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Educational Case

Educational Case: Medulloblastoma

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://doi.org/10.1016/j.acpath.2023.100086.[1]

Keywords: Pathology competencies, Organ system pathology, Nervous system, Central nervous system neoplasia, Brain tumors, Medulloblastoma

Primary objective

Objective NSC1.2: Classification of Brain Tumors. Compare and contrast the common types of brain tumors with respect to their location, age incidence, pathogenesis, molecular basis, morphology, and prognosis.

Competency 2: Organ System Pathology; Topic: Nervous System - Central Nervous System (NSC); Learning Goal 1: CNS Neoplasia.

Patient presentation

A 5-year-old boy is brought to the emergency department by his mother because he has had difficulty walking, with frequent falls and headache. Per the mother, her son has been complaining of a constant headache for the past two weeks that seems to be worse in the morning. The mother became worried today when her son could not walk across his bedroom without losing his balance and falling. Prior to these recent events, her son had been reaching normal developmental milestones and tracked along in the 70th percentile for weight and 75th percentile for height with no previous significant medical history. He is currently up to date on his vaccinations. The mother shared that there was no injury, trauma, or recent illness.

Diagnostic findings, Part 1

On physical examination, the child appears well-developed, well-nourished, and anxious. His head is normocephalic and atraumatic. On ocular exam, pupils are equal, round, and reactive to light. Papilledema is not noted upon fundoscopic examination. His neck is supple with a normal range of motion. Neurological examination demonstrates normal visual fields, no facial asymmetry, and no sensory deficit. He is fully alert and oriented to person, place, and time. When asked to walk in a straight line, even with support, the patient quickly loses balance and needs to sit down.

Questions/discussion points, Part 1

Based on the patient's clinical presentation and neurological examination, what should be considered in the differential diagnosis?

The patient is exhibiting signs of ataxia with a loss of coordination and gait abnormality, which suggests a pathologic involvement of the cerebellum. The presence of a constant, two-week headache cannot be ignored in this clinical context. It is imperative that consideration for increased intracranial pressure is given as the diagnostic workup begins. A thorough assessment needs to include a fundoscopic exam to look for papilledema as well as imaging studies to evaluate for mass lesions or other etiologies that cause increased intracranial pressure. Increased intracranial pressure is a medical emergency that can lead to herniation, particularly if a lumbar puncture is pursued, since the sudden escape of pressure leads to herniation and death. In this patient, there is also

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concern for an infectious cause for these neurologic symptoms, such as meningitis. While this is arguably less likely given the patient's lack of fever, absence of altered mentation, and up-to-date vaccination status, it is a serious concern that must be ruled out given the patient's headache. Other potential causes for the patient's symptoms include neurologic, inflammatory, endocrine, congenital, metabolic, and environmental (toxin or drug-induced). An arteriovenous malformation could also be considered; however, these tend to be rare in the pediatric population. Given the subacute presentation of this patient's symptoms, infectious or neoplastic etiologies appear the most likely, with neoplasm being favored.

What are the central nervous system pathologies that should be considered?

An intracranial mass is the leading diagnostic etiology of the patient's symptoms. The presence of a tumor would explain the initial headaches and the later manifestation of more severe neurological deficits, namely the ataxia. Pilocytic astrocytomas, as well as other posterior fossa tumors such as ependymoma and medulloblastoma, can present with nonspecific findings such as headache, nausea, vomiting, and ataxia, and all can be seen in patients in this age group.

What should the workup include?

Immediate neuroimaging should be performed to assess for a mass lesion or other intracranial process. A computed tomography (CT) scan is a relatively inexpensive and fast imaging approach which is readily available at most hospitals and should be the first step in the patient's workup. A CT will provide the general information needed to emergently treat the patient. However, a CT scan cannot provide detailed information about the characteristics of a tumor, so a magnetic resonance imaging (MRI) scan can be used as a follow-up to provide more detailed information about a mass lesion and thereby provide guidance for surgical planning. Additionally, MRIs, even at large medical centers, may be difficult to schedule, and waiting for imaging may delay needed care for the patient. Blood work should also be ordered with a basic metabolic panel (BMP) and a complete blood count (CBC). A lumbar puncture could also be considered to measure the patient's cerebrospinal fluid; however, as stated above, this must wait until after neuroimaging reveals no mass lesion in order to prevent herniation.

What does the imaging show?

An MRI was performed. A T1 post-contrast image is shown in Fig. 1.

Diagnostic findings, Part 2

Neuroimaging findings confirm the presence of a mass lesion in the posterior fossa. CT without contrast reveals a partially cystic hyperdense mass arising in the midline from the vermis with resulting effacement of the fourth ventricle and obstructive hydrocephalus. Follow-up MRI with and without contrast confirms a large posterior fossa mass, which is T1 hypointense and enhancing as seen in Fig. 1. The mass arises from the vermis and projects into the fourth ventricle without extension into the basal cisterns. The mass is hyperintense and heterogeneous on T2 and fluid-attenuated inversion recovery (FLAIR) images. Diffusion restriction is observed on diffusion-weighted imaging (DWI), suggesting hypercellularity. BMP and CBC are normal.

Questions/discussion points, Part 2

How do the initial studies help narrow down the differential?

Basic metabolic panel and complete blood count are normal, effectively ruling out the likelihood of an infectious or inflammatory process.

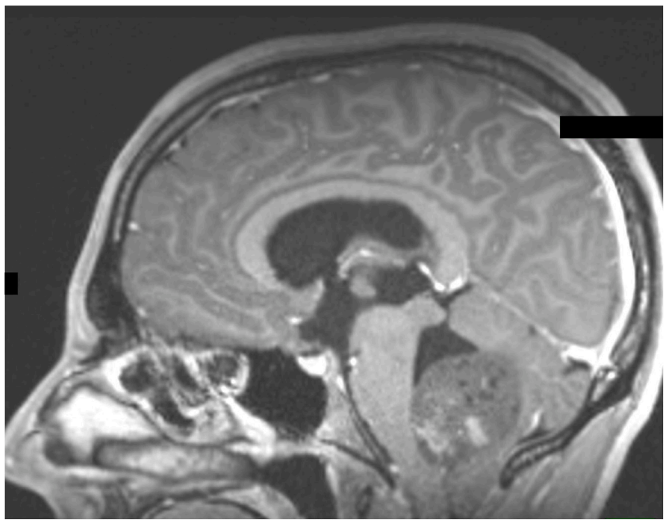

Fig. 1. T1 post-contrast MRI demonstrating large posterior fossa mass lesion causing obstruction of the 4th ventricle.

The patient's CT and MRI scans show no signs of cerebellar stroke or hemorrhage. The presence of a T1 hypointense, enhancing posterior fossa mass is diagnostic of a brain tumor. To definitively diagnose the mass, the patient should undergo resection of the tumor, or if the tumor is in a location where a full resection, called a gross total resection, is not possible, a biopsy can be pursued for a tissue diagnosis.

How do the imaging findings correlate with the patient's clinical presentation?

The cerebellar involvement in the patient's neuroimaging explains the ataxia and gait abnormalities. Compression of the 4th ventricle due to mass effect and obstructive hydrocephalus would also play a role in the patient's coordination issues and constant headache.

What are some of the common primary tumors of the central nervous system?

Primary brain tumors originate from the brain or its immediate surroundings as opposed to metastatic tumors that originate elsewhere in the body. Primary tumors rarely metastasize outside of the CNS, and their morbidity and mortality come primarily from their anatomic site and mass effect. Identification and classification depend on a variety of factors, including origin, histology, molecular features, and associated age of onset. Gliomas arise from the astrocytic, oligodendroglial, and ependymal cells in the brain. Neuronal tumors express neuronal cell markers and include gangliogliomas and neuroepithelial tumors, amongst others. Embryonal tumors are derived from neuroectodermal origin, the most common being medulloblastomas. Meningiomas are another primary CNS tumor that arises from meningothelial cells.[2]

What is the epidemiology of common pediatric brain tumors?

According to the American Cancer Society (ACS), more than 4000 brain and spinal cord tumors are diagnosed every year in children and teenagers; they account for about 25% of all childhood cancers.[3] The incidence rate has been largely unchanged at 5.67 per 100,000 person-years.[4] Common brain tumors in children include pilocytic astrocytomas, medulloblastomas, ependymomas, and craniopharyngiomas.[5] Low-grade gliomas are the most common type of brain tumor in children, making up roughly 40% of all CNS tumors in children younger than 18. Of these, pilocytic astrocytomas are the most common form, but a myriad of other subtypes exist as well.[4] Medulloblastomas are the most

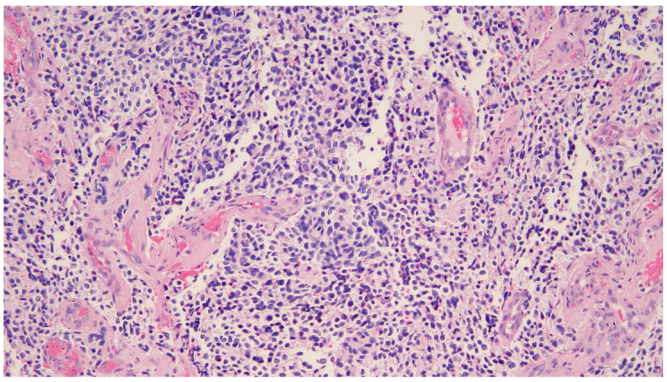

Fig. 2. Histologic section shows a densely cellular neoplasm. No distinct architectural features are present such as nodules, rosettes, or pseudorosettes. (H&E 20x).

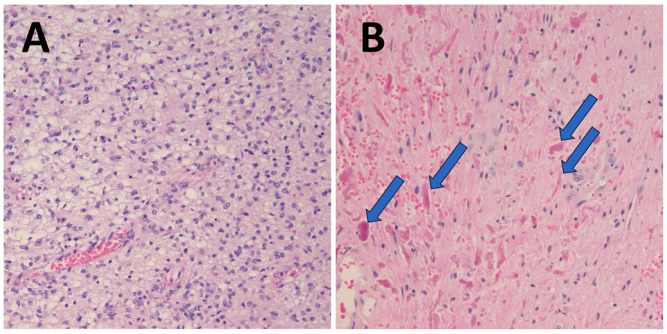

Fig. 3. Histologic sections of a pilocytic astrocytoma. Biphasic appearance with cystic areas, bland cytology, and no discernible mitotic activity (A). More compact portion of the tumor with abundant Rosenthal material present (arrows) (B). (H&E 20x).

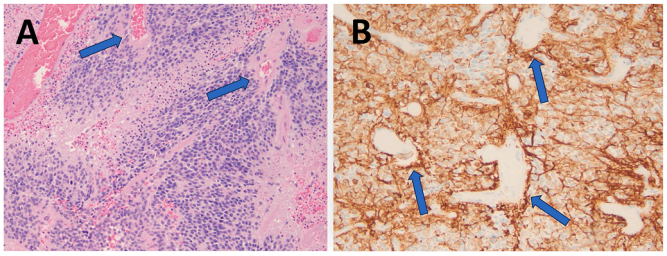

Fig. 4. Histologic sections of a posterior fossa ependymoma CNS WHO Grade 3 (20x). H&E section (A) shows perivascular pseudorosettes (arrows), highlighted on glial fibrillary acidic protein (GFAP) stain (arrows) (B).

common high-grade pediatric brain tumor and comprise 20% of all primary CNS tumors among children.[5] Most medulloblastomas occur in childhood, with a peak incidence at 5 years of age. A second smaller peak may occur in young adults 20–40 years.[6] Ependymomas also occur in children and account for approximately 10% of all childhood CNS tumors. Craniopharyngiomas account for roughly 5–10% of pediatric brain tumors and are located at the base of skull.[4]

Diagnostic findings, Part 3

The patient was taken to the operating room to resect the tumor. A sub-centimeter portion of tissue was submitted to pathology for evaluation. A photomicrograph of the permanent section is shown in Fig. 2.

Questions/discussion points, Part 3

Describe the histological findings seen in Fig. 2. How do the patient's histological findings distinguish between possible brain tumors?

Traditionally, medulloblastomas are histologically defined as highly cellular tumors with dark staining, round nuclei, and rosette formations known as Homer-Wright rosettes.[5] These are characterized by differentiated tumor cells grouped around a central region filled with neurofibrillary processes. The absence of rosettes in this case does not exclude medulloblastoma; these tumors vary in appearance. Along with some other tumors, medulloblastomas are described as small, round blue-cell tumors. Another possible pediatric brain tumor, pilocytic astrocytoma, has a microscopic morphology consisting of elongated, hair-like cell processes with cystic areas (Fig. 3). Rosenthal fibers, brightly eosinophilic structures within astrocytic processes, and eosinophilic granular bodies are often, but not always, seen in pilocytic astrocytomas. Ependymomas, another potential tumor on the differential, are histologically identified by ovoid nuclei with cytoplasmic processes forming pseudorosettes or true rosettes (Fig. 4).[6] Pseudorosettes contain a vessel at the center of the rosette. None of these findings are seen in the patient's specimen, which has a sheet-like architecture of small, round blue cells. The various tumors are derived from precursors from the astrocytic lineage (pilocytic astrocytoma), the ependymal lineage (ependymoma), and primitive neuroectodermal remnants (medulloblastoma).

What is the most likely diagnosis?

Together with the clinical and radiographic findings, the histologic features are consistent with a medulloblastoma. A medulloblastoma is a poorly differentiated neuroectodermal neoplasm that occurs in the cerebellum. Medulloblastomas are typically located in the vermis in younger children but can be found in the cerebellar hemispheres in older children and adults. Medulloblastomas are thought to arise from granule cell progenitors or multipotent progenitors from the ventricular zone. Complications include noncommunicating hydrocephalus, gait abnormalities, and dissemination through cerebrospinal fluid in “drop metastases” in the spinal canal.[6] The increased intracranial pressure from blockage of the 4th ventricle results in morning headache, nausea/vomiting, and irritability. This can develop into ataxia, frequent falls, papilledema, diplopia, nystagmus, and/or neck stiffness.

Table 1
Molecular classification of medulloblastoma highlighting immunohistochemical features and molecular alterations.

	WNT	SHH	Group 3 (NonWNT/NonSHH)	Group 4 (NonWNT/NonSHH)
Immunoprofile	Beta-catenin nuclear (+) in nuclei YAP1 (+) GAB1 (−)	Beta-catenin (−) YAP1 (+) GAB1 (−)	Beta-catenin (−) in nuclei; can be (+) in cytoplasm YAP1 (−) GAB1 (−)	Beta-catenin (−) in nuclei; can be (+) in cytoplasm YAP1 (−) GAB1 (−)
Prognostics and associated findings	Good prognosis in general	Good: MBEN Poor: TP53, MYCN, Gli2, metastatic disease	Poor: MYC, i17q, metastatic disease	Good: Chr 11 loss, Chr 17 gain Poor: Infants, metastatic disease
5-year survival[8]	>90%	70%	40%	70–80%

How are medulloblastomas categorized?

Medulloblastomas are now classified based on both histological and molecular features according to The World Health Organization (WHO) Classification of Tumors and Central Nervous System.[7] The traditional histological subgroups include classic, desmoplastic/nodular (D/N), medulloblastomas with extensive nodularity (MBEN), and large cell/anaplastic (LC/A).[4] Four molecular subgroups of medulloblastomas are defined. These include WNT-activated, SHH-activated, NonWNT/NonSHH-activated Group 3, and NonWNT/NonSHH-activated Group 4 (Table 1[8]). Different subgroups suggest that medulloblastomas are a heterogeneous disease and that medulloblastoma subgroups have distinct molecular, demographic, and clinical characteristics.[9] In practice, the workup for a medulloblastoma will include immunohistochemical analysis, which can be paired with molecular studies and methylation array studies to fully subclassify the tumor. Immunohistochemical features and other molecular markers are outlined in Table 1. Medulloblastomas that do not fit into the WNT-activated or SHH-activated categories are identified as Non-WNT/Non-SHH and are further designated as group 3 and group 4. The majority of medulloblastoma cases fall into this category, and there is considerable overlap between group 3 and group 4 on a molecular profile, leading to a spectrum consisting of 8 possible subtypes. Though delineating between the two is still a matter of debate, and immunohistochemistry does not help in identification, DNA methylation and RNA expression profiling can assist in classification and evaluating prognosis. In general, poor prognostic indicators in group 3 tumors include *MYC* amplification and metastatic disease. Group 4 tumors with chromosome 11 loss and chromosome 17 gain have a good prognosis, while those found at infancy and/or with evidence of metastasis are associated with worse outcomes.[9]

What are some of the key molecular features of other pediatric brain tumors?

Pilocytic astrocytomas are almost exclusively defined by alterations in the MAPK (mitogen-activated protein kinase) signaling pathway. The most common molecular driver by far is the *KIAA1549:BRAF* fusion, which accounts for over 80% of cases in pilocytic astrocytomas. It is highly specific and diagnostic for this tumor. Similar to medulloblastomas, ependymomas form a heterogenous group of tumors classified by histological and molecular features, as well as location. Supratentorial ependymomas are molecularly identified by the *ZFTA:RELA* fusion. The resultant fusion protein results in the pathological activation of the NF-kB signaling pathway. Posterior fossa ependymomas are further subgrouped as either Group A or Group B. The key molecular feature for Group A is the loss of H3K27 methylation, which is absent in Group B.[2]

How are brain tumors graded?

All brain tumors are assigned a grade by the WHO Classification of Tumors and Central Nervous System. This grade is based on the microscopic structure and molecular characteristics of the neoplasm and indicates how aggressive the tumor is and how it will typically respond to treatment. The concept of grading in CNS neoplasms continues to evolve. Not every tumor type has all grades represented, and conversely, not all tumor types are restricted to a single grade. In general, Grade 1 and Grade 2 tumors are referred to as low grade, while Grade 3 and Grade 4 tumors are referred to as high grade. As a rule, all medulloblastomas are classified as grade 4.[7] In contrast, the other tumors that are common in the posterior fossa in children tend to be low grade. Pilocytic astrocytomas are CNS WHO Grade 1, and posterior fossa ependymomas are Grade 2 or Grade 3, straddling the conceptual low vs high grade divide.

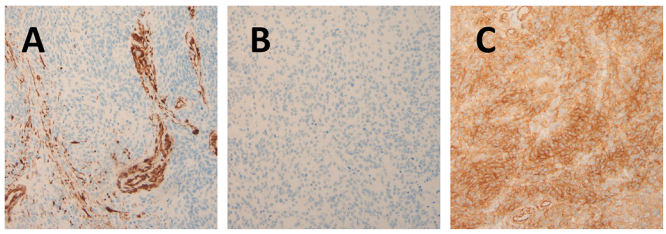

Fig. 5. Immunohistochemical stains (20x). YAP1 (A) shows negative staining in tumor cells, GAB1 (B) shows negative staining, and Beta-catenin (C) shows positive cytoplasmic staining. This staining pattern is characteristic of Non-WNT/Non-SHH medulloblastomas.

What is the final diagnosis in this case?

This patient had a tumor that showed positive cytoplasmic beta-catenin staining, and that was negative for YAP1 and GAB1 (Fig. 5). Methylation analysis further sub-classified the tumor as a Non-WNT/Non-SHH Group 3 tumor.

Overall prognosis and treatment options for children with medulloblastomas

The overall long-term survival rate in patients with medulloblastoma is 70%, but unfortunately with significant neurocognitive impairment.[5] High-risk features include age younger than three years at diagnosis, residual tumor after resection, anaplastic histology, and metastatic disease, and these features are associated with poor outcomes. Children with localized disease have a greater than 80% 5-year progression-free survival (PFS) compared to less than 40% 5-year PFS in disseminated disease.[5] Any treatment plan for a patient with medulloblastoma should involve consultation with a neurosurgeon, oncologist, and radiation oncologist. The treatment for medulloblastoma is multidisciplinary and involves options such as maximal surgical resection, craniospinal irradiation, and chemotherapy. An alternative treatment for patients younger than three years is to avoid radiation and use high-dose chemotherapy with autologous stem cell rescue.[5] Regardless of the treatment modality, patients and their families need to be informed of the risk of lifelong neurocognitive impairment resulting from both complications of the tumor itself as well as necessary therapeutic interventions.

Teaching points

- Brain tumors account for approximately one-quarter of tumors among children and adolescents.
- Evaluation for papilledema is critical since when it is identified, it reflects a marked increase in intracranial pressure and thereby identifies a patient at risk for herniation and death, constituting a medical emergency.
- Medulloblastomas are the most common malignant primary brain tumors among children, while other posterior fossa brain tumors such as pilocytic astrocytomas and ependymomas are also common CNS tumors in young children.
- Pilocytic astrocytomas are low-grade lesions (CNS WHO Grade 1) that have a bland histologic appearance and often contain Rosenthal material and/or eosinophilic granular bodies. These tumors derive from astrocytic precursors.
- Ependymomas are another tumor seen in children, which can be located in the posterior fossa. Ependymomas have a characteristic rosette appearance histologically. Ependymomas are graded as CNS WHO Grade 2 or 3 lesions based on histologic features.
- Medulloblastomas are traditionally categorized by their histological features into classic, desmoplastic/nodular (D/N), medulloblastomas with extensive nodularity (MBEN), and large cell/anaplastic (LC/A).

- Medulloblastomas are currently categorized on their molecular genetic profiles into four molecular subgroups: WNT-activated, SHH-activated, non-WNT/non-SHH group 3, and non-WNT/non-SHH group 4.
- The overall long-term survival rate of patients with medulloblastomas is variable, depending on the genetic and histologic features of the tumor.
- Potential complications of resection, radiation therapy, and chemotherapy at a young age include neurocognitive impairment (intellectual function, executive function, attention, processing speed, memory, fine motor control, etc.) and secondary neoplasms, including gliomas and other neoplasms.

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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