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Case Report

Intramedullary spinal cord metastasis of clear cell renal carcinoma in a Von Hippel–Lindau patient

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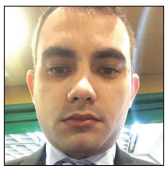

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ABSTRACT

Background: Intramedullary spinal cord metastasis is uncommon and represents only 0.6% of all spinal tumors. Renal cell carcinoma is even less frequent in this group than in lung and breast cancer. Patients with Von Hippel–Lindau disease (VHLd) present spinal hemangioblastoma more frequently.

Case Description: A 59-year-old female patient presented with medullary syndrome. There was a previous history of VHLd, with a cerebellar hemangioblastoma resection years ago. The radiological investigation showed a cervical intramedullary solid-cystic lesion. The patient has submitted a tumor resection, and a pathological and immunohistochemistry study confirmed clear cell renal carcinoma metastasis.

Conclusion: In patients with VHLd, the presence of an intramedullary solid-cystic lesion may not represent always a hemangioblastoma. Other diagnostic possibilities must be evaluated, despite being epidemiologically less frequent. Inside the group of patients with VHLd, only a previous case of intramedullary spinal cord renal cell carcinoma was reported in the literature.

Keywords: Hemangioblastoma, Metastasis, Neurosurgery, Renal Cell Carcinoma, Von Hippel–Lindau

INTRODUCTION

Intramedullary spinal cord metastasis (ISCM) is secondary tumors that grow in the parenchyma of the spinal cord (SC) and constitute the less common type of central nervous system (CNS) metastasis. The incidence is near 3.5% and represents only 0.6% of all spinal tumors.[21] Lung and breast cancers are the most common primary sites, being melanoma, ovarian, thyroid, and colorectal cancers as other possibilities, however less common.[4,13,28]

The clinical presentation is variable depending on the location of the lesion. The symptoms include pain, weakness, sensory loss, and sphincter dysfunction. Because the cervical spinal cord is the most affected, the more commonly described symptoms are weakness and sensory loss of upper and lower extremities besides sphincter dysfunction with urinary incontinence.[13]

Renal cell carcinoma (RCC) is the most common kidney cancer. During the past decade, is estimated that 350–400 thousand cases/year globally. Male patients that are living in developed countries are the most affected.[16,17]

There were described many subtypes of RCC. Recently, these entities changed their classification and have been considered independent cancers due to your behavior and your own genetic relationships. The clear cell renal carcinoma (ccRCC) is the most common, with approximately 70% of cases.[16]

ccRCC can present as metastatic disease of CNS, despite liver, lung, and bones being affected most frequently. On CNS, the brain is more commonly affected; however, few cases are reported in the literature with ISCM. The mechanism is like a hematogenous spread, with the arterial route.[18,28,32]

In cases that are associated with Von Hippel–Lindau Disease (VHLd), the diagnosis can be challenging. The radiological characteristics are similar between ccCCR and hemangioblastomas in several patients with intramedullary tumors. This possible confusion on diagnosis can late the appropriate treatment of ccCCR and prejudicated the patient. We present a case of a patient with VHLd and an ISCM of ccRCC. In a literature review, only 32 previous cases were reported.[1,2-4,6,8,9,11,12,15,20-33]

CASE REPORT

A 59-year-old female patient was referred to our hospital with weight loss, difficulty walking, and progressive weakness of the legs, besides bladder dysfunction. These symptoms started 6 months before admission. Previously, she had a history of brain surgery in 1994 with the diagnosis of hemangioblastoma.

On neurological examination, she presented with Glasgow Coma Scale 14 (she presented confused and did not understand her symptoms), left dysmetria, weakness and sensory loss of hands and lower limbs, and signs of pyramidal excitation as Hoffman and Babinski signs.

The patient was submitted to radiological investigation with MRI and CT scans. The MRI shows a 1.0 × 1.0 cm c2 intramedullary lesion which was demarcated as a homogeneous mass with a contrast-enhancing nodule associated with a cystic portion and flow voids that were characteristics of hemangioblastoma [Figure 1].

Due to neurological status and the presence of the cervical lesion, was decided to operate on the patient for maximal resection and spinal decompression. During the surgery, red color and high vascularized lesion were observed, with an excellent cleavage border. The pathological study showed neoplastic cells with clear cytoplasm, a hyperchromatic nucleus, and a small vascularized network between neoplastic cells [Figure 2]. The immunohistochemistry study was positive for the following markers: E29 (anti-EMA), SP67 (Anti-CD10), MRQ-50 (Anti-PAX8), and V9 (Anti-Vimentin). All these findings defined ccCCR as the diagnosis [Figure 3].

DISCUSSION

ccRCC is the most common entity of RCC, with approximately 70% of all cases. In general, when is present with metastasis, it has a vascular route of dissemination (arterial or venous). Lungs, liver, and bones are more commonly affected.[28,32]

The oncogenetic knowledge about ccRCC has exploded in advance since 1979 with the discovery of chromosome 3p

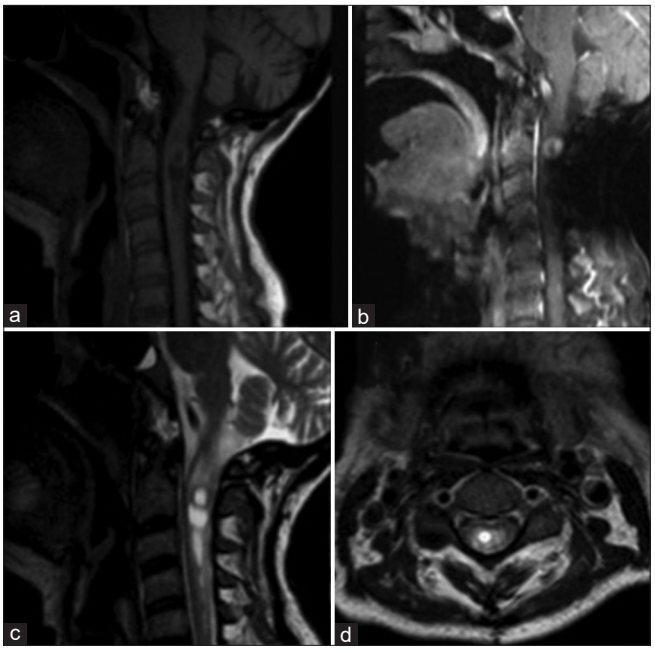

Figure 1: MRI with cervical spinal cord lesion: (a and b) (superior left and right, respectively) – T1 sagittal without and with contrast – 1.0 × 1.0 cm c2 intramedullary lesion with ring contrast enhancement. (c and d) (inferior left and right, respectively) T2 sagittal and axial.

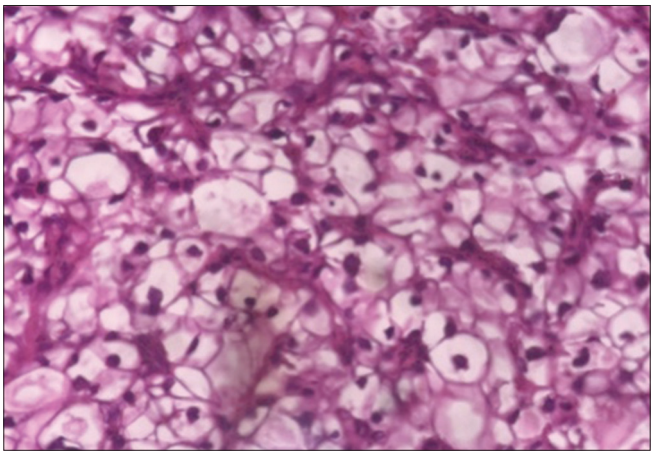

Figure 2: HISTOPATHOLOGIC STUDY: Neoplastic cells with clear cytoplasm, hyperchromatic nucleus and a small vascularized network between neoplastic cells.

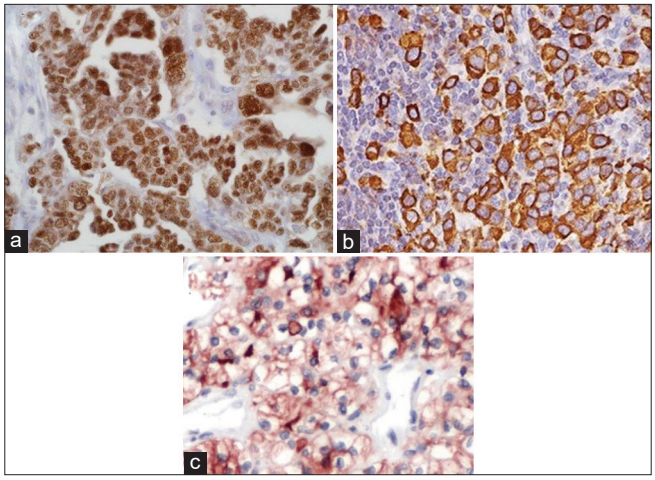

Figure 3: Immunohistochemistry: (a) – MRQ-50 (Anti-PAX8), (b) – E29 (anti-EMA), and (c) – SP67 (Anti-CD10).

loss. In 1993, the *vhl gene* was published, and additional oncogenes and mutations were described. Inside the genes related to metastases pathways, are important to cite PI3K activation, 9p, 14q loss, and 8q gain.[17]

The ccCCR can be present with VHLd which is an autosomal dominant syndrome described in 1904 that usually manifests in young adult patients and predisposes them to the development of other malignant and benign tumors such as hemangioblastomas of CNS, retinal angiomas, renal cysts, pancreatic cysts, pheochromocytomas, and neuroendocrine tumors. The principal genetic alteration is a mutation of both alleles of the *vhl gene* on 3p Chromosome.[5]

This pathology curses by two subtypes described. However, type 2 is the most important in this review context, mainly subtype 2b, characterized by retinal, CNS hemangioblastomas, and ccRCC.[5] The association between ccCCR and VHLd grows the risk of metastatic disease.[5,7,10]

Metastatic ccRCC can be present in 40% of cases of patients with VHLd and can be the cause of death of one-third of them. Patients with spinal metastatic ccRCC lesions can be confused with hemangioblastoma due to the prevalence of both pathologies and radiological characteristics. Both can be presented as solid lesions with homogeneous contrast uptake; however, other common characteristics can be present as a cystic portion and flow voids.[1]

The radiological overlap presentation could confuse medical staff. An important reminder is that hemangioblastomas on the spinal cord are found more commonly within the dorsal root entry zone.[7,23,33]

Immunohistochemistry is an important point to analyze. Some markers can present differentiation between ccRCC and VHLd despite the radiological overlap. In general, SP67 (Anti-CD10) and MRQ-50 (Anti-PAX8) are present in the ccRCC cases. Hemangioblastomas' markers are commonly NSE and S100 protein. V9 (Anti-Vimentin) and E29 (anti-EMA) can be present in both pathologies.[23,33]

The previous reviews suggest that only 4–9% of all intramedullary metastatic cases are secondary to ccRCC. An important reminder is that the ISCM represents only 0.1–2% of all spinal cord tumors. Most spinal lesions usually involve the extramedullary/extradural space, been lung and breast cancers are the most common primary sites.[4,32]

The symptoms and clinical presentation of ISCM are variable and depend on local space involvement (cervical, thoracic, or lumbar). The set of symptoms includes back or neck pain, weakness in the arms and/or legs, paresthesia, loss of sensibility, and sphincter dysfunction. Because the cervical spinal cord is the most affected, the more common previously described symptoms are weakness and sensory loss of upper and lower extremities besides sphincter dysfunction with urinary incontinence.[4,13]

The treatment with the microsurgery technique is the first-line therapy. This treatment's goal is to preserve preoperative neurologic function and avoid future worsening. Other classic options include radiation therapy and chemotherapy.[4,28]

Avoiding delays in the diagnosis are crucial for the patients. Late diagnosis and inadequate therapy drastically reduce the life expectancy.[4,28]

With the genetic understanding of the tumor, new options of therapies could be positioned on three major fronts: (1) targeting genomic vulnerabilities – here, the molecular taxonomy of ccRCC provides an opportunity to develop subtype-tailored therapeutic options; (2) targeting the tumor microenvironment – here, the therapeutics target the VEGF; and (3) targeting tumor heterogeneity – here, target agents again key driver mutations. Again, the most accurate and early diagnosis help the patient achieve potential treatment and increase life expectance.[1,2] Another potential treatment recently published for the group of MD Anderson Cancer Center is the MK-6482 inhibitor which is used in a group of ccRCC related to VHLd.[14,19]

The presence of ISCM for ccRCC is atypical. Only 33 cases were reported in the literature with our case [Table 1].[1-4,6,8,9,11,12,15,20-33] The mean age was 53.3 years (range 37–75 years). The Male gender was predominant with 78.7% of cases. The majorly affected is the cervical spine (48%); however, the thoracic spine is present in 42% of cases also. About 69.6% were submitted to surgery and 54.5% to radiotherapy. Only three patients were submitted to chemotherapy or immunotherapy. Other relevant information is that only two patients with the present case had the diagnosis of VHLd.

Table 1: Intramedullary spinal cord metastasis of clear cell renal carcinoma.

S. No.	Authors	Gender	Age	Location	VHLd	Extra Spinal Cord Involvement	Treatment	Follow-up/ Outcome
1.	Gaylor and Howie, 1938[11]	Male	62	Thoracic	-	Heart and Spleen	Not Described	Not Described
2.	Weitzner, 1969[31]	Male	44	Cervical	-	Bone	Radiotherapy	Not Described
3.	Kawakami and Mair, 1973[20]	Male	57	Cervical	-	Brain	Surgery	Not Described
4.	Schijns *et al.*, 2000[28]	Female	70	Cervical	-	Liver	Surgery	12 months
5.	Ateaque *et al.*, 2000[3]	Male	63	Cervical	-	Not Described	Surgery	1 month
6.	Poggi *et al.*, 2001[27]	Male	37	Thoracic	-	Lung, Bone and Brain	Radiotherapy	Not Described
7.	Fakih *et al.*, 2001[8]	Male	56	Cervical	-	Lung and Brain	Radiotherapy	6 months
8.	Fakih *et al.*, 2001[8]	Male	60	Thoracic	-	Lung and Brain	Surgery and Radiotherapy	5 months
9.	Fakih *et al.*, 2001[8]	Female	68	Thoracic-Lumbar	-	Not Described	Radiotherapy	16 months
10.	Fakih *et al.*, 2001[8]	Female	57	Cervical	-	Lung and Brain	Radiotherapy	5 months
11.	Fakih *et al.*, 2001[8]	Male	46	Thoracic	-	Lung and Brain	Radiotherapy and Alpha-interferon	4 months
12.	Fakih *et al.*, 2001[8]	Female	37	Cervical	-	Lung	Surgery	23 months
13.	Kaya *et al.*, 2003[21]	Male	43	Lumbar	-	Systemic	Surgery	6 months
14.	Altinoz *et al.*, 2005[1]	Male	43	Thoracic	Yes	Lung, Adrenal and Brain	Surgery	25 months
15.	Gómez de la Riva *et al.*, 2005[12]	Male	69	lumbar	-	Not Described	Surgery	14 months
16.	Donovan and Freeman, 2006[6]	Female	41	Cervical	-	Bone	Surgery and Radiotherapy	6 months
17.	Asadi *et al.*, 2009[2]	Female	51	Lumbar	-	Brain and Bone	Not Described	Not Described
18.	Parikh and Heron, 2009[22]	Male	50	Cervical	-	Brain	Surgery and Radiotherapy	28 months
19.	Komura *et al.*, 2011[22]	Male	57	Cervical	-	Not Described	Surgery	22 months
20.	Zakaria *et al.*, 2012[33]	Male	62	Cervical	-	Lung	Surgery, Radiotherapy and Immunotherapy	3 months
21.	Park *et al.*, 2013[26]	Male	44	Thoracic	-	Lung	Surgery and Radiotherapy	8 months
22.	Gao *et al.*, 2014[9]	Male	51	Thoracic	-	Not Described	Surgery	3 months
23.	Nomoto *et al.*, 2016[24]	Male	48	Thoracic	-	Not Described	Surgery and Radiotherapy	3 months

(Contd...)

Table 1: *(Continued).*

S. No.	Authors	Gender	Age	Location	VHLd	Extra Spinal Cord Involvement	Treatment	Follow-up/ Outcome
24.	Soga and Imanishi, 2016[29]	Male	69	Thoracic	-	Lung	Not Described	3 months
25.	Islam *et al.*, 2016[15]	Male	62	Thoracic	-	Bone	Radiotherapy	Not Described
26.	Weng *et al.*, 2018[32]	Male	58	Thoracic	-	Lung	Surgery and Radiotherapy	6 months
27.	Malik *et al.*, 2018[23]	Male	75	Thoracic	-	Not Described	Surgery and Radiotherapy	Not Described
28.	Strickland *et al.*, 2018[30]	Male	50	Cervical	-	Brain	Surgery	6 months
29.	Strickland *et al.*, 2018[30]	Male	50	Cervical	-	Brain	Surgery and Radiotherapy	3 months
30.	Strickland *et al.*, 2018[30]	Male	66	Thoracic	-	Brain	Surgery	65 months
31.	Strickland *et al.*, 2018[30]	Male	59	Cervical	-	Bone	Surgery and radiotherapy	65 months
32.	Barrie *et al.*, 2019[4]	Male	56	Cervical	-	Adrenal, Lung, Brain, Bone and Mediastinum	Surgery, Radiotherapy, Chemotherapy and Immunotherapy	25 months
33.	Authors Case, 2022	Female	59	Cervical	Yes	Lung	Surgery	2 months

VHLd: Von Hippel–Lindau disease

CONCLUSION

Despite a rare lesion with only few cases reported in the literature, ccRCC with ISCM must be reminded in the clinical reasoning of the medical team even in patients with VHLd, where spinal hemangioblastomas are more common.

With the actual natural history of cancer disease, due to the advance of all therapies and the more initial diagnosis, there is a growth of survival in general terms. These aspects must be led into consideration to remind that the possibility of finding in a patient with a SC tumor can be a metastatic pathology.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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