Medulloblastomas are invasive embryonal tumors of the posterior fossa and represent the most frequent malignant tumor of the CNS in childhood. They comprise between 15% and 20% of all childhood brain tumors. The rate of recurrence of pediatric medulloblastoma is between 35% and 40%. Screening for and diagnosing recurrent disease presents the clinician with significant diagnostic challenges, including the risk of misdiagnosis. The authors present the case of a young girl with a history of a treated standard-risk medulloblastoma that highlights the risk of assuming recurrence has occurred when clinical and/or imaging changes are observed. This girl developed both new clinical deficits and had radiographic evidence of recurrence. She subsequently experienced a complete resolution of symptoms and radiographic findings with steroids alone.

Key Words • medulloblastoma • magnetic resonance imaging • recurrent disease • oncology

Case Report

History and Examination. This girl initially presented at 6 years of age with 2 weeks of morning emesis, fatigue, and 2 days of diffuse headache. On examination she was sleepy, but arousable; no focal neurological deficits were noted. A CT scan was emergently obtained and revealed a posterior fossa mass, and MRI showed a mass in the posterior fossa with herniation of the cerebellar tonsils, effacement of the CSF space within the cisterna magna, and hydrocephalus (Fig. 1). Spinal MRI and CSF were negative for metastatic disease.

Operation and Postoperative Course. A gross-total resection was performed 2 days later and the histological diagnosis of medulloblastoma was confirmed. Pathological analysis demonstrated a small, round, blue-cell tumor with neuronal differentiation, which despite extensive reticulin deposition, did not show the nodular pattern of the classic nodular/desmoplastic variant. After initial resection she developed posterior fossa syndrome that slowly resolved. On postdischarge follow-up, she was noted to have a right-sided hand and arm tremor and dysconjugate gaze, but was ambulating well. The patient later received radiation and chemotherapy according to the Children's Oncology Group protocol (ACNS0331). She received a total of 23.40 Gy of cranial spine radiation therapy, followed by a posterior fossa boost of 30.60 Gy. Chemotherapy included vincristine, cisplatin, cyclophosphamide, lomustine, and supportive medications.

Second Presentation. The patient first presented to ophthalmology 6 months after initial presentation and treatment; at that time she demonstrated 20/20 vision in both eyes, and a mild palsy of the sixth cranial nerve. She
had no afferent pupillary defect and the rest of her examination was normal.

The patient’s treatment course was complicated by a persistent strabismus, weight loss greater than 10%, hearing deficits secondary to ototoxicity, chemotherapy delay secondary to thrombocytopenia, foot drop, and depression. She attended school and received occupational and physical therapy at a rehabilitation center. Treatment with chemotherapy was completed 1 year after initial diagnosis; it was stopped 2 cycles early due to her mother’s request.

Fourteen months after her last therapy, at 9 years of age, the patient presented for an urgent reevaluation. At that time, the mother noted her eyes “did not seem right,” and her teachers noted that she was not writing on the lines and was writing off of the page. Upon review of the patient’s systems, she was found to have experienced 2 weeks of increased fatigue and some decreased strength of the right arm. She underwent urgent evaluation by pediatric ophthalmology and was noted to have an acute change in vision; her visual acuity had dropped to 20/200 in the right eye and 20/400 in the left eye. The rest of her examination was completely normal, including a resolution of her sixth cranial nerve palsy.

An emergency MR image revealed multiple areas of enhancement that appeared to be recurrent disease (Figs. 2 and 3). An MR image of the spine revealed clumping of nerve roots in the lumbar spine as may be noted with leptomeningeal disease. The differential diagnosis included recurrent medulloblastoma, radiation myelitis, viral myelitis, Lyme disease, demyelinating disease, or sarcoidosis.

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The survival advantage of early detection may be limited by our ability to successfully treat recurrent disease. Patients with recurrent medulloblastoma following mul-
Misdiagnosing recurrent medulloblastoma

timodal therapy typically have tumors that are incurable despite further treatment. Salvage chemotherapy regimens, including alkylator-based high-dose chemotherapy with stem cell rescue, have been used to treat recurrent disease without significantly improved outcome.8,13,22 Newer, targeted therapies aimed at antiangiogenesis and other molecular pathways implicated in medulloblastoma are presently being studied. The current Children’s Oncology Group study for recurrent/refractory medulloblastoma (ACNS0821) is a Phase II randomized trial comparing the effectiveness of the combination of irinotecan and temozolomide with that of the same drugs combined with bevacizumab.11 Despite the lack of an established, effective salvage therapy, 1 advantage, as suggested by Shaw and colleagues,21 is that early detection of relapse with minimum disease may provide the best setting in which to test newer therapies.

Regardless of the lack of definitive evidence on its utility, current protocols not only employ surveillance scanning to detect recurrent disease, but also do not require histological confirmation. In the ACNS0821 protocol, the study authors define disease as tumor that is measurable in 2 perpendicular diameters on MRI and state that the patient must have had histological verification of the malignancy at original diagnosis or, but not necessarily, at the time of recurrence. Likewise, in the current Pediatric Brain Tumor Consortium Phase II study (PBTC-032) on recurrent/refractory medulloblastoma, the patients must only have bidimensionally measurable disease in the brain or spinal cord, defined as at least 1 lesion that can be accurately measured in at least 2 planes (PBTC-032).

Radiographic findings found on either routine or emergency imaging must be interpreted with caution. Clinicians must question if recurrent disease can be differentiated from treatment-induced changes, or pseudo-progression, on MRI. Abnormal findings following radiation therapy have been widely documented on MRI in children treated for brain tumors.5,24 There is also evidence to suggest that standard or high-dose chemotherapy can injure the normal brain,8 and there appears to be a compounding effect when radiation therapy and chemotherapy are used together.3,14,15,17,20 In a Phase I/II study evaluating the use of carboplatin during radiation therapy in patients with medulloblastoma, the authors found 4 metastatic patients with early progression of leptomeningeal disease who were long-term survivors following palliative chemotherapy alone. The authors, in retrospect, stated that these patients were not believed to have true progressive disease.15

Additionally, there is increased evidence of clinical and radiographic therapy-related alterations as a result of the more frequent use of high-dose chemotherapy combined with radiation therapy for pediatric brain tumors.16,25 Our patient was observed to have clinical symptoms and radiographic changes more than a year after therapy. It is important to note that radiation-induced MRI abnormalities can occur even a significant time after therapy. Spreafico and colleagues25 found that of the 49 children with malignant brain tumors, 18 had abnormal brain MRI findings occurring at a median of 8 months, but for as long as 39 months, after radiation therapy (6 of 25 with high-grade gliomas and 12 of 24 with primitive neuroectodermal tumors). Furthermore, as in our patient, they found that one-half of the patients had symptoms relating to the new radiographic findings.
Our patient also had evidence of leptomeningeal disease, both clinically and radiographically. Previous studies have shown that MRI of the brain and spine with a T1-weighted Gd-enhanced sequence is the standard and most sensitive way to detect leptomeningeal disease on neuroimaging. This raises the question of whether the presence of typical clinical features, in conjunction with appropriate neuroimaging abnormalities, is adequate to make the diagnosis of leptomeningeal disease even if CSF cytological results are negative.

In their review, Taillibert and colleagues stated that the most accurate way to diagnose recurrent leptomeningeal disease was by lumbar puncture, with detection of malignant cells being the most important finding. However, the initial cytology may be falsely negative in a significant proportion of cases. Prior studies in adults have shown that repeated sampling can significantly enhance the diagnostic yield. Therefore, in adults, some have recommended performing at least 3 lumbar punctures over several days if the initial cytology is negative.

Lumbar puncture may also be essential to differentiate leptomeningeal disease from infectious and inflammatory causes of subacute and chronic meningitis because they can produce similar images on MRI. For example, Fouladi and colleagues presented a case of a 16-year-old boy whose medulloblastoma had been successfully treated and underwent MRI that demonstrated asymptomatic nodular leptomeningeal enhancement of the brain and spinal cord, consistent with recurrent disease. Examination of the CSF, however, led to the diagnosis of bacterial meningitis, and after completing 2 weeks of antibiotic therapy, the findings on the original MRI resolved. The authors caution that even though nodular leptomeningeal enhancement is more commonly observed in neoplastic disease than infectious meningitis, it is imperative to consider all clinical and laboratory data, including results from a complete examination of the CSF, when interpreting the origin of new lesions revealed by MRI.

Even though they are rare, second tumors due to radiation therapy must also be considered. We know that pediatric patients with primary malignant brain tumors who received radiation therapy have an increased risk of developing a secondary malignant neoplasm, the majority of which are brain tumors and include meningioma, glioblastoma, and anaplastic astrocytoma. Studies have shown a high rate of mortality associated with secondary gliomas, but a high survival rate of secondary meningiomas.

The utility of screening for recurrent medulloblastoma remains controversial, especially in the absence of established effective salvage therapies; however, as current protocols still recommend routine surveillance scanning, the physician must be prepared to critically interpret positive results. As we have illustrated, caution must be taken when basing the diagnosis of recurrent medulloblastoma on symptomatology and MRI alone. While the differential diagnosis may be less common than tumor recurrence, it is important to consider the implications of a false positive finding on clinical or radiographic examination. Clinical trials do not require histological confirmation of recurrence, and therefore resolution of pseudoprogression may be interpreted as treatment response. For the patient, the risks associated with further neurosurgery, which are small with current techniques, may not outweigh the benefits of confirming recurrence. Furthermore, there exists the possibility of finding a more treatable condition, such as infection, or a secondary malignancy, such as a meningioma, which may have a good prognosis compared with recurrent disease.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Acquisition of data: Weintraub. Drafting the article: Weintraub. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Weintraub.

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Manuscript submitted May 13, 2013. Accepted October 3, 2013. Please include this information when citing this paper: published online November 8, 2013; DOI: 10.3171/2013.10.PEDS13231.

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