

**Case Report**

A Wilms Tumor Patient with Leptomeningeal Metastases, A Case Report and Literature Review of Early CNS Metastasis, At Presentation or During Treatment

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Abstract

Background: Wilms tumor (WT) is the most frequently occurring pediatric kidney cancer. Around 10-17% of patients with Wilms tumor present with metastatic disease, most commonly in the lungs and liver. In patients with Wilms tumor, central nervous system metastases are uncommon. This study was conducted with the aim of identifying patients with leptomeningeal metastases and their specific characteristics.

Methods: An in-depth case description of a patient with a Wilms tumor who developed leptomeningeal metastases during treatment was provided. For this narrative literature review, a PubMed data search was performed up until November 8, 2023. Articles were screened based on predefined inclusion and exclusion criteria.

Results: We report a three-year-old male presenting with stage IV, local stage III intermediate-risk Wilms tumor, with bone metastases and a solitary lung metastasis. Despite the initial response to treatment, the patient developed seizures during therapy, based on leptomeningeal metastases without obvious brain mass. A literature review on early central nervous system metastases in patients with Wilms tumor (at diagnosis, or during therapy) identified 10 additional patients with Wilms tumor showing central nervous system disease but did not identify any other patient with leptomeningeal disease (only).

Conclusions: Leptomeningeal metastases in Wilms tumor patients are rare and may not be recognized due to a lack of available literature and awareness. However, it is crucial to remain vigilant for symptoms of leptomeningeal metastases, even in patients with an intermediate-risk histology.

Keywords: Wilms tumor; leptomeningeal cancer; leptomeningeal metastases; pediatric; Wilms tumor metastases.

Introduction

Wilms tumor (WT), or nephroblastoma, is the most prevalent pediatric kidney cancer. Currently, the overall survival rate for patients with WT is around 90% [1]. Survival depends strongly on biological behavior, associated with histological subtype and staging. Patients with metastatic WT (stage IV) exhibit a 5-year event-free survival rate of about 28-73% [2-5]. Around 10-17% of all patients with WT present with metastatic disease [1,2]. These metastases present most commonly in the lungs and liver and rarely in the bones or in the central nervous system (CNS) [3]. In some patients, CNS metastases are present at diagnosis either as intracerebral metastases or reflect direct spinal infiltration [7,33-36]. Central nervous system metastases can involve the brain parenchyma, leptomeninges (pia, subarachnoid space and arachnoid mater), and the dura.

Here, we describe the characteristics and outcome of a 3-year-old boy that was diagnosed with a stage IV, local stage III intermediate WT who developed diffuse leptomeningeal metastases during treatment. We also pursued and present a narrative review of all patients with WTs with CNS metastases at diagnosis and during treatment, with the aim to identify other patients with leptomeningeal metastases and their specific characteristics, which revealed that leptomeningeal metastases only, had never been reported in children with WT.

Case Presentation

A 3-year-old male, born with a normal birth weight for gestational age, presented with abdominal extension, based on a right-sided renal tumor with a solitary lung metastasis (5 x 4 x 3 mm) and several bone metastases (Figure 1). According to the SIOP-RTSG-2016 UMBRELLA protocol (further referred to as UMBRELLA), based on the bone metastases, a tumor biopsy was performed [4]. Histology revealed a WT without anaplasia (Figure 2, Table 1) (Molecular testing showed a *MYCN* mutation, no 1q gain, and no loss of heterozygosity (LOH) of 16q). The patient started treatment according to UMBRELLA with six weeks of pre-operative chemotherapy, i.e. vincristine, doxorubicin, and actinomycinD (VAD). Repeated imaging showed partial response in week seven (all sites). Tumor-nephrectomy was performed and histology revealed local stage III intermediate-risk histology WT (mixed subtype) (two lymph nodes positive). Post-operative treatment included 34 weeks of chemotherapy (four drugs: carboplatin, etoposide, doxorubicin, and cyclophosphamide), and abdominal radiotherapy at postoperative week 10 (Total of 14.4Gy; lung metastases (CT scan) and bone metastases (total body MRI including brain) showed complete remission at week 10 post-operatively). Nine weeks into post-operative chemotherapy, the patient presented with a mechanical ileus for which adhesiolysis was performed. Radiotherapy to the right flank was given (8 fractions of 1.8Gy). Eighteen weeks into post-operative treatment, the patient experienced afebrile, nocturnal headaches, vomiting, a sudden onset of reduced consciousness (E4M4V1) and seizures,

after which he required intubation and PICU admission. MRI of the brain showed diffuse leptomeningeal enhancement with a broad differential diagnosis including infection, inflammation, and metastasis (Figure 1). Antiepileptic drugs, antibiotics, and aciclovir were administered. Upon neurological examination, asymmetry in pupil size (left pupil $>$ right pupil), but no signs of paresis were observed. Reflexes were symmetric. Plantar reflexes were bilaterally indifferent with a tendency towards the Babinski reflex on both sides. Cerebrospinal fluid (CSF) examination revealed an increased protein level (2.23 g/L), glucose <0.6 mmol/L, without elevated pressure measurement. Bacterial cultures, serum galactomannan, and viral PCR were negative. Histology of the CSF showed a few cells, difficult to classify, with some atypia, but did not identify nephroblastoma cells. One day later, post extubation, a cerebral and craniospinal MRI (T2), revealed increased leptomeningeal cerebrospinal enhancement without any CNS mass (Figure 1). Five days later, the patient further developed an unsteady gait and reported dizziness, indicative of progressive ataxia. CSF analysis was repeated, which did not reveal any malignant cells. Since CSF analysis did not provide conclusive results, a leptomeningeal biopsy via thoracal laminotomy was performed, of which histology demonstrated stromal type WT cells (Figure 2). No actionable targets were identified through molecular testing using next-generation sequencing in the

personalized medicine program (Figure 3). Fresh, viable material was obtained; however, organoid establishment was unsuccessful, and a compound screen was therefore not feasible [5,6]. Clinically, the headache and vomiting persisted and several atypical multifocal seizures with restless behavior and varying compulsion of the eyes occurred daily. In addition, there was an increase in myoclonus in the right arm and hand. Due to clinically and radiologically confirmed rapid disease progression during therapy, craniospinal radiotherapy was administered and chemotherapy was switched to ifosfamide, carboplatin, and etoposide (ICE), with the aim to administer four courses followed by high-dose chemotherapy (HD-CEM; carboplatin, etoposide, melphalan), and autologous stem cell rescue. After one ICE course, MRI showed a diffuse decrease in leptomeningeal enhancement, intracranially as well as along the spinal axis, and the second ICE course was administered. Unfortunately, after two courses of ICE, craniospinal MRI revealed further progression of leptomeningeal disease. Subsequently, shared decision-making with parents led to the preference for palliative treatment (radiotherapy and oral temozolamide). Fourteen weeks later, a CT scan of the brain showed disease progression with an expansion of ventricles, increased hydrocephalus, and growth of the leptomeningeal metastases. The patient subsequently died due to disease progression (Figure 4).

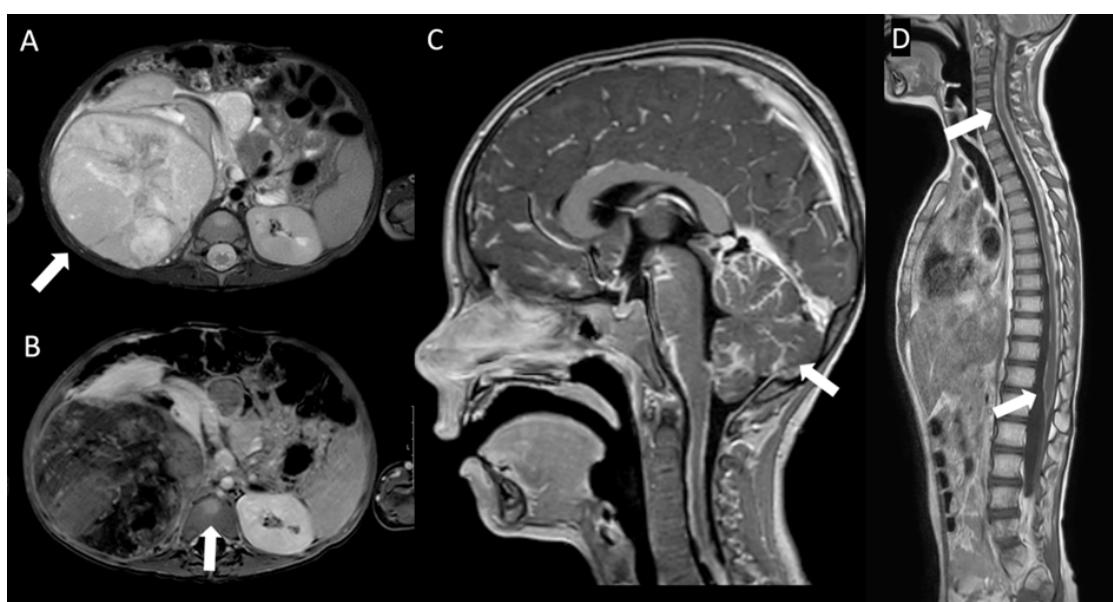


Figure 1: Imaging of Wilms Tumor at primary diagnosis and at leptomeningeal metastases. A: A mass in the left kidney with band-like enhancement, radiologically indicative of a WT. B: Visible on MRI is capsular bleeding, a suspect lymph node, and multiple enhancing lesions in the bone marrow of the pelvis, proximal femora, and spine. C: Abnormally increased leptomeningeal enhancement is observed in the cerebrum. D: Increased enhancement along the spinal cord consistent with the biopsy-proven leptomeningeal disease.

Histology	Microscopic	TB	WT without anaplasia (IR-WT)
		TN	Mixed type WT without anaplasia (IR-WT), 2 positive lymph nodes (anterior of right renal artery, and para-aortal)
		LB	Histological similarities with the stromal component of the primary WT
	Immunohistochemistry	TB	WT1 ⁺ , PAX8 ⁺ , CD56 ⁺ blastemal cells, pankeratin ⁺ , and EMA ⁺ epithelial cells. INI1 and BRG1 preserved. Myogenin ⁻ , MyoD1 ⁻ , TdT, CD45 ⁻ , synaptophysin ⁻ , chromogranin ⁻ , and S100 ⁻ .
		LB	Desmin ⁺ , PAX8 ⁺ . Focal weak positive for WT1. INI1 and BRG1 preserved.
Germline genetics	No pathogenic variants were detected within the pediatric kidney tumor WES gene panel*		
Molecular	TB	**WES: <i>MYCN</i> variant c.131C>T RNA sequencing: no clinically relevant gene fusions no CNVs, no 1q gain, no LOH 12p, no LOH 16q	
	TN	**WES: <i>MYCN</i> variant c.131C>T, <i>CTNNB1</i> variant c.1161T>A RNA sequencing: no clinically relevant gene fusions no CNVs, no 1q gain, no LOH 12p, no LOH 16q, <i>MYCN</i> variant c.131C>T, <i>CTNNB1</i> variant c.1161T>A	
	LB	**WES: <i>NRAS</i> variant c.181C>A, gain of chr 2, 8, 13, 14, and 19, no 1q gain, no LOH 12p, no LOH 16q RNA sequencing: <i>NRAS</i> variant c.181C>A	

Table 1: Tumor characteristics of current case. Histologic, genetic, and molecular characteristics of the patient described in this report. TB= tumor biopsy, TN= total nephrectomy specimen, LB= leptomeningeal biopsy, IR-WT= intermediate-risk Wilms tumor, WES= whole exome sequencing, CNV= copy number variation, chr= chromosome, LOH= loss of heterozygosity. *Germline gene panel = AMER1, ASXL1, BLM, BRCA2, BUB1B, CDC73, CDKN1C, CEP57, CTR9, DICER1, DIS3L2, FBXW7, GPC3, GPC4, HACE1, MLH1, MSH2, MSH6, NF1, NYNRIN, PALB2, PMS2, PIK3CA, REST, TP53, TRIM28, TRIM37, TRIP13, and WT138. **WES all samples: highly focal CN-LOH on chromosome 11p. Beckwith Wiedeman syndrome negative.

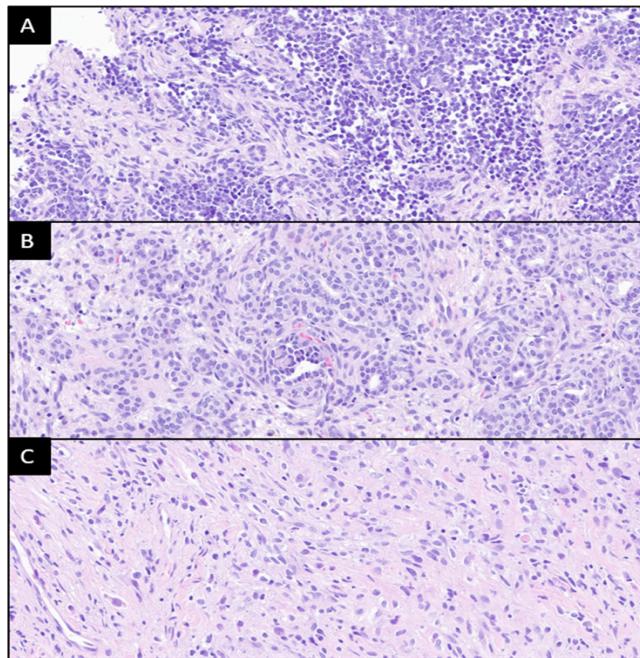


Figure 2: Histology of tumor biopsy, total nephrectomy, and leptomeningeal biopsy. (A) Hematoxylin and eosin-stained images of the initial tumor biopsy showing triphasic Wilms tumor with predominant blastemal component, in addition to minor epithelial and stromal areas. (B) The nephrectomy specimen shows a mixture of mature epithelium and stroma, with only minor areas of blastema (not present in this image). (C) In the leptomeningeal metastases the stromal component predominates, as seen in image. Stromal cells display immunoreactivity for desmin (not shown). All images x400 magnification.

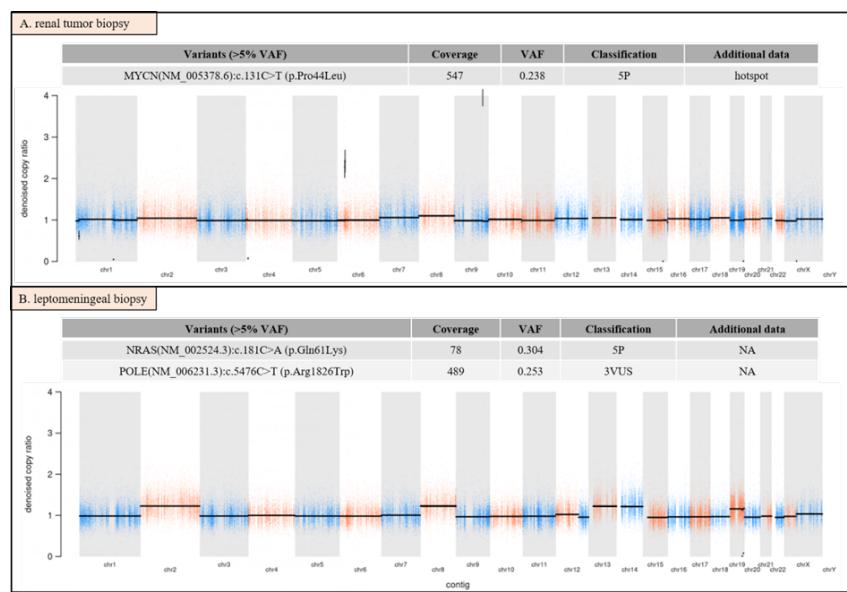


Figure 3: Molecular testing results. Next generation sequencing at molecular testing for both renal tumor (A) and leptomeningeal metastases (B). Renal tumor biopsy molecular testing revealed a *MYCN* gene mutation, no copy number variations (CNVs), no 1q gain, no LOH 12p, and no LOH 16q. Leptomeningeal biopsy molecular testing revealed an *NRAS* gene mutation, and a *POLE* mutation (variant of unknown significance), a gain of chr 2, 8, 13, 14, and 19, no 1q gain, no LOH 12p, and no LOH 16q.

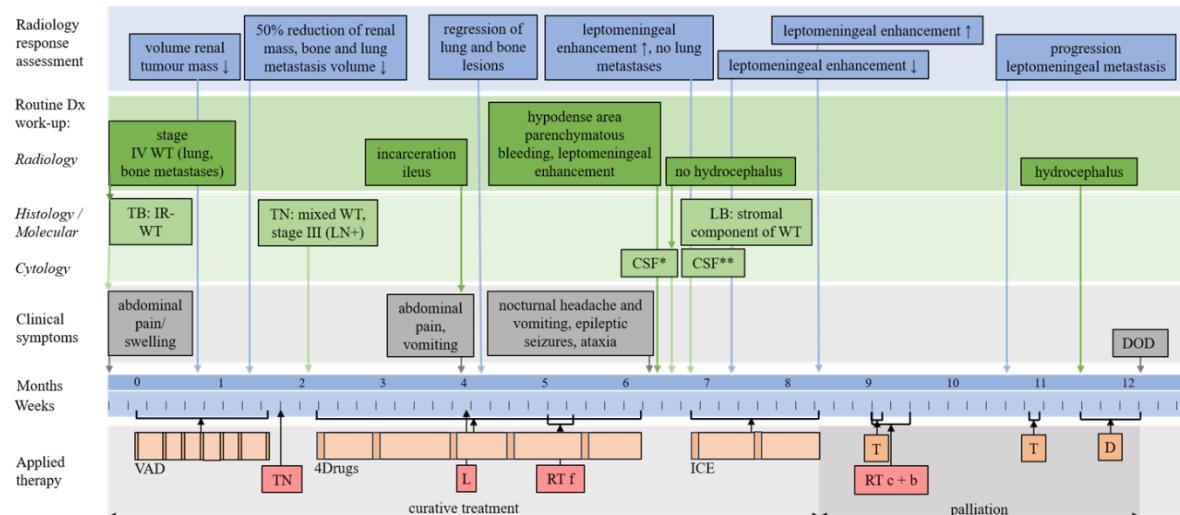


Figure 4: Presentation and evolvement of disease of the patient with WT. Timeline of symptoms, diagnostics, and treatment of the patient described in the current patient case. TB= tumor biopsy, CSF= cerebrospinal fluid, CSF*= cytology: no malignant cells, CSF**= no malignant cells, leptomeninges: stromal component WT, LN+= 2 positive lymph nodes. VAD= cycles of combinations of vincristine + actinomycin + doxorubicin following UMBRELLA protocol. 4Drugs= cycles of combinations of cyclophosphamide + doxorubicin + carboplatin + etoposide following UMBRELLA protocol. ICE= cycles of ifosfamid + carboplatin + etoposide. T= temozolamide, D= dexamethasone 2dd1mg, TN= total nephrectomy, L= laparotomy, RT f = radiotherapy right flank (total cumulative dose 14.4 Gy), RT c + b = radiotherapy craniospinal axis + brain (total cumulative dose 20 Gy).

Narrative literature review

We performed a literature search for the occurrence of CNS metastases at diagnosis or during WT treatment up until November 8, 2023. PubMed database was searched using synonyms for “Wilms tumor”, and “CNS metastases” (full search strategy see Supplementary Table 1). The search yielded 451 articles. All articles, written in English, describing several types of CNS metastases, were eligible for inclusion. Articles concerning non-Wilms kidney tumors and all reports describing relapses after the end of therapy, were excluded. After title and abstract screening, a total of 70 articles were eligible for full-text screening, after which 62 articles were excluded. We extracted information on patient characteristics, WT features, treatment, time to CNS metastasis, and the management of CNS metastases, along with their respective outcomes, from the eight included articles. A cross-reference check was also performed and yielded two additional articles (Supplementary Figure 1).

Summary of existing cases including literature and our case (n=11)

In the literature, we identified 10 well-documented patients with WT and CNS metastases at diagnosis or during treatment. We

summarized clinical characteristics, including the patient described in this report, resulting in 11 patients in total, as depicted in Table 2.

Among all 11 patients, there were six boys and five girls. The median age at WT diagnosis was 4 years (range: 4 months - 14 years), with six out of 11 patients being under five years of age. None of the patients were reported to exhibit an underlying predisposition syndrome associated with WT.

At the time of WT diagnosis, three patients had localized disease, and eight patients had metastasized disease (stage IV) WT (other than CNS, metastatic sites included vertebral bone n=3, bone n=2, pulmonary n=4, liver n=1, and extradural n=1). No patients were reported to have stage I or stage V at the time of diagnosis. Five out of 11 tumors exhibited high-risk histology (blastemal n=3, diffuse anaplastic n=2), and six out of 11 exhibited an intermediate-risk histology. Immunohistochemistry was reported for three patients, revealing WT1 expression in two out of three patients (Table 2). Our patient was the only patient with available molecular testing. He revealed an activating somatic *MYCN* mutation (c.131C>T (p.Pro44Leu)), no 1qgain, and no LOH of 16q or 1p (Table 1 and 2).

CNS metastases were identified in five patients at WT diagnosis, with the following distribution; epidural (n=1), epidural and intraspinal (n=1), tectal plate and ventricular (n=1), intradural (n=1), and unspecified (n=1). One CNS metastasis caused hydrocephalus and CSF contained tumor cells, however, CNS location was not further specified. Three patients had received preoperative chemotherapy (five did not, and three were not described). After surgery, three patients had received chemotherapy only, and seven had a combination of radiotherapy (brain n=3) and chemotherapy. Therapy for CNS metastasis was not described for the remaining patient.

In six patients (stage II n=1, stage III n=2, and stage IV n=3), CNS metastases (parenchyma n=2, epidural n=3, and in the current patient leptomeningeal n=1) developed during treatment, with a median time from diagnosis to CNS metastasis of 37.5 weeks (3 weeks - 52 weeks). Our patient presented with CNS metastases during treatment for WT, and a combination of metastases also reported by Sudour-Bonnange et al [7]. The latter patient with a blastemal type WT who underwent surgery, received chemotherapy and vertebral radiotherapy, responded well and survived.

All patients exhibited symptoms consistent with CNS involvement, most commonly back pain (n=6) and paresthesia (n=6), at the onset of CNS metastasis (Supplementary Table 2). Epileptic seizures and ataxia were only reported in the current patient and were not documented in the other patients with CNS metastases, at diagnosis or during treatment (Table 3). However, no other patients with WT and leptomeningeal metastases were reported in these studies. Therapy in patients with the development of CNS metastases during treatment encompassed surgery, chemotherapy, or variable combinations of surgery, and/or chemotherapy, and/or radiotherapy, and/or dexamethasone (Table 2).

Five of the 11 patients with WT survived, and six patients died of disease. Of all surviving patients one had favorable histology, one had unfavorable histology with focal anaplasia, and three had blastemal histology subtype. Of all patients who died of disease one had favorable histology, one had mixed histology, one had epithelial histology, two had diffuse anaplastic histology subtypes, and for one patient histology was not described. The patients with blastemal WT survived.

Discussion

We here reported the first patient with WT who developed leptomeningeal metastases during treatment (without CNS mass). At diagnosis, the patient presented with multiple bone metastases and a solitary lung metastasis without signs of CNS metastases. This was in a patient that responded well to treatment (tumor volume decreased from 1236 ml to 560 ml after six weeks of upfront VAD and metastases in the lungs and bones were no longer visible on whole-body MRI and CT thorax), 10 weeks postoperatively.

However, in postoperative week 18, the patient exhibited epileptic seizures and ataxia, due to via laminectomy obtained tissue-proven leptomeningeal disease.

Leptomeningeal metastases in patients with WT have not been previously described in the literature. This absence of prior reports describing leptomeningeal metastases in patients with WT contrasts with their described presence in other pediatric cancers [8,9]. In the current patient, the absence of a tumor mass in adjacent structures, such as bones, makes it unlikely, that the metastasis originated from nearby tissue to the CNS. Despite the protective nature of the blood-brain barrier, which shields the CNS from bloodstream components, metastasis seems to be most likely due to hematogenous spread. Hematogenous spread is described via arachnoid vessels or choroid plexus and also speculated via the retrograde venous pathways along the Valveless Batson's venous plexus [10-12]. Considering the complexity of breaching the blood-brain barrier, spreading to the CNS without a primary tumor nearby points to the adaptability of tumor cells [13].

WTs are known to metastasize predominantly to the lungs and liver [4]. Bone metastases are rare, having been reported in only 0.44% of WT cases, with a higher likelihood of occurrence at relapse, namely in 76% of bone metastatic cases [14,15]. Additionally, intracranial metastases in WT are very uncommon, occurring in less than 1% of patients with WT, and if so they mainly appear at relapse [3,16,17]. Interestingly, our patient presented with multiple bone metastases at diagnosis. In our case, we had not searched for CNS metastases, and after 18 weeks into post-operative therapy, seizures appeared, for which enhanced MRI was necessary to identify the metastases. It needs to be determined whether, in patients with bone metastasis, baseline staging with this radiological tool should include the CNS screening as standard of care, as bone metastasis has been described to occur together with CNS involvement in several cases now. However, it is unclear whether our patient had the metastases at presentation, and whether we would have been able to rescue the (otherwise well-responding) patient by application of CNS irradiation at an earlier stage. The disease progression of our patient case illustrates the aggressiveness of the disease, despite the initial sensitivity and response to standard treatment with chemotherapy for WT.

Leptomeningeal metastases typically arise as a late-stage complication of cancer, leading to increased intracranial pressure and neurological symptoms [12]. Cancer cells infiltrate the leptomeninges and CSF via direct invasion from adjacent structures, hematogenous spread, or entry through the choroid plexus [10]. Metastatic leptomeningeal cancer cells exhibit distinct phenotypic characteristics and can be localized in the CSF or adhere to the pia and arachnoid mater, respectively 'floating cells' or 'pia-attached' (MRI positive) cancer cells. Patients with CSF, i.e. floating cell, leptomeningeal metastases have a worse prognosis [18]. Overall,

leptomeningeal metastases result in poor overall survival in other cancers, with survival periods ranging from 2.6 to 6.9 months [19].

Our patient developed clinical symptoms based on leptomeningeal metastases without apparent CNS mass. Our current literature review on CNS positive WTs, shows that only 11 well-documented *de novo* patients (including our patient) have been reported so far. The ten published cases presented with tumor mass. High-risk (HR) tumor characteristics, such as advanced stage, blastemal or diffuse anaplastic histology subtype associated with a more aggressive course, are prevalent. Again, the occurrence of bone metastases seems to be more likely in WT patients with CNS metastases (three out of 11 patients), compared to the described 0.44% in sporadic patients with WT [14]. Recurrent molecular characteristics, such as loss of p53 function in anaplastic tumors, 1p and 16q loss, and 1q gain, potential indicators of poor outcomes, were not studied and thus reported in any, apart from our, CNS metastatic WT patient [20–23]. No pathogenic germline variants were detected in our patient (Table 1). In our patient, a *MYCN* somatic mutation was identified in the WT, however not in the leptomeningeal biopsy, where a *de novo* *NRAS* somatic mutation was detected. *MYCN* mutations in WTs are associated with relapses and poor outcome [22,24]. Research into the biological characteristics and development of kidney tumors (SIOP) and relapses is expanding, and research performed by the COG (Children's Oncology Group) provides indications of an association between specific gene expression signatures and relapses in stage III favorable histology (FH)-WT [25]. However, due to the rarity, studies on the molecular characteristics, that play a role in the development of homing of WT cells towards the CNS specifically, are not to find [2,25]. Hence, further studies are needed to identify molecular and tumor-associated indicators for CNS metastases.

Our patient presented with epileptic seizures and ataxia leading to a suspicion of CNS involvement. Nevertheless, brain CT as well as CSF examination did not explain the patient's symptoms. CSF cytology is the gold standard for the identification of leptomeningeal metastases, however, it only has a sensitivity of 44-67% for detecting leptomeningeal metastases [26]. CSF diagnostics can detect the freely floating cancer cells, however, the pia mater attached cancer cell form of leptomeningeal metastases is better visualized on MRI [18]. Therefore, even though leptomeningeal metastases are very rare and have not previously been described in patients with WT, given the severity, it is important to perform further diagnostics starting with contrast-enhanced MRI. If a

combination of MRI and CSF analysis is inconclusive, our patient case shows, that leptomeningeal biopsy to detect leptomeningeal metastases may be of help.

Leptomeningeal metastases are challenging to treat, and the outcome of CNS disseminated disease seems poor. Early identification and CNS penetrating treatment focuses on postponing neurological deterioration and is important, as performance status expressed in Lansky score at diagnosis is described to be the most important prognostic factor [27,28]. For the treatment of CNS metastases, it is crucial that CNS-penetrating chemotherapeutic agents are administered. This is guaranteed in the current SIOP RTSG Umbrella protocol, partly in upfront treatment through vincristine, but even better in the 4-drug regimen that includes etoposide and carboplatin [4]. However, crossing the blood-brain barrier is challenging and several compounds have a difference in distribution, resulting in different CSF plasma ratios, which affects the treatment efficiency [29]. Regarding the performance status, our patient received upfront therapy with VAD based on WT stage IV with lung and bone metastases. For WT patients with bone metastases, it is currently under investigation, whether the poor outcome that, as reported by the COG renal tumor committee (survival rate only 0-13%) represents a WT subset survival rate of 0-13%, also represents a subset of such poor children in the SIOP_RTSG where pre-operative chemotherapy is applied, and whether a more intensive chemotherapy approach should be considered [4,30,31]. Whether the co-presence of CNS disease is an independent adverse prognostic factor, will be obviously difficult to explore, given the rarity of these cases.

Hence, our study is limited by the scarcity of available studies on patients with WT and CNS metastases, and in particular leptomeningeal metastases. Also, most of these studies did not describe molecular and tumor characteristics. Therefore, identifying indicators for CNS metastases in patients with WT is not conclusive using these limited studies. More, at least, descriptive studies and in-depth molecular and tumor characteristics of CNS metastasized WT patients are needed for early identification of CNS metastases in WTs. Although growing epithelial, stromal, and blastemal components in WT organoids is promising, the organoids from this patient did not grow sufficiently, and compound screening for personalized medicine was not feasible. However, for future exploration of individual treatment options, use of 3D patient derived models will remain of value [32].

Reference	Gender	Age at Dx	Synd	Stage (non CNS sites)	Histology before treatment	Molecular (+/-)	Pre-op	Surgery	Post-op	Time to CNS metastases	CNS location of metastases	Treatment CNS metastases	Other metastases at CNS metastasis	Outcome
[7]	F	5.5y	ND	IV (B/P/V)	BT*	ND	VAD	TN	CT, RT	Dx	epidural	S, CT, RT	B/P/V	A
[33]	F	14y	No	IV (extradural/PaLN/V)	BT, FH**	ND	ND	TN	RT, VDD > AADD	Dx	epidural, intra-spinal	S, RT, VDD > AADD	extradural/ PaLN/V	A
[34]	M	8m	ND	IV (-)	NC	ND	No	TN	VAdC	Dx	tectal plate, ventricle	S, VAdC, RT	No	DOD
[35]	M	5.5y	ND	IV (ND)	DA	ND	ND	ND	ND	Dx	intradural	Dm, RT	ND	DOD
[36]	M	4m	ND	IV (extra-renal extension)	DA	ND	No	TN	AV	Dx	unspecified (CSF)	ND	ND	DOD
[37]	F	18m	ND	III	FH	ND	ND	TN	VAD, ICE, RT	39w	Brain (frontal region)	S, ICE	No (history of P)	A
[38]	M	20m	ND	III	FH	ND	VCD > VDa	Yes, ND	Da	+/- 52w	cerebellar	S, RT	No	DOD
[39]	M	8y	ND	IV (P/L/ PaLN)	ET	ND	No	TN	AVAC, RT	3w	epidural	RT, JET	V, L, PaLN	DOD
[40]	F	5y	ND	IV (P)	BT	ND	No	TN	RT, VAD	36w	epidural	S, RT, VEIE	No	A
[41]	F	4y	ND	II	UH, FA	ND	No	TN	RT, DVD	39w	epidural	Dm, S, RT, CT (>CVD)	Extradural/P	A
Current case	M	3y	No	IV (B/V/P)	mixed***	MYCN mutation, no CNVs/1q gain/ LOH 12p/LOH 16q	VAD	TN	RT, 4D	26w	leptomeningeal	ICE, RT	No	DOD

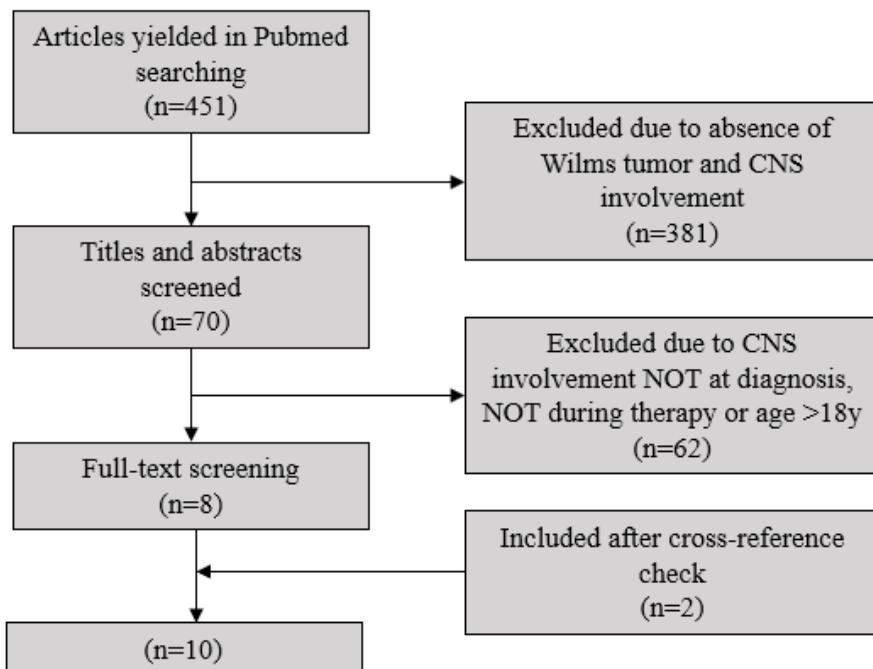
* immunohistochemistry: strong WT1+ expression, ** immunohistochemistry: cytokeratin+, synaptophysin-, neurofilament protein-, CD99-, *** Mixed, sub-classification stromal Wilms tumor (score 0.77). Immunohistochemistry: WT1+, PAX8+, CD56+, pankeratin+, EMA+. INII/BRG1 preserved. Myogenin-, MyoD1-, CD45-, synapto-, chromo-, s1000

Synd= syndrome, CNS= central nervous system, pre-op= pre-operative treatment, post-op= post-operative treatment, M= male, F= female, ND= not described, BT= blastemal, ET= epithelial, ST= stromal FA= focal anaplasia, DA= diffuse anaplastic, FH= favorable histology, UH= unfavorable histology, LOH= loss of heterozygosity, NC= not classified, RT= radiotherapy, CT= chemotherapy, S= surgery, TN= total nephrectomy, Dx= at diagnosis, A= alive; DOD= died of disease, DM= dexamethasone, AV= actinomycin and vincristine; VAD= vincristine, actinomycin-D, and doxorubicin, AVAC = actinomycin, vincristine, doxorubicin, and cyclofosfamide, Da = dactinomycin, 4D = carboplatin, etoposide, doxorubicin, and cyclophosphamide, ICE = ifosfamide, carboplatin, and etoposide, VCD= vincristine, cyclophosphamide, and doxorubicin; VDA= vincristine and dactinomycin, JET = high-dose carboplatin and etoposide, VEIE= vincristine, etoposide, ifosfamide, and epirubicin, DVD= dactinomycin, vincristine sulfate, and doxorubicin hydrochloride, CVD=cyclophosphamide, vincristine sulfate, and doxorubicin hydrochloride, VAdC = vincristine, Adriamycin, and cyclophosphamide, VDD = vincristine, dactinomycin, and doxorubicin, AADD= actinomycin-D, Adriamycin, dactomycin, and doxorubicin, V= vertebral; P= pulmonal, B= bone other than vertebral metastases, L= liver, PaLN= para-aortic lymph nodes, >= switch of chemotherapy

Table 2: Characteristics and outcome of WT with CNS metastases at diagnosis (Dx) or progression under therapy. Clinical patients and tumor characteristics of all well-documented CNS metastases in patients with WT diagnosed with or presenting during treatment for WT.

Search strategy for Pubmed database
1. Wilms tumor: (wilms tumor) OR (wilms' tumor) OR (wilm tumor) OR (wilm's tumor) OR (nephroblastoma)
2. Metastases: (metastases) OR (metastasis) OR (carcinomatosis)
3. Central nervous system: (leptomeningeal) OR (meningeal) OR (brain) OR (intracranial) OR (cerebral) OR (spine) OR (spinal) OR (spinal column) OR (vertebral column) OR (vertebra) OR (vertebrae) OR (bone) OR (epidural) OR (intradural) OR (extradural)

Supplementary Table 1: Search strategy. Search strategy for Pubmed database with a combination search: 1 AND 2 AND 3.



Supplementary Figure 1: Flowchart searching and selection strategy. The initial Pubmed article search identified 451 articles. Title, abstract, and full-text screening on inclusion and exclusion criteria yielded 8 articles, on which cross-reference checking was applied. In total 10 articles were included in this narrative review of literature.

Reference	Time of presentation of CNS involvement		Back pain	Leg pain	Weakness of lower limbs	Uro-genital symptoms ¹	Signs of intracranial pressure ²	Diminished/absent tendon reflexes	Paresthesia / paresis / paralysis ³	Epileptic seizures	Other ⁴
	At Dx	during treatment									
[7]	x		x			x			x		
[33]	x		x							x	
[34]	x						x				x
[35]	x		x	x				x	x		x

[36]	x					x				x
[37]		x				x				
[38]		x				x		x		x
[39]		x	x					x		
[40]		x	x	x	x			x		
[41]		x	x		x			x		
current patient		x				x*			x	x*

All symptoms reported just before or at the moment of diagnosis of central nervous system metastasis in patients with Wilms tumor.
1 sphincter disorder [7], urinary incontinence [40,41]
2 headache*, nausea/emesis [38]*, vomiting*, sunset phenomenon [34], hydrocephalus [36,38]*
3 paraparesis causing loss of ambulation [7], unable to walk [38,41], numbness in feet [35], lower limb paralysis [35], complete flaccid paraplegia [35], sensory loss/neuropathy [35], neuropathy [38], spastic paraplegia [41]
4 tiredness [33], drowsiness [38], unsteadiness [38], myoclonus/ataxia*, greater head circumference/size [34,36], muscle spasm [35], inappropriate ADH secretion [36]
CNS= central nervous system, Dx= at diagnosis

Supplementary Table 2: Presenting symptoms CNS metastases in WT at diagnosis or progression under therapy.

Conclusions

We report the first patient with stage IV, local stage III IR WT, who developed leptomeningeal metastases during treatment. Our literature review indicates that, in general, any CNS metastasis in patients with WT at diagnosis or during therapy is rare, are shown by a mass on imaging, and that leptomeningeal metastases in patients with WT may not be recognized due to the fact that contrast enhanced MRI is not part of our regular diagnostic work-up, especially in non-symptomatic disease, and given the rarity of this metastatic site. Because of the reported adverse outcomes in WT patients with CNS metastases, it is crucial to remain vigilant for symptoms that may reflect CNS metastases, especially in children with bone metastasis, even in patients with intermediate-risk histology.

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der Salm, Lennart Kester, Geert Janssens, and Martine van Grotel.; Resources, all authors.; Data Curation, all authors contributed to data collection regarding the reported patient. The data extraction was performed by Roos Valk and Francis Wens for the narrative review.; Writing – Original Draft Preparation, Roos Valk, Francis Wens, Martine van Grotel, and Marry van den Heuvel-Eibrink.; Writing – Review & Editing, all authors.; Visualization, Roos Valk, Francis Wens, Annemieke Littooij, Ronald de Krijger, Sophie van Peer, and Karin Langenberg.; Supervision, Martine van Grotel and Marry van den Heuvel-Eibrink.; Project Administration, Marry van den Heuvel-Eibrink.; Funding Acquisition, not applicable.

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