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Leptomeningeal dissemination in pediatric brain tumors

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ABSTRACT

Leptomeningeal disease (LMD) in pediatric brain tumors (PBTs) is a poorly understood and categorized phenomenon. LMD incidence rates, as well as diagnosis, treatment, and screening practices, vary greatly depending on the primary tumor pathology. While LMD is encountered most frequently in medulloblastoma, reports of LMD have been described across a wide variety of PBT pathologies. LMD may be diagnosed simultaneously with the primary tumor, at time of recurrence, or as primary LMD without a primary intraparenchymal lesion. Dissemination and seeding of the cerebrospinal fluid (CSF) involves a modified invasion-metastasis cascade and is often the result of direct deposition of tumor cells into the CSF. Cells develop select environmental advantages to survive the harsh, nutrient poor and turbulent environment of the CSF and leptomeninges. Improved understanding of the molecular mechanisms that underlie LMD, along with improved diagnostic and treatment approaches, will help the prognosis of children affected by primary brain tumors.

Introduction

Leptomeningeal disease (LMD), also known as "leptomeningeal carcinomatosis", "carcinomatous meningitis", "leptomeningeal metastasis" or "leptomeningeal dissemination" is defined as the detection of cancer cells in the leptomeninges (arachnoid and pia maters), subarachnoid space or within the cerebrospinal fluid (CSF) compartments (Fig. 1) [1]. In this review, "LMD" will include all terms. LMD may occur with any adult or pediatric malignant tumor. In adults higher incidences have been observed in breast cancer (5-8%), lung cancer (9-25%) and melanoma (6-18%) [2]. Independent of the nature of the primary tumor, the presence of LMD confers a dismal prognosis with an average survival range of 3 to 6 months for both adult and pediatric tumors [3]. Disseminated cells within the leptomeninges often lead to perturbations in CSF flow and absorption, with frequent development of raised intracranial pressure, hydrocephalus and increased mortality [2].

With respect to brain tumors, LMD has an incidence of 1% to 2% [4]. Within pediatric brain tumors (PBTs), it is most commonly detected in medulloblastoma (MB) [5] and primary central nervous system (CNS) lymphomas [6], but also observed in other pathologies including pineoblastoma (PB) [7], craniopharyngioma (CP) [8], Diffuse Intrinsic Pontine Glioma (DIPG) [9,10], Atypical Teratoid Rhabdoid Tumor (ATRT) [11], low grade gliomas such as pilocytic astrocytoma [12] as well as high-grade gliomas [13]. The overall prevalence of LMD in PBTs is difficult to determine as it is likely underdiagnosed due to lack of uniformity in screening across the different pathologies, both at the time of diagnosis and throughout the course of the disease. In many pathologies, the overall survival (OS) has increased due to advancements in surgical techniques and both focal and systemic therapies. Therefore, LMD is more frequently observed as a late complication of cancer progression or recurrence.

As in all forms of metastases, in LMD, the ability of cancer cells to spread from the primary tumor site and to settle in the new environment involves a genetically and epigenetically selective multi-step process [14]. Only a small proportion of circulating tumor cells (CTCs) survive this process and can successfully establish a metastatic colony

Abbreviations: LMD, Leptomeningeal Disease; CSF, Cerebrospinal Fluid; MB, Medulloblastoma; CTCs, Circulating Tumor Cells; PBTs, Pediatric Brain Tumors; CP, Craniopharyngioma; CPC, Choroid Plexus Carcinoma; CSI, Craniospinal Irradiation; GCT, Germ Cell Tumor; ATRT, Atypical Teratoid Rhabdoid Tumor; DIPG, Diffuse Intrinsic Pontine Glioma; DMG, Diffuse midline glioma; ABAT, 4-aminobutyrate transaminase; IGF-1, Insulin Growth Factor 1; SRT, Stereotactic Radiation Therapy; GTR, Gross Total Resection; CPP, Chorioid Plexus Papilloma; NCGCT, Non-Germinomatous Germ Cell Tumor; WV-RT, Whole Ventricular radiation therapy; GBM, Glioblastoma; DLGNT, Diffuse Leptomeningeal GlioneuronalTumor; WBRT, Whole Brain Radiation Therapy; IV, Intravenous; IT, Intrathecal; CAR T, Chimeric Antigen Receptor T.

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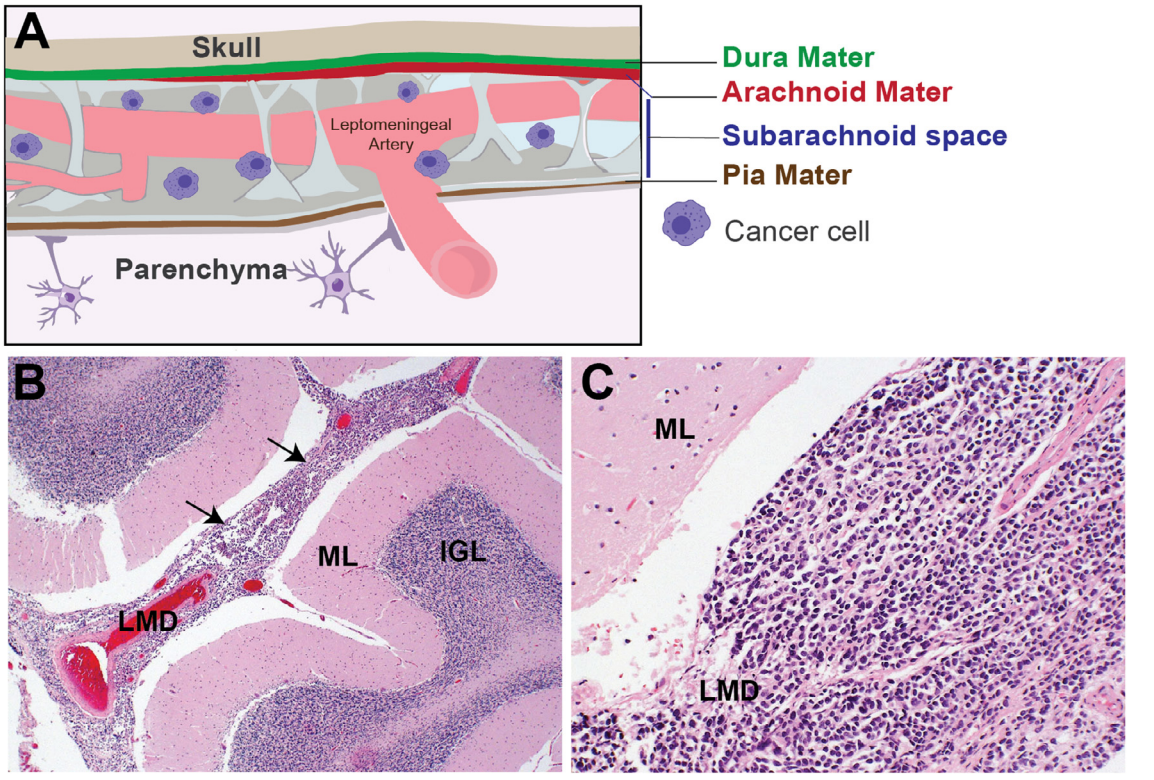

Fig. 1. **(A)** Graphic representation of the leptomeninges, which include the arachnoid mater, the subarachnoid space and the pia mater. **(B-C)** Histological section of the perivascular leptomeningeal infiltration (arrows) of a pineoblastoma at the level of the cerebellum. LMD: leptomeningeal dissemination; ML: molecular layer; IGL: Internal Granular Layer. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[15]. CTCs may infiltrate host sites through direct spread within the subarachnoid space or more distantly travelling via CSF [5]. The hematogenous route for brain tumors LMD has also been proposed. Indeed, MB cells were detected in human MB patients' bloodstream and parabiosis experiments showed that mouse MB tumors may disseminate via this route [16]. The anatomy of the leptomeninges makes the microenvironment physically and metabolically challenging for CTCs, as the CSF lacks significant nutrients and is characterized by a turbulent flow [17]. To overcome such environment, CTCs may undergo dormancy [18,19], developing resistance to radiation and chemotherapy. Clinically, the presence of dormant cells may manifest as late recurrences and underscores the need of prolonged follow-ups. For these reasons, LMD remains a major challenge to achieve long-term control of PBTs. Unfortunately, due to a paucity of pre-clinical models, and the difficulty in obtaining LMD samples matched with primary tumors, the mechanisms underlying PBTs LMD remain poorly understood. Therapeutic approaches to primary brain tumors, including surgical resection, cranio-spinal irradiation (CSI) and chemotherapy, are designed to minimize the spread of CTCs within the neuroaxis [20]. However, in pediatrics, dose-limitations to avoid irreversible side-effects on developing brains, and systemic toxicities often restrict the treatment options. In addition, genetic differences between the primary tumor and LMD [15,21], localization within the leptomeninges, and early dissemination prior to initial treatment make eradication of LMD extremely difficult.

Within PBTs, MB LMD has been the most studied and we refer to excellent reviews on the subject (e.g. [22,23]). In the present review, we will comprehensively examine the state of LMD in all PBTs with an emphasis on incidence, clinical presentation, and therapeutic management with the goal of providing novel insights into this therapeutically challenging disease.

Clinical presentation and incidence of LMD in pediatric brain tumors

Pediatric LMD is a rare entity with incidence rates varying widely depending on the primary tumor. Given the breadth of primary tumor types, there is no consensus on surveillance nor treatment of LMD. In addition, the timing of LMD detection greatly influences the treatment options available. LMD may either be diagnosed simultaneously with the primary tumor, at recurrence of primary tumor, or as primary LMD without a primary intracranial lesion. In addition, there is concern that CSF diversion procedures may potentiate the dissemination of malignant cells [24]. Magnetic resonance imaging (MRI) is the standard of care imaging modality to diagnose LMD. However, LMD diagnosis based on neuroimaging analysis is often challenging. In 2018, Harris et. al [25] published a study examining the diagnostic reliability for LMD using Gadolinium-based MRI and found inter-observer variability in diagnosis and poor agreement among imaging experts. While a standardized imaging score-based methodology for the assessment of LMD was suggested [26], it failed to provide significant clinical utility. There remains no neuroradiological standardized approach for patients with suspected LMD accepted across the community. Currently, the presence of LMD on imaging is routinely confirmed with CSF cytologic analysis looking for tumor cells [27].

Within this section, we review the most common PBTs LMD. We also present 3 unique cases of LMD not previously reported in the literature.

Medulloblastoma

MB is an embryonal tumor of the cerebellum which affects about 5 cases per million individuals per year, making it the most common malignant PBT [28]. The current standard of care consists of gross total

resection (GTR), chemotherapy and CSI for patients older than 3 years. Based on DNA methylation and transcriptomic profiling, the 2021 World Health Organization (WHO) classified MBs into 4 subtypes: *1)* WNT-activated, *2)* Sonic hedgehog (SHH)-activated *P53* wild type (WT), *2)* SHH-activated *P53* mutated and *4)* non-WNT/non-SHH MB (this group includes the previous Group 3 and Group 4 MB) [29]. Incidence of metastasis in MB is variable depending on the subgroup and subtypes as defined in Cavalli et al. [30]: between 8.6 to 21.4% for WNT MBs, between 8.9 to 33% for SHH MBs, between 20 to 43.4 % for Group 3 MBs and between 38.7 to 40.7% for Group 4 MBs. The presence of LMD at diagnosis, together with the molecular features of the tumor (such as *MYC* amplification and tumor subtype), are considered strong predictors of poor outcome [22]. For all MB subtypes, patients who are not eligible for GTR (due to tumor location/dissemination) or CSI, relapsed and had poorest survival [31]. LMD is the predominant pattern of metastasis described in MB [22]. Very rare cases of primary leptomeningeal disseminated MB have also been described. In this review, we present an additional case of primary leptomeningeal MB, not yet reported in the literature (Fig. 2A-D).

Several studies [31–34] explored the genetics and patterns of relapse among the different subtypes of MB, taking into account clinical history, histology and molecular features of the tumor at diagnosis. For all subtypes, the genetic landscape at relapse was stable compared to the primary tumor and about 60% of the genetic aberrations found at diagnosis were maintained in the metastases [33]. Non-WNT/non-SHH MBs had the highest incidence of relapse, and metastases mainly occurred at distant sites (spine), both with a nodular and diffuse pattern along the leptomeninges [28,32]. Within this subtype, the former Group 4 MBs were the most genetically divergent between primary tumor and metastases while Group 3 MBs were mostly genetically stable at relapse. SHH-MB mainly recurred with nodular lesions, both at local and distant sites. Distant and diffuse disease was observed in patients with *MYCN* amplification at diagnosis and who had received CSI [32]. Patients diagnosed with *MYC* amplified MB are considered “high risk” for recurrence and are usually treated with very aggressive therapeutical protocols [28].

To elucidate the genetic evolution of SHH MBs at relapse, Richardson and colleagues [33] subdivided the SHH-MB subtype into $SHH_{non\text{-}infant}$ and SHH_{infant}. $SHH_{non\text{-}infant}$ were more genetically divergent at relapse when compared to SHH_{infant} MBs, and a significant enrichment in 4p/4q gain and 10p loss was observed between the 2 groups. Such mutations strongly correlated with the *TP53* status of the tumors [33]. WNT MBs have the lowest risk of relapse [28] and are genetically stable by retaining the driver mutation found at diagnosis (*CTNNB1* and chromosome 6 monosomy) [28,33]. The mutations found at relapse are either acquired during LMD or are the result of a clonal selection from the primary tumor. Previous studies [15,21] proposed that dominant clones at relapse are the result of treatment driven genetic divergency of a subset of clones present at diagnosis in the primary tumor.

The genetic divergence acquired during relapse, likely helps the cells to adapt and colonize a different environment (such as the CSF) [22]. A recent study has suggested a role for the inhibitory neurotransmitter γ-Aminobutyric acid (GABA) metabolism in the metastatic behavior of MB [19]. In bacteria, GABA can be physiologically converted by the enzyme GABA transaminase (4-aminobutyrate transaminase or ABAT) to succinate to sustain cell survival in conditions of nutrient deprivation and stress [35]. ABAT was shown to be upregulated in MB LMD samples and it was found to promote dormancy in MB CTCs [19]. Recent studies using animal models and patient derived xenografts [36,37] highlighted the transcription factor OLIG2 as a marker expressed by a clone of quiescent cells responsible of tumor relapse. Interestingly, *OLIG2* mRNA expression correlates with metastatic state and poor survival in both SHH and Group3 MBs [36]. The interaction between quiescent cells and leptomeninges is likely necessary at least to exit from dormancy. Insulin Growth Factor 1 (IGF-1) hormone plays a role in the proliferation, survival and expansion of granule progenitor cells [38]. The availability of IGF-1 in the CSF depends on the metalloprotease cleavage of the IGF-sequestering IGF binding protein 3 (IGFBP3) [39]. CTCs in the CSF express the IGF-1 receptor (IGF1-R) and rely on IGF-1 for survival and proliferation. Svalina et al. showed that the high expression of protease in the leptomeninges facilitates the availability of IGF-1 through the cleavage of IGFBP3, and therefore supports tumor cell survival [39].

The paucity of pre-clinical models has hampered the discovery of the mechanism underlying MB LMD. Using the Sleeping Beauty transposon system in neural cells, Wu et al. [15] identified a list of candidate genes that when disrupted led to a metastatic phenotype in a Shh-based mouse model of MB, which is typically non-metastatic. Genes such as *Gdi2* or *Ccrk* were identified in this study for potentially playing a role in MB LMD and were further investigated in this process as reviewed in [22,40]

Among PBTs, studies on MB LMD are definitively the most numerous and have paved the way for studies in other PBTs. However, LMD remains a major obstacle in the management of MBs. Further genetic and functional preclinical studies are still needed to fully decipher the mechanisms underlying LMD in MB and to identify new therapeutic targets.

Craniopharyngioma

Craniopharyngiomas (CPs) are typically benign intracranial neoplasms that arise from the embryonic remnants of Rathke’s pouch epithelium [41], represent 1.2 to 4% of PBTs and are located in the sellar and suprasellar regions [42]. According to the WHO classification, CPs are Grade 1 tumors which can be classified in 2 histological type: adamantinomatous (ACP) and papillary craniopharyngioma (PCP). ACPs are characterized by an increased stability of β catenin due to a somatic mutation in the exon 3 of the *CTNNB1* gene, and are mainly described in children [41]. PCP typically arises in adults and are characterized by a $BRAF^{V600E}$ mutation, which induces a sustained activation of the MAPK signaling [41]. Due to their localization (in proximity to the optical tract, pituitary gland and hypothalamus), GTR of CPs is not always possible and the incidence of relapse is extremely high for subtotal resection (~50% of the cases) [43]. Ectopic recurrences along the surgical tract are the most reported in literature [44]. Metastatic leptomeningeal CP have been described both in the spine and at the intracranial compartment [8,41,45]. Here, we present an additional case of metastatic leptomeningeal CP not yet reported in the literature (Fig. 2E-I).

Atypical teratoid rhabdoid tumor

Atypical Teratoid Rhabdoid Tumor (ATRT) is a malignant embryonal tumor of the CNS typically characterized by a large heterogeneous mass with both cystic and solid components, intra-tumoral hemorrhage, and calcifications [46]. The median age at diagnosis is 1 year of age, with children less than 2 years of age accounting for 65.7% of patients diagnosed with ATRT and an incidence rate of 0.07 per 100,000 [47]. The underlying predominant genetic mutation is a biallelic mutation of *SMARCB1*, encoding a member of the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex [48]. Three main consensus molecular subgroups have been described following transcriptome and DNA methylation profiling: Tyrosinase (ATRT-TYR), SHH (ATRT-SHH) and MYC (ATRT-MYC) [49]. Of note, ATRT-SHH was further classified into ATRT-SHH-1 (supratentorial) and ATRT-SHH-2 (infratentorial) due to molecular heterogeneity between the groups. Detection of metastasis at diagnosis is common in ATRT patients. Depending on the studies, the incidence of metastases in ATRT patients varies from 30% to 46.2% [50–52]. The stage of metastasis M1 vs M2-M4 according to Chang’s classification [53], does not seem to affect survival [51].

Choroid plexus tumors

Choroid plexus (CP) tumors originate from the choroid plexus which lines the ventricular walls and produces CSF. Genomic profiling using

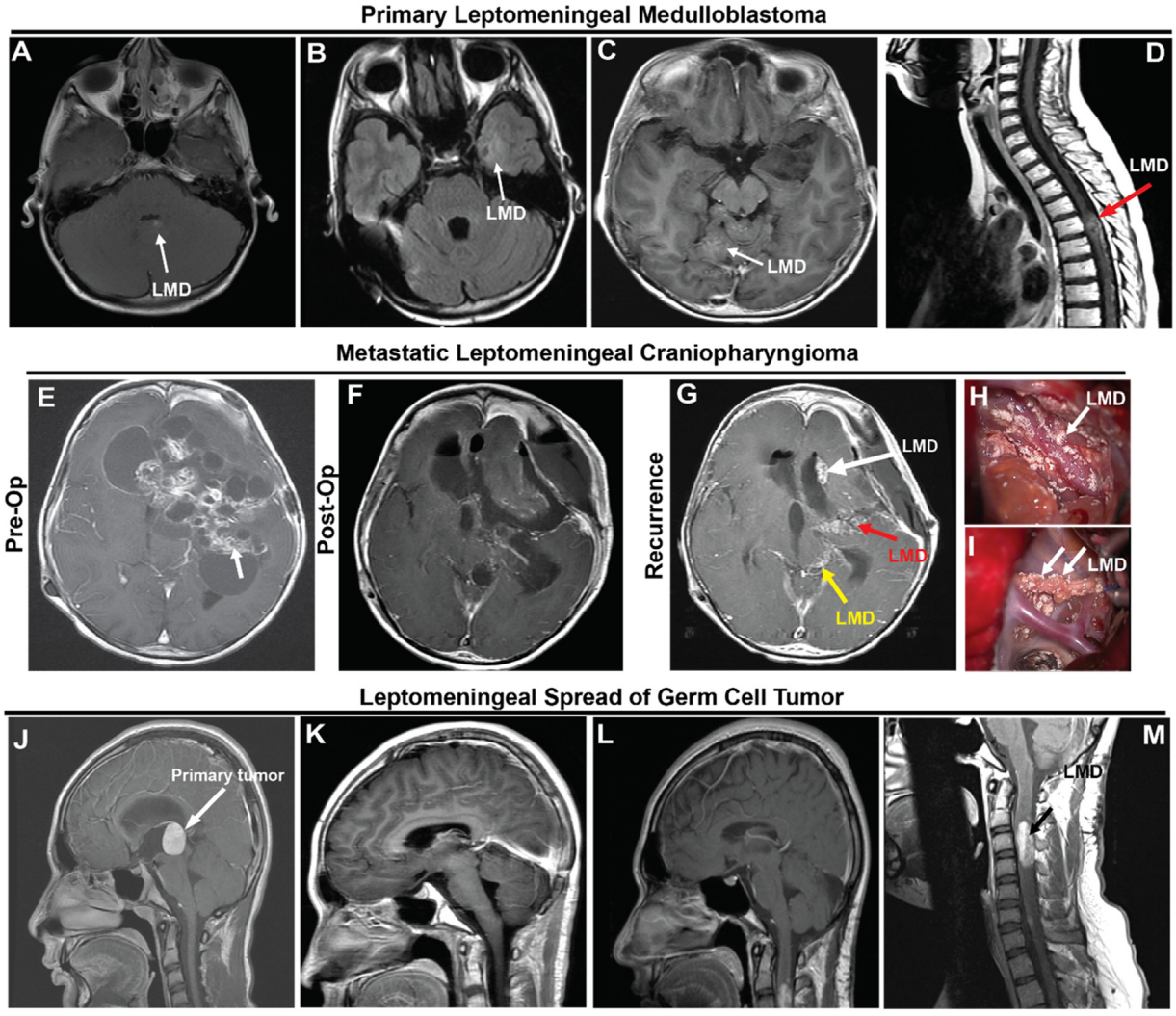

Fig. 2. Examples of LMD patterns in pediatric brain tumors. (**A-D**) **Primary Leptomeningeal Medulloblastoma:** A 12-year-old right-handed male developed nausea, vomiting, blurred and double vision. On ophthalmological evaluation, he was found to have Grade IV papilledema and bilateral VIth nerve palsy. Lumbar puncture was performed with an opening pressure of 55 cm of H20 and CSF cytology was negative for malignant cells. He was started on diamox without improvement in symptoms. MRI demonstrated findings consistent with intracranial hypertension, including papilledema and tonsillar herniation. Magnetic Resonance Venography (MRV) showed occlusion of left transverse sinus with dominant right venous system. On MRI, there were regions of T1 and T2 prolongation in bilateral frontal and temporal lobes, as well as small foci of superficial enhancement along cerebellar vermis with a differential including leptomeningeal disease. Post-contrast T1 MRI showed superficial enhancement along cerebellar vermis (**A**, white arrow) and FLAIR T2 pre-contrast demonstrates hyperintensity along the medial aspect of the left temporal lobe (**B**, white arrow). He was evaluated by neurosurgery for placement of ventriculoperitoneal shunt given concern for idiopathic intracranial hypertension versus LMD of unknown etiology. CSF was collected from the ventricular system at time of shunt placement and demonstrated a high grade non-hematopoietic neoplasm. Given the inability to determine the etiology of the malignant cells, he underwent suboccipital craniotomy for biopsy and re-sampling of CSF. Pathologic analysis of the cerebellum, tonsil and vermis showed MB WHO Grade IV and arachnoid with tumor infiltration, consistent with primary leptomeningeal MB. He underwent bilateral optic nerve fenestrations, proton CSI with boost to posterior fossa, and started on chemotherapy. Three years later, MR was concerning for progression of disease, and he underwent surgical excision of a left temporal lesion. Repeat imaging showed continued progression of LMD and dissemination, with increased bulky LMD along cerebellar vermis **(C,** white arrow**)** and thoracic spine. (D, red arrow**)** on sagittal T1 post-contrast. He remained on chemotherapy regimens 4 years after initial diagnosis. (**E-I**) **Recurrent giant craniopharyngioma with leptomeningeal dissemination:** A 4-year-old male presenting with vomiting, strabismus, visual disturbances and obtundation was found to have a multi-compartmental giant craniopharyngioma encompassing the anterior and frontal cranial fossa, the left middle cranial fossa, as well as the posterior fossa **(E)**. He underwent shunt placement, followed by near total resection with residual disease within the prepontine cistern. Post-operative MRI demonstrated resection of mass through left pterional craniotomy **(F)** with residual tumor in the posterior fossa and pathology was consistent with ACP. On follow-up imaging, he experienced rapid progression of his recurrent ACP within multiple areas and underwent 3 surgical resections in addition to multiple shunting and revision procedures including placement of 4th ventricular stent. As evidenced by an MRI demonstrating enhancement along the ependymal surface of left frontal horn (**G**, white arrow), along left middle cerebral artery M1 segment and M1 bifurcation (red arrow), and residual tumor within the left prepontine cistern (yellow arrow) and confirmed on intraoperative findings, he experienced significant LMD. Intraoperative images during resection show LMD along the middle cerebral artery (MCA) (**H**) and optic nerve (**I**). Given the extensive nature of the lesion, he would have required whole brain radiation, which was deferred to high side effects, but was started on lomustine and doxorubicin for progression of disease. He died at age 7 due to progression of disease. **(J-M) Case of leptomeningeal spread of germ cell tumor**: An 11-year-old male developed headaches, dizziness, nausea and vomiting and was found to have a pineal region and third ventricular mass. Initially, T1-post contrast MR from 2014 demonstrated a 2.5 × 2.1 cm non-diffusion restricting enhancing lesion within the pineal recess along the posterior aspect of the third ventricle (**J**, arrow). He underwent endoscopic third ventriculostomy with sampling of CSF and tumor biopsy. Ventricular cytology was negative for malignant cells, but CSF had elevated alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG). He was started on chemotherapy with ifosfamide/etoposide for NCGCT. With normalization of his CSF AFP and b-HCG levels, he underwent suboccipital craniotomy for resection of remaining pineal

DNA methylation array divided CP tumors into 3 DNA methylation subgroups: choroid plexus papilloma (CPP) WHO grade I (benign), atypical CPP WHO grade II and choroid plexus carcinoma (CPC) WHO grade III (malignant) [29,54,55]. Except for *TP53* (which is mutated in about 50% of the cases), pediatric CP cancers are devoid of recurrent driver mutations [56–59]. Despite the rarity of LMD in CPP, several cases in children have been reported with supratentorial, infratentorial, and spinal dissemination [60–64].

Three large studies described the incidence of LMD in CPC in a cohort of respectively 11, [65] 54, [66] and 13 patients [57]. In the first study [65], 5/11 patients presented LMD at diagnosis, in the second study 11/54 subjects had dissemination [66], while in the third case [57], 8 cases had metastatic disease at diagnosis, with 7/8 (87.5%) of patients having LMD confirmed on MRI. Among these 8 patients with metastatic disease, *TP53* mutations were detected in 5 of them [57]. *TP53* mutational status was the only significant predictor of outcome. Indeed, patients with wild type *TP53* responded better to radiotherapy and displayed longer overall survival [57]. Surprisingly, the presence of metastases did not impact the patient outcome. Three additional cases of CPC LMD were reported in the literature [67–69].

Ependymoma

Ependymomas are neoplasms that arise from the ependymal lining within the ventricles and central canal remnants of the spinal cord [70]. The median age of diagnosis for pediatric ependymoma is 3.6 years with 24% having supratentorial (ST) and 78% infratentorial ependymomas [71] as reported in 1 large multicenter analysis. While the molecular underpinnings of ependymoma remain most uncharacterized, the most common genetic abnormalities in pediatric ependymomas are chromosome 1q gain and chromosome 22q loss [72,73]. The 2021 WHO Classification of CNS tumors [29] updated the subtypes of ependymomas based on molecular characteristics: ST-ZFTA (previously known as ST-*RELA* tumor type), ST-YAP1, and ST-NEC (Not Elsewhere Classified) or ST-NOS (Not Otherwise Specified) [74]. The 2 main posterior fossa (PF) ependymoma subtypes remained as PF-A and PF-B. Intracranial and spinal LMD has been described in multiple cases of pediatric ependymomas [75–79]. In a study containing 33 pediatric patients, the CSF of 21.2% patients contained neoplastic cells [70]. In another large study of 402 individuals with intracranial ependymoma, 3/402 (1.0%) had positive CSF cytology at the time of diagnosis [80]. In a subset of spinal ependymomas (SP-EPN), focal amplification of *MYCN* has been described. This subset of tumors named SP-EPN-*MYCN*, showed a particularly aggressive behavior, characterized by early metastasis onset, LMD, rapid progression and poor prognosis [81]. Investigations into the molecularly aggressive intracranial ependymoma phenotypes are an active area of research. For example, for pediatric ST-ZFTA, *Cyclin-dependent kinase inhibitor 2A (CDKN2A)* deletion is associated with a poor prognosis but also represents a potential therapeutic target [82]. For intracranial ependymomas, a copy number gain of 1q25 is associated with poor progression-free and more frequent distant relapses [83–85].

Diffuse Intrinsic pontine glioma (Diffuse Midline Glioma)

Diffuse Intrinsic Pontine Glioma (DIPG), now classified as Diffuse Midline Gliomas (DMG), is characterized by the histone mutation H3.3 K27M in 80% of the cases. They are highly lethal lesions that are predominately located in the brainstem and account for 10% of all PBTs [86,87]. *TP53, ACVR1* and *PDGFRA* are frequent genomic mutations in these diffuse gliomas along with others at lower frequency (*ATRX, MYCN, MAPK, RAS*) [29,88,89]. While it is still unclear how these mutations affect DIPG with LMD, studies indicate that these genetic alterations may promote tumor cells migration and aggressiveness [29,88,90,91].

There are few reported cases of LMD in children with DIPG [9,10,13,92–99]. Lu at al. [95] reported a case of a 9-year-old female revealing a single pontine lesion at diagnosis and 6 months later, LMD was observed on MRI throughout the brain and spine. In a larger study, Wagner et al. highlighted 110 patients diagnosed with DIPG, of which 13% presented secondary dissemination in the spine, ventricular and cerebral regions 8.2 months following diagnosis [13]. Similarly, Buczkowicz et al. [99] reviewed 72 DIPG patients with 1/3 presenting LMD within the spinal cord and/or thalamic region. While LMD is rarely observed at diagnosis in DIPG, it is estimated to be present in 20-30% of cases as the tumor progresses [93,100].

Germ cell tumor

Germ cell tumors (GCTs) of the CNS are a heterogeneous group of extragonadal neoplasms originating from germline cells. They can be divided into 2 main categories: germinomas, which are more common, and non-germinomatous GCT (NCGCT) [101]. Non-germinomatous GCT include mature and immature teratomas, embryonal carcinomas, choriocarcinomas, and yolk sac tumors [101]. GCT comprise about 1% of pediatric and young adult brain tumors and are prevalently located in the pineal region and in the suprasellar region [101,102]. The general management of GCT is centered on a multimodal approach involving chemotherapy and radiation. Germinomas are extremely radiosensitive. For localized germinomas, treatment usually involves chemotherapy and whole ventricular irradiation (WV-RT). For metastatic germinomas, CSI is utilized. Due to proximity with the ventricular system and intracranial CSF spacing, the theoretic risk of LMD seeding remains high. As LMD at the level of the ventricular system is a common place of relapse in GCT tumors, WV-RT has emerged as a crucial factor in prolonging progression free survival (PFS) [103]. LMD should be considered if embryonic markers have not normalized after treatment and concern for leptomeningeal enhancement is present on MRI [104]. The estimated rate of CSF dissemination within patients diagnosed with GCT is 10%. In a study with 100 patients studying local or regional tumor dissemination, there were 6 cases of LMD GCT (6%). LMD was noted on MRI in 2 cases (CSF cytology positive in 1, negative in the other), and 4 other patients had positive CSF cytology without evidence of LMD on MRI [105]. Furthermore, the need for CSF diversion procedures for GCT causing obstructive hydrocephalus, including ventriculoperitoneal shunt placement or endoscopic third ventriculostomy (ETV), could promote LMD of disease [106]. Here, we present a case of leptomeningeal spread of GCT 8 years after ETV (Fig. 2J-M).

Gliomas: diffuse leptomeningeal glioneuronal tumor

Pediatric gliomas encompass a wide range of pathologies ranging from pediatric low-grade gliomas and glioneuronal tumors to pediatric high-grade gliomas including glioblastoma (GBM), anaplastic astrocytoma, and diffuse midline gliomas. All these entities have reports of

region tumor. He then underwent radiation to ventricles with boost to pineal region. Sagittal T1-post contrast MRI of the brain from 2014 confirmed no residual tumor after chemotherapy, radiation, and suboccipital craniotomy for tumor excision. (**K**). At 4- and 6-years follow-up, MRI of the spine and brain, respectively, showed no evidence of recurrent or residual disease. He re-presented in 2022 at age 19 with 2 weeks of bilateral neck pain that radiates down shoulders, numbness of the left arm, handgrip weakness, and overall weakness and heaviness in the legs. Sagittal T1-post contrast of brain from 2022 does not demonstrate intracranial relapse or LMD (**L**). However, MRI of the spine demonstrated a 1.9 × 1.3 cm x 3.3 cm expansive intramedullary lesion that extended from C2 to C4 with T2 hyperintense signal (**M**, arrow), as well as other areas of nodular enhancement, concerning for LMD. He underwent C2-4 laminectomy with biopsy of intradural intramedullary mass, with pathology consistent with LMD of GCT. He underwent emergent radiation and was started on chemotherapy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Literature review of immunotherapy based clinical trials for CNS tumors with LMD.

Study title	Conditions	Treatment	Delivery route	Age - year	Sponsor	ID
Iodine I 131 Monoclonal Antibody 3F8 in Treating Patients With Central Nervous System Cancer or Leptomeningeal Cancer	CNS tumors, intraocular melanoma, lung cancer	131 I-3F8	IT	Child, adult	Memorial Sloan Kettering Cancer Center	NCT00445965
131I-omburtamab Radioimmunotherapy for Neuroblastoma Central Nervous System/Leptomeningeal Metastases	Neuroblastoma, CNS metastases, LMD	131 I-omburtamab	IT	up to 18	Y-mAbs Therapeutics	NCT03275402
Radiolabeled Monoclonal Antibody Therapy in Treating Patients With Refractory, Recurrent, or Advanced CNS or Leptomeningeal Cancer	Brain and CNS, Neuroblastoma	131 I-omburtamab	IT	Child, adult	Y-mAbs Therapeutics	NCT00089245
131I-omburtamab for the Treatment of Central Nervous System/Leptomeningeal Neoplasms in Children and Young Adults	Central Nervous System/LMD Neoplasms	131 I-omburtamab	IT	Child, adult	Memorial Sloan Kettering Cancer Center	NCT05064306
131I-Omburtamab, in Recurrent Medulloblastoma and Ependymoma	Recurrent MD, ependymoma	Irinotecan, temozolomide, bevacizumab, 131 I-omburtamab, liothyronine, dexamethasone	IT/IV/Oral	up to 21	Pediatric Brain Tumor Consortium	NCT04743661
Study of B7-H3-Specific CAR T Cell Locoregional Immunotherapy for Diffuse Intrinsic Pontine Glioma/Diffuse Midline Glioma and Recurrent or Refractory Pediatric Central Nervous System Tumors	Recurrent CNS tumors, DIPG	CAR T-B7H3	Intratumoral	1 to 26	Seattle Children's Hospital	NCT04185038
CAR T Cells After Lymphodepletion for the Treatment of IL13Rα2 Positive Recurrent or Refractory Brain Tumors in Children	Recurrent CNS tumors	CAR T-B7H3	IT/IV	4 to 25	City of Hope Medical Center	NCT04510051
Brain Tumor-Specific Immune Cells (IL13Ralpha2-CAR T Cells) for the Treatment of Leptomeningeal Glioblastoma, Ependymoma, or Medulloblastoma	Ependymoma, glioblastoma, MB	CAR T-B7H3	IT	18 and older	City of Hope Medical Center	NCT04661384
EGFR806-specific CAR T Cell Locoregional Immunotherapy for EGFR-positive Recurrent or Refractory Pediatric CNS Tumors	Recurrent CNS tumors	CAR T-EGFR	IT	1 to 26	Seattle Children's Hospital	NCT03638167

LMD [107]. In addition, the 2016 WHO classification of tumors of the CNS added a distinct entity: Diffuse Leptomeningeal Glioneuronal Tumor (DLGNT) [108,109,110]. This lesion is characterized by nodular LMD with or without an intraparenchymal mass. The most common mutation identified in DLGNT patients is the *KIAA1549:BRAF* fusion, a fusion identified in pediatric gliomas such as pilocytic astrocytoma and which leads to constitutive activation of the MAPK pathway [111].

Management of LMD

Many current chemotherapeutic or radiation-based treatments for PBTs do not achieve desired efficacy and cause significant toxicity to the developing CNS. The failure of these treatments is thought to be due, in part, to the presence of the blood-brain barrier, the blood-CSF barrier and the blood-tumor barrier that may limit the efficacy of drug delivery and the patient's innate immunologic response. Molecular differences between the primary (often the only biopsied site) and the leptomeningeal tumors may also contribute to poor outcomes [112]. Current treatment of LMD in children include radiation, surgery, chemotherapy, targeted therapy, or immunotherapy.

Surgery

While LMD is not a disease that surgical resection can address given the diffuse nature and localization of the tumor cells, surgical adjuncts are needed in the management of the disease. Surgical interventions for LMD include ventriculoperitoneal shunt placement for relief of raised intracranial pressure, and Ommaya reservoir placement for repeated administration of chemotherapeutic agents or for CSF sampling to serially evaluate patients for CTCs and disease status [113]. The role of routine, temporally spaced sampling of CSF to help diagnosis and monitor response to treatment is an area of active research. Sampling variability is a known challenge for interpreting the results; in a group of ependymoma patients routine surveillance via CSF sampling for cytology evaluation was shown to be very inconsistent during treatment [114].

Radiation treatment

Both whole brain radiation therapy (WBRT) and CSI have been used for decades to prevent or treat LMD [115]. Patients diagnosed with LMD will most likely undergo radiation at one point as part of their treatment, except children younger than 3 years old, where radiotherapy is typically avoided or delayed as much as possible to minimize acute and late toxicities [116]. Radiotherapy can be given alone or together with chemotherapy. For patients with LMD who have not received CSI before, palliative CSI is the treatment of choice. In a reported case of midline H3K27M-mutant tumor glioma with LMD along the entire neuroaxis, palliative CSI with a boost given to the primary tumor in the thalamus resulted in marked response in the supratentorial and infratentorial leptomeningeal enhancement [107].

Local stereotactic radiation therapy (SRT) can be used in patients with prior CSI to control LMD, especially in bulky disease. In a small cohort, King et al [117] assessed the efficacy and tolerance of SRT in 3 children who received CSI at diagnosis with metastatic relapse of MB. The CSF space is uniquely suited to compartmental radiotherapy for leptomeningeal malignancies. Radiolabeled drugs, like ^{131}I-omburtamab administered intrathecally [118,119] can deliver small amount of radi-

Table 2
Literature review of chemotherapy based clinical trials for CNS tumors with LMD.

Study title	Conditions	Treatment	Delivery route	Age - year	Sponsor	ID
Infusion of 5-Azacytidine (5-AZA) Into the Fourth Ventricle in Patients With Recurrent Posterior Fossa Ependymoma	Recurrent Ependymoma	5-Azacytidine	IT	1 to 80	The University of Texas Health Science Center	NCT03572530
Combination Intraventricular Chemotherapy Pilot Study: 5-Azacytidine (5-AZA) and Trastuzumab Infusions Into the Fourth Ventricle or Resection Cavity in Children and Adults With Recurrent or Residual Posterior Fossa Ependymoma	Posterior Fossa Ependymoma	5-Azacytidine, trastuzumab	IT	1 to 80	The University of Texas Health Science Center	NCT04958486
Antiangiogenic Therapy for Children With Recurrent Medulloblastoma, Ependymoma and ATRT	Recurrent AT/RT, ependymoma, MB	Bevacizumab, thalidomide, celecoxib, fenofibric acid, etoposide, cyclophosphamide, etoposide phosphate, cytarabine	IT/IV/Oral	up to 19	Medical University of Vienna	NCT01356290
Lutathera for Treatment of Recurrent or Progressive High-Grade CNS Tumors or Meningiomas Expressing SST2A	Recurrent HHG	Lutathera®	IV	4 and older	Children's Hospital Medical Center, Cincinnati	NCT05278208
Methotrexate and Etoposide Infusions Into the Fourth Ventricle in Children With Recurrent Posterior Fossa Brain Tumors	Brain Tumor Recurrent	Methotrexate, Etoposide	IT	1 to 80	The University of Texas Health Science Center	NCT02905110
Infusion of Panobinostat (MTX110) Into the Fourth Ventricle in Children and Adults With Recurrent Medulloblastoma	Recurrent MB	Panobinostat - MTX110	IT	1 to 80	The University of Texas Health Science Center	NCT04315064
Infusion of 5-Azacytidine (5-AZA) Into the Fourth Ventricle in Patients With Recurrent Posterior Fossa Ependymoma	Recurrent Ependymoma	5-Azacytidine	IT	1 to 80	The University of Texas Health Science Center	NCT03572530
Combination Intraventricular Chemotherapy Pilot Study: 5-Azacytidine (5-AZA) and Trastuzumab Infusions Into the Fourth Ventricle or Resection Cavity in Children and Adults With Recurrent or Residual Posterior Fossa Ependymoma	Fossa Ependymoma	5-Azacytidine, trastuzumab	IT	1 to 80	The University of Texas Health Science Center	NCT04958486

ation locally, targeting CTCs and small bulky tumors (less than 1 cm) (Table 1).

Chemotherapy/drug delivery

Drug delivery for LMD treatment may be performed using systemic (intravenous or IV) or local (intrathecal or IT, e.g., intraventricular, lumbar cistern) routes. Assuming CSF flow is not obstructed, IT is usually preferred over IV delivery as systemic chemotherapies do not offer a high CSF penetration of drugs and therefore do not achieve an active pharmaceutical dose against LMD. In addition, IT delivery offers a more uniform drug distribution and allows short half-life drugs to be more optimally delivered [120].

Despite the pharmacologic advantages of IT chemotherapy, there are some disadvantages: (*i*) IT drug administration may be associated with higher complication rate and post-procedural pain; (*ii*) radioisotope studies have shown that in as many as 10% of lumbar punctures, drug may be inadvertently administered into the epidural or subdural space, and not to the intended subarachnoid space [121]; (*iii*) distribution of the drug within the neuroaxis after IT infusion may not be homogeneous as it varies with CSF bulk flow and patient position [122] and (*iiii*) following IT drug administration, based on bolus administration, penetration into tissue is minimal, thereby limiting potential efficacy in patients who have bulky leptomeningeal or parenchymal tumors [123]. Ventricular access devices facilitate repeated access to the IT space, resulting in confirmed drug delivery into the CSF and greater flexibility in dosing schedules, thus improving the efficiency and toxicity of the treatment. In a pilot study with 5 patients [124], a catheter was surgically placed into the fourth ventricle and attached to a ventricular access device and patients were treated with 4 consecutive daily methotrexate bolus infusions (2 mg). Five patients (3 with MB and 2 with ependymoma) received 18, 18, 12, 9, and 3 cycles, respectively. There were no serious adverse events or new neurological deficits attributed to methotrexate. All 3 patients with MB had partial response or stable disease until 1 patient had progressive disease after cycle 18. Both patients with ependymoma had progressive disease after 9 and 3 cycles, respectively. Some patients with recurrent MB experienced a beneficial anti-tumor effect both within the fourth ventricle and at distant sites [124]. Similarly, in a pilot study with 5 ependymoma patients using a weekly bolus of 5-azacytidine into the fourth ventricle no serious adverse events or neurologic deficits were observed. All patients unfortunately progressed, however, with partial response observed in 2 patients [125]. In addition to bolus administrations in the fourth ventricle, another study has shown that chronic continuous IT administration of chemotherapy is also safe. Tran et al [126] evaluated the toxicity and survival benefit from a continuous IT injection of topotecan in a patient with recurrent ependymoma. Topotecan was given at a rate of 0.6 mL/h for 7 days with a daily dose of 0.2 mg for a total of 1.4 mg over the course of treatment. After 2 courses, the patient had no neurological adverse events and showed signs of disease stabilization.

The above suggests that ventricular and continuous chronic IT delivery of chemotherapy is safe and has proven to be efficient in several CNS tumors [51,127–129] The drugs commonly used for IT chemotherapy are methotrexate, liposomal cytarabine, etoposide, and topotecan. However, there is currently no standard of care for LMD in PBTs and most treatments are individualized and institutionalized. Novel therapeutics as well as delivery methods to address LMD are currently being investigated. For example, a recent preclinical study identified Ephrin type-A receptor 2 (EPHA2), Human epidermal growth factor receptor-2 (HER2) and interleukin 13 receptor α2 (IL13Rα2) as targets for chimeric antigen receptor T (CAR-T) cell-based therapy for LMD and other CNS tumors and phase 1 studies are under way [130]. The clinical outcomes of CAR-T cell therapies have proven remarkably efficient and long-lasting, rendering them an appealing treatment for several human cancers [131]. In addition, the administration of modified human neural stem cells carrying cytosine deaminase gene improved the OS in a mouse model of MB with LMD [132]. Additionally, IT delivery of a novel retinoid receptor agonist UAB30 led to a significant

reduction of tumor growth in a group 3 MB (D341 cells) intraventricular mouse model [133]. Clinically, a current phase I clinical trial (NCT04661384) investigates the feasibility and side effects of IL13Rα2 hinge-optimized 41BB-co-stimulatory CAR truncated CD19-expressing T-lymphocytes (IL13Rα2-CAR T cells) via intracerebroventricular (ICV) delivery in patients diagnosed with LMD derived from primary GBM, MB or ependymoma. Another targeted approach for the treatment of LMD is radioimmunotherapy which targets and delivers a small amount of radionuclide to the cancer cells thereby reducing radiation exposure to healthy tissues [134]. Current radiopharmaceutical used via IT delivery are ^{131}I-omburtamab, a monoclonal antibody (mAb) directed to B7-H3 (NCT03275402, NCT04743661, NCT00089245, NCT05064306) and ^{131}I-3F8 specific to GD2 (NCT00445965). An extensive list of current immunotherapy and chemotherapy clinical trials for CNS tumors with LMD, which include pediatric patients is presented in Tables 1 and 2 respectively.

Conclusion

LMD is the ultimate challenge in the treatment of almost every brain tumor in children. In PBTs, improved OS due to improvement in surgical techniques and systemic therapeutics, together with more sophisticated diagnostic methods, is leading to an increased incidence and recognition of LMD. Better understanding of the biology underlying this particular and lethal form of metastasis and the development of specific therapeutical approaches is a crucial priority. Unfortunately, due to the rarity of the disease, very few preclinical models are available. The genetic analysis, especially changes observed in the disseminated tumor cells compared to the primary tumor, are also limited due to lack of matched samples. Additional studies involving PBTs matched primary and LMD samples should be performed for all pediatric tumors presenting LMD, which will potentially help identify targetable mutations and understand the biology behind LMD. Given the rarity of PBTs, we expect that international consortia for collecting, sequencing, and establishing patient-derived xenografts models of PBTs LMD will play a major role in future studies aiming at determining the commonalities and differences of mechanisms involved in PBTs LMD.

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.

CRediT authorship contribution statement

Carolina Cocito: Writing – review & editing. **Brice Martin:** Writing – review & editing. **Alexandra M. Giantini-Larsen:** Writing – review & editing. **Marcus Valcarce-Aspegren:** Writing – review & editing. **Mark M. Souweidane:** Writing – review & editing. **Luca Szalontay:** Writing – review & editing. **Nadia Dahmane:** Writing – review & editing. **Jeffrey P. Greenfield:** Writing – review & editing.

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