Case Report

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

Tiago S. F. Holanda, Edson Lopes Jr
Department of Neurosurgery, General Hospital of Fortaleza, Fortaleza, Brazil.
E-mail: *Tiago S. F. Holanda - tiago_holanda@hotmail.com; Edson Lopes Jr - neurocirurgiatiagoholanda@outlook.com

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. Lung and breast cancers are the most common primary sites, being melanoma, ovarian, thyroid, and colorectal cancers as other possibilities, however less common.

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.

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

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.\(^\text{[18,28,32]}\)

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.\(^\text{[1,2-4,6,8,9,11,12,15,20-33]}\)

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.\(^\text{[28,32]}\)

The oncogenetic knowledge about ccRCC has exploded in advance since 1979 with the discovery of chromosome 3p...
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 expectancy.\[1,2\] 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. 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.

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**Figure 3:** Immunohistochemistry: (a) – MRQ-50 (Anti-PAX8), (b) – E29 (anti-EMA), and (c) – SP67 (Anti-CD10).
### 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/Optume |
|--------|------------------------------|--------|-----|-------------|------|------------------------------|--------------------------------|------------------|
| 1.     | Gaylor and Howie, 1938       | Male   | 62  | Thoracic    | -    | Heart and Spleen             | Not Described                 | Not Described    |
| 2.     | Weitzner, 1969              | Male   | 44  | Cervical    | -    | Bone                         | Radiotherapy                   | Not Described    |
| 3.     | Kawakami and Mair, 1973     | Male   | 57  | Cervical    | -    | Brain                        | Surgery                       | Not Described    |
| 4.     | Schijns et al., 2000        | Female | 70  | Cervical    | -    | Liver                        | Surgery                       | 12 months        |
| 5.     | Ateaque et al., 2000        | Male   | 63  | Cervical    | -    | Not Described                | Surgery                       | 1 month          |
| 6.     | Poggi et al., 2001          | Male   | 37  | Thoracic    | -    | Lung, Bone and Brain         | Radiotherapy                   | Not Described    |
| 7.     | Fakh et al., 2001           | Male   | 56  | Cervical    | -    | Lung and Brain               | Radiotherapy                   | 6 months         |
| 8.     | Fakh et al., 2001           | Male   | 60  | Thoracic    | -    | Lung and Brain               | Surgery and Radiotherapy      | 5 months         |
| 9.     | Fakh et al., 2001           | Female | 68  | Thoracic-Lumbar | - | Not Described                | Radiotherapy                   | 16 months        |
| 10.    | Fakh et al., 2001           | Female | 57  | Cervical    | -    | Lung and Brain               | Radiotherapy                   | 5 months         |
| 11.    | Fakh et al., 2001           | Male   | 46  | Thoracic    | -    | Lung and Brain               | Radiotherapy and Alpha-interferon | 4 months |
| 12.    | Fakh et al., 2001           | Female | 37  | Cervical    | -    | Lung                         | Surgery                       | 23 months        |
| 13.    | Kaya et al., 2003           | Male   | 43  | Lumbar      | -    | Systemic                     | Surgery                       | 6 months         |
| 14.    | Altinoz et al., 2005        | Male   | 43  | Thoracic    | Yes  | Lung, Adrenal and Brain      | Surgery                       | 25 months        |
| 15.    | Gómez de la Riva et al., 2005 | Male | 69  | lumbar      | -    | Not Described                | Surgery                       | 14 months        |
| 16.    | Donovan and Freeman, 2000   | Female | 41  | Cervical    | -    | Bone                         | Surgery and Radiotherapy      | 6 months         |
| 17.    | Asadi et al., 2009          | Female | 51  | Lumbar      | -    | Brain and Bone               | Not Described                 | Not Described    |
| 18.    | Parikh and Heron, 2009      | Male   | 50  | Cervical    | -    | Brain                        | Surgery and Radiotherapy      | 28 months        |
| 19.    | Komura et al., 2011         | Male   | 57  | Cervical    | -    | Not Described                | Surgery                       | 22 months        |
| 20.    | Zakaria et al., 2012        | Male   | 62  | Cervical    | -    | Lung                         | Surgery, Radiotherapy and Immunotherapy | 3 months |
| 21.    | Park et al., 2013           | Male   | 44  | Thoracic    | -    | Lung                         | Surgery and Radiotherapy      | 8 months         |
| 22.    | Gao et al., 2014            | Male   | 51  | Thoracic    | -    | Not Described                | Surgery                       | 3 months         |
| 23.    | Nomoto et al., 2016         | Male   | 48  | Thoracic    | -    | Not Described                | Surgery and Radiotherapy      | 3 months         |

(Contd...)
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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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Altinoz MA, Santaguida C, Guiot MC, Del Maestrob RF. Spinal hemangioblastoma containing metastatic renal cell carcinoma in von hippel-lindau disease. Case report and review of the literature. J Neurosurg Spine 2005;3:495-500.
2. Asadi M, Rokni-Yazdi H, Salehinia F, Allamh FS. Metastatic renal cell carcinoma initially presented with an intramedullary spinal cord lesion: A case report. Cases J 2009;2:7805.
3. Ateaque A, Martim JL, O’Brien C. Intramedullary spinal cord metastases from a hypernephroma 11 years following the diagnosis and treatment of the primary lesion. Br J Neurosurg 2000;14:474-6.
4. Barrie U, Elguindy M, Pernik M, Adeyemo E, Aoun SG, Hall K, et al. Intramedullary spinal metastatic renal cell carcinoma: Systematic review of disease presentation, treatment, and prognosis with case illustration. World Neurosurg 2020;134:584-93.
5. Ben-Skowronek I, Kozaczuk S. Von hippel-lindau syndrom. Homone Res Pediatr 2015;84:145-52.
6. Donovan DJ, Freeman JH. Solitary intramedullary spinal cord tumor presenting as the initial manifestation of metastatic renal cell carcinoma: Case report. Spine (Phila Pa 1976) 2006;31:E460-3.
7. Dornbos D 3rd, Kim HJ, Butman JA, Lonser R. Review of the neurological implications of von hippel-lindau disease. JAMA Neurol 2018;75:620-7.
8. Fakh M, Schiff D, Erlich R, Logan TF. Intramedullary spinal cord metastasis (ISCM) in renal cell carcinoma: A series of six cases. Ann Oncol 2001;12:1173-7.

9. Gao J, Li Y, Yang Z, Wang R. Intramedullary spinal cord metastasis of renal cell carcinoma 6 years following the nephrectomy. Turk Neurosurg 2014;24:294-6.

10. Glasker S, Vergauwen E, Koch CA, Kutikov A, Vortmeyer AO. Von hippel-lindau disease: Current challenges and future prospects. Onco Targets Ther 2020;13:5669-90.

11. Gaylor JB, Howie JW. Brow-sequat syndrome: A case of unusual etiology. J Neurol Psychiatry 1938;1:301-5.

12. Gómez de la Riva A, Isla A, Perez-Lopez C, Budke M, Gutierrez M, Frutos R. Intramedullary spinal cord metastasis as the first manifestation of a renal carcinoma. Neurocirurgia (Astur) 2005;16:359-64.

13. Goyal A, Yolcu Y, Kerezoudis P, Alvi MA, Krauss WE, Bydon M. Intramedullary spinal cord metastases: An institutional review of survival and outcomes. J Neurooncocol 2019;142:347-54.

14. Hasanov E, Jonasch E. MK-6482 as a potential treatment for von hippel-lindau disease-associated clear cell renal carcinoma. Expert Opin Investig Drugs 2021;30:495-504.

15. Islam R, Habib R, Rahman A, Bhowmik NB, Haque A, Rahman T. Renal cell carcinoma presented with an intramedullary spinal cord metastasis: A case report. Bangladesh Crit Care J 2016;4:51-3.

16. Jonasch E, Gao J, Rathmell WK. Renal cell carcinoma. BMJ 2014;349:g4797.

17. Jonasch E, Walker CL, Rathmell WK. Clear cell renal cell carcinoma: Oncology and mechanisms of lethality. Nat Rev Nephrol 2021;17:245-61.

18. Kalimutthu LM, Ora M, Gamdbhir S. Recurrent renal carcinoma with solitary intramedullary spinal cord metastasis. Indian J Nucl Med 2020;17:4245-61.

19. Kanno H, Yamamoto I, Nishikawa R, Matsutani M, Wakabayashi T, Yoshida J, et al. Spinal cord hemangioblastomas in von hippel-lindau disease. Spinal Cord 2009;47:447-52.

20. Kawakami Y, Mair WG. Haematomyelia associated with anticoagulant therapy, an intramedullary ependymoma and schwann cells. Acta Neuropathol 1973;26:253-8.

21. Kaya RA, Dalkicilic T, Ozler F, Aydin Y. Intramedullary spinal cord metastasis: A rare and devastating complication of cancer: Two case reports. Neurol Med Chir (Tokyo) 2003;43:612-5.

22. Komura S, Hosoe H, Iwata A, Hirose Y, Shimizu K, Miyamoto K. Intramedullary spinal cord metastasis from renal cell carcinoma mimicking hemangioblastoma. Eur J Orthop Surg Traumatol 2011;21:597-9.

23. Malik MT, Kazmi SJ, Turner S. Teaching neuroimages: Intradural, intramedullary spinal cord metastasis from primary renal cell carcinoma. Neurology 2018;90:e911-2.

24. Nomoto Y, Tsukie T, Kurita A, Seki K, Suzuki H, Yamazaki K. Metastatic renal cell carcinoma initially presented with longitudinally extensive spinal cord lesion on MRI. Rinsho Shinkeigaku 2016;56:348-51.

25. Parikh S, Heron DE. Fractionated radiosurgical management of intramedullary spinal cord metastasis: A case report and review of literature. Clin Neurol Neurosurg 2009;111:858-61.

26. Park J, Chung SW, Kim KT, Cho DC, Hwang JH, Sung JK, et al. Intramedullary spinal cord metastasis in renal cell carcinoma: A case report of the surgical experience. J Korean Med Sci 2013;28:1253-6.

27. Poggi MM, Patronas N, Buttmann JA, Hewitt SM, Fuller B. Intramedullary spinal cord metastasis from renal cell carcinoma: Detection by positron emission tomography. Clin Nucl Med 2001;26:837-9.

28. Schijns OE, Kurt E, Wessels P, Luijkx G, Beuls EA. Intramedullary spinal cord metastasis as a first manifestation of a renal cell carcinoma: Report of a case and review of the literature. Clin Neurol Neurosurg 2000;102:249-54.

29. Soga H, Imanishi O. Case of intramedullary spinal cord metastasis of renal cell carcinoma. World J Urol 2016;5:72-4.

30. Strickland BA, McCutcheon IE, Chakrabarti I, Rhines LD, Weinberg JS. The surgical treatment of metastatic spine tumors within intramedullary compartment. J Neurosurg Spine 2018;28:79-87.

31. Weitnzer S. Coexistent intramedullary metastasis and syringomyelia of cervical spinal cord. Report of a case. Neurology 1969;19:674-8.

32. Weng Y, Zhan R, Shen J, Pan J, Jiang H, Huang K, et al. Intramedullary spinal cord metastasis from renal cell carcinoma: A systematic review of the literature. Biomed Res Int 2018;2018:7485020.

33. Zakaria Z, Fenton E, Jansen M, O’Brien D. The occult nature of intramedullary spinal cord metastases from renal cell carcinoma. BMJ Case Rep 2012;2012:bcr2012007476.

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