**CNS/Brain Tumors**

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1. A 9-year-old boy presents to the emergency department with emesis and headache of 3 weeks’ duration. MRI reveals a large heterogeneous mass in the posterior fossa. He undergoes a resection, and the pathology is most consistent with a classic medulloblastoma. There are no signs of residual tumor on postoperative MRI. The molecular evaluation reveals a non-Wingless and non–Sonic Hedgehog medulloblastoma most consistent with a group 3 or group 4 tumor.

In addition to these findings, which of the following is necessary to determine the best treatment strategy?

A. Serum and CSF AFP and beta-HCG

B. Circulating tumor DNA levels

C. A full spine MRI and lumbar CSF cytology evaluation

D. Ventricular fluid CSF cytology

E. PET scan

**Explanation**

Although molecular classification is slowly becoming part of prognostication and treatment paradigms for medulloblastoma, the most accepted and studied risk groups are standard- and high-risk medulloblastoma. In addition to histology (classic, desmoplastic, extremely nodular, and anaplastic/large cell), the other characteristics that define risk group are age, amount of residual disease, and metastases. This child’s age, lack of residual disease, and classic histology place him in a standard risk group. Both lumbar CSF cytology and a full spine MRI are necessary to evaluate for metastatic disease. Spinal MRI should be done preoperatively or 10 to 14 days postoperatively to avoid postoperative changes that can make interpretation difficult. Lumbar CSF cytology also should be done 10 to 14 days postoperatively. Metastatic disease would increase the patient’s risk level to high and change treatment. Medulloblastoma does not secrete tumor markers. Ventricular fluid is not universally accepted or performed as part of staging. Circulating tumor DNA currently is not part of medulloblastoma evaluation. PET scans typically are not performed or useful. Medulloblastoma metastases typically are confined to the brain and spine.

2. A 20-month-old girl presents with persistent emesis and increased sleepiness. Brain MRI reveals a posterior fossa mass and associated hydrocephalus. She undergoes a complete resection of the mass. While awaiting the final pathology, the parents ask about high-dose chemotherapy and autologous hematopoietic stem cell rescue treatment approaches.

For which of the following diagnoses would this treatment be the most widely accepted and successful strategy for this child?

A. Low-grade glioma

B. Choroid plexus papilloma

C. Ependymoma

D. Medulloblastoma

**Explanation**

The use of high-dose chemotherapy and autologous hematopoietic cell rescue has been tested in many infant brain tumors in an effort to reduce, delay, or avoid radiotherapy, given the late effects associated with craniospinal radiation and the developing infant brain (ie, neurocognitive dysfunction, ototoxicity, endocrine dysfunction, secondary malignancy). Medulloblastoma is among the diagnoses listed as having the most evidence and success with this approach. Most practitioners would use this approach for a child younger than 3 years with a diagnosis of medulloblastoma. Although this approach has been tested in ependymoma, it is not universally accepted, and most practitioners would treat a 20-month-old with a posterior fossa ependymoma with a resection followed by focal radiotherapy. In fact, most current studies use focal radiation of the posterior fossa down to age 12 months for children with ependymoma. Neither choroid plexus papilloma or low-grade glioma is treated with this approach.

3. An 11-year-old girl presents with ataxia, headaches and emesis that has worsened over the last several weeks. CT in the emergency department reveals a large mass in the cerebellum with associated hydrocephalus. After she is stabilized, the patient undergoes a complete resection of the mass that preliminarily is most consistent with a classic medulloblastoma. Molecular testing has been sent, but the results are not yet available.

Which of the following molecular aberrations would be most consistent with a medulloblastoma with excellent survival?

A. Wingless (WNT) pathway abnormality

B. Loss-of-function alterations in neurofibromin 1

C. BRAFv600e mutation

D. Tuberous sclerosis complex-1 (TSC-1) abnormality

E. Sonic Hedgehog (SHH)

**Explanation**

Although classifications are constantly evolving as new insights are obtained, most researchers and clinicians subgroup medulloblastoma into four broad molecular subgroups: WNT, SHH, Group 3, and Group 4. The WNT subgroup is the most rare and typically occurs in children between 10 and 12 years old, has a classic histology, and, based on historic data and developing prospective data, has excellent survival outcomes (more than 95% in most series). None of the other answer choices is associated with medulloblastoma. Loss-of-function alterations in neurofibromin 1 are associated with a diagnosis of neurofibromatosis type 1 and low-grade glioma development. BRAFv600e aberrations, such as BRAF V600E mutation and the BRAF KIAA-1549 fusion, are common in pilocytic astrocytomas, the most common low-grade glioma in children. TSC-1 abnormality is seen in children with tuberous sclerosis who have an increased risk of developing subependymal giant cell astrocytomas. Although SHH is a subgroup of medulloblastoma, it has variable outcome depending on other factors, such as the presence or absence of p53.

4. A 22-month-old girl presents with 6 months of failure to thrive despite eating normally. She currently is at less than 3% for weight on the growth curve, and 8 months ago she was at the 50%. She has had an extensive GI, endocrinological, and genetic evaluation, but no etiology has been identified. Over the last week, she has developed new persistent emesis. MRI of her brain reveals a large mass in the hypothalamus with associated hydrocephalus. A third ventriculostomy and biopsy are performed.

This history is most consistent with what pathologic diagnosis?

A. Ependymoma

B. Pilocytic astrocytoma

C. Medulloblastoma

D. Thalamic cyst

**Explanation**

This vignette is a classic case of diencephalic syndrome. This syndrome most commonly is seen in infants and young children. It is characterized by failure to thrive and severe emaciation despite normal or only slightly decreased intake. It also sometimes presents with hyperactivity and euphoria. It can go undiagnosed for many months because typically it does not initially present with the classic findings of obstructive hydrocephalus such as headaches and emesis. Although other histologies have been described, it is most commonly caused by a low-grade glioma such as a pilocytic astrocytoma in the hypothalamic region. A complete and thorough understanding of the pathophysiology of these associated symptoms has not been achieved. Typically these patients are treated with low-grade glioma chemotherapy such as carboplatin/vincristine. Most commonly the failure to thrive improves with treatment. It should be noted that this is a very rare cause of failure to thrive, but if all other etiologies have been eliminated, one should at least consider brain imaging.

5. A 6-year-old boy presents with a 6-month history of “clumsiness.” Initially his family thought it was due to him needing glasses, but it has persisted and slightly worsened over the last month despite a new eyeglass prescription. Over the last 2 days he has complained of headaches and developed some right-handed weakness. Outpatient MRI of his brain reveals a mass in the left frontal-parietal region of the brain with very mild associated hydrocephalus. He undergoes a resection of the mass that is consistent with a pilocytic astrocytoma. Postoperative imaging reveals a gross total resection without any evidence of residual disease.

What is the best postoperative treatment course for this patient?

A. Craniospinal radiation

B. High-dose chemotherapy with autologous hematopoietic cell rescue

C. Observation with regularly scheduled surveillance imaging

D. A combination of low-grade chemotherapy followed by focal radiotherapy

**Explanation**

For children with a completely resected low-grade glioma (LGG) such as pilocytic astrocytoma, the most accepted treatment paradigm is observation alone because both progression-free and overall survival after a gross total resection are excellent (greater than 90%). For children with LGG and residual disease after surgery or associated symptoms such as vision dysfunction (as seen in optic pathway LGG), the usual first-line treatment is LGG chemotherapy alone.

6. A 6-year-old boy presents with a 6-month history of “clumsiness.” Initially his family thought it was due to him needing glasses, but it has persisted and slightly worsened over the last month despite a new eyeglass prescription. Over the last 2 days he has complained of headaches and developed some right-handed weakness. Outpatient MRI of his brain reveals a mass in the left frontal-parietal region of the brain with very mild associated hydrocephalus. He undergoes a resection of the mass that is consistent with a pilocytic astrocytoma. Postoperative imaging reveals a gross total resection without any evidence of residual disease.

If this patient’s tumor is sent for molecular testing, which of the following is the most likely abnormality to be found?

A. Aberrations in the MAPK pathway such as a BRAF fusion

B. Sonic Hedgehog (SHH) abnormalities

C. Tuberous sclerosis complex-2 (TSC-2) abnormality

D. TP53 mutation

**Explanation**

Over the last decade, it has become understood that the most common molecular abnormalities in pediatric low-grade glioma are abnormalities of the MAPK pathway. The most common specific abnormality is the BRAFKIAA1549 fusion, which is estimated to be present in more than 60% of all pilocytic astrocytomas. SHH is associated with medulloblastoma; TSC-2 is associated with tuberous sclerosis and subependymal giant cell astrocytomas and dysregulates the mTOR pathway. In fact, if resection is not feasible or safe, a first-line therapy is the use of mTOR inhibition, which has been very effective. In CNS tumors, TP53 abnormalities are most commonly seen in high-grade gliomas and medulloblastomas. Germline mutations of TP53 are seen in Li-Fraumeni, a tumor predisposition syndrome.

7. A 6-year-old boy with neurofibromatosis type 1 (NF-1) is noted to have decreasing visual acuity on serial eye exams. Recent MRI of his brain and orbits reveals slight progression of a known optic chiasm mass, most consistent with an optic pathway glioma.

If the visual acuity worsening is verified on serial exams, what is the best next treatment option?

A. Initiation of low-grade glioma (LGG) chemotherapy

B. Focal radiotherapy

C. Complete resection of the mass

D. Laser therapy to the blood supply supplying the tumor

**Explanation**

Children with NF-1 have about a 15% to 20% risk of developing LGG, most commonly in the optic pathway. These tumors are often indolent and do not necessitate any therapy at all. However, most would agree that, when visual acuity is affected by the tumor, treatment is indicated to prevent further vision decline and possibly improve vision in some patients. The best-known current therapy is LGG chemotherapy. Common first-line LGG chemotherapies are combinations of carboplatin/vincristine, vinblastine alone, or a combination of thioguanine, procarbazine, CCNU, and vincristine (TPCV). TPCV often is avoided for patients with NF-1 because the risks of secondary malignancy and alkylator use are concerning. Radiotherapy is avoided for children with NF-1 because of the high risk of secondary malignancy. A complete resection of a chiasmatic LGG would be very difficult and probably lead to loss of vision. Laser therapy is a technique used in retinoblastoma, not for LGG of the optic pathway.

8. A 14-year-old boy presents with a 2-week history of worsening headaches and left-sided weakness. MRI reveals a 2-cm × 2-cm mass in the right cerebrum with associated mild midline shift. A complete resection is performed, and the pathology is consistent with a World Health Organization grade IV high-grade glioma (HGG).

Which of the following is the most likely survival outcome for a 14-year-old patient with HGG treated with a combination of focal radiotherapy and HGG chemotherapy?

A. 5-year overall survival of 50%

B. 5-year overall survival of 90%

C. No survivals have been reported

D. 5-year survival of 15% to 20%

**Explanation**

The survival rates for children with HGG are dismal, with most prospective and historic reports showing 15% to 20% overall survival at 5 years. However, there are some survivors, but we are only just beginning to understand the molecular features that distinguish those patients who survive from those who do not.

9. A 14-year-old boy presents with a 2-week history of worsening headaches and left-sided weakness. MRI reveals a 2-cm × 2-cm mass in the right cerebrum with associated mild midline shift. A complete resection is performed, and the pathology is consistent with a World Health Organization grade IV high-grade glioma (HGG). After meeting with the patient’s family, you discover that his maternal uncle died of a “brain tumor” at age 40, his maternal first cousin developed an undifferentiated sarcoma in her 20s, and his mother was just diagnosed with an adrenocortical carcinoma.

Which of the following molecular findings would be most consistent with this family’s history?

A. A germline mutation in TP53

B. Loss-of-function alterations in neurofibromin 1

C. Mutations in the NF-2 gene

D. No molecular abnormality

**Explanation**

This family history, with multiple high-grade gliomas (adrenocortical carcinoma and sarcomas), is most consistent with a diagnosis of Li-Fraumeni syndrome, a cancer predisposition syndrome characterized by a germline mutation in TP53, a tumor suppressor gene. Loss-of-function alterations in neurofibromin 1 are seen in patients with NF-1 and are associated with low-grade glioma. Mutations in NF-2 are associated with a diagnosis of neurofibromatosis type 2, and these patients are at risk for developing acoustic schwannomas and ependymomas. It would be much less likely to *not* find a molecular abnormality in a history this strong for cancers, especially in young patients.

10. A 6-year-old boy presents with emesis for 3 weeks and new ataxia over the last 2 days. MRI reveals a large posterior fossa mass with associated hydrocephalus. He undergoes a tumor resection, and the pathology is most consistent with an ependymoma. Postoperative imaging reveals no residual disease, and there are no signs of metastases on spine MRI or lumbar CSF cytology.

What is the most accepted postoperative treatment approach?

A. Focal radiotherapy

B. High-dose chemotherapy with hematopoietic cell rescue

C. Craniospinal radiation followed by 6 months of dose-intense chemotherapy

D. Intrathecal chemotherapy

E. Observation

**Explanation**

The best known treatment for ependymoma is a gross total resection followed by focal radiotherapy. Some practitioners may use a radiation-delaying approach in very young children, but in a 6-year-old, focal radiotherapy is the most widely accepted postsurgical treatment approach with the best-reported outcomes among the answer choices listed. Observation is not universally accepted for a 6-year-old child with a posterior fossa ependymoma. There are ongoing studies evaluating observation alone for patients with supratentorial ependymoma, but this is controversial.

11. A 14-year-old boy is admitted to the hospital with a 3-month history of increased thirst and urination. Laboratory results evaluating his serum and urine reveal a diagnosis consistent with diabetes insipidus (DI). He initiates treatment with desmopressin with subsequent improvement. Over the next several months, however, he develops worsening headaches and emesis. MRI of his brain reveals 2 distinct masses with associated obstructive hydrocephalus, one in the suprasellar region and one in the pineal region.

Which of the following is the most likely histologic diagnosis?

A. Metastatic medulloblastoma

B. Metastatic ependymoma

C. Langerhans cell histiocytosis (LCH)

D. Bifocal CNS germ cell tumor (GCT)

**Explanation**

This prolonged history with endocrine symptoms (DI) is a common finding in patients with CNS GCTs in the suprasellar/pituitary region. The concomitant presence of a mass in the pineal region is known as a bifocal or doublet lesion. This constellation of findings is most consistent with a CNS GCT, probably a germinoma. Medulloblastoma is defined by its presence in the posterior fossa, and therefore the locations of his masses exclude option A. It would be very unusual to have a metastatic ependymoma with this distinct pattern on MRI, especially when the patient presents with DI. Finally, although LCH can present with DI, the presence of a concomitant pineal mass makes this option very unlikely.

12. An 8-year-old girl presents with increased urination and declining vision. Imaging reveals a large suprasellar/pituitary mass with compression of the optic chiasm.

Which of the following findings would be most consistent with a diagnosis of a CNS nongerminomatous germ cell tumor (NGGCT)?

A. A serum AFP greater than 1000 IU/L (normal is less than 10 IU/L)

B. Lumbar CSF cytology positive for tumor cells

C. Normal levels of serum and CSF beta-HCG

D. Elevated carcinoembryonic antigen (CEA) levels

**Explanation**

CNS germ cell tumors (GCTs) are rare CNS tumors that sometimes can be diagnosed without tissue. There are two main categories of CNS GCT: germinomas and NGGCTs. The NGGCTs often secrete tumor markers (AFP and beta-HCG) that can be quantified in serum and CSF, but this alone does not distinguish the two categories. The most common tumor locations for all CNS GCTs are the suprasellar and pineal regions. CNS GCTs in the suprasellar region often present with diabetes insipidus and vision difficulties. High levels of AFP and beta-HCG are most indicative of NGGCT. With a mass in the suprasellar region and elevated AFP, this scenario is most consistent with CNS NGGCT. Tumor cells in the CSF cannot confirm a diagnosis. Although normal levels of beta-HCG do not exclude the diagnosis of CNS NGGCT, they do not confirm it, ether. Tissue would be necessary to confirm a diagnosis of CNS GCT in the presence of normal markers. CEA is not typically evaluated in pediatric CNS GCT and does not confirm a diagnosis.

13. A 3-month-old boy presents with rapidly increasing head circumference noted by his pediatrician. Imaging reveals a large mass in the posterior fossa. The infant is also noted to have mild hematuria, and a renal ultrasound is performed revealing a large left-sided renal mass.

Which of the following abnormalities is most consistent with this pattern of findings?

A. BRAFv600e mutation in the tumors

B. Diagnosis of neurofibromatosis type 1 (NF-1)

C. Diagnosis of neurofibromatosis type 2 (NF-2)

D. Germline mutation in SMARCB1/INI-1

**Explanation**

This scenario is most consistent with an atypical teratoid rhabdoid tumor (AT/RT) in the brain. The presentation before age 12 months and the concomitant renal mass are most suggestive of a germline mutation. AT/RT and malignant rhabdoid tumors are characterized by abnormalities in SMARCB1/INI-1, which often are pathognomonic. Germline mutations in SMARCB1/INI-1 predispose patients and families to rhabdoid tumors and schwannomatosis. BRAFv600e is most commonly seen in low-grade glioma (LGG) in children. NF-1 predisposes to LGG, especially of the optic pathway. NF-2 predisposes to acoustic schwannomas and ependymomas.

14. A 5-year-old boy presents with a 3-week history of his right eye “not moving to the right side.” The remainder of his neurologic exam is normal with the exception of a weak gag. MRI of the brain reveals a diffusely infiltrative mass in the pons.

If treated with focal radiotherapy, what is the expected survival outcome for this patient?

A. Most children succumb to this disease within 10 to 12 months of diagnosis.

B. 5-year overall survival is approximately 50%.

C. 5-year overall survival is close to 95%.

D. A prognosis cannot be made without a tissue diagnosis.

**Explanation**

This child has a diffuse intrinsic pontine glioma (DIPG). These patients commonly present with a short duration of cranial nerve findings (such as weak gag, lateral rectus palsy, and hoarse voice). Characteristic imaging typically reveals a large, diffuse infiltrative mass with its epicenter in the pons. Although tissue biopsy for molecular testing has become more common, it is still not required for a diagnosis. The diagnosis can be made by MRI alone. Recent advancements over the last decade have revealed a characteristic histone mutation in DIPG and other midline high-grade gliomas in H3 K27M. Outcomes are almost universally poor, with a median survival of 10 to 12 months in most series.

15. A 22-year-old man with a history of a medulloblastoma treated when he was 12 years old with a combination of craniospinal radiation and chemotherapy presents with 4 weeks of worsening headaches. Imaging reveals a large mass in his right thalamus.

What is the most likely diagnosis?

A. Recurrent medulloblastoma

B. Radiation-induced high-grade glioma (HGG)

C. Atypical teratoid rhabdoid tumor (AT/RT)

D. CNS lymphoma

**Explanation**

This question highlights the risk of late effects of CNS tumor therapy. A child treated with CS radiation therapy is at risk of developing a secondary malignancy. The time frame for a radiation-induced secondary HGG is typically 8 to 10 years after initial therapy. Most radiation-induced malignancies in the CNS are either HGG or meningioma. Recurrent medulloblastoma would be very unlikely 10 years after therapy. Most medulloblastoma recurrences occur within the first 2 years after therapy, although rare recurrences can happen beyond this timeframe. AT/RT is unlikely given the history and the age of the patient. Finally, CNS lymphoma is most commonly seen in patients with immunodeficiencies, but medulloblastoma treatment should not cause a significant or prolonged weakened immune system in survivors.