

REVIEW ARTICLE

Pediatric primary central nervous system melanoma: A current review of diagnosis and emerging therapies

Adriene Pavék*, Justin Lyon, Dillon Stevens, Annabelle Huntsman, and Grace Bradford

School of Medicine, University of Utah, Salt Lake City, Utah, United States of America

Abstract

Pediatric primary central nervous system (CNS) melanoma is a rare and aggressive malignancy, often arising in association with neurocutaneous melanosis but also reported in sporadic cases. Children typically present with signs of increased intracranial pressure, seizures, or focal neurological deficits. Median age at diagnosis is 2.8–3.7 years, that is, under four years, although cases spanning infancy to early adolescence have been reported. Median survival rarely exceeds one year despite multimodal therapy. Melanogenesis may directly influence tumor behavior, as intermediates generate oxidative stress and contribute to radioresistance and variable immunotherapy response. Pediatric CNS melanomas frequently harbor activating mutations in *GNAQ*, *GNA11*, or *NRAS*, which drive mitogen-activated protein kinase and phosphoinositide 3-kinase–AKT signaling to promote proliferation and confer resistance to apoptosis. Additional alterations, such as *CDKN2A* and *TP53* loss, may be linked to accelerated progression. Unlike cutaneous melanoma, *BRAF* mutations are uncommon. Maximal surgical resection remains the cornerstone of therapy, offering the greatest survival benefit. Adjuvant radiotherapy or chemoradiation provides limited efficacy due to the intrinsic radioresistance of melanoma cells and the restricted delivery of therapeutic agents across the blood–brain barrier (BBB). Among chemotherapies, temozolomide has modest CNS activity, whereas checkpoint inhibitors and targeted agents have shown only transient responses in pediatric case reports. These therapeutic challenges underscore the urgent need for novel strategies that can overcome BBB-related barriers to drug delivery and melanin-mediated resistance. Advances in molecular profiling and targeted drug development, coupled with education for early diagnosis, may improve survival in patients with this aggressive disease.

***Corresponding author:**Adriene Pavék
(adriene.pavek@hsc.utah.edu)

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1. Introduction

Melanoma is a malignant tumor most discussed in the context of its cutaneous form, often associated with risk factors such as prolonged lifetime sun exposure and genetic predisposition.¹ Originating from melanocytes, the pigment-producing cells of the skin,

melanoma can also present in other areas of the body, including the eyes, mucous membranes, and leptomeninges (membranes covering the brain and spinal cord). Melanin pigment, known for its essential role in protecting against harmful ultraviolet (UV) radiation, is produced through the enzymatic conversion of *L*-tyrosine to dopaquinone.² A subsequent cascade leads to the formation of the two main melanin polymers, eumelanin and pheomelanin. Eumelanin, a potent antioxidant, provides photoprotection, while pheomelanin, its chemically less stable counterpart, can promote a mutagenic environment under UV exposure. Factors that influence the biosynthesis of melanin include sun exposure as well as hormonal and non-hormonal regulators at the tissue and cellular levels.³ An understanding of these factors is essential for discussion of melanoma development and progression, as melanin synthesis is frequently deregulated, leading to pro-tumorigenic conditions that promote growth, invasion, and oxidative stress.⁴ Furthermore, melanin plays a dual role, contributing both to protection against skin cancers and, under certain conditions, to their development. This paradox is partly related to the requirement for pigment-producing melanocytes in melanogenesis, despite their role in UV protection.⁵ Melanogenesis has been thought to contribute to the development of malignancy, given the presence of highly reactive intermediates that can contribute to cytotoxic and mutagenic effects.⁴ These intermediates have secondary metabolic sequelae that activate hypoxia-inducible factor-1 alpha, which can further modulate the tumor microenvironment, contributing to melanoma progression and resistance to biologic therapies.⁴

The embryonic origin of melanoma is also thought to contribute to its dualistic features.⁶ Melanoma arises from neural crest-derived precursor cells that act transiently during development, generating multipotent cells that migrate to multiple sites and differentiate according to the physical and metabolic demands of the target organ.⁴ As a result, this feature is thought to contribute to the ability of melanomas to migrate, settle within niches, and progress rapidly.⁴

While cutaneous melanoma is the most prevalent form, it is important to delineate the differences in molecular characteristics between intracranial melanocytic neoplasms and their cutaneous counterparts. As discussed above, melanin pigmentation and melanocyte activity are regulated by a complex interplay of hormonal and molecular mechanisms.^{4,7} Examples of these mechanisms include actions from melanocortin, corticosteroids, and biogenic amines.⁷ For example, alpha-melanocyte-stimulating hormone and adrenocorticotrophic hormone play a role in stimulating melanogenesis through the melanocortin 1 receptor. Enzymatic cascades occurring secondary to

intracellular elevations of cAMP promote the expression of the key enzyme in melanin synthesis—tyrosinase.^{4,7,8} As a result, the relationship between melanocyte activity and sun exposure has been well documented as an etiologic factor for the development of cutaneous melanoma.^{2,3,4,7,8} In contrast, intracranial neoplasms exhibit a distinct molecular and genetic background, lacking the UV-induced mutational signatures often seen in cutaneous melanoma. The molecular alterations include mutations in *GNAQ*, *GNA11*, *PLCB4*, or *CYSLTR2*.⁹ The presence of these tumors in sun-protected regions such as the leptomeninges suggests an alternative pathophysiologic process that may be associated with neuroendocrine and developmental factors rather than environmental triggers. As a result, it is important to consider the anatomical and embryological context of intracranial melanomas when evaluating disease progression and prospective therapeutic targets.¹⁰ While subtypes of melanoma may share some similar features (metastatic potential, cell origin, and histopathology), this review focuses on a rare subtype of pediatric central nervous system (CNS) melanoma. A comparison between the two is summarized in [Table 1](#).

Pediatric CNS melanoma is an uncommon but notably aggressive form of melanoma. It can present in two forms: as a primary CNS melanoma originating from melanocytes within the leptomeningeal or brain parenchyma, without evidence of extracranial disease, or in the setting of neurocutaneous melanocytosis, particularly in children with multiple, large congenital melanocytic nevi (CMN), frequently in the context of *NRAS* mutations.¹³ This subtype is further categorized as primary or secondary based on tumor origin. Primary CNS melanoma refers to tumors that arise in melanocytes housed within the CNS. In contrast, secondary CNS melanoma is defined by systemic melanoma that has crossed the blood–brain barrier (BBB) and metastasized to this area of the body.¹⁴ Given that the location of these tumors often lies within the confined space of the skull, presenting clinical features are associated with increased intracranial pressure, such as headaches and seizures, as well as focal neurologic deficits and hydrocephalus.¹⁵ Although the pathogenesis has not been fully elucidated, the importance of adequate education surrounding this condition is imperative due to the cancer's highly aggressive biological behavior and distinct presentation, differentiating itself from other types of melanomas.¹¹ Furthermore, pediatric CNS melanomas are identified by distinct genetic mutations (*NRAS*) compared to adult forms, which have diagnostic and prognostic implications.¹⁴ Given the notably poor prognosis, it is essential that clinicians have appropriate training and clinical skills to evaluate and diagnose patients with this condition to match them with the most effective

Table 1. Comparison of cutaneous melanoma and pediatric primary central nervous system (CNS) melanoma^{11,12}

Feature	Cutaneous melanoma all ages	Pediatric primary CNS melanoma
Location	Skin, particularly sun-exposed areas like the back, face, and upper back.	CNS, including the posterior cranial fossa, spinal cord, and Meckel's cave.
Incidence	More common than primary CNS melanoma.	Rare, <1% of all melanomas.
Risk factors	Sun exposure, fair skin, family history.	Limited understanding, but may involve neurocutaneous melanosis or other genetic factors.
Clinical presentation	Pigmented brown or black macule or nodule, sometimes ulcerated, with amelanotic lesions also possible.	May present with signs of raised intracranial pressure, focal neurological symptoms, seizures, or subarachnoid hemorrhage. Spinal tumors may cause back pain, weakness, or incontinence.
Diagnosis	Histopathological analysis of a biopsy.	Requires exclusion of metastatic melanoma from other sites.
Prognosis	80% 5-year survival	Mean survival time is 0.4 years in neurocutaneous melanocytosis
Incidence	Increasing	Stable
Median age at diagnosis	55	2.8–3.7
Staging scheme	UICC/American Joint Committee on Cancer and TNM	WHO-defined CNS classification
Treatment	Surgery (excision), possibly including sentinel lymph node biopsy.	Surgery, radiation therapy, targeted therapy, immunotherapy, and chemotherapy, with limited efficacy.
Molecular features	<i>BRAF</i> or <i>NRAS</i> (superficial spreading and nodular melanomas) mutations	Unique molecular alterations, including <i>GNAQ</i> or <i>GNA11</i> mutations in adults, and <i>NRAS</i> mutations in children with neurocutaneous melanosis.

Abbreviations: UICC: Union for International Cancer Control; TNM: Tumor, node, and metastasis; WHO: World Health Organization.

evidence-based treatment guidelines to promote optimal patient outcomes and minimize harmful side effects. As a result, patients with high suspicion for pediatric CNS melanoma should be evaluated with a thorough neurologic examination, detailed family history for neurocutaneous syndromes, and prompt radiological (contrast-enhanced magnetic resonance imaging [MRI]) and histopathological (S100, human melanoma black [HMB-45], and Melan-A) assessment.¹⁶ Moreover, each patient interaction provides an additional opportunity to drive research innovations that may lead to the discovery of novel therapeutic targets. A clear understanding of the natural course of these tumors provides a steadfast foundation for healthcare professionals to offer education, support, and realistic expectations to patients' families, helping them to navigate the complexities and uncertainties of this challenging diagnosis.

In summary, this review aims to provide a comprehensive and current overview of the literature on primary CNS melanoma in the pediatric population.

2. Epidemiology

Pediatric CNS melanoma, as discussed previously, is an extremely rare subtype of melanoma often associated with congenital conditions, specifically, neurocutaneous melanocytosis. Due to the scarcity of cases that have been reported, limited data currently exist in relation to annual prevalence, incidence, and geographic distributions. However, estimates have been elucidated from population

studies (age ≤ 19 years), identifying 84 cases of primary CNS melanoma between 1973 and 2015 with an age-adjusted incidence rate for all ages of 0.52/10,000,000 person-years.¹⁷ The median age at diagnosis ranges 2.8–3.7 years, though cases spanning infancy to early adolescence have also been reported.^{18,19} Pediatric cases have been shown to be more aggressive, leading to rapid progression after diagnosis and poor prognosis. Current data have shown a median survival averaging less than one year, with no cases reported beyond one year after diagnosis, despite the use of evidence-based multimodal therapy.^{18,19} Past studies have not been able to identify a sex predilection or determine risk factors associated with a higher likelihood of intracranial versus spinal involvement.¹⁸ Due to the presence of only isolated cases occurring sporadically worldwide (<100 cases), the limited scope and foundational knowledge of this condition pose significant challenges for healthcare providers. This is mainly in the context of leptomeningeal dissemination, which commonly occurs by the time the patient presents with features leading to diagnosis.¹⁹ As research continues to investigate therapeutic targets and outline the pathophysiology, the National Comprehensive Cancer Network has published data emphasizing the differences in pediatric CNS tumors vs. adult CNS tumors, both histologically and when examining molecular profiles.²⁰

Neurocutaneous melanocytosis has become a prominent risk factor, with clinical features including large or multiple CMN dispersed across the trunk, head,

and neck.²¹ Neurological manifestations vary based on the extent of disease and invasion into the CNS, but may include signs of elevated intracranial pressure, cranial nerve palsies, developmental delay, or motor/sensory deficits.^{21,22} Risk stratification for CNS involvement can be guided based on the number of satellite nevi and the size/extent of CMN distribution.²² Furthermore, this condition is molecularly driven by *NRAS* gene mutations, specifically postzygotic activating mutations in codon 61, resulting in somatic mosaicism.²¹ These mutations have been strongly implicated in the pathogenesis of pediatric CNS melanoma, largely because they result in constitutive activation of the RAS/mitogen-activated protein kinase (MAPK) pathway, promoting proliferation of melanocytes in both the skin and CNS.^{23–26} These mutations have been found in most pediatric CNS melanomas, accounting for 75–88% of cases where molecular studies have been conducted.^{18,25} As shown here, the use of molecular profiling technologies such as next-generation sequencing, immunohistochemistry (IHC), fluorescent *in situ* hybridization, and quantitative polymerase chain reaction has become an essential tool in guiding medical decision-making and the indication for targeted therapies such as mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors, although curative treatment has yet to be established.^{18,23}

3. Pathogenesis

The pathophysiology of pediatric primary CNS melanoma is complex and poorly understood. While metastatic CNS melanoma typically arises from a cutaneous (epidermal) primary lesion, primary CNS melanoma is unique in that it originates from the leptomeninges and rarely CNS parenchyma, in the absence of an extracranial primary lesion.^{27,28} These pediatric cases often present in association with a neurocutaneous syndrome, such as neurocutaneous melanosis, but sporadic cases are also documented in the literature.^{29,30} This dual presentation of pediatric melanoma, with syndrome associations or sporadic cases, further illustrates the complex etiology of this disease.

Meninges refer to the three membranes surrounding the CNS parenchyma: The dura mater, the arachnoid mater, and the pia mater. The leptomeninges specifically refer to the arachnoid and pia mater, characterized as the two innermost layers surrounding the brain and spinal cord.^{31,32} During development, melanocytes differentiate from neural crest cells following migration to the leptomeninges, epidermis, uveal tract of the eye, and some mucosal sites.^{33,34} It is from melanocytes that melanoma arises following mutations.³⁴ The leptomeningeal location could likewise play a role in the rapid progression of pediatric CNS melanoma, as the CNS experiences a degree of segregation from the immune system by the BBB.^{19,20}

Essentially, a lower immune involvement could translate into lower resistance to tumor progression.³⁵

The embryological process of neural cell migration may provide insight into the association between pediatric primary CNS melanoma and congenital abnormalities such as neurocutaneous melanosis.³⁶ Neurocutaneous melanosis is a neurocutaneous disorder characterized by the presence of large, numerous melanocytic nevi of the skin with associated increased CNS melanocyte proliferation.^{37,38} It is hypothesized that neurocutaneous melanosis is a consequence of postzygotic activating mutations affecting melanocyte progenitors. These progenitors ultimately colonize both the skin and the leptomeninges, thus causing melanocytic dysfunction in both the skin and the CNS, with one possible CNS complication being pediatric primary CNS melanoma.^{39,40}

Genetic mutations further define the pathogenesis of pediatric primary CNS melanoma, which differs substantially from cutaneous melanoma and even adult primary CNS melanoma. Pediatric primary CNS melanoma is frequently driven by *NRAS* mutations, most often at codon 61 (Q61R and Q61K), particularly in cases associated with neurocutaneous melanosis.^{10,23,36} Neuroblastoma RAS viral oncogene homolog (*NRAS*) is a known upstream activator of the MAPK and phosphoinositide 3-kinase (PI3K)–AKT pathway, and gain-of-function *NRAS* mutations subsequently lead to pathway activation, promoting sustained cell proliferation and resistance to apoptosis.^{10,41–44}

An important aspect of pediatric primary CNS melanoma is its defining features that set it apart from cutaneous melanoma. While *BRAF* mutations, especially V600E substitution, are common in cutaneous melanomas, they rarely arise in pediatric CNS melanomas.^{24,36,45} Further, *NRAS* mutations that often arise in pediatric CNS melanoma occur in much less frequency in cutaneous melanomas.^{24,36} While this may be diagnostically helpful in differentiating pediatric primary CNS melanoma from metastatic melanoma, it also complicates therapeutic decision-making because there is no established curative treatment. Many therapies that target the B-Raf proto-oncogene, serine/threonine kinase (*BRAF*)—such as vemurafenib, encorafenib—are only modestly effective as monotherapy in *NRAS*-mutant tumors, such as those seen in many pediatric primary CNS melanomas.^{46,47} Although *NRAS* is an activator of *BRAF*, it also targets other RAF isoforms, including CRAF and ARAF, which lead to persistent MAPK activation despite *BRAF* inhibition.⁴⁸

GNAQ and *GNA11* mutations, specifically occurring at codon 209, are common drivers of sporadic cases of primary CNS melanoma existing without association

with neurocutaneous melanosis.⁴⁴⁻⁴⁷ Guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) and guanine nucleotide-binding protein subunit alpha-11 (GNA11) are early activators of the MAPK pathway, and activating mutations initiate inappropriate activation of the MAPK pathway, resulting in unregulated growth and proliferation.⁴⁸ Furthermore, they are rarely found in cutaneous melanoma, making them relatively specific for primary CNS melanoma.^{47,49}

Secondary alterations, including loss of *CDKN2A* and *TP53*, contribute to aggressive growth and malignant transformation by disabling tumor suppressor checkpoints.^{43,44} These molecular features not only distinguish pediatric CNS melanoma from cutaneous forms but also have therapeutic implications. For example, MEK inhibitors, such as trametinib, targeting MAPK signaling have shown limited benefit in case reports, and PI3K-AKT inhibitors are under early clinical investigation.^{41,42}

Advanced melanomas can promote tumor growth and progression through the release of neuroendocrine mediators, affecting both local and systemic homeostasis.⁵⁰ This mechanism allows for tumor cells to evade the host's immune-mediated eradication system, while recruiting surrounding cells that may contribute to the neoplastic process.⁵⁰ This occurs through tumor-produced cytokines, neurotransmitters, and neuroactive peptides (catecholamines, corticotropin-releasing hormone [CRH], urocortins, growth hormone-releasing hormone, thyroid-releasing hormone, biogenic amines, melatonin, proinflammatory cytokines, among others) that influence the central and peripheral neuroendocrine axes to favor tumor progression.⁵⁰ The release of these compounds promotes downstream activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to the expression of neuromodulatory receptors on target organs. Respectively, CRH and urocortins produced by melanomas can interact with CRH receptor 1 (CRH-R1), leading to the activation of the pituitary-adrenal axis. Subsequent activation of CRH-R1 and CRH-receptor 2 (CRH R2) expressed in nearly all organs follows, resulting in peripheral homeostatic alterations.⁵¹ The capacity of melanomas, in their advanced form, to influence systemic homeostasis is thought to be related to their neural crest-derived origin.⁵⁰ Furthermore, the expression of these HPA axis regulators has been shown to be positively correlated with tumor progression and malignant behavior.^{52,53} Future directions have begun to investigate how tumor cells instruct immune cells to produce neuroendocrine factors that contribute to the development of pathology; however, this has not been fully elucidated.⁵⁴

4. Clinical presentation

The clinical manifestations of primary CNS melanomas often vary, with presentations ranging from asymptomatic to symptoms that depend on the primary tumor location. Symptoms are frequently associated with increased intracranial pressure due to a space-occupying lesion or spinal cord compression.^{55,56} For example, in a case report of a 15-year-old patient with primary intracranial malignant melanoma (PIMM), the patient presented with headaches accompanied by nausea and photophobia.²⁰ Alternatively, another case report detailed a 12-year-old patient with primary intracranial melanoma who presented with a sudden onset of severe headache and associated neurological deficits.¹

Other reported clinical symptoms include seizures and developmental regression.⁵⁷ For example, a case report of a 17-year-old patient with a primary brain melanoma presented with a tonic-clonic seizure with no focal neurologic deficits on exam.⁵⁸⁻⁶⁰ In addition, these symptoms may progress to hydrocephalus and severe neurological impairment triggered by a proliferation of melanocytic cells.³⁷

The non-specific symptoms, such as headaches and seizures, can mimic infectious or inflammatory CNS etiologies, including a brain abscess.⁶¹ In one reported case, a 7-year-old patient presented with a fever, headache, and vomiting suspicious for infectious meningitis was diagnosed with primary diffuse leptomeningeal melanoma, and a 5-year-old patient with primary malignant melanoma of the meninges presented with an atypical clinical presentation of meningitis.^{62,63} The non-specific variety of clinical symptoms, in combination with the rarity of primary CNS melanoma in the pediatric population, often leads to diagnostic difficulty.

5. Diagnostic evaluation

Due to its rarity, there is no standardized approach for diagnosing pediatric primary CNS melanoma. The diagnosis relies on several diagnostic modalities combined with the exclusion of all other differential diagnoses. Diagnostic tools include neuroimaging, cerebrospinal fluid (CSF) analysis, biopsy histopathology, and molecular testing. Differential diagnoses that need to be ruled out include metastatic melanoma and other primary CNS lesions such as meningioma, schwannoma, and melanocytoma.

The relatively non-invasive nature of MRI makes it a preferred choice for the first step in diagnosing a suspected primary CNS melanoma. Melanin has paramagnetic properties that result in T1-weighted hyperintensity of the

melanoma lesions as seen in Figure 1.²⁵⁻²⁷ The lesions may show hypointensity on T2-weighted imaging, although the literature suggests this is less reliable than T1-weighted imaging.^{5,64}

The hyperintense lesions often appear as leptomeningeal enhancement, either as a solitary tumor or diffusely, depending on the malignancy and invasive behavior of the CNS melanoma.^{16,64,65} Although MRI can be helpful to rule in CNS melanoma, it cannot reliably rule out the other differential diagnoses of malignant melanoma or other primary CNS tumors. This reflects the variability in the presentation of primary CNS melanoma, which causes excessive overlap with other CNS pathologies.^{16,23} It is therefore imperative to use imaging in conjunction with biopsy evidence to make a primary CNS melanoma diagnosis.

Another technique for evaluating suspected primary CNS melanoma is CSF analysis. Obtaining a CNS biopsy is highly invasive, so exploring CSF analysis as a possible alternative is of interest. There are a few documented cases from the 1990s and early 2000s that describe obtaining circulating melanoma cells from CSF and identifying them with IHC staining.^{35,66,67} This is possible due to the association of primary CNS melanoma with the leptomeninges, which are in proximity to the CSF. Primary CNS melanoma is rare, and this specific technique is especially understudied. Sensitivity is often limited, especially in earlier-presenting primary CNS melanoma, due to a lack of metastasis and low circulating cells.⁵⁸ More recent research shows promise of using PCR to characterize circulating tumor DNA in the CSF as a means for detecting and identifying CNS tumors, though sensitivities and specificities are still suboptimal, and ongoing research is needed.^{18,67,68}

Gross examination of a primary CNS melanoma biopsy often shows a pigmented lesion with variable margins, depending on the degree of malignancy, seen in Figure 2.^{37,38,64,65} Subsequent microscopic findings may include pleomorphic epithelioid cells with melanin pigment, as well as associated non-specific hypercellularity, occasional mitotic figures, and areas of necrosis.³⁴

IHC is crucial for narrowing a differential diagnosis list and can provide significant evidence for pediatric primary CNS melanoma. Because melanocytic tumors such as CNS melanoma are of neural crest origin, S-100 staining has high sensitivity but limited specificity.^{16,33} More specific stains include HMB-45 and Melan-A, which are melanocytic-specific but do not discriminate between melanomas, such as a primary CNS melanoma and metastatic melanoma.^{16,33} Examples of staining patterns are shown in Figure 3.³⁸

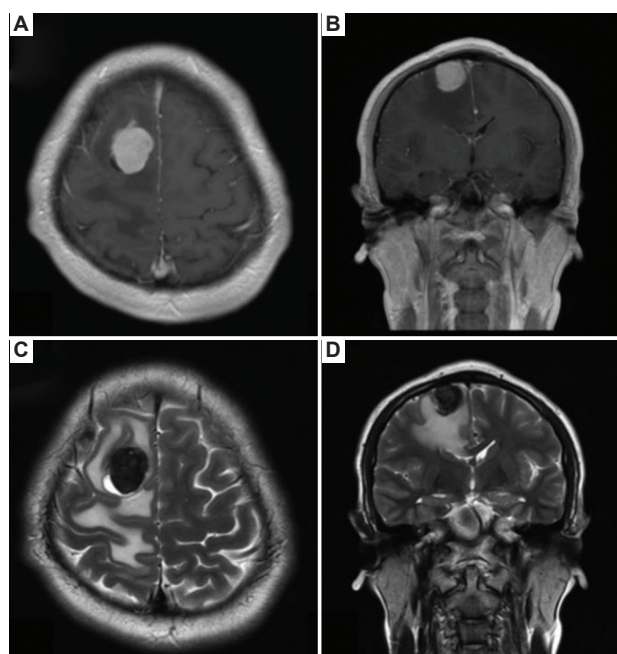


Figure 1. Magnetic resonance imaging of intracranial melanoma in an adolescent in the right parasagittal frontal region, surrounded by vasogenic edema. (A) Tumor mass enhancing with contrast on axial. (B) Tumor mass enhancing with contrast on coronal T1-weighted images. (C) Cystic component in the tumor mass on axial. (D) Cystic component in the tumor mass on coronal T2-weighted images. Adapted from Golden *et al.*²⁷

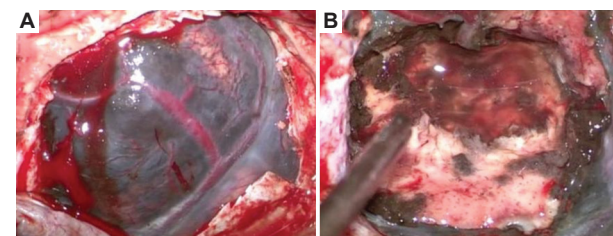


Figure 2. Intraoperative view of adolescent primary melanoma taken (A) pre- and (B) post-excision. Adapted from Golden *et al.*²⁷

Genetic analysis can be exceptionally valuable for characterizing pediatric primary CNS melanoma and differentiating it from metastatic melanoma. *NRAS* mutations are frequently observed in pediatric primary CNS melanoma, especially in cases associated with neurocutaneous melanosis. In contrast, these mutations are less frequent in cutaneous melanoma. Further, *BRAF* V600E is a characteristic of cutaneous melanoma and is rarely seen in primary CNS melanoma. *GNAQ* and *GNA11* mutations are often seen in adult primary CNS melanoma and sporadic type pediatric CNS melanoma, but not in cutaneous melanomas. Therefore, *NRAS*, *GNAQ*, and *GNA11* mutations are suggestive of primary CNS melanoma, while *BRAF* V600E mutations are more suggestive of cutaneous melanoma metastasis.^{10,24,68,69}

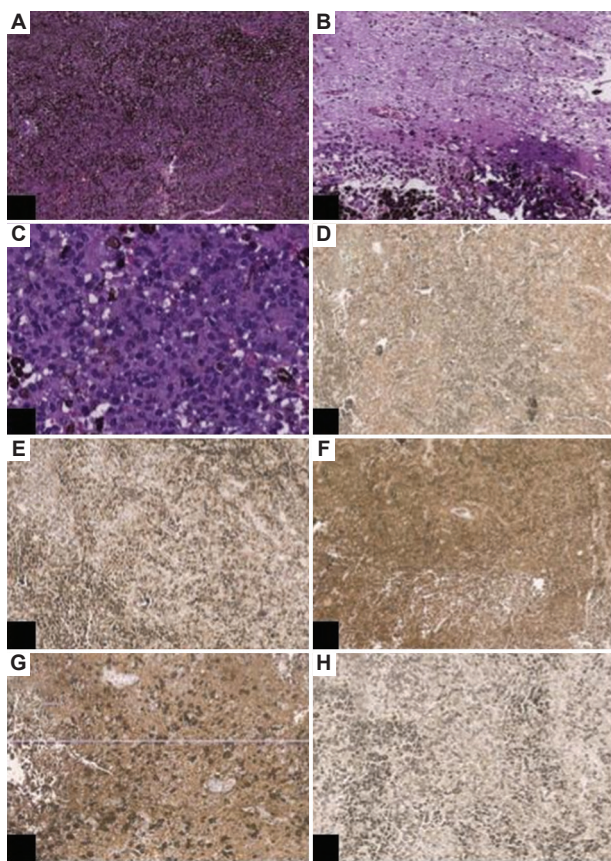


Figure 3. Histopathological findings of melanoma in an adolescent. (A) Tumor mass consisting of diffuse proliferation of neoplastic cells with dense melanin pigment deposition (hematoxylin and eosin [H&E] stain; magnification: 40×). (B) Infiltrative tumor cells are seen among the brain tissue (H&E stain; magnification: 100×). (C) The tumor cells exhibit round to oval, polygonal to spindle morphology, with partially extensive eosinophilic cytoplasm, an increased nuclear to cytoplasmic ratio, and pleomorphic nuclei (H&E stain; magnification: 200×). (D-H) Immunohistochemistry (IHC) shows positive staining for (D) Melan A, (E) human melanoma black-45, (F) S100, (G) glial fibrillary acidic protein, and (H) epithelial membrane antigen. Image adapted from Golden *et al.*²⁷

When considering a pediatric primary CNS melanoma as a diagnosis, it is important to keep a broad list of differential diagnoses because other tumors may present in a similar way and are much more common.^{14,16,69,70} For that reason, it is crucial that a primary CNS melanoma diagnosis be a diagnosis of exclusion. Some differential diagnoses to rule out include:

- **Metastatic melanoma:** Full examinations are required to screen for any primary sites of cutaneous melanoma. Metastatic melanoma can present as multiple leptomeningeal lesions on MRI, which is similar to some pediatric primary CNS melanoma presentations. Furthermore, both stain positive for S100, HMB-45, and Melan-A on IHC. Genetic studies are useful in differentiating the two, as *BRAF*

mutations are suggestive of cutaneous melanomas, while *NRAS*, *GNAQ*, and *GNA11* mutations are more suggestive of primary CNS melanoma.^{10,24,68,69}

- **Melanocytoma:** A melanocytoma is a benign melanocytic lesion of the CNS. It can present as a well-demarcated lesion and microscopically shows well-differentiated melanocytes without invasion. This is in contrast to the atypia, necrosis, and invasion seen in primary CNS melanoma.^{33,47}
- **Meningioma:** A meningioma can present in similar locations as a primary CNS melanoma, with even more overlapping presentation in cases of pigmented or hemorrhagic meningiomas. Meningiomas are histologically characterized by whorled cells, psammoma bodies, and positive staining for epithelial membrane antigen (EMA). They are negative for melanocytic-specific stains such as HMB-45 and Melan-A, as seen in primary CNS melanomas. Primary CNS melanomas likewise stain negative for EMA.^{33,63}
- **Schwannoma:** Melanotic schwannomas can have a presentation that overlaps with primary CNS melanoma. They can have a similar appearance and location on MRI, and both can stain positive for melanocytic IHC stains. Melanotic schwannomas are characterized microscopically by spindled epithelioid cells in fascicles with less cellular atypia than that seen in CNS melanomas. Genetic testing can further help differentiate the two, with Schwannomas often showing *PRKARIA* mutations.⁶⁶

6. Classification and histopathology

The most widely accepted, up-to-date classification and categorization system of CNS-derived tumors is defined by the World Health Organization (WHO), specifically, the 2021 fifth edition, based on histopathological and molecular features that define these neoplasms.⁶⁹ This resource organizes tumors into major families based on their cell lineage, pathogenesis, and genetic markers to provide clinicians with directed guidelines for diagnosis, prognosis, and surgical/medical therapy.⁷⁰ Tumors are graded on a scale from 1 to 4 as outlined by the following:

- Grade 1: Tumors with a favorable prognosis, low proliferative/metastatic potential; local surgical resection is normally curative (i.e., pilocytic astrocytoma).⁶⁹
- Grade 2: Tumors that are locally invasive, with low proliferative potential but have a higher propensity to recur compared to Grade 1 (i.e., oligodendroglioma).⁶⁹
- Grade 3: Tumors with histological findings consistent with malignancy, including increased mitotic activity, an elevated nucleus-to-cytoplasm ratio,

and other features of cellular atypia (i.e., anaplastic meningioma).⁶⁹

- (iv) Grade 4: Tumors with high metastatic potential or advanced disease due to rapid proliferation, necrosis, or specific genetic markers/mutations (i.e., glioblastoma and isocitrate dehydrogenase-wildtype).⁶⁹

The use of additional subgrades within the same class (i.e., 3A and 3B) was introduced to provide context in relation to the presence or absence of specific histopathological findings. This is most easily described in the case of a Grade 2A vs. Grade 2B meningioma, where Grade A tumors meet the mitotic criteria but lack additional risk factors such as parenchymal invasion or specific molecular alterations, which are present in Grade B tumors.⁶⁹

The WHO discloses that these classification guidelines only pertain to CNS tumors and are not generally applicable to other organ systems.⁷¹ In this review, we applied these guidelines to differentiate the following CNS tumors: primary CNS melanoma, melanocytoma, and metastatic melanoma. In addition, notable variants of melanoma, epithelioid and spindle cell, are described.

Primary CNS melanoma, a WHO Grade 4 neoplasm, is defined histologically by the presence of cytologic atypia, high mitotic activity, necrosis, and local brain parenchymal invasion. As described previously, these tumors arise from leptomeningeal melanocytes, leading to signs of increased intracranial pressure. Molecularly, activating mutations in *GNAQ* or *GNA11* lead to aberrant G-protein signaling that contributes to oncogenic pathways.^{10,24}

Activating mutations in *GNAQ* and *GNA11* result in constitutive activation of phospholipase C β (PLC β). This leads to hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3), with DAG activating protein kinase C (PKC).⁷² PKC subsequently stimulates the MAPK/extracellular signal-regulated kinase (ERK) cascade through RAF–MEK–ERK signaling, driving proliferation. In parallel, mutant G α_q can also activate PI3K, leading to AKT phosphorylation and downstream pro-survival signaling activation.⁷³ Similarly, activating mutations in *NRAS*, a small GTPase, lock it in the GTP-bound “on” state, resulting in persistent recruitment of RAF kinases and activation of the MAPK pathway, as well as direct engagement of PI3K, enhancing AKT-mediated cell survival and metabolic regulation. Together, these mutations converge on MAPK and PI3K–AKT signaling to promote uncontrolled growth, survival, and oncogenesis.⁷³

Epithelioid variants are defined by large, polygonal cells with abundant eosinophilic cytoplasm and prominent

nucleoli.⁶⁹ Features of this variant include signs of metastatic potential such as cellular atypia, high mitotic activity, and brain parenchymal invasion. In contrast, the spindle-cell variant consists of fibroblast-like cells that are elongated, fusiform, and arranged in bundles called fascicles, without features of rapid proliferation/malignant potential (minimal atypia, low mitotic activity).⁶⁹ Although both variants are WHO Grade 4 neoplasms, epithelioid is generally considered the more aggressive of the two.⁶⁹

In contrast, CNS melanocytomas are benign, WHO Grade I tumors derived from leptomeningeal melanocytes.¹⁰ Grossly, these tumors are often well-circumscribed with histologic characteristics that are generally opposite to those seen in primary CNS melanoma. These include low cellular atypia, minimal mitotic figures, infrequent brain invasion, and absence of necrosis.¹⁰ IHC assays show common melanocytic markers such as HMB-45 and S-100. When in combination with reassuring historical findings, this is normally definitive for diagnosis.¹⁰ The spindle-cell variant is more common than epithelioid morphology, and the presence of epithelioid features should precipitate subsequent clinical investigation for malignancy.^{69,70}

Finally, we discuss metastatic (secondary) CNS melanoma. This form of melanoma is more common than primary CNS melanoma and often results from systemic spread of a cutaneous melanoma.⁶⁸ The melanoma presents with multiple, well-circumscribed lesions that track along the gray–white matter junction, often with signs of local hemorrhage. Historically, secondary CNS melanomas are indistinguishable from primary lesions.^{68,73} As a result, molecular profiling methods are utilized to differentiate these two CNS tumors. Metastatic melanomas characteristically involve BRAF, which is normally absent in primary CNS melanoma.⁷³ The *NRAS* mutation is present in approximately 20% of cutaneous melanoma, is absent in adult primary CNS melanoma, but is associated with many cases of pediatric primary CNS melanoma.^{73,74} Epithelioid and spindle-cell variants mirror those seen in primary CNS melanoma and should be evaluated as discussed in the setting of the patient's clinical picture, including a known melanoma skin cancer, which can help provide additional clues to identify the source of the malignant tumor.^{69,70}

7. Management strategies

Given the rarity of primary CNS melanomas in pediatric patients, there is no established standard of care or prospective clinical trials, leaving treatment options limited. However, the mainstay treatment often involves complete surgical resection.⁷⁵ Literature has noted a longer life expectancy of <22 months in pediatric patients with

primary intracranial metastatic melanoma who undergo gross tumor resection compared to patients who did not undergo resection.⁷⁶

Radiation or chemoradiation as definitive treatment remains uncertain in primary CNS melanomas, but often plays a crucial role after surgery.⁷⁷ Adjuvant radiotherapy is frequently used in the setting of residual disease.^{78,79} Radiotherapy options, including stereotactic radiosurgery, where high doses of radiation are delivered to the tumor, and whole brain radiotherapy, are often used in cutaneous melanoma that has metastasized to the brain.⁸⁰ However, melanoma is often relatively resistant to radiation, and higher doses per fraction are frequently required to improve local control.⁸¹ The potential toxicities of radiation therapy, especially in the pediatric population, must be carefully weighed against its benefits when selecting treatment options. *In vivo* studies in mice have demonstrated that melanin can have a radioprotective effect through inhibition of radiation-induced damage, and survival curves of melanoma cells suggest a higher ability to repair sublethal damage after irradiation compared to other cells.^{82,83} In addition, there is a lack of universal recommendations for the use of radiotherapy for intracranial melanoma, other than in uveal melanoma.⁸⁴

Similar to its relative radioresistance, melanoma also exhibits intrinsic chemoresistance, and the treatment of primary CNS melanoma is further constrained by the limited penetration of chemotherapeutic agents across the BBB.⁸⁵ Temozolomide and dacarbazine are the most commonly used medications, and a retrospective study performed by Paul *et al.*⁸⁶ found a significant difference in favor of temozolomide as a replacement for dacarbazine, as it has the benefit of better penetration into the CNS. Chemotherapy is used in combination with radiation.

Immunotherapy, particularly immune checkpoint inhibitors (ICIs), such as pembrolizumab—an anti-programmed cell death protein 1 (PD-1) agent—and ipilimumab—an anti-cytotoxic T-lymphocyte-associated protein 4 agent—has become a well-established treatment for patients with cutaneous melanoma.⁸⁷ In the setting of primary CNS melanoma, data on immunotherapy are limited and consist primarily of a few case reports. In one case report, a 14-year-old patient was treated with trametinib and everolimus, followed by ICI agents nivolumab and ipilimumab, resulting in temporary clinical improvement and survival for 7 months.⁸⁸

While ICIs offer potential survival benefits, they also carry risks of immune-related adverse events (dermatitis, colitis, and endocrinopathies) and systemic toxicities such as fatigue and hepatotoxicity.⁸⁹ In pediatric patients, these side effects may be more challenging to manage due

to developmental vulnerabilities and long-term toxicity risks, although some literature suggests that children may tolerate ICIs better than adults.⁸⁹

The BBB has historically made it difficult to treat brain tumors and metastasis with immunotherapy. However, some immunotherapies, particularly those using nanoparticles to facilitate BBB crossing, have shown promise in reaching tumors in the brain.⁹⁰ Immunotherapy also has its own spectrum of side effects, including diarrhea, hepatotoxicity, skin eruptions, fatigue, and immune-related adverse events, necessitating symptomatic treatment, endocrine replacement therapy, corticosteroids, or other immunosuppressant medications.⁹¹ While most health insurance plans cover the high cost of many immunotherapy medications, varying plan-specific coverage can lead to patients facing significant out-of-pocket expenses.

Targeted treatment options are a form of precision medicine and another therapeutic approach that has been utilized in primary CNS melanomas. The most common gene mutation in melanoma is the *BRAFV600E* variant. Specific targets of BRAF kinase, such as dabrafenib in combination with trametinib, a MEK1 and MEK2 inhibitor, have shown promising results in the treatment of metastatic melanoma. However, there is limited data for its use in primary CNS melanomas. A case series of pediatric primary tumors (non-melanoma CNS tumors) found that dual BRAF/MEK inhibition led to a substantial clinical response compared to single-agent dabrafenib.⁸⁸ One case report of a patient with leptomeningeal disease had remained stable for 18 months after whole-body radiation followed by vemurafenib, a BRAF inhibitor.⁹² This suggests a potential treatment with trametinib and dabrafenib for patients with primary CNS melanomas who harbor the *BRAFV600E* mutation. However, this mutation occurs less frequently in primary CNS melanoma, so BRAF inhibitors may benefit only a minority of primary CNS melanoma patients.

A common mutation in melanomas is the *NRAS* mutation.¹¹ In one study using mouse models, researchers concluded that *Nras* mutation in melanocytes is a significant risk factor for early CNS melanoma.⁹³ MEK inhibitors such as trametinib or PD0325901 act downstream of NRAS and may represent a potential treatment option in patients with *NRAS* mutations.⁹⁴ Targeted therapies also face difficulties in crossing the BBB. There is ongoing research to improve BBB crossing for targeted therapies using ligands, physical disruption via ultrasound with microbubbles, and targeted nanocarriers such as liposomes.⁹⁴

Hydrocephalus can be a complication of primary CNS melanomas, and ventriculoperitoneal shunts have been

reported to relieve elevated intracranial pressure. However, shunts can pose a risk of peritoneal seeding or malignant ascites; hence, they should be used with extreme caution.⁹⁵

8. Prognosis and outcomes

Prognosis in patients with pediatric primary CNS melanoma is influenced by an array of factors, including histopathologic features, molecular pathway variations, and tumor-specific properties related to invasion and distant metastasis.² Literature to date has found universally fatal outcomes with a median survival time of 0.4 years (0.1–0.9) and no reported cases exceeding the one-year mark in patients with neurocutaneous melanocytosis.^{2,7} As a result, this association has been deemed the most important prognostic factor, largely due to its association with *NRAS* mutations and the downstream melanocytic growth and proliferation that characterize the condition.² In pediatric cases without neurocutaneous melanocytosis, studies have shown improved prognosis with some cases exceeding one year; however, the overall prognosis remains poor in relation to other pediatric melanomas.⁹⁶ As a whole, pediatric patients tend to have a better prognosis than adult patients, yet within the pediatric cohort, no specific age range has been deemed more protective against disease progression.^{97–99} Furthermore, tumor characteristics such as location (infratentorial vs. supratentorial) have not been shown to affect prognosis, whereas tumor depth of invasion has been associated with worse outcomes despite treatment.⁹⁹ Despite these findings, as with most malignancies, the extent of disease defined as leptomeningeal dissemination or the presence of lesions in multiple areas of the brain (multifocality) has been associated with poor prognostic outcomes.^{97–99} Few studies have extrapolated characteristic mutations associated with worse prognosis; however, the presence of a *CDKN2A* homozygous deletion, a tumor suppressor gene associated with both melanomas and pancreatic cancer, has been linked to reduced survival.¹⁰⁰ Identification of prognostic factors is imperative for clinical decision-making and patient education. Additional work is needed to provide comprehensive insight into the factors that contribute to patient mortality in pediatric primary CNS melanoma.

9. Case reports and literature

Given the rarity of pediatric primary CNS melanoma, we identified 22 published case reports and briefly summarized their findings here and in [Table 2](#). According to published case reports, pediatric patients with primary CNS melanoma have a median age at onset of 14 ± 3.19 years, an age range of 7–17 years, equal distribution between males and females, and a median survival time of only 8 months.¹⁰¹

A 14-year-old female who presented with headache, vomiting, and photophobia was found to be HMB-45-positive and with variable *Ki67* profiles, suggesting a primary diffuse leptomeningeal melanomatosis (PDLM).¹ She was treated with surgical resection and both temozolomide and dexamethasone. She subsequently developed hydrocephalus, needing a ventriculoperitoneal shunt, and passed away 4 months after her diagnosis. A 27-month-old female, who presented with vomiting and mild intermittent strabismus, was found to have *NRAS*-positive leptomeningeal melanoma.²⁴ She was treated with radiation, temozolomide, cisplatin, and vindesine. She passed away 11 months after her diagnosis. Likewise, a 15-year-old male had PIMM with *NRAS* Q61K mutation.⁹⁵ He was treated with whole-brain radiotherapy, ipilimumab, and nivolumab. A five-year-old female was reported to have amelanotic primary CNS melanoma.¹⁰⁷ This was a rare case, given that her tumor was amelanotic. She was treated with cisplatin, etoposide, and temozolomide and survived for 10 months. These four cases showcase the typical presentation, treatment, and outcomes in patients with pediatric CNS melanoma.

A rarer presentation was seen in a 3-year-old male with PDLM, which was the first case described to have extracranial metastatic disease with response to a combination of radiation, immunotherapy, and MEK inhibitor therapy.¹⁰² He had metastasis to the peritoneum and within the abdomen. His treatment consisted of radiation, ipilimumab, nivolumab, and binimetinib (MEK inhibitor).

One case of pediatric primary CNS melanoma involves an 18-year-old male with a history of a left-sided nevus of Ota and 3 years of headache associated with ptosis, who presented after four weeks of worsening headaches, polydipsia, polyuria, nausea, and vomiting.¹¹² Brain MRI demonstrated an increasing left frontal lobe mass. Initial diagnostic evaluation and treatment included craniotomy with subtotal resection, after which pathology supported a diagnosis of CNS melanoma with immunochemistry positive for microphthalmia-associated transcription factor, Melan-A, and S100. DNA sequencing of the tumor revealed a *GNAQ* R183Q mutation, suggesting a clonal relation to his nevus of Ota. Staging studies during diagnostic workup showed leptomeningeal disease. After surgical resection, the patient underwent radiotherapy and immunotherapy with nivolumab and ipilimumab. Unfortunately, he experienced no response to immunotherapy, and 6 months after surgical resection, imaging demonstrated progressive leptomeningeal disease. This worsening disease was associated with

Table 2. Summary of pediatric central nervous system (CNS) melanoma case reports

Diagnosis subtype	Age	Sex	Mutation status	Treatment (s)	Outcome/Follow-up	Source
Primary leptomeningeal melanoma	2	F	NRAS	Radiation; temozolomide, cisplatin, vindesine	11-month survival	24
Primary intracranial melanoma	12	F	NRAS, Ki67 proliferation	Surgical resection; ipilimumab, nivolumab	7-month survival	57
Primary intracranial malignant melanoma (PIMM)	17	F	NRAS and TP53 variants detected (molecular profiling)	Surgical resection; adjuvant therapy; toripalimab	Survived at least 5 months after surgery	101
Primary diffuse leptomeningeal melanomatosis (PDLM)	3	M	NRAS Q61R mutation	Radiation; ipilimumab, nivolumab, binimetinib (MEK inhibitor)	Survived 7 months, passed away from complications of RSV, Klebsiella, and subdural hemorrhage	102
PDLM	4	F	Variable Ki67	Surgical resection; temozolomide, dexamethasone	4-month survival	103
PIMM	15	M	NRAS Q61K	Surgical resection; whole-brain radiotherapy; ipilimumab, nivolumab	Rapid clinical deterioration	15
Primary brain melanoma	17	M	10% Ki67-positive	Surgical resection; radiation; pembrolizumab, nivolumab, ipilimumab	13-month survival	74
Non-syndromic PDLM	14	F	Not reported	Not reported	Not reported	104
PDLM	13	M	Not reported	Surgery only (no further oncologic therapy)	Survived 5 months after surgery	14
Pediatric PIMM	16	M	S100	Surgical resection; radiation	5-month survival	105
Primary intracranial meningeal melanoma mimicking meningitis	6	F	S100	Whole-brain radiation	1.5-month survival	106
Primary CNS malignant melanoma	Pediatric	Not reported	Not reported	Temozolomide, etoposide	Rapid clinical deterioration	95
Primary amelanotic leptomeningeal melanomatosis	5	F	Amelanotic	Cisplatin, etoposide, temozolomide	10-month survival	107
Primary leptomeningeal melanoma	3	M	Not reported	Not reported	Not reported, but patients tolerated 8 cycles	108
Leptomeningeal melanoma	Pediatric	M	Not reported	Vincristine, carboplatin, etoposide	6-month survival	109
Primary malignant melanoma of the meninges	5	M	S100	Dexamethasone, immunoglobulin, nimodipine	At least 3 months, no further data	58
Primary CNS melanoma	11	F	Not reported	Surgical resection	2-month survival	110
Primary diffuse leptomeningeal melanomatosis (PDLMM)	14	M	NRAS Q61R mutation	Surgical resection; trametinib, everolimus, etoposide, cytarabine, topotecan (IVT), nivolumab, ipilimumab	7-month survival	87
Meningeal melanosis	16	F	Not reported	Not reported	Not reported, but patients tolerated 8 cycles	111
Primary meningeal melanomatosis	17	M	S100, 10% Ki-67	Whole brain radiation; dacarbazine, carmustine, cisplatin, tamoxifen	Not reported, but patients tolerated 8 cycles	93
Primary CNS malignant melanoma	Pediatric	Not reported	Not reported	Case 2: Multiple resections+radiation therapy+ipilimumab	Rapid clinical deterioration	109

hydrocephalus and seizures, requiring management with a ventriculoperitoneal shunt. He was then treated with

palliative temozolomide and transitioned to hospice care. He succumbed to his illness 9 months after diagnosis.

Nevus of Ota is known to be associated with *GNAQ* mutations, which are also commonly seen in certain types of melanoma. Although nevus of Ota is infrequently associated with CNS melanoma, this case demonstrates the importance of monitoring and investigating focal neurologic findings in patients with nevus of Ota.⁵⁷

Compared to the more chronic presentation of symptoms demonstrated in the previous case, some other cases of pediatric CNS melanoma present more acutely. A previously healthy 12-year-old female presented with a sudden, severe headache and neurologic symptoms.¹¹³ Head computed tomography (CT) revealed what was initially thought to be an arteriovenous malformation (AVM), and she soon developed intracerebral hemorrhage, which was managed conservatively, and was discharged home. She presented again with syncope, and a repeat head CT revealed worsening bleeding and midline shift. After craniectomy for hematoma evacuation and partial resection of the presumed AVM, she experienced initial symptom improvement. A repeat resection was performed to remove the majority of the remaining mass. Pathology confirmed a melanoma diagnosis. There was no evidence of melanoma elsewhere, supporting the presence of primary CNS melanoma. On hospital day 22, she received her first course of intravenous immunotherapy. Leptomeningeal metastases were seen on MRI, and her clinical course was characterized by rapid neurological decline related to hydrocephalus. This case demonstrates the importance of distinguishing primary CNS melanoma from other lesions, such as AVM, on brain imaging. This will promote earlier intervention for these tumors, ideally resulting in more favorable outcomes. Both cases discussed highlight the limitations of current treatment regimens, characterized by surgical resection, radiation, and immunotherapy, amongst pediatric populations. Both also demonstrate the difficulty of diagnosis of these cancers, as initial presentations can be variable.

10. Future directions and research gaps

As demonstrated in the cases explored previously, the medical community faces many obstacles in identifying and treating primary CNS melanoma in pediatric patients. Primarily due to the infrequency of this condition in pediatric patients, there is limited data on its management. Because of this, there are no current established guidelines for treatment in children; therefore, most treatment approaches are extrapolated from an adult population. These treatments, which often include surgical resection, radiation, and immunotherapy, have proven to be largely ineffective, given the high mortality rate of pediatric primary CNS melanoma.¹ To improve these outcomes, pediatric-specific clinical trials that investigate the efficacy

and safety of various treatment options are vital. While investigating pediatric-specific treatment strategies, it is vital to continue to explore the molecular and genetic characterization of pediatric CNS melanoma. Although it is known that *GNAQ* and *NRAS* mutations are implicated in these tumors, the full spectrum of potential mutations and their corresponding therapies is yet to be discovered.¹¹ The rare occurrence of pediatric cancers and the low frequency of genomic mutations in them significantly limit the use of targeted therapies, underscoring the need for further research on targeted therapies in precision medicine.¹¹⁴ Another factor that may contribute to the development of pediatric-specific treatment regimens is the establishment of a pediatric tumor registry or other research collaboration platforms. Registries for pediatric melanocytic lesions that integrate molecular analysis have allowed for more individualized treatments for patients with these lesions.¹¹³ Developing this type of collaborative space for pediatric primary CNS melanoma may allow for greater access to information that will guide future treatment strategies, especially in the case of such a rare condition.

11. Conclusion

Pediatric primary CNS melanoma is a rare but aggressive form of melanoma. Primary CNS melanoma originates from the leptomeninges rather than the CNS parenchyma, and this location, in combination with the BBB, partly shields the tumor from effective immune surveillance. It often occurs with an associated neurocutaneous syndrome, specifically neurocutaneous melanosis, but there are reports of sporadic cases. Pediatric patients with primary CNS melanoma often present with clinical features of increased intracranial pressure, hydrocephalus, headaches, seizures, and focal neurological deficits.

The non-specific clinical symptoms of pediatric primary CNS melanoma, combined with the rarity of this entity, often lead to diagnostic difficulty and delayed treatment. This, in combination with pediatric primary CNS melanoma's aggressive nature, necessitates that patients in whom pediatric CNS melanoma is strongly suspected be evaluated with a thorough neurological examination, family history for neurocutaneous syndromes, radiological (MRI), and histopathological assessment. To improve treatment outcomes and prognosis, further research is essential, including a better understanding of the genetic profile, the establishment of a pediatric tumor registry and collaborative research platform, and the development of pediatric-specific treatment guidelines.

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Author contributions

Conceptualization: Adriene Pavsek, Annabelle Huntsman, Grace Bradford

Writing—original draft: All authors

Writing—review & editing: All authors

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