

# Intradural spinal metastasis of renal cell cancer. Report of a case and review of 26 published cases

Gregory Jost · Stephan Zimmerer · Stephan Frank · Dominik Cordier · Adrian Merlo

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**Abstract** Metastatic disease in the intradural compartment of the spine is a rare manifestation of cancer. We report the case of an 82-year-old patient with an intradural, extra-medullary metastasis of renal cell carcinoma in the cervical spine. A literature search for intradural spinal metastases of renal cell carcinoma yielded a total of 26 further cases. 18 patients had sporadic renal cell carcinoma, and 9 patients had von Hippel-Lindau disease (VHL) in which the metastases of the renal cell carcinoma were embedded within spinal haemangioblastomas. Patients presented with paresis, back pain, altered sensation or, less frequently, bladder dysfunction. Intradural spinal metastases were diagnosed at an earlier age in VHL patients than in sporadic cases (mean  $43 \pm 5$  years vs.  $60 \pm 14.5$  years). The metastasis was surgically removed in 81% of patients. Pain improved in all patients, paresis in 90%, hypaesthesia in 38% and bladder dysfunction in 50%. Death occurred as a result of systemic cancer progression. 93% of patients in the sporadic renal cell cancer group died within 1.5 years, whereas two thirds of the VHL patients were alive after 2 years.

**Keywords** Renal cell carcinoma · Renal cell cancer · Intradural metastasis · Intramedullary metastasis · Spine · VHL · von Hippel-Lindau disease

G. Jost (✉) · S. Zimmerer · D. Cordier · A. Merlo  
Department of Neurosurgery,  
University Hospital Basel,  
Spitalstrasse 21, 4031 Basel, Switzerland  
e-mail: gregoryjost@gmx.ch

S. Frank  
Department of Neuropathology,  
Institute of Pathology,  
University Hospital Basel,  
Schoenbeinstrasse 40, 4056 Basel, Switzerland

## Introduction

Metastatic disease in the intradural compartment of the spine is a rare manifestation of cancer with an incidence of less than 1% in patients dying from systemic malignancies [9]. The most commonly associated primary tumours are cancers of the lung, breast, kidney and skin [38, 44]. Renal cell carcinoma is usually diagnosed at a disseminated stage [35]. Advanced disease predominantly presents as metastases to the lung (50%), bones (49%), lymph nodes (6–32%), liver (8%) and occasionally brain (3–10%) [32]. We present an 82 year old patient with an intradural metastasis of renal cell carcinoma (RCC) in the cervical spine and discuss it in the context of a further 26 previously published examples of this condition.

## Literature review

The Medline database (PubMed, <http://www.ncbi.nlm.nih.gov/PubMed/>) was searched for the keywords *intradural renal cell carcinoma* and *renal spinal metastasis*. After screening of titles and abstracts, all suitable reports and important cross-references were obtained as full copies. Where appropriate, their authors were contacted by mail for follow-up information, such as progression of local or systemic disease and survival since publication.

## Clinical details

An 82 year old man presented with progressive, moderately severe left hemiparesis and neck pain aggravated by coughing. A year earlier, he had sustained an infarction in the territory of the right middle cerebral artery, from which

he had completely recovered. Six years earlier, he had undergone a nephrectomy for clear-cell renal carcinoma. He had also undergone orchidectomy for prostatic carcinoma.

Neurological examination revealed a left-sided spastic hemiparesis of grade III–IV on the Medical Research Council Scale [18] and was otherwise unremarkable, as was the general physical examination.

Magnetic resonance imaging (MRI) of the entire spine revealed a solitary, well-circumscribed intradural tumour at C6/7, compressing and displacing the spinal cord to the right. The lesion was iso-intense on T1- and hypo-intense on T2-weighted images, with slight homogeneous contrast enhancement (Fig. 1). MRI of the brain disclosed a small 0.8×0.6 cm extra-axial contrast enhancing lesion at the left foramen of Luschka (Fig. 2). In consideration of the patient's advanced age and the small size of the cerebral lesion, Gamma Knife therapy was planned. Surgery was recommended for the symptomatic, space-occupying, well-defined tumour in the spine. A C6 laminectomy was performed. When the dura mater was opened, the tumour was found to be attached to the left C6 root. Macroscopically, it displayed a nerve sheath tumour-like aspect with a rubbery consistency and a well demarcated cleavage plane. Histopathology of the completely removed lesion revealed partly haemorrhagic, highly vascularised tissue consisting of clear cells arranged in small lobules (Fig. 3). The tumour cells had pronounced cytoplasmic accumulations of PAS-positive granules, reflecting glycogen deposition. Immunohistochemical staining revealed strong reactivity with the pan-cytokeratin marker CK22 as well as with a renal cell carcinoma marker (NCL-RCC, clone 66.4.C2). Post-operatively, the left hemiparesis improved progressively. Adjuvant local irradiation was administered. One year after



**Fig. 1** T2-weighted sagittal MRI of the cervical spine revealed a sharply circumscribed, intradural/extramedullary, hypointense tumour at C6/7 with dorsal displacement of the spinal cord



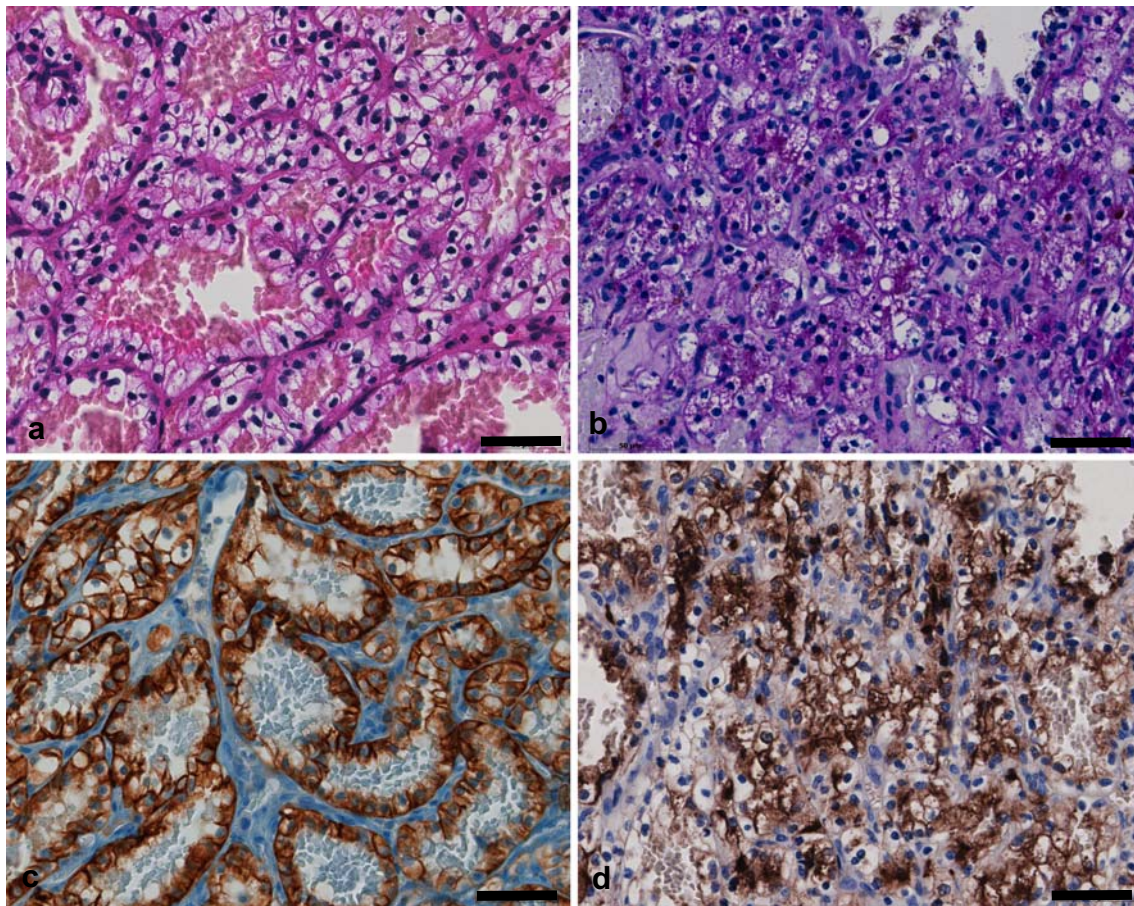
**Fig. 2** Contrast-enhanced, T1-weighted axial MRI of the brain showed a small, homogeneously enhancing lesion at the left foramen of Luschka

surgery, the patient is doing well and is able to walk unaided.

## Results

A Medline literature search yielded 19 articles dating from 1990 to 2007 concerning 32 examples of intradural spinal cord metastases (ISCM) of renal cell carcinoma [1, 2, 4, 5, 11, 13, 15, 19, 20, 22–24, 28, 29, 33, 38, 39, 41, 42]. Six of these dated from the pre-CT and pre-MRI era and were therefore discarded from the analysis [15]. A total of 18 patients, including our patient, had sporadic RCC (Table 1) [2, 4, 5, 12, 14, 19, 23, 24, 28, 29, 39, 41], while 9 patients had von Hippel-Lindau disease (VHL) (Table 2) [1, 4, 13, 19, 20]. In the latter group of patients, RCC was found within haemangioblastomas of the spinal cord as a tumour-to-tumour metastasis. Eleven of the patients with sporadic RCC were male, and 7 were female. In the VHL group, female patients (n=6) predominated over male patients (n=3). Nine ISCM were located in the cervical, 8 in the thoracic, 9 in the lumbar, and one in the sacral spine. All intradural metastases occurring between C1 and L1-2 were intramedullary except for our patient in whom the lesion mimicked an extradural extramedullary nerve sheath tumour. All intradural metastases below the conus medullaris were extramedullary, as expected.

Patients presented with limb paresis (n=20, 74%), back pain (n=15, 56%), hypaesthesia or paraesthesia (n=13, 48%) and bladder dysfunction (n=6, 22%). In 4 patients



**Fig. 3** On conventional H&E stains, the clear-cell aspect of the partly haemorrhagic tumour could easily be appreciated (a). The tumour cell cytoplasm featured conspicuous PAS-positive granula, corresponding to glycogen deposits (b). Upon immunohistochemical examination,

tumour cells were found to express cytokeratin (c) as well as a renal cell carcinoma-specific antigen (d). See text for details. Scale bar 50  $\mu$ m, all images same magnification

(15%), cervical or upper thoracic ISCM caused at least a partial Brown-Séquard syndrome [11, 13, 39]. The lesion was surgically resected in 22 (81%) patients. In four (15%) adjuvant post-operative radiotherapy was administered [11, 15, 28]. Five (19%) patients received external beam radiotherapy without surgery [13, 33]. All patients experienced pain relief. Muscle strength improved in 18 of 20 patients (90%), hypaesthesia in 5 of 13 (38%) and urinary disturbance in 3 of 6 (50%). Histopathology confirmed metastatic renal cell cancer in all patients; the metastases were admixed with a haemangioblastoma lesion in the patients with VHL [1, 4, 13, 19, 20, 34].

#### Sporadic cases

The mean age at diagnosis of RCC and ISCM was  $57 \pm 13$  years (range, 36 to 78) and  $60 \pm 14.5$  years (range, 36 to 84), respectively. In the majority of sporadic cases (13 of 18, 72%), ISCM occurred after renal cell carcinoma had already been diagnosed, at a mean latency of 4.3 years (range 2 months to 15 years). In the remaining 5 patients

(28%), ISCM was the first manifestation of disease [11, 13, 16, 19, 39]. When ISCM was diagnosed, 6 patients (33%) had no other metastases [2, 5, 13, 23, 29, 39]. Among the 12 patients (66%) with systemic disease, 9 (50%) had involvement of the lungs [11, 13, 16, 24, 33, 41] and 4 (22%) of the brain [13, 15], while a further 4 patients developed brain metastases later on [13, 33, 41]. Metastasis to the brain was a frequent event in RCC (44% of all patients). Brain metastases were treated with external beam radiotherapy (n=5) [13, 15, 33], with corticosteroids (n=2) [13] and with surgery (n=1) [33]. In 5 patients, lung metastases appeared before ISCM was diagnosed [13, 24, 33, 41]. Interestingly, an aggressive strategy consisting of nephrectomy, resection of lung metastases and chemotherapy was associated with late development of ISCM, namely 6, 7 and 15 years after the diagnosis of RCC [13, 24, 41]. In the patients that had been treated with nephrectomy and chemo- or immunotherapy alone, ISCM was diagnosed within a few months [13, 33].

In general, the prognosis was poor. Survival times were available for 14 patients. Seven (50%) died within 6 months

**Table 1** Data from patients with intradural spinal cord metastases (ISCM) from sporadic renal cancer

Case report Author, year	Age at RCC, sex	Time to ISCM (months)	level	Other RCC metastases	Treatment	Signs & symptoms before / after treatment				Time to death after ISCM (months)
						pain	motor	sens.	bladder	
Alfieri, 2005	67,f	48	L3-L5	-	n, r	+/-	+/-	-/-	+/-	?
Ateaque, 2000	52,m	132	C2-C3	-	n,r,st	-/-	+/+	+/+	+/+	1
Donovan, 2006	41,f	0	C4	l,bo	r,xbo,xiscm	-/-	+/-	+/+	-/-	2
Fakih, 2001	56,m	0	C4	l,br	xbo,xbr,xiscm,st	-/?	+/?	?/?	+/+	6
Fakih, 2001	57,f	0	C7	l,br	xbo,xbr,xiscm,st	+/-	+/-	+/?	-/-	5
Fakih, 2001	60,m	180	T1-T2	l,br	n,ch,st,r,xbr,xiscm	-/-	+/-	?/?	-/-	2
Fakih, 2001	46,m	2	T5	l,br	xbo,xiscm,inf,st,ret	-/-	+/-	+/?	+/-	5
Fakih, 2001	68,f	2	T2	-	xiscm,st	-/-	+/-	?/?	-/-	16
Gaetani, 2004	36,f	4	L3-L4	br,vi,spi	n,r, xbr,xiscm	+/-	+/-	+/-	-/-	12
Gomez, 2005	69,m	0	L1	l,vi	r	+/-	+/-	+/-	-/-	16
Kaya, 2003	43,f	12	L1	-	n,r	+/-	+/-	-/-	+/-	6
Kubota, 2003	61,m	84	L3	l	n,r	+/-	-/-	?/?	-/-	?
Mak, 2001	52,m	84	L3-L4	spi	n,r,xiscm	-/-	+/-	?/?	-/-	18
Maxwell, 1999	78,m	72	L2-L3	-	n,r	+/-	-/-	-/-	-/-	?
Poggi, 2001	37,m	2	T12	l,bo,br	n,xbo,xbr,xiscm,inf,il	+/?	+/?	+/+	-/-	?
Schijns, 2000	70,f	0	C7	-	r	+/?	+/-	+/-	-/-	13
Takada, 2003	55,m	72	L3	l,br	r,inf	+/-	+/+	+/+	+/+	36
Present case	76,m	72	C6-C7	br	n,r,st	+/-	+/-	-/-	-/-	>12

*l* lungs, *bo* bones, *br* brain, *vi* visceral, *spi* vertebra of the spine, *n* nephrectomy, *r* resection of the intraspinal metastasis, *xbo* radiotherapy to bones, *xiscm* to the ISCM, *xbr* to the brain, *st* steroids, *ch* chemotherapy, *inf* interferon, *ret* cis-retinoic, *il* interleukin-2, ? not reported, + present, - not present.

[5, 11, 13, 23] and 13 (93%) within 1.5 years [5, 11, 13, 15, 16, 23, 28, 39]. Only 1 patient survived for 3 years [41]. The overall mean survival time for sporadic RCC was 11 months. Death always manifested as a result of systemic progression of RCC.

#### VHL patients

In VHL patients, ISCM was diagnosed at a mean age of 43±5 years (range, 36 to 52). All but two of the VHL patients had already been diagnosed with this syndrome; for

**Table 2** Data from VHL patients with intradural spinal cord metastases (ISCM) of renal cancer

Case report Author, year	Age at RCC, sex	Time to ISCM (months)	level	Other RCC metastases	Treatment	Signs & symptoms before / after treatment				Time to death after ISCM (months)
						pain	motor	sens.	bladder	
A-Hamden, 2003	39,m	0	C1-C4	?	n,r	-/-	+/-	+/+	-/-	?
Altinoz, 2005	43,m	24	T6-T7	l,br,adr	n,il,xbr,r,sut	+/-	-/-	-/-	-/-	>96
Fakih, 2001	37,f	24	C2	l	n,il,r	+/-	+/-	+/-	-/-	23
Hamazaki, 2001	47,f	0	T5-6,T9	-	n,r	-/-	+/?	+/?	-/-	>24
Jarrel, 2006	36 <sup>a</sup> ,f	?	sacrum	-	r	+/-	-/-	-/-	-/-	>36
Jarrel, 2006	44 <sup>a</sup> ,f	?	thoracic	-	r	+/-	-/-	-/-	-/-	>12
Jarrel, 2006	41 <sup>a</sup> ,m	?	thoracic	l	r	-/-	+/-	-/-	-/-	3
Jarrel, 2006	50 <sup>a</sup> ,f	?	lumbar	-	r	?/?	?/?	?/?	?/?	?
Polydorides, 2007	46,f	72	cervical	?	n,r	-/-	-/-	+/?	-/-	?

<sup>a</sup> age at diagnosis of intradural spinal cord metastasis (ISCM), *l* lungs, *br* brain, *adr* adrenals, *n* nephrectomy, *r* resection of the ISCM, *xbr* radiotherapy to the brain, *il* interleukin-2, *sut* sunitinib, ? not reported, + present, - not present.

two of them, however, it was the spinal tumour that brought the underlying VHL to clinical attention [1, 19]. On average, the time from diagnosis of RCC to diagnosis of an intradural spinal metastasis was only 1 year. Most of the VHL patients had known CNS haemangioblastomas. Two of 8 patients (25%) had lung metastases of RCC 2 years before diagnosis of ISCM, treated with immunotherapy [4, 13]. One of these (13%) developed a brain metastasis 3 years after ISCM, which was irradiated and resected. This particular patient also received systemic interleukin-2, chemotherapy and the anti-angiogenic protein kinase inhibitor sunitinib and was still alive 6 years after removal of the ISCM [4, 12]. One patient declined resection of the primary RCC and died 3 months later of intestinal obstruction [20]. Two thirds of VHL patients were alive after 2 years.

## Discussion

Intradural metastatic disease to the spine is a rare complication of cancer. It accounts for only 0.8–3.9% of all symptomatic spinal metastases [9]. The strategic localisation within the intradural spinal compartment often leads to irreversible neurological deficits. Patients with ISCM commonly suffer from advanced disease [26]. Therefore, the main goal of therapy is palliation. Most patients analysed in this systematic review of published reports underwent surgical removal of the ISCM, which relieved pain and improved motor function. Sensory and urinary dysfunction were less likely to recover. Five patients received radiotherapy instead of surgery because of advanced disease [13, 33]. In experienced hands, the microsurgical resection of an intradural spinal tumour is a safe procedure [8] and is associated with longer survival than conservative therapy [21], though selection bias is likely to play a part in the latter finding. The resection of metastases provides an effective local treatment and thus plays an important role in the management of radio-resistant tumours such as RCC [30]. In this historical and retrospective series, the male to female distribution in sporadic RCC reflected the same 1.5 :1 predominance of men over women found in other studies [27]. In the VHL group, there were twice as many women as men, but the number of patients was small. The mean age at presentation of ISCM in sporadic RCC, 60 years, matched Kalayci's and Schiff's findings in 138 and 40 patients, respectively, with mixed ISCM [21, 38]. Presumably, because of the hereditary factor, ISCM of RCC manifested much earlier in patients with VHL than in sporadic cases. In 40–70% of VHL patients RCC develop at a mean age of 37 years, as opposed to a peak incidence between 60 and 70 years for sporadic RCC [27]. Typically, CNS haemangioblastomas in

VHL cases become symptomatic in the third decade, and RCC is then detected during screening. In this disease, germ-line mutations of the tumour suppressor gene VHL on the short arm of chromosome 3 leads to deficient ubiquitination of hypoxia-inducible factor, which is involved in the molecular pathogenesis of CNS haemangioblastomas, pheochromocytomas, pancreatic cysts as well as islet cell tumours, papillary cystadenomas of the epididymis, renal cysts and carcinoma [40]. Consequently, individuals with VHL have a reduced average life expectancy of less than 50 years [14].

Intradural spinal cord metastasis is a sign of advanced disease and therefore associated with a poor prognosis, irrespective of whether it is intra- or extramedullary. According to the modified Robson staging system for RCC, patients with distant metastasis have stage IV cancer [36], with a 5-year survival from 0 to 10 percent [10]. Indeed, 93% of patients with sporadic RCC were dead 15 months after diagnosis of ISCM (mean survival 11 months), whereas two-thirds of the VHL patients were alive after 2 years. The cause of death was always systemic progression of cancer. The bulk of tumours causing symptomatic ISCM in VHL patients were haemangioblastomas that contained nests of renal cell cancer as a minor component. Thus, RCC was detected and treated at an earlier stage. Accordingly, the apparently faster diagnosis of the spinal metastasis after primary renal cell carcinoma and the apparently longer survival after ISCM of RCC is probably due, at least in part, to accelerated diagnosis because of the co-existing haemangioblastoma. In reports of ISCM from multiple sources and with mixed treatment strategies, the mean survival was 3 to 7.3 months, and 9.4 months if only surgically treated cases were considered [21, 38]. At the outset, 41% of patients had concomitant brain metastases [21], and 57.5% developed metastatic brain lesions over the course of their disease [38], a slightly higher figure than was found in the present study. Given this high probability of brain involvement in patients with ISCM, as opposed to only 5% of patients with RCC at initial presentation [30], imaging studies of the head should be performed as part of staging.

Half the patients had metastases in the lungs. In fact, the results of 687 post mortems suggested that RCC follows a metastatic “cascade” in which the lungs are the first site of haematogeneous spread [45]. Arterial embolism of pulmonary metastases might seed to other sites but would be an unlikely means of spread to the spinal cord. Nevertheless, the absence of pulmonary metastases in our patient suggests an alternative mechanism of spread via the vertebral venous plexus, as first proposed by Batson [7] and recently reviewed by Tobinick and Vega [43]. In addition to connections with the cranial venous system, the vertebral venous plexus communicates via widespread anastomoses

with systemic veins, including the inferior and superior venae cavae, the left renal and suprarenal veins, and the azygos and portal venous systems [6, 17]. As blood flow in the vertebral venous system has been shown to be bidirectional [7, 17], this venous route provides an accepted pathway of metastatic seeding [31, 37]. Moreover, angiographic studies have demonstrated retrograde (inward) flow in the radicular veins and hence a communication between extra- and intradural compartments of the spine [25]. We suggest this route as the probable mechanism in our patient, whose metastasis was located close to the dorsal root. An alternative pathway is seeding via the cerebrospinal fluid (CSF), which, given the co-existent brain metastasis, would also have been possible in our patient. However, the CSF route seems less likely in patients with no prior or concomitant brain involvement. Finally, dissemination along the subarachnoid space via lymph vessels of peripheral nerves can lead to leptomeningeal invasion [46]. On the other hand, vertebral bone metastases can directly invade and/or seed to the CSF [28].

## Conclusion

Surgery for ISCM from RCC leads to favourable functional results and may, in combination with aggressive therapy of systemic disease progression, prolong survival. Considering the high risk of brain involvement, imaging of the brain is mandatory in the staging of patients with ISCM. The prognosis for patients with ISCM of RCC is as poor as that of patients with ISCM of other primary tumours. Mortality is mainly due to the systemic disease.

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## Comment

The article by Dr. Jost and colleagues focuses on intradural spinal metastasis of renal cell cancer. Although intraspinal spread of neoplasms has been repeatedly reported, the occurrence of metastasis in the intradural compartment of the spine caused by renal carcinoma is highly uncommon. The novel and interesting aspects of the present work particularly lie in the detailed current literature review including both cases of metastasis to haemangioblastomas in von Hippel-Lindau disease and sporadic cases of renal cell carcinoma metastasis, and the conclusion that, although optimal treatment after diagnosis of intradural spinal metastatic disease in renal cell carcinoma remains controversial, selected patients may have substantially increased survival and acceptable clinical outcome after surgical resection and adequate multidisciplinary management. This clearly written and well arranged review and case presentation of a rare condition is a valuable contribution to our literature on spinal cord metastasis from systemic cancer.

Markus Florian Oertel  
Germany