JOURNAL OF NEUROSURGERY:
Case Lessons

J Neurosurg Case Lessons 5(1): CASE22466, 2023
DOI: 10.3171/CASE22466

Mother and daughter with a *SMARCE1* mutation resulting in a cervical clear cell meningioma at an identical location: illustrative cases

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BACKGROUND A rare meningioma subtype is a clear cell (CC) meningioma, which can be associated with a *SMARCE1* gene mutation. Manifestation of a CC meningioma in the cervical spine is unusual. In the current case, both mother and daughter present with a CC meningioma at an identical cervical location.

OBSERVATIONS A 67-year-old patient with an intradural extramedullary mass at the level of C5 presented with progressive myelopathy. The mass was resected through a ventral approach by a two-level corpectomy with an expandable cage and instrumentation. The daughter of this patient appeared to have had an intradural extramedullary mass at C5 at the age of 20, which was resected through a posterior approach. Pathological investigation of both tumors revealed CC meningioma. Genetic testing of the daughter revealed a *SMARCE1* mutation.

LESSONS It is of major importance to consider a *SMARCE1* mutation in elderly presenting with a CC meningioma, which is still uncommon in current practice. This could lead to timely diagnostics in the succeeding generation. Complete resection of a CC meningioma is important because of the high recurrence rate. Routine follow-up should therefore be performed in the postoperative period. An anterior approach should be considered for a ventral cervical CC meningioma.

https://thejns.org/doi/abs/10.3171/CASE22466

KEYWORDS cervical spine; meningioma; spinal tumors; clear cell meningioma; genetics

Meningiomas are tumors that arise from the dura mater and primarily occur in the brain and spinal cord.[1] Intradural extramedullary meningiomas are the most common, which account for approximately 45% of all intradural spinal tumors.[2,3] Extradural spinal meningiomas occur less frequently.[2] Meningiomas are generally benign tumors and are rarely malignant. Because these tumors grow slowly, symptoms often arise when the tumor is already fairly large. Meningiomas are commonly found in all regions of the skull and along the spinal cord.[3,4] The majority (67%–84%) of spinal meningiomas occur in the thoracic area, whereas only 2%–14% occur in the cervical spine.[3]

Meningiomas can be divided into three categories, as classified by the World Health Organization (WHO);[1,5] Grade I entails slow growing benign tumors, Grade II entails atypical tumors with high recurrence rate, and Grade III entails malignant, fast-growing tumors. A rare, WHO Grade II type of meningioma is the clear cell (CC) meningioma.[6,7] CC meningiomas are characterized by clear sheets of cells, abundant collagen, chicken wire vasculature and accumulation of glycogen. They can be associated with loss of the *SMARCE1* gene function.[6] The majority of CC meningiomas are familial cases, suggesting that CC meningioma is a hereditary disease.

Switch/sucrose nonfermentable (SWI/SNF)-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1 (*SMARCE1*) is a gene that provides information for making proteins that form subunits of the SWI/SNF complex. The SWI/SNF complex is involved in gene activity by chromatin remodeling, which means that SWI/SNF complexes are important in DNA repair and controlling growth of cells. This indicates that the *SMARCE1* gene acts as a tumor suppressor.[6,8,9] Tumor suppressors normally slow down

ABBREVIATIONS ADL = activities of daily living; CC = clear cell; CPA = cerebellopontine angle; MRI = magnetic resonance imaging; SNF = sucrose nonfermentable; SWI = switch; WHO = World Health Organization.

INCLUDE WHEN CITING Published January 2, 2023; DOI: 10.3171/CASE22466.
SUBMITTED October 28, 2022. **ACCEPTED** November 29, 2022.

cell division, repair DNA mistakes or initiate programmed cell death. When these genes are turned off due to loss-of-function mutation, the tumor suppressor function is inactivated leading to uncontrolled cell growth.[10] Almost all tumors with *SMARCE1* mutation, and thereby loss of the tumor suppressor function, cause clear cell morphology.

Regular meningiomas occur more often in middle-aged people. However, CC meningiomas occur more often in children and young adults; the mean age of onset is around 26 years of age.[6,7,9,11] The occurrence of CC meningiomas is nearly equal in men and women, while regular meningiomas have a higher incidence in females.[11] The recurrence rate of CC meningiomas is high, at an estimated 38% in 2 years. The reported mortality rate of patients with CC meningiomas is 8.8%, within the same time span.[6] Due to the combination of a high recurrence rate and a strong penetration of the mutation to the next generation, patients diagnosed with CC meningioma and their relatives should be genetically screened and followed.[6,7]

The radiological presentation of CC meningiomas is in many aspects similar to regular meningiomas. Both meningiomas and CC meningiomas typically have an iso to mildly high signal intensity on both T1- and T2-weighted magnetic resonance imaging (MRI).[12] They are usually strongly homogeneously enhanced on gadolinium contrast T1-weighted imaging.[13,14] Moreover, CC meningiomas rarely show peritumoral edema or tumor cysts.[12] However, in some aspects they can appear different from other meningiomas upon imaging. As described by Zhang et al.,[13] spinal CC meningiomas more commonly adhere to the roots, and not to the dura. The typical dural tail of a meningioma can thus be absent upon imaging. Spinal CC meningiomas might thus strongly resemble schwannomas upon imaging.[13,15]

Even though meningiomas are often benign, they can cause severe complaints. The common treatment option for meningiomas, and thus CC meningiomas, is surgical removal of the tumor. Usually no additional radiotherapy is needed, however, when complete resection is not possible and/or the meningioma is a WHO Grade II, radiotherapy is advised in addition to the surgery.[4,16] To date, there is no effective chemotherapy treatment option for meningiomas.[4]

CC meningiomas with loss of *SMARCE1* function have the tendency to occur in the spinal cord, cerebellopontine angle (CPA) and intracranially.[6,7] However, there is inconsistency in the reported frequency of CC meningioma occurrence in these locations. In the available literature/case reports, CC meningiomas are often found in the lumbar spine, CPA, and cranially.[17–20]

Therefore, it is of interest to investigate the current case in which both mother and daughter presented with a cervical spinal CC meningioma at the same location.

Illustrative Cases

Case 1

A 67-year-old woman with a history of diabetes mellitus type 2 and cardiovascular disease presented with a tingling feeling in the hands and feet. She had persistent complaints of neck pain in the past 2.5 years, which recently started to aggravate. Over the course of 4 months, the paresthesia's in hands and feet had progressed to deep hypoesthesia. This was first considered to be a result of diabetic neuropathy. However, symptoms slowly worsened over the following 2 months, the strength in the hands was declining, and she developed difficulty walking. Within 6 months the patient lost independency in activities of daily living (ADL).

MRI of the cervical spine and the cranium revealed a large mass from C4 to C6 with a length of approximately 37 mm. The mass was located intradural and extramedullary, ventral to the spinal cord (Fig. 1). The differential diagnosis comprised schwannoma, meningioma, or neurofibroma. Considering the severity of complaints, surgical treatment was the preferred treatment strategy. Resection of the tumor was performed by the neurosurgeon through a ventral approach requiring a two-level corpectomy. Perioperatively the tumor did not appear adherent to the dura, but to a ventral cervical rootlet. The tumor was removed in toto with resection of the adherent part of the rootlet. The dura was sutured and sealed with fibrin glue. An expandable cage was used and plate fixation from C3 to C6 was performed (Fig. 2A). No perioperative complications occurred. The patient recovered quickly postoperatively and neurological deficits diminished. She was discharged on postoperative day 10.

After immunohistochemical staining the pathologist determined that the tumor was a clear cell meningioma WHO Grade II. The standard postoperative control radiograph after 6 weeks revealed subsidence of the cage with secondary kyphosis (Fig. 2B). A secondary surgery was performed to prevent further deformity. The plate was revised and a dorsal instrumentation of C3 to C6 was performed. The patient recovered well and went home on postoperative day 9. Imaging 4 weeks later showed a good and stable position of the cage and plate (Fig. 2C).

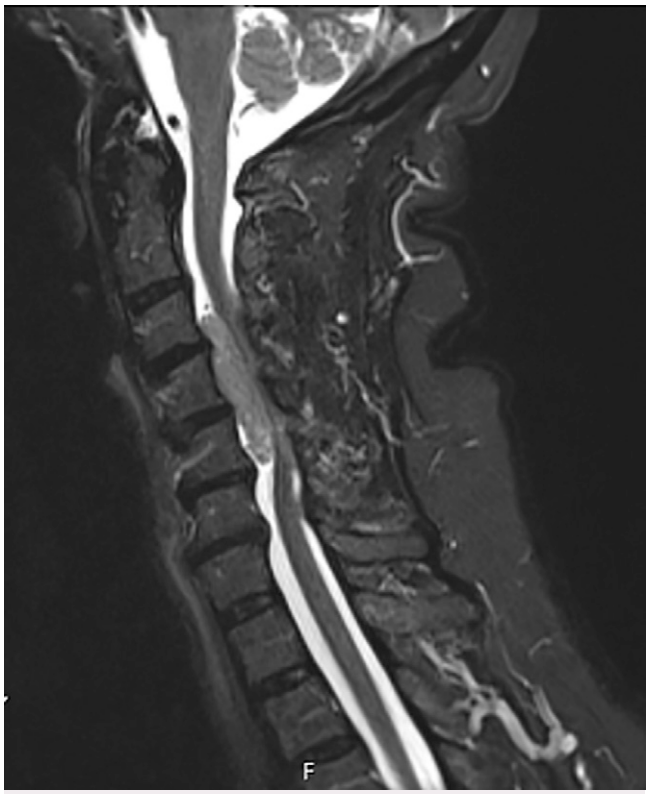

FIG. 1. Sagittal T2-weighed MRI revealing an intradural extramedullary mass located at C3–5 in the 67-year-old patient.

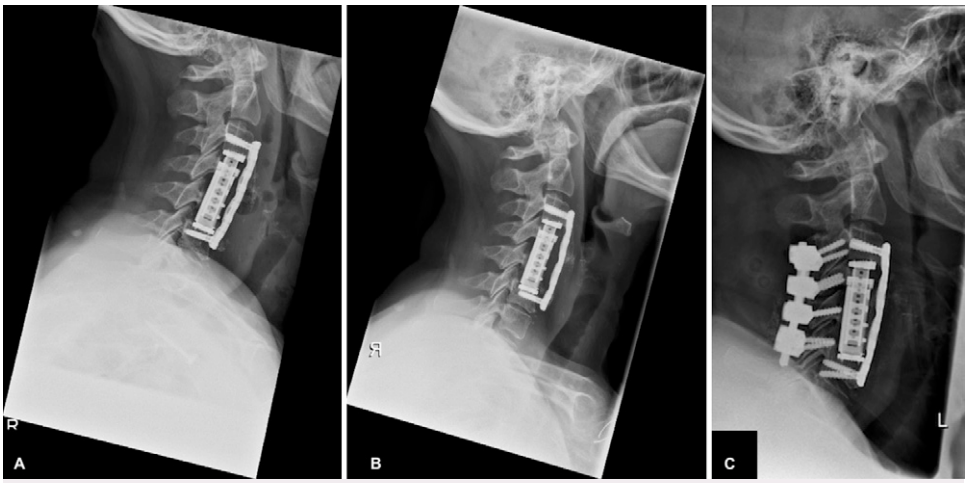

FIG. 2. Postoperative images obtained in the 67-year-old patient. **A:** Radiograph obtained directly postresection and corpectomy. **B:** Radiograph with visible subsidence of the cage, obtained 4 weeks postoperatively. **C:** Radiograph obtained directly after revision of cage and instrumentation.

Over the 2-year follow-up period the sensation in the hands and fingertips improved, as well as the strength in the hands. She regained independent ADL ability. Moreover, the patient's walking improved. Unfortunately, the hypoesthesia in the feet remained. Routine MRI studies were performed every 6 months; there was no residual tumor, and to date there is no sign of tumor recurrence.

Case 2

After further inquiry it appeared that the patient's daughter also had a cervical CC meningioma at the age of 20. Approximately 20 years ago, the daughter presented with paresthesia and hypoesthesia in the hands, which had developed over the course of 2 years. Later, over the course of a month, a progressive paresis in the hands, balance issues, and difficulty walking developed. An MRI of the cervical spine was performed and revealed an intradural and extramedullary mass at C5, extending to C7, with substantial spinal cord compression (Fig. 3A). This was also located ventral to the spinal cord. The differential diagnosis of the mass considered was meningioma or neurofibroma. A laminectomy from C5 to C7 and resection of the complete tumor was performed (Fig. 3B). Intraoperatively, two posterior radiculi of C7 on the right were severed. Postoperatively the paresthesia and hypoesthesia in the upper limbs worsened. Moreover, the strength in the legs decreased, the patient suffered from quadriparesis. Due to her nonambulatory condition, the patient was admitted to a rehabilitation institution 7-days postoperatively. After 2 months of rehabilitation, she regained ambulatory function and use of her arms and hands, as well as being independent again. Her further recovery was uncomplicated and symptoms improved.

Pathological investigation similarly revealed a CC meningioma WHO Grade II. The patient was stable for 6 years. MRI studies were regularly performed, and no recurrence was seen. New complaints developed 6 years later. Next to complaints of severe nausea, she developed new, prominent paresthesia and hypoesthesia in the upper limbs. The MRI did not reveal recurrence of the tumor, but extensive adhesions and syringomyelia (Fig. 4). A second surgery was performed at the time, during which the spinal cord was untethered. Again, the patient initially worsened neurologically and had to recover in a rehabilitation institution. Four weeks postoperative she regained ambulatory function and was able to function independently. Paresthesia in the upper limbs remained.

Three years later, a progressive kyphosis of the cervical spine was clearly apparent on the follow-up radiographs (Fig. 5A). A

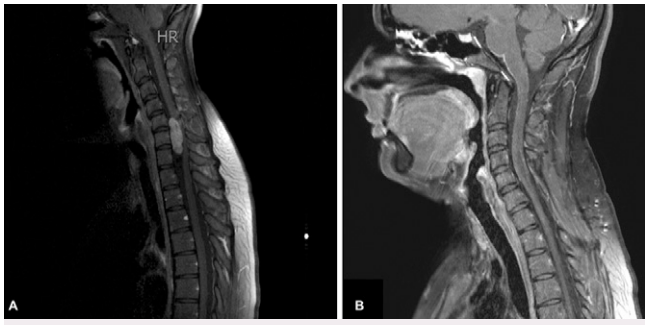

FIG. 3. A: Sagittal T1-weighed MRI with gadolinium obtained in the daughter at the age of 20, revealing a large intradural extramedullary mass at C5–7. **B:** Sagittal T1-weighed MRI of the daughter obtained directly after tumor resection and laminectomy.

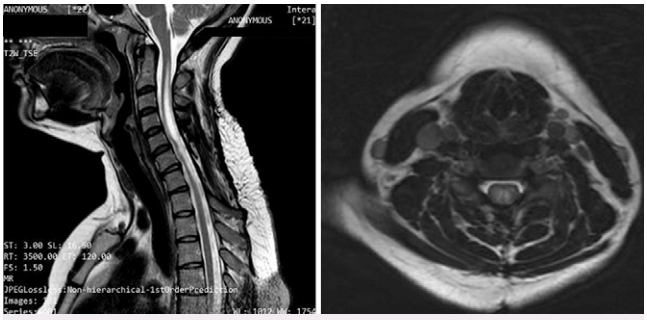

FIG. 4. T2-weighed MRI of the daughter on her second presentation, revealing extensive adhesions in light of syringomyelia. A sagittal view (**A**) and transverse view (**B**) with visible adhesion.

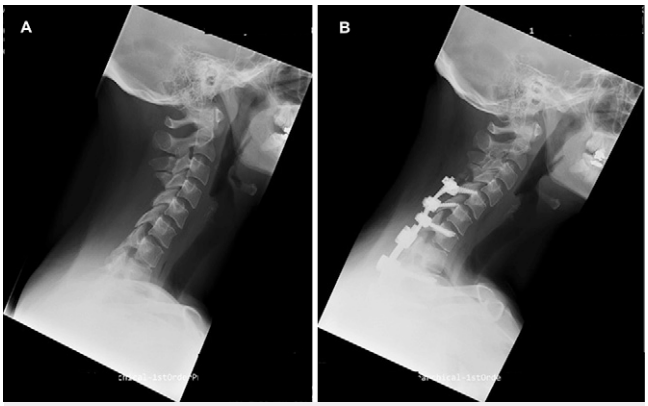

FIG. 5. Images of the daughter obtained at her third presentation. **A:** Radiograph with progressive kyphosis of the cervical spine. **B:** Radiograph obtained directly postoperatively.

dorsal instrumentation from C5 to T3 was performed 6 months later because of progressive walking disability (Fig. 5B and C). The patient recovered well and was discharged postoperative day 9. Again, the patient was followed for years. To date, symptoms are stable, MRIs show a slowly progressive syrinx but no tumor recurrence.

Initially, no genetic investigation was conducted. However, the unlikely presentation of both mother and daughter with a cervical CC meningioma resulted in genetic screening of the daughter one year ago. This screening revealed that the daughter has the *SMARCE1* mutation. The 67-year-old mother was not screened because it was obvious that the daughter inherited the autosomal dominant mutation from her. However, the patient's sister was screened and was negative for a *SMARCE1* mutation. The children of the daughter, the grandchildren of our patient, were not yet genetically tested, but will be regularly screened with MRI until they are 18 years old. On reaching the age of 18, they can opt for genetic screening if desired. One of the grandchildren reported mild complaints of paresthesia and hypoesthesia in hands and feet, but no tumor is visible on MRI. An important thing to consider is that the *SMARCE1* mutation is autosomal dominantly inherited, but the penetrance is incomplete and dependent on epigenetic factors, like environmental factors.[21]

Additional inquiry from the 67-year-old patient revealed that a niece had a cerebral tumor, which was resected, in combination with a *SMARCE1* mutation. Unfortunately, documentation is missing, and it remains unclear whether this was a CC meningioma.

Discussion

Both mother and daughter initially presented with paresthesia and hypoesthesia in the upper limbs and later on in the lower limbs, followed by a progressive quadriparesis and difficulty walking. The complaints appeared to be caused by an anterior CC meningioma around C5. Interestingly, the initial treatment differed. A posterior approach was chosen for the daughter, while the mother received anterior surgery. Moreover, the daughter was considerably younger when the tumor was discovered. In both cases, complications occurred, however they were more extensive in the case of the daughter.

Observations

To the best our knowledge, this is the first case of a mother and daughter with a CC meningioma found at an identical location. Moreover, this is the first Dutch case where both mother and daughter, both have a cervical meningioma. Gerkens et al.[7] did report a familial case of *SMARCE1*-mutated meningioma in The Netherlands. However, in this situation, the grandmother and grandson were affected, and the CC meningiomas occurred at different locations. The grandmother had a spinal CC meningioma, whereas the grandson had a CC meningioma in the right CPA.

As described by Smith et al.,[22] only 10% of meningiomas occur in the spinal region. As reported by Kwee et al.,[3] spinal meningiomas are more commonly found in the thoracic region than in the cervical or lumbar region of the spine. Common locations for CC meningiomas are the lumbosacral region, intracranial or at the CPA.[7,11,17–20,22,23] To the best of our knowledge, only one of the cases found indicated the tumor to be located cervical,[11] the other spinal cases were not found in the cervical region or did not specify the spinal location.[11,17–20,22,23] Therefore, cervical CC meningiomas are considered to be more rare than lumbar CC meningiomas. Therefore, it is exceptional to find that in this case, both the mother and daughter had a CC meningioma, not only at the same cervical level, but both ventral to the spinal cord.

Not only the late age of onset in the mother's case, but also the occurrence at the same location as the daughter is a unique feature of this case. CC meningiomas usually have an earlier age of onset than regular meningiomas.[6,7,9,11] Although our patient was in her 60s when she was diagnosed with a CC meningioma, the daughter was a young adult when the tumor was discovered, which fits the early time of onset of a CC meningioma.[6,9] To date, only one CC meningioma case has been reported in which the patient was 72 years of age when the tumor was discovered. The remaining cases in the literature concern patients younger than 60.[11]

SMARCE1 mutations always result in clear cell morphology, and familial CC meningioma is associated with germline *SMARCE1* mutations.[7,11,17–20,22,23] As *SMARCE1*-associated CC meningiomas almost always occur in younger patients, it is uncommon to consider a meningioma in an elderly patient to be a CC meningioma associated with a *SMARCE1* mutation. This might be the reason why less *SMARCE1* screening is performed in elderly. The other way around, this might just be the reason for the infrequently discovery of *SMARCE1* mutations in older people with meningiomas.

When a patient is diagnosed with CC meningioma it is important to perform a complete resection because CC meningiomas have a high recurrence rate (∼38%), therefore, regular follow-up with imaging is important.[6,24,25] Radiological follow-up is recommended 1 to 2 years postoperative every 6 months.[7,26] When no tumor recurrence is observed in this period, it can be chosen to extend the interval to annual check-ups.

Screening should also be performed in the succeeding generation. According to national guidelines predictive genetic testing is not advised in children unless it is a treatable condition and treatment should start before the age of 18. This is why it is advised to perform routine MRI until the age of 18, after which they can opt for genetic testing.

The appearance of the tumor of the daughter differed from the typical meningiomas upon MRI. Although the gadolinium-contrast T1-weighted imaging was strongly enhanced just like with normal meningiomas, it was not attached to the dura mater.[13] Therefore, it resembled a schwannoma on imaging.[13,15] This was also the case

for the mother's MRI, which broadened the differential diagnosis based on imaging. Moreover, both in the mother and daughter, the tumor was located more ventral to the spinal cord.

The CC meningiomas in both cases were located at exactly the same place. The initial surgical approach was different. In the case of the mother, a ventral approach was performed, whereas for the daughter a posterior approach was chosen. Both appear to be surgeries associated with a high risk of complications, which in these cases occurred.[27,28] However, in the ventral surgery the complications originate from a purely mechanical nature, whereas in the posterior approach both mechanical complications as well as intradural complications arose, the latter having more severe consequences. The daughter developed severe complaints due to adhesions. A secondary untethering was performed, after which symptoms partly resolved, but soon recurred, subsequently a third surgery followed because of progressive kyphosis. The daughter required intense rehabilitation twice due to her recurrent complaints and surgery. The mother, however, did not develop new neurological complaints, but additional instrumentation was performed because of radiological subsidence. One could argue that a 360-degree approach could have been performed initially. This was not done at the index surgery because the posterior elements were all intact, there was good a cervical lordosis, and bony purchase of the screws was good.

Lessons

This case lessons shows that older individuals can also present with a CC meningioma and that a *SMARCE1* mutation should be considered in elderly, which is still uncommon in current practice. When the person is diagnosed with CC meningioma it is important to perform a complete resection because CC meningiomas have a high recurrence rate, therefore regular follow-up with imaging is important.

Another important factor is awareness surrounding *SMARCE1* mutation and the occurrence of CC meningiomas. If a *SMARCE1* mutation is detected, family should be informed and be given the option to be screened as well.

Furthermore, an anterior surgical approach should be considered for an anteriorly located cervical meningioma.

Acknowledgments

We are thankful to the patients for cooperating in the writing of this paper.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Schuermans, Van de Goor, Boselie. Acquisition of data: Schuermans, Van de Goor, Broen. Analysis and interpretation of data: Schuermans, Boselie. Drafting the article: Schuermans, Van de Goor. Critically revising the article: all authors. Reviewed submitted version of manuscript: Broen. Approved the final version of the manuscript on behalf of all authors: Schuermans. Administrative/technical/material support: Van de Goor.

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