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Case Report

MR imaging findings in primary spinal cord glioblastoma [☆]Paolo Ferrante, MD^{a,b}, Juan Andres Mora, MD^{b,c}, Lourdes Salazar, MD^d, Elena Martínez Sáez, MD^d, Cristina Auger, MD^{b,e}, Àlex Rovira, MD^{b,e,f,*}^a Diagnostica per Immagini e Radiologia Interventistica, Policlinico Tor Vergata, University Rome “Tor Vergata”, Rome, Italy^b Section of Neuroradiology, Department of Radiology, Vall d’Hebron University Hospital, Hospital Vall d’Hebron, Passeig de la Vall d’Hebron, 119-129 | 08035, Barcelona, Spain^c Fundació Universitaria Sanitas, Clínica Reina Sofia, Bogotá, Colombia^d Neuropathology Unit, Pathology Department, Vall d’Hebron University Hospital, Hospital Vall d’Hebron. Barcelona, Spain^e Vall d’Hebron Institut de Recerca (VHIR), Vall d’Hebron University Hospital, Barcelona, Spain^f Universitat Autònoma de Barcelona, Bellaterra, Spain

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ABSTRACT

Spinal cord glioblastoma is a rare disease, with an aggressive course and a poor prognosis. We describe magnetic resonance imaging (MRI) findings, in 3 adult cases of biopsy-confirmed glioblastoma.

Conventional MRI findings were unclear with regard to the differential diagnosis between this rare tumor and other more common spinal cord lesions, including less aggressive tumors such as ependymoma or pilocytic astrocytoma, abscesses or tumefactive demyelinating lesions. After reasonable exclusion of infectious/inflammatory conditions, a final diagnosis of glioblastoma was established based on histopathological analysis. The cases reported reflect the difficulty of early radiological diagnosis of spinal cord glioblastoma, and indicate the need to perform a biopsy once inflammatory-infectious conditions are excluded with appropriate laboratory tests.

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Introduction

Although glioblastoma (GB) is the most common primary malignant tumor of the central nervous system (CNS), their location in the spinal cord is extremely rare with less than 200

cases reported in the medical literature [1]. This tumor accounts for approximately 7.5% of all intramedullary gliomas and 1.5% of all spinal cord tumors [1]. It has a highly aggressive course with a very poor prognosis due to its infiltrative growth and the impossibility of complete surgical resection. Median survival rate is approximately 14 months, even in the setting

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* Corresponding author.

E-mail address: alex.rovira.idi@gencat.cat (À. Rovira).<https://doi.org/10.1016/j.radcr.2020.10.043>1930-0433/© 2020 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

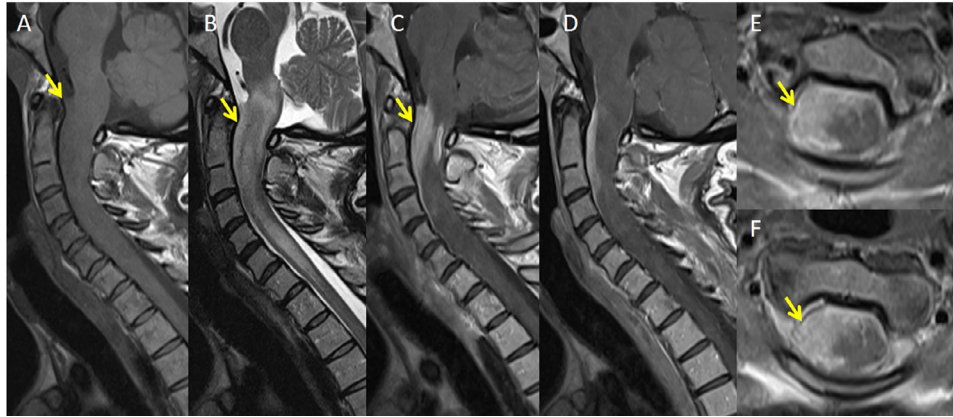


Fig. 1 – Spinal cord MRI from patient 1. Sagittal T1-weighted image shows an iso- to hypointense mass in the cervical cord (A). The lesion is better demarcated on the sagittal T2-weighted sequence (B). An intense peripheral enhancement is shown on the contrast enhanced axial and sagittal T1-weighted images (C-F). Observe the exophytic component of the lesion in its upper portion on the right side (arrows in E and F).

of aggressive multimodality treatment [2]. The highest incidence is between the second and third decade of life [2], and the most common location is the cervical and thoracic spinal cord. Less commonly, it can occur in the conus medullaris [3]. Due to its rarity, spinal cord GB might be misdiagnosed radiologically with infectious and inflammatory conditions, or with less malignant and more common types of spinal cord tumors.

We report 3 cases of spinal cord GB, analyze the imaging features, and discuss differential diagnoses of this rare disease.

Case 1

A 34-year-old woman with a history of neurofibromatosis type 1 (NF1), presented to the emergency department with motor weakness of the right arm and sensory disturbances of the lower limbs that started 4 days before admission. The patient had no fever or systemic symptoms, and no previous history of cancer or trauma. On neurological examination, the patient showed paraparesis and hypoesthesia of the upper extremities and general hyper-reflexia of the lower limbs. A cervical spine MRI showed an extensive intraspinal - intradural infiltrative expansile lesion with an exophytic component, which involved nearly the entire cervical spinal cord, and extended cranially to the lower part of the medulla oblongata including the area postrema (Fig. 1). The lesion showed a homogeneous peripheral and eccentric enhancement of both the intramedullary and exophytic components of the lesion at its proximal segment (Fig. 1). Brain MRI showed only bilateral subcutaneous epicranial lesions in the occipital regions, compatible with neurofibromas, and a left parotid lesion suggestive of a plexiform neurofibroma. Oligoclonal bands in CSF and serum antibodies to aquaporin-4 (AQP4-Ab) were negative. A spinal cord biopsy was performed, and a highly cellular lesion composed of medium-sized, oval nuclei with granular chromatin and eosinophilic cytoplasm was

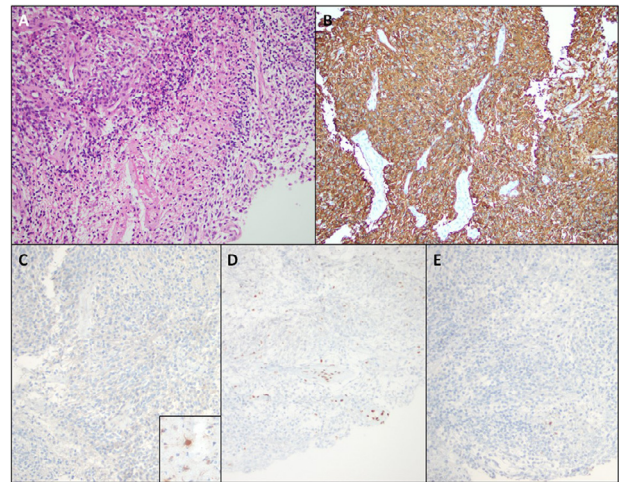


Fig. 2 – Histological images from patient 1, showing a hypercellular proliferation composed of round-to-oval medium-sized nuclei, with foci of necrosis (A. hematoxylin and eosin stains, 200 x), with strong and diffuse GFAP expression (B, 200 x). Absence of IDH1 R132H mutation (C, 200 x, with positive control in the inset), absence of ATRX expression with positive internal control, consistent with ATRX mutation (D, 200 x), absence of p53 overexpression (E, 200 x).

found on histological analysis. Two mitoses were identified in the whole material, with frequent foci of necrosis and endothelial hyperplasia. The neoplastic cells expressed glial fibrillary acidic protein (GFAP), with loss of ATRX expression. No isocitrate dehydrogenase (IDH), BRAF nor H3 K27M mutations were found and no p53 overexpression was seen. The proliferation index (measured by Ki67) reached 7%. These findings were consistent with a grade IV, IDH-wild type GB (WHO 2016) (Fig. 2). Due to the location and histopathology

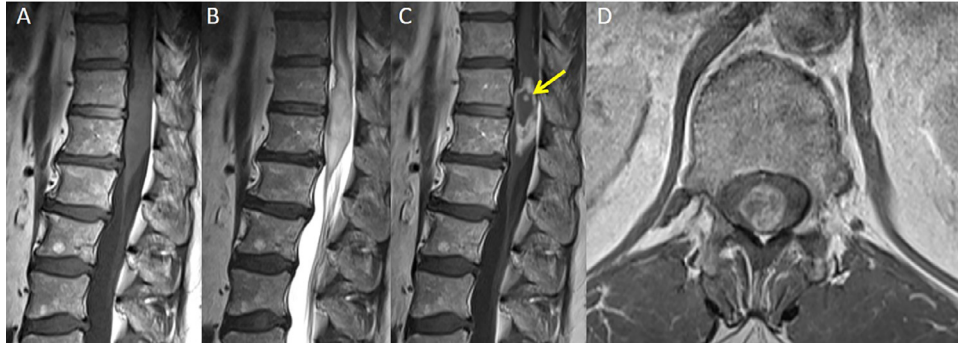


Fig. 3 – Spinal cord MRI from patient 2. Sagittal T1-weighted image shows an iso- to hypointense mass in the conus medullaris (A). The lesion is better demarcated on the sagittal T2-weighted sequence (B). An intense peripheral enhancement delimiting a central area of necrosis associated with an eccentric enhancing nodule (arrow in C) is shown on the contrast-enhanced sagittal and axial T1-weighted images (C and D).

of the tumor, and the rapid clinical deterioration, it was decided not to perform any treatment. The patient developed hydrocephalus and passed away 2 months after admission, most likely to rapid disease progression.

Case 2

A 64-year-old man without any past medical history presented to the emergency department after a 3-week history of motor weakness of the lower extremities with associated sensory disturbances. Neurological examination showed paraparesis and decreased sensation in the anterior region of both thighs and in the genital and the perianal areas. There were no neurologic abnormalities of the upper limbs and cranial nerves and no sphincter dysfunction. A lumbar spine MRI revealed an ovoid, intramedullary, expansile lesion involving the conus medullaris with homogeneous hyperintense signal intensity on T2-weighted images. After injection of contrast, the lesion demonstrated an irregular, thick peripheral enhancement, delineating a central area of necrosis associated with an eccentric enhancing nodule (Fig. 3). These imaging features were consistent with a spinal cord tumor, although an infectious lesion was also considered. Serological testing for different infectious diseases including *Toxoplasma gondii* was all negative. The patient was surgically treated with partial resection of the lesion. Histologically, a moderately cellular lesion composed of medium-sized, oval, hyperchromatic nuclei with scant cytoplasm was identified, with a prominent myxoid background (Fig. 4). Mitotic activity reached 5 mitoses/10 high power fields, with necrosis and vascular proliferation. The neoplastic cells expressed GFAP and preserved ATRX expression. No IDH mutations, epidermal growth factor receptor (EGFR) amplification nor BRAF translocation were found. P53 expression reached 40%. The proliferation index (measured by Ki67) reached 30%. These findings were consistent with a grade IV, IDH-wild type GB (WHO 2016). The patients started treatment with radiotherapy and chemotherapy, but recurrent disease was demonstrated 13 months later, and he passed away 20 months after his initial diagnosis.

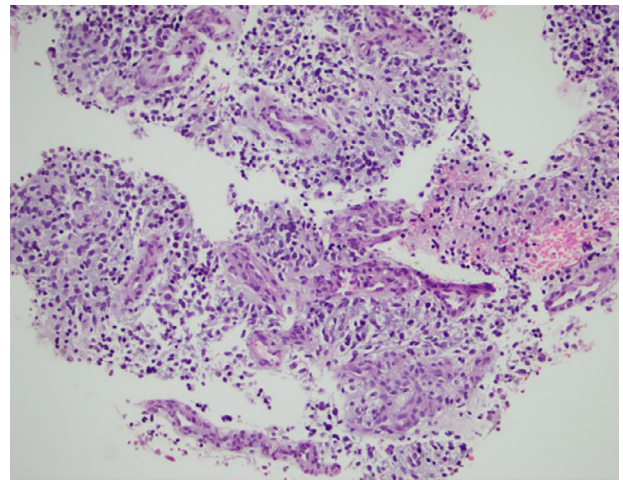


Fig. 4 – Histological images from patient 2 (hematoxylin and eosin stains, 200x). The sample shows hypercellular proliferation composed of oval medium-sized nuclei, with mitotic activity and endothelial hyperplasia.

Case 3

A 47-year-old patient with a history of hyperuricemia and arterial hypertension presented to the hospital with 18 months history of progressive spinal cord symptoms with paresthesia in the lower right extremity starting in the foot and ascending to the leg, accompanied by episodes of intense pain, loss of thermic sensitivity, and numbness of left arm. A cervicothoracic spine MRI was performed in another institution that showed 2 tumefactive intramedullary lesions involving the cervical and thoracic segments. A diagnosis of tumefactive inflammatory lesions was initially suggested and the patient was treated with corticosteroids, without clinical improvement. Oligoclonal bands in CSF and serum antibodies to aquaporin-4 (AQP4-Ab) and myelin oligodendrocyte glycoprotein (MOG) were negative. The patient clinically progressed over the next 4 weeks, developing motor weakness of his left

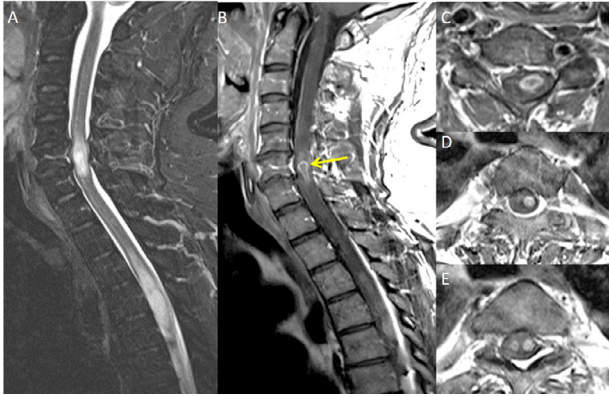


Fig. 5. – Spinal cord MRI from patient 3. Sagittal STIR image shows multifocal lesion that affects the cervical (C5–C7) and dorsal (D3–D5) spinal cord segments (A). Contrast-enhanced sagittal and axial T1-weighted images (B–E) demonstrates peripheral enhancement and a small necrotic center (arrows).

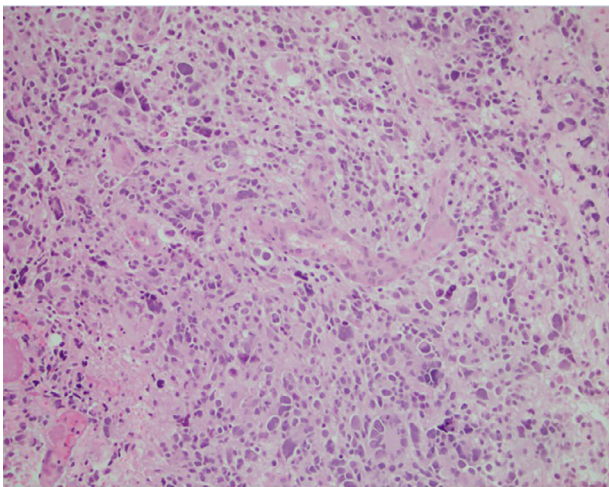


Fig. 6 – Histological images from patient 3 (hematoxylin and eosin stains, 200x). Observe the hypercellular proliferation composed of large and medium-sized nuclei, multinucleated cells, and atypical mitoses, with endothelial hyperplasia.

arm, and came to our institution for a more extensive diagnostic work-up. A new cervicothoracic spine MRI revealed 2 fusiform expanding lesions involving the C5–C7 and T3–T5 spinal cord segments, with contrast-uptake delineating central areas of necrosis (Fig. 5). A spinal cord biopsy was performed on the cervical cord lesion, which showed a highly cellular tumor, composed of large and irregular nuclei, with frequent bizarre and multinucleated cells, and a high mitotic index (reaching 13/10 high power fields). Frequent images of vascular proliferation and necrosis were found (Fig. 6). The neoplastic cells expressed GFAP. No p53 overexpression, EGFR amplification nor IDH and BRAF mutations were present. The proliferation index (measured by Ki67) reached 65%.

These findings were consistent with a grade IV, IDH-wild type GB (WHO 2016). The patient was treated with radiotherapy and chemotherapy but rapidly progressed clinically and radiologically and passed away 10 months after first hospital admission.

Discussion

Glioblastoma is the most frequent malignant tumor of the CNS, and constitutes 12%–15% of all intracranial neoplasms [4], but it is a rare entity in the spinal cord, with only less than 200 cases reported in the literature [1]. Spinal cord GB has a predilection to develop from the cervical cord segment and has a tendency to develop at a younger age compared to those primarily involving the brain [5].

Histopathologically, spinal cord and brain GB are identical. However, there is no molecular marker specific for spinal cord GB and markers such as IDH-1 and O6-methylguanine-DNA methyltransferase promoter methylation only have prognostic significance for supratentorial GBs [6].

Its location at the cervical spinal cords segment is more frequent and clinical symptoms depend on the degree of spinal cord damage [7]. These tumors frequently show contiguous dissemination, and through cerebrospinal fluid also disseminate to distant sites, which significantly reduce survival [8].

Spinal cord MRI is considered the gold standard imaging modality to diagnose spinal intramedullary tumors, although differentiation of primary spinal cord GB from other spinal cord diseases, such as infectious and inflammatory disorders, or other intramedullary tumors, is challenging, since primary spinal cord GBs show MRI features that are similar to these conditions (intramedullary longitudinally extensive lesions with patchy heterogeneous enhancement and intralesional cysts or necrosis). Therefore, a definitive diagnosis requires tissue biopsy and histopathological evaluation. The majority of primary spinal cord GBs appear as infiltrative expansive masses with iso or low signal on T1-weighted, and high signal on T2-weighted images, and heterogeneous enhancement on contrast-enhanced T1-weighted images [1]. Nonconventional MRI sequences could provide additional useful features, such decrease in fractional anisotropy on diffusion tensor images that correlates with the severity of infiltration and destruction of spinal nerve tissue [9] and increase in relative blood volume (>1.8) on dynamic susceptibility contrast MRI perfusion caused by the angiogenesis that characterized these tumors [9].

In the first patient, the lesion had an exophytic extension, defined as the growth of tumor beyond the pia mater and into the subarachnoid space, which has been previously described in spinal cord GB [10]. In this case, the initial differential diagnosis included, in addition to GB, pilocytic astrocytoma, ependymoma, and neuromyelitis optica spectrum disorder (NMOSD). Pilocytic astrocytoma is the most common intramedullary tumor in patients with NF1 [11], and mainly involves the cervical segment arising eccentrically within the cord. Additional imaging features are a cystic mass with a mural nodule showing a diffuse nonhomogeneous contrast enhancement [12]. Ependymomas have been also described

as associated with NF-1, but we could not find in the medical literature and association between NF-1 and GB. NMOSD was considered in the differential diagnosis, as the lesion extended to the area postrema in the lower part of the brainstem, an MRI feature initially considered to be specific to NMOSD, but later seen in other conditions associated with longitudinally extensive cervical cord lesions [13]. Also, the presence of the exophytic component suggested this diagnosis, as leptomeningeal enhancement has been described in this condition [14]. However, this diagnosis was excluded as AQP4 antibodies were not detected and there was no additional clinical involvement beside the spinal cord, which is a requirement to establish this diagnosis according to the 2015 NMOSD diagnostic criteria [15].

The second case was a GB located in the conus medullaris, which is a very rare location for this tumor. A retrospective study that collected 128 cases from 1938 to 2015, showed that 42.2% of spinal cord GBs were located in the thoracic spine, 29.7% in the cervical spine, while those located in the conus level only accounted for 14% of cases [3,4]. In fact, we did not even consider a GB in the initial differential diagnosis, while our first suggestion was of a myxopapillary astrocytoma, a slow-growing variant of spinal cord ependymoma, due to its location in the conus medullaris. However, myxopapillary astrocytomas, which mainly affect young adults, appear as circumscribed enhancing masses with a tendency to show cystic and hemorrhagic changes [16]. Another diagnosis that could be considered in this case is a spinal cord embryonal tumor, a rare and aggressive tumor, with a poor prognosis [17], which similar imaging features to GB (heterogeneous enhancement and necrosis), although tumor tend to manifest in young children [16]. Finally, the presence of an eccentric enhancing nodule also suggested the diagnosis of toxoplasmosis, as the eccentric target sign has been considered pathognomonic for cerebral toxoplasmosis [18]. However, toxoplasmic myelitis, a rare condition seen in immunocompromised hosts, was excluded in our patient through appropriated laboratory testing.

In the third case, the initial diagnosis was a tumefactive inflammatory lesion, as presence of longitudinally extensive lesions with at least 2 noncontiguous lesions has been frequently described in MOG-IgG myelitis and rarely in AQP4-IgG myelitis [19]. However, these conditions were excluded as serum analysis of these antibodies was negative. Moreover, the rapid clinical and MRI progression suggested the diagnosis of an aggressive tumor, and spinal cord biopsy finally established the diagnosis of GB.

Conclusion

Spinal cord GBs are extremely rare entity and are generally associated with a dismal outcome. Although MRI plays a vital role in the diagnosis of spinal cord tumors, imaging features are not specific and commonly unable to differentiate glioblastoma from other less aggressive and more common spinal cord tumors, and from infectious and inflammatory conditions. However, tumefactive spinal cord lesions with enhancement and necrosis in a young adult patient should raise the diagnosis of GB and a prompt biopsy should be performed

to confirm this diagnosis, after reasonable exclusion of infectious and inflammatory conditions through appropriate laboratory tests.

Patients Consent Statement

Written informed consent could not be obtained from the patients as they all were exitus few months after diagnosis. All the images included in this Case report are entirely unidentifiable and there are no personal details on individuals reported

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