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Spinal Invasion as a Rare Presentation in Children with a Wilms Tumour: 2 Cases and a Review of the Literature

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Abstract

Spinal invasion is a rare complication of Wilms tumour. We here describe two patients with spinal invasion, as a result of direct extension from the primary tumour or from vertebral bone metastasis. They both presented with symptoms of spinal cord compression, including muscle weakness and sensory disturbances. We conducted a search of all previously described cases of spinal invasion caused by either direct extension of the primary tumour or vertebral metastasis, and were able to identify five additional cases from the literature. In total, three out of seven patients presented with an extra-renal Wilms tumour. No correlations with histology, nor germline or somatic mutations or other molecular characteristics, were described. There was a personalised diagnostic and therapeutic approach. Six out of seven patients survived, with two patients achieving full neurological recovery and four patients experiencing residual neurological deficits. We show that very rarely malignant spinal cord compression occurs in children with a Wilms tumour as a result of direct extension from the primary tumour or vertebral metastases. Early detection and personalised interventions are necessary to prevent permanent neurological damage. Therefore, awareness that malignant spinal cord compression can occur in children with Wilms tumour at diagnosis is important.

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Introduction

Wilms tumours (WTs) are the most common type of paediatric renal cancer, comprising 80% of renal neoplasms occurring before the age of 15 [1,2]. The overall survival of WTs is ~90%, however there remain subtypes with a more adverse outcome [3-5]. Around 10-15% of WTs present with metastatic disease, most commonly affecting lungs, liver, and more rarely bone marrow and/or the central nervous system (CNS) [6]. The vast majority of WTs are unilateral, intra-renal tumours that arise sporadically with a peak incidence between 1-4 years of age [1,6]. WTs can arise as bilateral and multifocal disease, which most often occur in the context of a genetic predisposition syndrome. Extra-renal WTs are rare, arising from migrating embryonal kidney precursors thereby illustrating the embryonal origin of WTs [7,8].

The most common presentation of a child with WT is a distended abdomen. Less common presenting symptoms are haematuria, constipation, fever, pain and weight loss [6]. Rarely, patients may present with symptoms arising from compression of surrounding organs or vascular or lymphatic infiltration [6]. This can include neurological symptoms from malignant spinal cord compression (MSCC). MSCC most commonly occurs in neuroblastoma, sarcomas and lymphomas [7,8]. However, MSCC has occasionally been described in patients with WT as a complication of CNS metastasis [9-11]. The latter, however, most commonly occurs at relapse [12,13]. Here, we report two patients with WT and early-onset spinal cord compression resulting from direct extension of the primary tumour or as a result of vertebral bone metastasis. We also present a review of patients described in the literature.

Case Presentation

Case 1

A 4-year-old girl, born full term with no dysmorphic features, presented with stomach pain

and a left abdominal palpable mass. On abdominal ultrasound and chest CT two separate lesions in the left kidney were found, as well as pulmonary metastases. Abdominal MRI confirmed the renal origin of the tumours and detected several bone marrow metastases (T8-10 and T12) with intraspinal extension and cord compression (Figure 1). This corresponded with the clinical picture of progressive bilateral weakness in the lower limbs (right side: MRC 0 in all muscle groups except for MRC 2 in m. tibialis anterior, left side: MRC 0 in iliopsoas and MRC 1-2 in other muscle groups) and a sensory level at T6-T7 with absent abdominal reflexes, urinary retention and a triple response of the plantar reflex (Table 1). Dexamethasone was administered followed by a laminectomy of T7-9 to decompress the spinal cord. The specimen revealed a non-anaplastic nephroblastoma with somatic *SIX1* and *DROSHA* mutations. Sensory and motor recovery was observed within 48 hours post-operatively.

Preoperative chemotherapy according to the SIOP-RTSG-2016-UMBRELLA protocol for metastatic WT was started (6-week course of vincristine, actinomycin D and doxorubicin (VAD)) (Table 1) [14]. A subsequent unilateral nephrectomy revealed one completely necrotic, stage I tumour and a second, regressive type, stage III tumour with invasion of the adrenal gland, perinephric fat and surrounding adipose tissue with positive resection margins [15]. Nephrogenic rests were observed near both the stage I and stage III tumour. No further molecular diagnostic testing was performed. The patient received 34 weeks of adjuvant chemotherapy with alternating cycles of cyclophosphamide/doxorubicin and carboplatin/etoposide, as well as left flank and vertebral column radiotherapy [14]. Through an intensive rehabilitation programme, the patient regained full motor function of the left leg and a MRC 5- score of all muscle groups in the right leg. Sensory function was fully regained. No disease recurrence has developed in the 4 years following initial diagnosis.

Case 2

A 7-month-old boy, born at 36+3 weeks of gestational age weighing 2400 grams (SDS: -1) with no dysmorphic features, presented with a three-day history of fever, diarrhoea and loss of appetite. On clinical examination a palpable abdominal mass and paralysis of the left leg was observed. An abdominal ultrasound and CT confirmed the presence of a cystic necrotic tumour with inhomogeneous enhancement, located outside but in contact with the left kidney which was dislocated by the mass. The tumour invaded the spinal canal through the L3-L4 and L4-L5 vertebral foramina (Figure 2). A tumour thrombus extension was present in the inferior vena cava (IVC). CT thorax was negative for metastases. Dexamethasone was started and an emergency laminectomy of L3-L4 for spinal decompression and open biopsy was performed. The biopsy revealed a non-anaplastic nephroblastoma of mixed type: epithelial with small percentage of blastema (20%) [15]. A 6-week course of VAD chemotherapy was started [14], and completed of which vincristine was omitted in the last two doses due to the development of vocal cord paralysis, clinically reflected by a hoarse voice and swallowing difficulties requiring a nasogastric tube.

An MRI after six weeks of pre-operative chemotherapy showed persisting intraspinal invasion through the vertebral foramen at L4-L5 and a remaining IVC thrombus, with clinical improvement in muscle power in the left leg. One extra cycle of carboplatin/etoposide chemotherapy was administered with the aim to further reduce the volume and viability of the tumour thrombus pre-operatively. A second laminectomy was performed, followed by a complete nephrectomy with IVC thrombus removal. Unfortunately, the patient developed a pseudomonas meningitis post-operatively, not associated with aplasia, for which an external ventricular drain was inserted. Tumour histology confirmed a mixed-type stage III extra-renal Wilms tumour, due to positive resection margins [15]. No clinically relevant somatic mutations were found in the intraspinal tumour sample, whilst the extrarenal tumour resection showed a somatic *CTNNB1* mutation and partial gain of chromosomal arm 11p and partial loss of 11q. Postoperative chemotherapy and flank radiotherapy were administered. Subsequently, a 34-week four drug chemotherapy course (without vincristine) was completed (Table 1). The patient currently suffers from ongoing paresis of the left L3-4 innervated muscles, but with functional improvement. On EMG, muscle action potentials were present in the biceps femoris.

Literature Review

Materials and Methods

A literature review, using the PubMed database was performed. Up until January 19th 2024 the PubMed database was searched for studies on WT with spinal invasion. Our search criteria are depicted in Supplementary Table 1. No language restrictions were applied to our search. Cross reference check was performed to identify any additional studies. Exclusion criteria included Metastatic Spinal Cord Compression (MSCC) caused by CNS metastasis or recurrent local disease, and patients with (occult) spinal dysraphism. The literature search and cross-reference checks were independently pursued by two authors (I.T. and F.W).

Results

The literature search yielded a total of 121 studies. After title and abstract screening, a total of 11 studies were selected for eligibility. After full-text review, eight studies were excluded for the following reasons: article could not be accessed (n=3); MSCC caused by CNS metastasis (n=2), recurrent local disease (n=1) or associated with spinal dysraphism (n=2). Two additional articles were included after cross-reference checks. As a result, five studies were included, describing five individual patients (Figure 3).

Summarised clinical characteristics of the five patients in the literature and the two patients from our centre are depicted in Table 1 (three boys and four girls). The median age at diagnosis was 48 months (range: 2 months-14 years). Four patients had direct extension from the primary tumour and three patients had vertebral bone metastases causing MSCC. All patients presented with symptoms attributed to spinal invasion, ranging from isolated back pain (n=1) to sensory and motor deficits (n=6). Three patients presented with cauda equina syndrome.

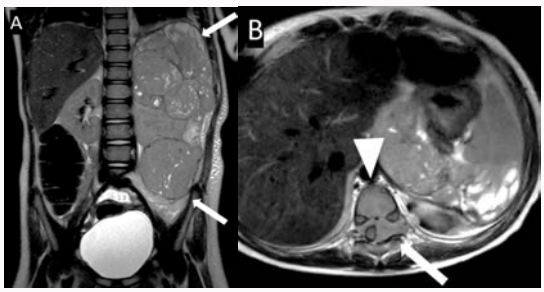

Figure 1: Imaging studies for case 1. A) Abdominal CT depicting two distinct tumours of the left kidney. B) MRI of the spine depicting bone marrow metastases with intraspinal extension and cord compression.

Table 1: Clinical characteristics and outcome of patients with Wilms tumour and spinal invasion in the literature.

Study	Sex	Age	Presenting symptoms	CNS locus	Neurological intervention	1° tumour	Other disease	Local stage	Histology	Molecular aberrations	Pre-op	Sx	Post-op	Neurological outcome	Pt status
[22]	F	14y	Abdominal pain and mass, flaccid paraplegia, loss of bladder and bowel function	T9-L1	None	Intra-renal	Lung metastasis	NA	Epithelial (percutaneous biopsy). ?mono-phasic epithelial pre-dominant	NA	VAD[i]	None	None	NA	Died
[23]	M	2m	Symptoms of gastro-enteritis, flaccid paraplegia, loss of bladder and bowel function	L4	Emergency CT (EC[ii]), surgical resection	Extra-renal	None	NA	Triphasic – 60% epithelial, 20% blastemous, 20% rhabdo-myoblastic (surgical biopsy)	11p13 deletion	VA	NF	VEpA	Complete motor deficit of S1 roots, partial motor deficit of L4 + L5 roots, complete S1 + S3 + S4 + S5 sensory deficit	Alive
[24]	F	3y	Abdominal mass, leg pain, paraesthesia	T11-L1	Cortico-steroids	Extra-renal	Lung metastasis	I	Regressive (IR)	NA	VAD	NF	VAD	No deficit	Alive
[25]	M	5y	Lumbar back pain, generalised afebrile seizure	L2	Surgical resection	Intra-renal	Lymph node involvement	II	Triphasic: blastemal, stromal, epithelial (favourable histology)	NA	None	NF	NA[iii]	Motor deficit in lower limbs (3/5 right and 4/5 left), urinary and faecal incontinence	Alive
[26]	F	5y	Lower back pain, progressive paraparesis, sphincter dysfunction	T12-L1	T12-L1 laminectomy	Intra-renal	Lung and bone metastasis	II	Regressive (IR)	NA	VAD	NF	VAD	Sequelar bilateral equinovarus	Alive
This report	F	4y	Stomach pain, unsettled, bilateral leg paralysis, abnormal sensation, urinary retention	T6-10	T7-9 laminectomy, cortico-steroids	Intra-renal (two tumours)	Lung and bone metastasis	I & III	Completely necrotic (LR); Regressive (IR); Associated NB	Somatic SIX1 + DROSHA	VAD	NF	HR 4 drugs	No deficit	Alive
This report	M	7m	Fever, diarrhoea, poor feeding, unsettled, left leg paralysis	L3-5	L3-5 laminectomy (x2), cortico-steroids	Extra-renal	IVC thrombus	III	Mixed type (IR)	Somatic CTNNB1, partial gain 11p, partial loss of 11q	VAD[iv] + CE	NF	HR 4 drugs	Partial motor deficit of L3-L4 innervated muscles	Alive

CNS= central nervous system. Pre/post-op= pre/post-operative, Sx = surgery, Pt= patient. Dx= diagnosis. NA= not available. IR= intermediate risk. HR= high risk. NB= nephroblastomatosis. NF = nephrectomy. CT= chemotherapy. VAD= vincristine, dactinomycin, doxorubicin. VA= vincristine, actinomycin. EC= etoposide, carboplatin. VepA= vincristine, epirubicin, actinomycin. HR 4 drugs= etoposide, carboplatin, cyclophosphamide, doxorubicin.. IVC = inferior vena cava. i) patient died before initiation of neoadjuvant chemotherapy. ii) initially treated as an hourglassneuroblastoma according to the French Society of Paediatric Oncology guidelines. iii) patient received adjuvant chemotherapy and radiotherapy, with no further details available. iv) two doses vincristine omitted because of vocal cord paralysis, upstaged to HR 4 drug treatment due to vincristine toxicity.

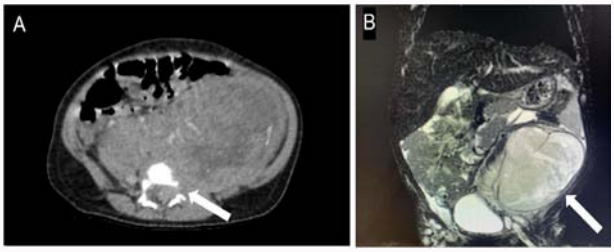

Figure 2: Imaging studies for case 2. A) Abdominal CT depicting a cystic-solid mass in contact with the left kidney with invasion of the spinal canal through L3-L4 and L4-L5. B) MRI of the spine depicting the left abdominal mass with dislocation of the left kidney superiorly and laterally.

Four out of seven patients had a rare presentation of WT, of whom three patients had an extra-renal tumour and one patient had multi-focal disease. No patients had a phenotype suggestive of a predisposing genetic syndrome. The majority of patients (n=6) had extensive disease at diagnosis which was either metastatic (n=4) or locally advanced (n=2) disease. No specific local stage, histology or molecular characteristics were observed (Table 1).

Immediate treatment for MSCC was started in six patients, with one patient dying before treatment was administered (cause of death unknown). Three patients received dexamethasone, four patients underwent emergency neurosurgery and one patient received chemotherapy for suspected neuroblastoma. Six patients received multimodality WT treatment, including pre-operative chemotherapy (n=5), nephrectomy (n=6), post-operative chemotherapy (n=6) and radiotherapy (n=4). Six patients survived, of which two patients fully recovered and four patients experienced residual neurological deficits (Table 1).

Discussion and Conclusion

Malignant spinal cord compression (MSCC) is a rare complication of paediatric malignancies which typically occurs in children with neuroblastoma, sarcoma, lymphoma or leukaemia [8]. It may arise from haematogenous metastasis to either the CNS or vertebral bones, lymphogenic or perineurial invasion, and direct invasion through the

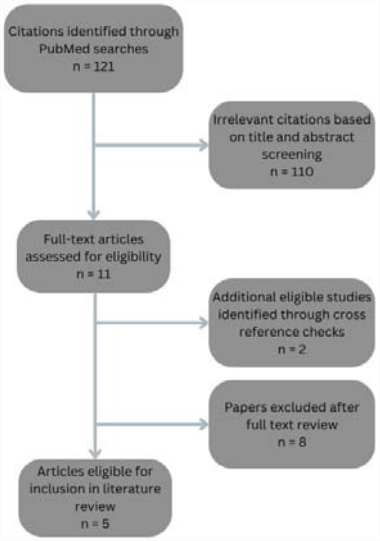

Figure 3: Flowchart showing the process for inclusion of studies.

intervertebral foramina from a paravertebral tumour [16,17]. MSCC has previously been reported in WT, however, most commonly as a result of CNS metastasis [9-11]. To our knowledge here we present the first literature review of MSCC caused by direct extension from the primary tumour or vertebral metastasis in WT.

All patients included in this case study presented with symptoms of spinal cord compression at diagnosis. The majority of patients presented with neurological deficits, including muscle weakness and sphincter disturbance. One patient presented solely with back pain. These findings are in accordance with findings in larger cohorts of paediatric MSCC patients with any cancer type [7,8]. It emphasises the importance of recognising MSCC in a child with (suspected) malignancy if back pain is the presenting symptom, even in the absence of focal neurological deficits. MSCC appears to be associated with advanced disease at diagnosis, especially with lung metastasis which is the most common metastatic site in WT in general (85%). Bone and CNS metastasis are rare presentations (<1%) [6]. The patients included in this study had a wide age range (2 months-14 years), despite a peak incidence of WT at 1-4 years [6]. Additionally, two out of six patients were <12 months which increases the difficulty of diagnosing MSCC at an early stage [18].

Tumour characteristics varied between the cases. Molecular characteristics were not reported for most of the patients described in the literature. Two patients in the literature only had histology reported from biopsy rather than from the nephrectomy. Those that had histology reported after nephrectomy showed varying local stage (I-III), but most were classified as intermediate-risk. Three patients reported here presented with an extra-renal WT, which are considered to arise from embryonal kidney precursor cells anywhere along their craniocaudal migration pathway. Whilst extra-renal WTs represent <1% of all WT cases, they predispose to spinal cord compression due to the fact they arise closer to the spinal cord [19]. Extra-renal WT can present as paraspinal tumours with direct extension into the spinal cord, thereby mimicking neuroblastoma. These tumours have previously been associated with spinal dysraphism [19,20]. No spinal dysraphism or genetic syndromes were reported in any patients included in this study, but it is unclear whether genetic predisposition has been studied in depth in the current patient group.

Immediate intervention in MSCC is important for preventing permanent neurological damage [18,21]. A shorter interval between symptom onset and diagnosis has been shown to be associated with greater full neurological recovery rates. This underlines the need for early recognition of symptoms [21]. Clinical management may include any combination of high dose corticosteroids, chemo-radiotherapy and surgical resection depending on patient status, primary malignancy, spinal disease extent, duration of neurological deficit and availability of surgical expertise [8,9]. However, an expert patient-tailored approach is important. Early multidisciplinary involvement and management with consideration of (a combination of) chemotherapy, radiotherapy and emergency neurosurgical decompression, needs to be considered in every case [8,9,21].

We conclude that MSCC is a rare condition in children with WT. It may arise as a consequence of CNS or vertebral metastasis, or direct extension from the primary tumour. Personalised approaches without delay are indicated, and therefore awareness that malignant spinal cord compression can occur in children with WT at diagnosis is important.

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