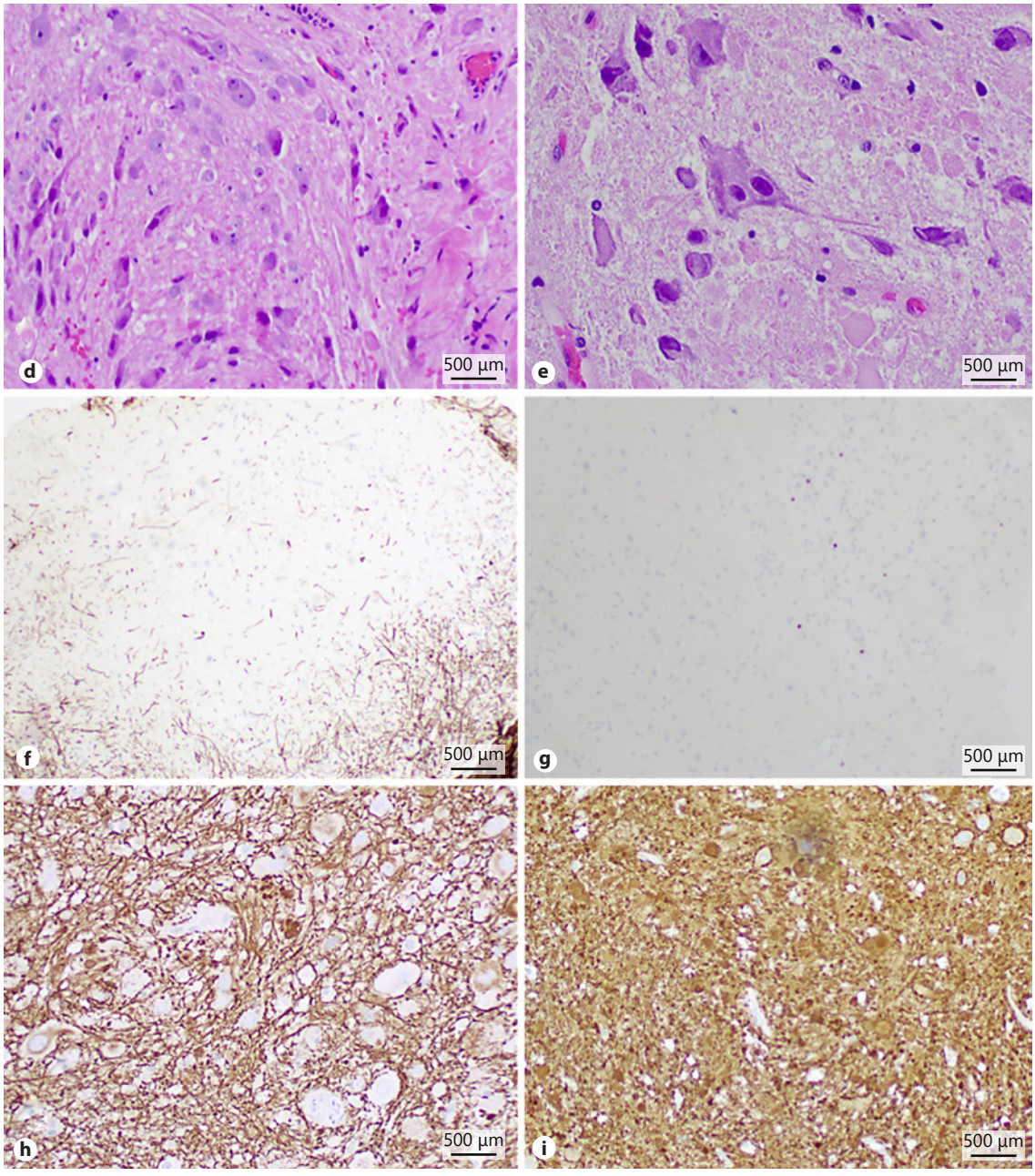

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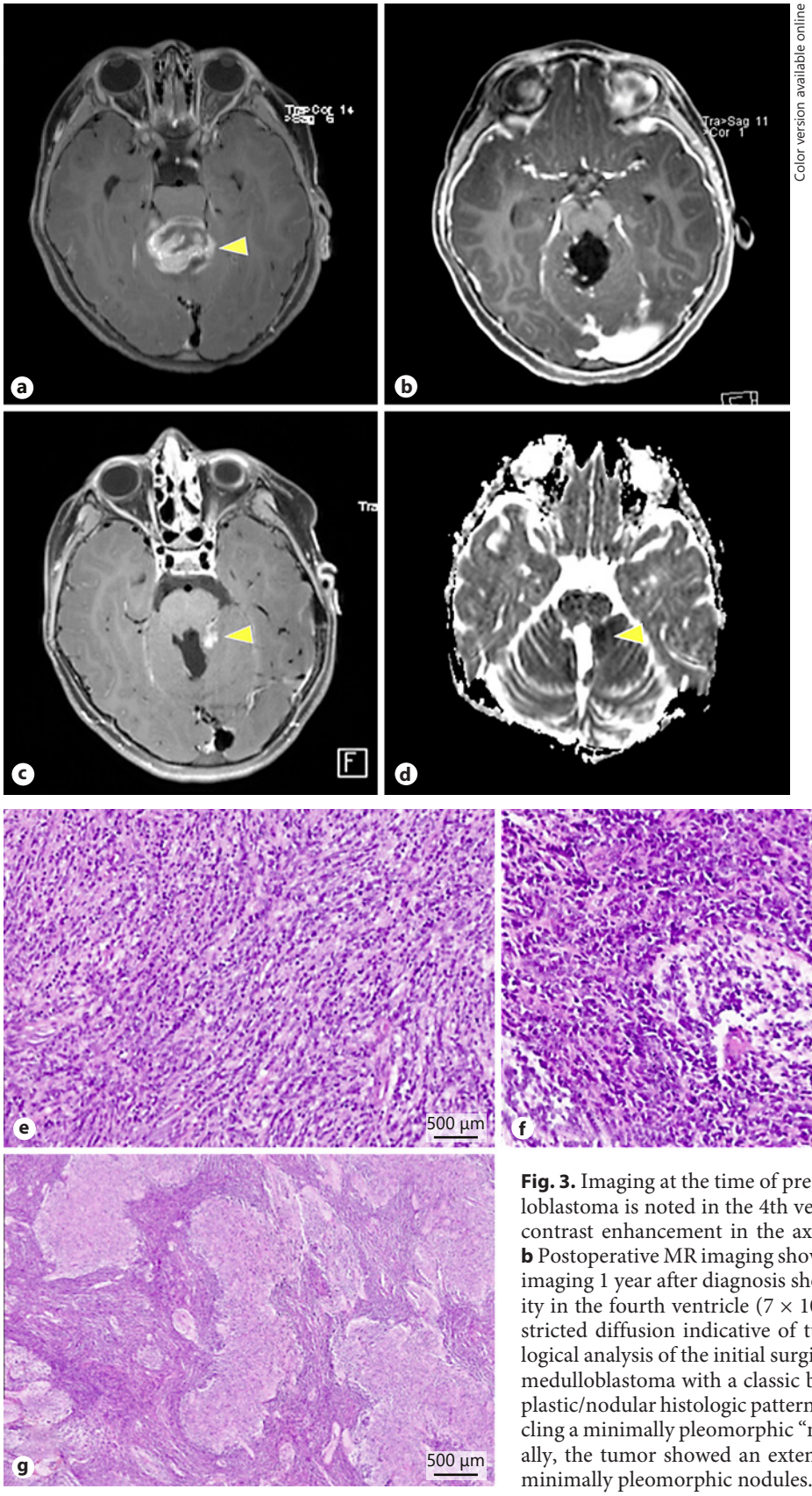

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Fig. 3. Imaging at the time of presentation for the patient in case 2. **a** Medulloblastoma is noted in the 4th ventricle, which demonstrates heterogeneous contrast enhancement in the axial T1 postcontrast sequence (arrowhead). **b** Postoperative MR imaging shows gross total resection. T1 postcontrast MR imaging 1 year after diagnosis shows disease recurrence in the resection cavity in the fourth ventricle (7 × 10 mm; **c**, arrowhead), which also shows restricted diffusion indicative of tumor recurrence (**d**, arrowhead). **e** Pathological analysis of the initial surgical specimen for the patient in case 2 shows medulloblastoma with a classic blue cell sheet-like architecture. **f** A desmoplastic/nodular histologic pattern was observed with desmoplastic cells encircling a minimally pleomorphic "neurocytic"-like central nodule. **g** Additionally, the tumor showed an extensive nodular histologic pattern with large, minimally pleomorphic nodules.

Discussion

Medulloblastoma is the most common primary central nervous system malignancy in children and accounts for roughly 10% of all childhood brain tumors [9]. Medulloblastoma occurs in the posterior fossa and presents most commonly with headaches, nausea, emesis, ataxia, hydrocephalus, and/or cranial nerve deficits. The overall survival for children in the USA diagnosed with medulloblastoma at 1, 5, and 10 years is estimated at 86, 70, and 63%, respectively [10]. Standard treatment includes surgical resection, craniospinal irradiation (in children above the age of 3 years), and combination chemotherapy. The most common cause of death among patients diagnosed with medulloblastoma is progressive leptomeningeal disease [11].

Medulloblastoma has various classification systems, with the earliest classification based exclusively on histology [12]. Classification based on histology alone has been a suboptimal marker of disease behavior and overall prognosis. More recent classification based on molecular subgroups (WNT, SHH, group 3, and group 4) has been more successful in terms of predicting the treatment response and prognosis [13, 14]. In 2016, the WHO developed a consensus model that incorporates both histological and molecular subgroups to refine the classification of medulloblastoma to better predict treatment response and prognosis [15].

When recurrent tumor is treated with surgical resection, pathological analysis almost universally reveals recurrent medulloblastoma. Only 6 prior case reports (8 patients in total) have described medulloblastoma undergoing posttreatment maturation into a benign neoplasm [3–8]. Of the 8 patients previously described, 3 underwent maturation into gangliocytoma. The remaining 5 patients after maturation, respectively, showed pathology consistent with neuronal differentiation, classic medulloblastoma, mature neuronal elements, ganglioneurocytoma, and ganglioglioma. Chelliah et al. [4] described a 22-month-old boy who underwent gross total surgical re-

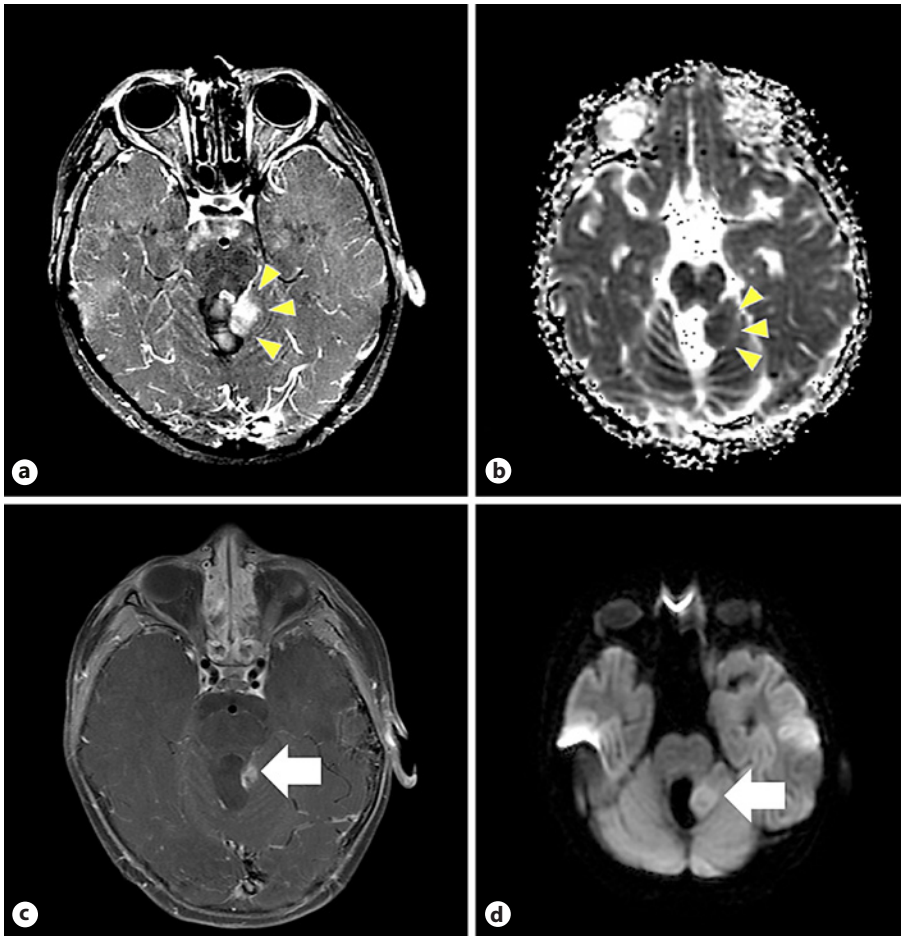

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Fig. 4. Imaging at the time of progression postradiotherapy in case 2 (30 months from diagnosis and 18 months from first relapse). A tumor nodule (11 × 16 mm; arrowheads) is noted in the 4th ventricle that shows heterogeneous contrast enhancement (**a**, axial T1 postcontrast) and restricted diffusion (**b**). MRI prior to the second resection in case 2. **c** A contrast-enhancing tumor nodule is noted within the left superior vermis (arrow). **d** The tumor displays restricted diffusion on DWI sequence (arrow). **e** Pathological analysis at the time of recurrence in case 2 showing gangliocytoma. **f** Synaptophysin stain shows robust perikaryal staining of the mature ganglion cells. **g** The postoperative scan after the second resection shows subtotal resection (arrowhead; axial T1 postcontrast).

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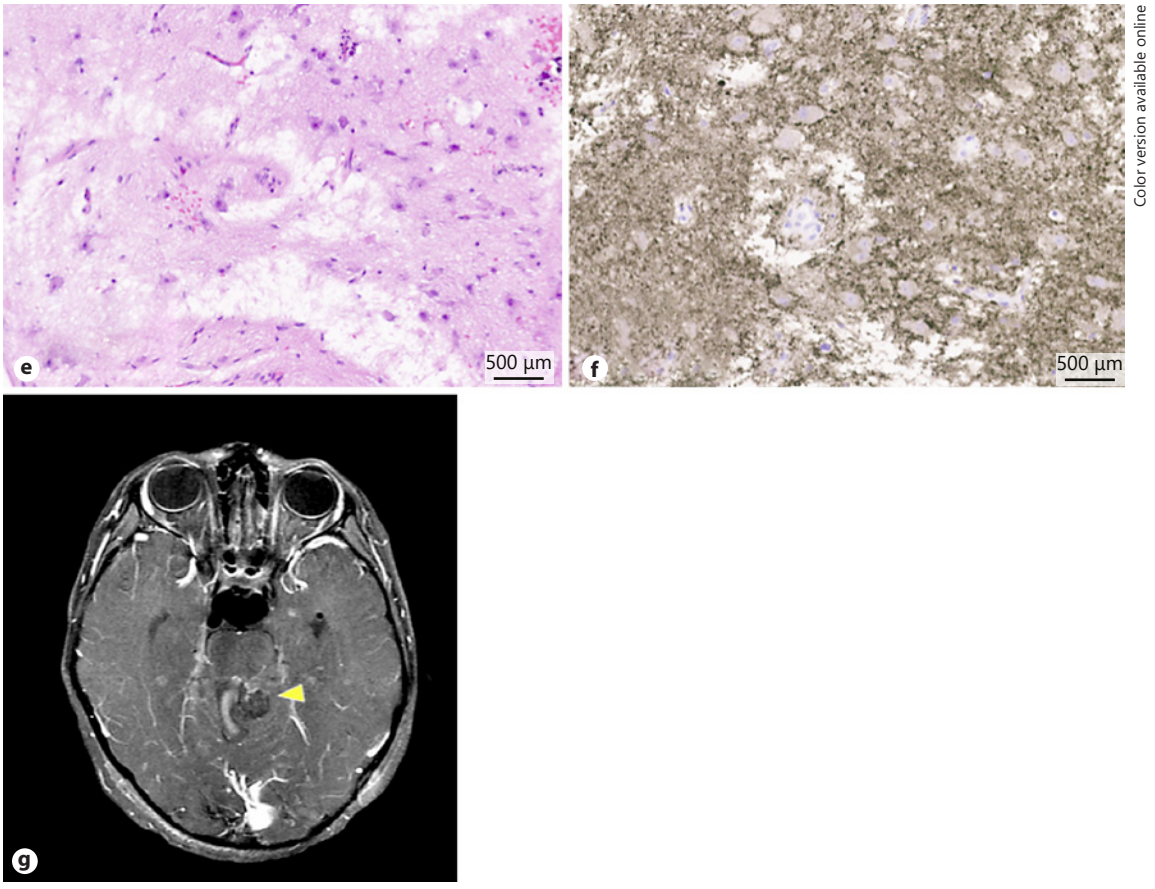

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section followed by adjuvant systemic chemotherapy. The initial pathology was consistent with medulloblastoma with extensive nodularity (MBEN). After recurrence 7 months later, the patient underwent a second surgical resection followed by craniospinal irradiation with a boost to the posterior fossa along with further chemotherapy. Ten years later, the patient underwent surgical resection of recurrent posterior fossa tumor, with a resultant diagnosis of gangliocytoma.

Two cases of posttreatment maturation of medulloblastoma into gangliocytoma were described by Wu et al. [8]. In the first case, a 13-month-old girl presented with a right cerebellar hemisphere tumor. Subtotal resection yielded a histopathologic diagnosis of MBEN, with treatment comprising cyclophosphamide, cisplatin, and vincristine, utilizing the chemotherapy protocol described by Rutkowski et al. [16]. She subsequently underwent craniospinal irradiation with a boost to the posterior fossa. Thirty months after the initial surgery, local recurrence was identified on surveillance imaging, and pathological analysis showed gangliocytoma. In a second case described by the same authors, a 2-year-old girl presented with a left cerebellar hemisphere tumor that was diagnosed as MBEN after subtotal resection. Treatment comprised of cyclophosphamide, cisplatin, and vincristine, along with craniospinal irradiation with a boost to the posterior fossa. After 6 months recurrence was noted, and reoperation yielded a diagnosis of gangliocytoma [8].

Posttreatment maturation is a rare phenomenon that has been described in other malignancies outside of the central nervous system [17–20]. The etiology of maturation is poorly understood but may be related to differentiation induced by chemotherapy and radiation. Three prior published cases have demonstrated MBEN (generally with a more favorable prognosis) undergoing posttreatment maturation [4, 8]. However, here we present 2 cases of more aggressive subtypes of desmoplastic/nodular and classic medulloblastoma undergoing maturation into gangliocytoma.

Interestingly, neuroblastoma represents a subtype of central nervous system malignancy which demonstrates regression, posttreatment maturation, or progression in

spite of treatment. The behavior of neuroblastoma may give insight into mechanisms of posttreatment maturation in medulloblastoma. With neuroblastoma, there have been several proposed mechanisms of regression, including neurotrophin-mediated regression, relative telomerase activity, immune-mediated, and genetic/epigenetic factors [21]. These mechanisms of regression, specifically genetic and epigenetic analysis, could lead to understanding of how posttreatment maturation occurs. We propose that examining the gene expression and methylation patterns of pretreated medulloblastoma with the maturation product could lead to new methods of targeted therapy. In neuroblastoma, it has been shown that 13-cis retinoic acid has been associated with alterations in gene expression and differentiation [22]. Similarly, examining the effects of chemotherapy on gene expression and its association with maturation would be beneficial. Currently, given that cases of postmaturation are very rare, there has not been extensive investigation into this process.

Conclusion

Here we have reported 2 cases of high-risk medulloblastoma with complete maturation into gangliocytoma after undergoing surgical resection, craniospinal irradiation, and chemotherapy. Although rare, maturation into a benign neoplasm should be considered in the differential diagnosis of recurrent tumor in patients diagnosed with medulloblastoma.

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Statement of Ethics

Written consent was obtained from both subjects for all of the aforementioned treatments including consent for surgical intervention. No identifying information, images, or descriptions of the patients are included within this manuscript. IRB approval was not required as this case series included fewer than 3 patients in our report. The parents of each patient gave their written informed consent for the publication of data and images. The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Dr. Matthew Mullarkey, Grace Nehme, Sana Mohiuddin, and Darshan Trivedi assisted with the acquisition and interpretation of data as well as drafting/revising the work. Dr. Leomar Ballester, Meenakshi Bhattacharjee, and Gregory Fuller provided pathology data and analysis along with drafting/revising the manuscript. Dr. David Sandberg, Manish Shah, and Wafik Zaky assisted in data acquisition, analysis, and the interpretation of data. They also assisted with drafting and revising the manuscript.

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