Case Report

Intramedullary clear cell ependymoma of the lower thoracic spinal cord: report of a new case

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ABSTRACT

Background: Clear cell ependymomas (CCEs) are a rare variant of tumors of the nervous system, the main location is the intracranial compartment. Special differential diagnosis should be done with oligodendrogliomas, neurocytoma, glioneurocytoma, astrocytoma, or metastatic renal cell carcinoma, lesions that somehow share cells with clear cytoplasm. Most of these lesions are benign but differential diagnosis is essential to decide further treatment. Few case reports of intramedullary CCEs have being published and there is no strict consensus on the diagnostic criteria.

Case Description: We hereby describe a new case of an intramedullary clear CCE with very few neurological symptoms, surgical treatment is satisfactory, histological and immunohistochemical analysis was confirmatory. After gross total resection and 3-year follow-up no recurrence of the lesion is evident.

Conclusion: After this case presentation and review of the limited literature, it is evident that methodical clinical suspicion, radiological imaging combined with histological, and modern immunohistochemical techniques are essential for the diagnosis. Surgical options with gross total resection remain the cornerstone of its treatment. Neurophysiological monitoring is extremely useful to avoid postoperative morbidity.

Keywords: Clear cell, Ependymoma, Intramedullary, Surgical treatment

INTRODUCTION

Clear cell ependymomas (CCEs) constitute a rare variant of tumors of the central nervous system. Most of them are located intracranially and specially in the supratentorial compartment. Spinal cord CCEs have being described previously and constitute a rare but very benign variant of intramedullary tumors.3-14 Despite the fact that the number of reported cases is not yet significant, the individual descriptions that have been made demonstrate more specific parameters that allow unification in the diagnosis criteria. We present a new case of a thoracic intramedullary CCE and a review of previous cases emphasizing the importance of clinical, radiological, and histopathological criteria for its diagnosis.

CASE REPORT

A 57-year-old Mexican woman was referred to neurosurgical consultation after being reviewed by the Clinical Neurology Department at our hospital. She assisted complaining with a 36-week...
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The initial neurologic evaluation demonstrated a dissociated sensory disturbance below Th11 level and decreased deep tendon reflex in both lower limbs. Strength was 4/5 on the left iliopsoas and quadriceps muscles associated with negative extensor plantar reflex. Gait disturbances were prominent preventing her to perform Tandem, Romberg sign and walking instability were evident as other proprioceptive alterations.

Magnetic resonance image (MRI) of the thoracolumbar spine [Figure 1a] exhibits a remarkable intramedullary isointense lesion on T1-W sequence expanding the thickness of the spinal cord and filum terminalis, a moderate homogenous enhancement was noticed after Gadolium injection [Figure 1b]. T2-W sequences confirmed an hyperintense lesion occupying almost the whole diameter of the spinal cord with foamy-like well-defined characteristics that extended from the superior border of Th11 to the inferior border of Th12, remarkable spinal cord, and filum terminalis vasogenic edema could be observed. Cranial syrinx was evident immediately adjacent to the tumor and extended from Th11 to Th4 with an important intramedullary cystic cavity [Figures 1c-e].

The patient was scheduled to a Th9–Th12 laminectomy, tumor resection, and laminoplasty, which was performed under neurophysiological monitoring with motor evoked potentials (MEP's) and microsurgical techniques. After identifying the posterior medullary sulcus and performing a midline myelotomy, we could observe a highly vascularized grayish lesion that was firmly attached to the ependymal walls. Despite having a firm texture, no clear plane of cleavage was evident except in its upper pole where a cystic cavity containing xanthochromic fluid was emerging. An estimated 95% resection of the tumor could be achieved with ultrasonic aspiration assistance without eventualities. Medullary pia was slightly closed just to juxtapose the posterior columns using 7–0 non-absorbable stitches and allowing the syrinx to drain into the subarachnoid compartment. While the tumor was manipulated, a moderate and transient decrease in MEP’s amplitude was detected, however progressive recovery of the registry allowed us to continue with the procedure. Postsurgical evolution was satisfactory and the patient did not show any increase of her previous neurological manifestations. After the 5th postoperative day, she was discharged from the hospital to her home under a physical therapy program for her legs. Tumor recurrence is discarded after 24 months of follow-up MRI [Figure 1f].

For histological purposes, 3–4 μm-thick sections were stained with hematoxylin and eosin, finding an extensive proliferation of monotonic round to oval cells with clear fibrillary cytoplasm and large central round nucleus with indistinct nucleoli disposed in a diffuse pattern and scarce mitotic activity than normal tissues. Entrapped blood vessels showed moderate perivascular hyalinization and the presence of pseudorosettes suggesting; thus, the diagnosis of CCE without anaplasia [Figure 2]. Immunohistochemical
analysis results consisted in a strong positivity (3+) to anti-glial fibrillary acidic protein (GFAP) with a Ki67 (MIB-1) labeling index at 1%, and negative for both chromogranin A and anti-epithelial membrane antigen (EMA) antibodies [Figure 3].

DISCUSSION

Ependymoma is a group of tumors that have their origin from the ependymal cells of the ventricular system of the brain and in the central canal of the spinal cord. Most of intracranial cases are predominant in childhood, whereas the intramedullary cases usually occur in adults with a characteristic preference for the cervical and thoracic regions in the spinal cord. Primary intramedullary ependymomas are the most frequent tumors within the spinal cord consisting between 30 and 45% of them. Ependymal tumors usually appear in the fourth decade of life and 75% of these usually occur in adults making up 25% of intramedullary spinal cord tumors, with an estimated incidence of 1.1 cases per 100,000. These are only a 2% of primary central nervous system neoplasms.

It is well recognized that most ependymomas are usually of benign etiology and their symptoms derive from the neurological deficit caused by the underlying affected structures without presenting infiltrative characteristics. Cysts associated with intramedullary ependymomas are frequent, their presence is near to 80% of cases and it is considered that the volume of the cysts is proportional to the severity of symptoms presented by patients.

Table 1 contains the results of an exhaustive search in the English written literature including our case. There are nine documented cases of CCE within the spinal cord (seven benign and two malignant). Seven are women and two men with an average age of 46.44 years (range: 3.5–85 years old). To the best of our knowledge, the only anaplastic variant was described by Eshraghi et al. and is considered as the youngest patient in the group. In spite, Bekci’s et al. report was confirmed as CCE without anaplastic characteristics; its recurrence with metastatic subarachnoid spread forced the authors to propose radiotherapy as complementary treatment. The rest of the clinical cases identified were confirmed to be benign.

The predominant location is the thoracic region, followed by high lumbar and the cervical segments (5, 3, and 1 cases, respectively). Akatsu et al. in 2000, reported the only patient with cervical location to date, it is about a female that experienced ulnar numbness and moderate spastic weakness of the lower limbs. Clinically, the main symptom reported in most of the patients is long-term back or neck pain depending on the location. This is followed by radicular manifestations referred either as itchy sensations or cramps sometimes with multiple root involvement or even bilateral presentation. Sensitive dissociation, dermatomal numbness, or hypoalgesia, followed by hyperactive reflexes and mild weakness of the lower extremities, were the most relevant findings during neurological examination, thus suggesting syringomyelia symptoms. Notwithstanding, the predominance of gait disturbances in patients with thoracic lesions, all of them preserved the ability to walk. These lesions are considerable large; however, due to their clinical
Table 1. Summary of cases reported with Intramedullary Clear Cell Ependymoma

| Author                  | Gender | Age | Location                | MRI Imaging                              | Syrinx | Histology                                                                 | Immunochemistry                                                                 |
|-------------------------|--------|-----|-------------------------|------------------------------------------|--------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Akutsu et al. (2000)    | Female | 42  | Cervical (C6-Th1)       | Well defined T1 isointense              | +      | Round nuclei with clear cytoplasm and perinuclear halos, Ependymal rossettes and perivascular pseudorosettes | GFAP +, Vimentin T +, Chromogranin A -, Synaptophysin -, Neuron-specific enolase - and EMA - |
| Kim et al. (2003)       | Male   | 59  | Thoracic (Th3-Th4)     | 3.5 cm well defined T1 isointense T2 isointense Hetero enhancement | + (Th2-Th3) | Clear cells with round nucleus. Bright cytoplasm +++, and foamy cells proliferation +++ | GFAP +, EMA +, Vimentin +, Cytokeratine - , Synaptophysin - and MIB-1 staining index = 0.25 %, GFAP +, S-100 protein +, NSE and Vimentin +, EMA, Desmin, Synaptophysin - , Chromogranin & S-3 protein - , Ki-67 index 1% |
| Kim et al. (2007)       | Female | 73  | Thoracic (Th12)        | 2 cm well defined T1 isointense T2 hyperintense No contrast | None | Round to oval cells, large central nuclei, indistinct nuclei & clear cytoplasm with perinuclear halo. Entrapped blood vessels with perivascular hyalinization and pseudorosettes. No criteria for anaplasia. Granular cytoplasm PAS +, Multifocal clear-cell regions, perivascular pseudorosettes, focal tanyctic -like pattern, some mitosis, slight nuclear pleomorphism and polychromasia, microvascular proliferation and regions of tumor necrosis. | GPAF +, S-100 protein +, NSE and Vimentin +, EMA, Desmin, Synaptophysin - , Chromogranin & S-3 protein - , Ki-67 index 1% |
| Bapuraj et al. (2007)   | Female | 10  | Lumbar (L1-L3)         | 5.5 cm well-defined T1 hyperintense T2 hyperintense Homo enhancement | None | Not referred                                                                 | Not referred                                                                 |
| Rajabiani et al. (2011) | Female | 57  | Lumbar (L1-L2)         | 2 cm well defined T1 Not referred T2 Not referred Homo enhancement | + (L1) | Round to oval cells with large central nuclei and clear cytoplasm. Nuclear grooves with intranuclear inclusions were rarely found. Rare ependymal clefts, perivascular hyalinization & pseudorosettes. | GPAF +, S-100 protein +, NSE and Vimentin +, EMA, Desmin, Chromogranin - , Pancytokeratin +, Synaptophysin - , P53 - , Ki67 index < 1 % |
| Eshraghi et al. (2012)  | Female | 3   | Lumbar (L1-L2)         | T1 isointense T2 isointense Homo enhancement Cystic component hyperintense | None | No details                                                                 | Not referred                                                                 |
| Camelo-Piragua et al. (2012) | Female | 85  | Thoracic (Th7-Th8)     | Not Referred Not Referred | Clear cells round nuclei and few nuclear pleomorphism, areas devoid of nuclei around blood vessels, eosinophilic processes forming | GFAP +, EMA + focal perinuclear |

(Contd...)
Concerning their morphology, normal ependymal cells can vary considerably ranging from ciliated or cuboidal epithelial cells to elongate and fibrillated glial cells also known as tanycytes. The same is true for ependymomas, resulting in three histopathological variants: papillary ependymoma (PE), CCE, and tanycytic ependymoma being this last the most recently recognized ependymoma variant. However, one genetically defined ependymoma subtype has been added to the 2016 CNS WHO as a novel entity: ependymoma, RELA fusion-positive.

Histologically, ependymoma shows characteristic diagnostic perivascular pseudorosettes and/or true rosettes called ependymal rosettes and ependymal tubes or canals. In exceptional cases, when there are no distinct histological features of ependymoma, immunohistochemical approach (including EMA and GFAP positivity), and/or ultrastructural findings such as combined epithelial and glial phenotype, such as intracellular lumina or abortive tubule formation, microvilli, occasional cilia, complex desmosome-like junctions, and glial fibers contribute to a definite diagnosis. Clear cells or oligodendroglia-like cells have been noticed in ependymomas for many years. This morphologically distinctive subtype is characterized by sheets and lobules of crowded, uniform cells with round nuclei, central nucleoli, and conspicuous perinuclear cytoplasmic clearing so it could be misdiagnosed as oligodendroglioma or other potentially clear cell neoplasms including neurocytoma, glioneurocytoma, astrocytoma, or metastatic renal cell carcinoma.

Microscopically, these tumors are composed by a moderately round to oval cell population with large central round nuclei and clear cytoplasm, but without atypical features. Nuclear grooves and intranuclear inclusions are rarely found in the specimens but a very well-defined fibrillary background can be easily noticed in certain portions of tumor. Rare ependymal clefts, perivascular hyalinization and pseudorosettes may also be identified.

In a review and analysis of different clear-cell tumors of the central nervous system, an adequate identification of the origin of these neoplasms is possible by combining GFAP, EMA, and synaptophysin. Immunohistochemical staining techniques demonstrate that CCEs are diffusely and strongly positive for both antivimentin and anti-GFAP antibodies in the cytoplasm, reflecting its biological behavior. A positive result for anti EMA antibody is usually focal and dot-like. A few of the tumor cells may also be positive for cytokeratin
AE1/AE3. Neuronal markers including synaptophysin, neurofilaments, neuron-specific enolase, and chromogranin A are usually negative, and as very distinctive characteristic is that most of them show a low Ki-67 (MIB-1) labeling index even at the very positive immunoreactive protein areas and very few p53-positive cells. Using anti-NEUN, anti-VIM, and anti-EMA on representative tumor specimens allows an appropriate differential diagnosis between CCE and other central nervous system tumors.

Although very strict immune reactive characteristics have been well defined for ependymomas, electron microscopy (EM) has showed some specific diagnostic peculiarities, highlighting complex intercellular junctions, surface microvilli, and cilia as well as micro rosettes formation. However, lack of secretory granules, vesicles, absence of peripheral parts of the cytoplasm including organelles, and synapses may appeared to be electron lucent and suggestive of cellular edema, which might explain the clear cell features, so the use of EM should be considered in questionable situations. However, it is well accepted that under the basic principle of an adequate histological description associated with modern immunohistochemical techniques, the precise diagnosis of these lesions can be simplified.

Radiologically, unlike the cellular or myxopapillary spinal cord ependymomas, CCEs are homogeneously isointense to hyperintense on T1-W images and hyperintense on T2-W images, sometimes showing homogeneous enhancement after gadolinium administration and their margins are well defined and they appear nonaggressive. Rostral or caudal adjacent cysts are frequently associated to ependymomas either due to cerebrospinal fluid obstruction or secretory properties attributed to the neoplasm. Some authors consider their presence either intratumoral or peripheral to the solid portion of the tumor with a rate around 50–85%; this characteristic may provide a better cleavage plane thus probably facilitating the opportunity to perform an ideal gross total resection. Other descriptions include mildly hyperintense encapsulated mass on T1-W images. On T2-W images, these lesions appeared homogeneously hyperintense. After contrast agent administration, they may show uniform and marked enhancement. Although some lesions may be of considerable size, intramedullary, and exophytic components have been described.

Amatya et al. described the lesion as “cystic,” because the tumor appeared to have solid as well as cystic components on MR images. The isodense solid component enhanced uniformly while the cystic component did not. T2-W sequences were clearly hyperintense with irregular borders but well defined from the spinal cord tissue. In our patient, an important adjacent cystic cavity was observed and practically the whole thickness of the spinal cord was involved extending from Th10 to Th12. To the best of our knowledge, the present case could be the most extensive intramedullary CCE reported to date.

Surgical management is by far the best option of treatment for these neoplasms. The goal of the treatment is focused on gross total excision preserving surrounding tissues; good surgical results are achievable through radical resection with minimal resultant morbidity. These lesions should be operated when they cause moderate symptoms, it is well accepted that early surgery is associated with better outcome because severe and long-lasting preoperative symptoms rarely improve after surgery. Extent of the resection for spinal cord ependymoma depends of tumor location, size, the existence of a capsule, and cystic cavity (providing a plane of cleavage). In a series of 39 intramedullary ependymomas, tumors in the thoracic region had a worse outcome than tumors of the cervical or lumbar region. Gross total resection of the lesion determines the long-term control of the tumor.

Maintenance of the capsule is an important component of tumor excision to obtain an in-bloc resection, a careful circumferential dissection of the spinal cord interphase is performed, this may decrease the chances for a tumor dissemination simultaneously. It is very often that an intratumor debulking should be considered to allow a safe dislodge of the capsule from the surrounding spinal cord tissue, at this moment, an adequate control of tumor vascularity is necessary. The vast majority of these lesions obtain their blood supply by supplemental feeders surrounding the capsule and from small branches of the anterior spinal artery. Cautious coagulation and cutting of these vessels should be done as far away as possible from the neural tissue, especially from the anterior border of the cord. Small pedicle feeders from the anterior spinal cord artery are not unusual, excessive arterial tension should not be applied reducing the risk vascular compromise. Unfortunately, in some cases, by distinctive conformational characteristics of these neoplasms, this technique may not be possible to be reached; thus, we recommend meticulous piecemeal removal with the aim of microsurgical techniques and ultrasonic aspiration; however, the risks of dissemination must be determined.

Routinely, we attempt to decrease in postoperative morbidity using neurophysiologic monitoring during surgery. Prevention of injury to motor pathways and further neurological deficit can be achieved with continue MEP monitoring, while the spinal cord is operated. Although somatosensory evoked potential monitoring has not predicted functional outcomes, we usually monitor them while the dorsal midline myelotomy is performed. We focus this step on preserving spinal blood flow by minimal dissection and manipulation of the arachnoid membrane with supportive traction sutures. If any of the two modalities of evoked potentials decrease while the
spinal cord is manipulated (50% decrease of its baseline amplitude), the procedure should be stopped and wait until the cord potential recovers by increasing spinal cord blood flow with mild systemic hypertension and gentle warm irrigation. Sala et al. could really confirm that intraoperative neuromonitoring significantly improves clinical outcome with surgical resection of intramedullary ependymomas, less so in astrocytomas.\[20\]

If a total resection is achieved, no further therapy with radiation or chemotherapy is necessary. Surgical options are not different from other intramedullary tumors, but a great effort is sometimes required to obtain the most extensive resection to avoid a possible recurrence.\[21\] Complete extraction yielding reported local rates of 90–100%, tumor recurrence after gross total resection is less than 10%, but this can be delayed by the slow growth rate of ependymomas. With subtotal resection, tumor recurrence is seen in 50–70% of cases, but if recurrence does occur, a new excision should be performed.\[20\] Involved-field external beam radiotherapy at a dose of 45–54 Gy is indicated for partially resected or biopsied WHO Grade 2 ependymomas or malignant WHO Grade 3 tumors.\[29\]

CONCLUSION

With few reported cases, the diagnosis of CCEs requires very straight neuroimaging, histologic and ultrastructural correlation, especially when limited biopsy fragments are available. Current immunohistochemical techniques demonstrate very specific parameters for the differential diagnosis of clear-cell tumors. Radical surgical resection is considered the optimal treatment option. Satisfactory surgical outcome depends on adequate pre-operative planning, fine operative manipulation, and continuous intra-operative monitoring. Determining an adequate plane of cleavage allows preservation of functional spinal cord tissue. Despite being considered as benign lesions, radiotherapy should be considered in those cases with malignant characteristics or with evidence of meningeal dissemination. The importance of an adequate recognition is the avoidance of alternative misdiagnosis and inappropriate therapies.

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.

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