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A rare case of atypical intradural extramedullary glioblastoma diagnosed utilizing next-generation sequencing and methylation profiling: illustrative case

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BACKGROUND Primary spinal cord tumors, especially primary spinal cord glioblastoma multiforme (PSC-GBM), are exceptionally rare, accounting for less than 1.5% of all spinal tumors. Their infrequency and aggressive yet atypical presentation make diagnosis challenging. In uncertain cases, a surgical approach for tissue diagnosis is often optimal.

OBSERVATIONS A 76-year-old male presented with a rapidly progressing clinical history marked by worsening extremity weakness, urinary retention, and periodic fecal incontinence alongside diffuse changes on neuraxis imaging. The patient, in whom subacute polyneuropathy was initially diagnosed, received multiple rounds of steroids and intravenous immunoglobulin without clinical improvement. Histopathological review of the biopsy tissue yielded an initial diagnosis of spindle cell neoplasm. Next-generation sequencing (NGS) is done routinely on all neuropathology specimens at the authors' institution, and methylation profiling is pursued in difficult cases. Ultimately, NGS and methylation profiling results were essential to an integrated final diagnosis of GBM.

LESSONS PSC-GBM is a rare but highly aggressive occurrence of this tumor. Prolonged back pain, rapid neurological decline, and imaging changes warrant the consideration of lesional biopsy for precise disease characterization. In inconclusive cases, NGS has proved invaluable for clinical clarification and diagnosis, underscoring its importance for integrated diagnoses in guiding appropriate treatment strategies.

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KEYWORDS spinal GBM; biopsy; next-generation sequencing; methylation profiling

Of the primary neoplasms of the central nervous system (CNS), primary spinal cord tumors (SCTs) are rare, representing approximately 2%–4% of cases in the population.[1] These tumors are subcategorized on the basis of their location relative to the thecal sac of the spinal cord, consisting of extradural, intradural extramedullary, and intramedullary. Across these variants, astrocytoma, ependymoma, ganglioglioma, oligodendroglioma, and subependymoma are commonly observed, with the intradural-extramedullary classification in particular comprising 70%–80% of these neoplasms.[2,3]

Still rarer among these rarities is primary spinal cord glioblastoma multiforme (PSC-GBM). GBM, a high-grade malignant glioma, is among the most intractable and fatal of the primary brain neoplasms, with a median 1-year survival rate of 21%.[4] Despite representing the most common neurogenic malignancy of the brain in adults, GBM accounts for less than 1.5% of all neoplasms of the spine and is especially challenging to treat, given both its rarity and extensive metastatic potential.[5] PSC-GBMs are notorious for their genetic, clinical, and etiological heterogeneity, with distinguishing features complicated by a low disease incidence and a corresponding lack of documentation alongside high treatment morbidity.[6] Despite aggressive therapy, the prognosis for this disease is quite poor, with the average life expectancy ranging from 10 to 14 months following diagnosis.[7,8]

Generally, these tumors are most often observed in young adults, are more commonly associated with men, and characteristically manifest in the cervicothoracic region.[9] In contrast to cranial GBM, patients with PSC-GBM may initially experience silent symptoms, such as untreatable

ABBREVIATIONS CNS = central nervous system; CSF = cerebrospinal fluid; GBM = glioblastoma multiforme; GFAP = glial fibrillary acidic protein; IDH = isocitrate dehydrogenase; IVIG = intravenous immunoglobulin; MPNST = malignant peripheral nerve sheath tumor; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PSC = primary spinal cord; SCT = spinal cord tumor.

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back pain, followed by a more aggressive clinical course wherein leptomeningeal penetration and early brain metastases become possible, given the accessibility of the subarachnoid space.[10] Common clinical presentations of such neoplasms consist of pain in the originating vertebral region coupled with sensorimotor symptoms such as paresthesia and progressive weakness.[11] Given the difficulties of characterizing such a sparsely documented tumor subtype, patients are often provided with limited therapeutic interventions upon diagnosis. Nevertheless, a study by Cheng et al.[12] showed that complete resection with a focus on functional preservation coupled with postoperative radiotherapy and temozolomide regimens contributed most to prognostic improvement. However, the infiltrative pathology of PSC-GBM complicates effective tumor margination and likewise supports alternative findings that gross-total resection does not improve outcomes and may instead contribute to higher mortality.[9,13]

In this article, we present a case of an elderly male who exhibited a long-standing clinical history of progressive bilateral lower-limb weakness with posterior findings of a PSC-GBM. Clinical, histological, and immunohistochemical findings were combined with next-generation sequencing (NGS) and methylation profiling to ultimately arrive at this diagnosis, highlighting the importance of integrated multimodal approaches to characterize CNS lesions more accurately. This case involved multiple nondiagnostic cerebrospinal fluid (CSF) studies and an initially inconclusive pathology that was later identified through the conjunction of multimodal approaches.

Illustrative Case

A 76-year-old male was referred to our institution for evaluation of worsening lower-leg weakness, urinary retention, and periodic fecal incontinence. He presented with a 4-month history of progressive bilateral lower-extremity weakness initially diagnosed as subacute polyneuropathy. Spinal magnetic resonance imaging (MRI) at the time revealed diffuse dural enhancement in the cervicothoracic spinal cord with nodular areas of enhancement in the distal segments and diffuse nodular thickening of the cauda equina nerve roots. The patient received two rounds of intravenous immunoglobulin (IVIG) and intravenous steroids with tapering, yielding minimal improvement. Of clinical note, further review of his history revealed that the patient had experienced cervical and lumbar pain over the past 3 years.

Two months prior to admission at our institution, the patient revisited the same healthcare facility for worsening weakness. Serial lumbar punctures were negative for both infection and cytology. Neuroaxis MRI indicated the persistence of the aforementioned findings, most notably the diffuse dural enhancement with ventral intradural-extramedullary nodular enhancement at L2–3 past the conus and additional abnormal enhancement of cranial nerves V, VI, and VII (Fig. 1). An additional computed tomography scan of the chest and pelvis showed no primary lesions. During this encounter, the clinical symptoms were rediagnosed as progressive radiculopathy with myelopathy. The patient received further treatment, including tapering intravenous steroids and an additional five doses of IVIG, before being referred to rehabilitation. Despite these interventions, the patient's weakness continued to deteriorate, leading to repeated visits to the emergency room, where an indwelling urinary catheter was ultimately required to relieve his worsening urinary retention.

The patient was initially admitted to our institution under the care of the neurology department. Neurological examination at admission revealed ptosis, bilateral lower motor nerve VII cranial palsy (right > left),

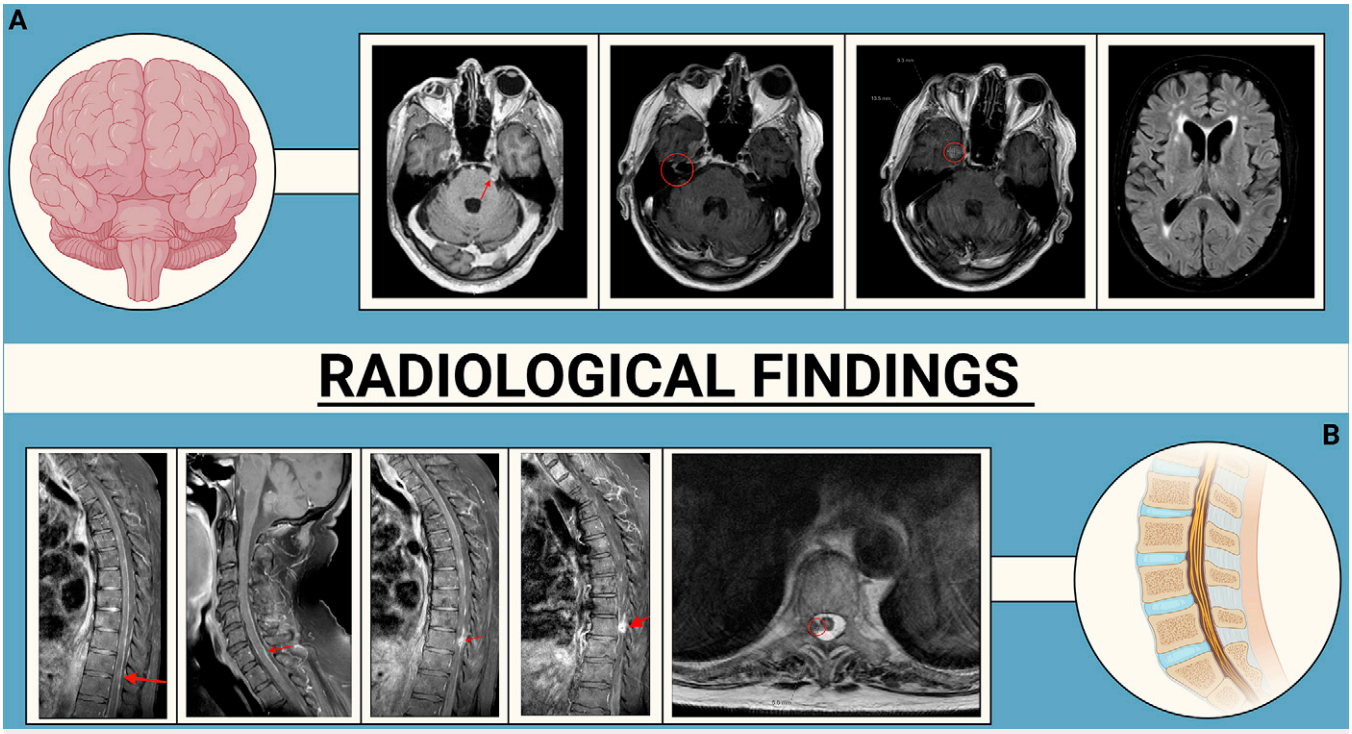

FIG. 1. T1-weighted MRI of the brain (**A**) and spine (**B**) showcasing (from left to right, *red arrow* and *circles*, upper row) abnormal enhancement of the left fifth and right seventh cranial nerves, with extraaxial enhancement in the inferomedial aspect of the temporal lobe adjacent to the cavernous sinus and periventricular leukoaraiosis. MRI of the spine shows diffuse dural enhancement with a ventral intradural-extramedullary nodular enhancement at the thoracic segments of the spinal cord. Created with BioRender.com..

and hypotonic paraplegia with loss of position sense. A comprehensive diagnostic workup was initiated with presumption of a chronic progressive syndrome of myeloradiculitis with multiple cranial neuropathies. The differential diagnosis included autoimmune disease, neoplastic processes, and granulomatous processes. A lumbar puncture was performed, with the CSF profile consistent with hypoglycorrhachia, elevated protein levels, and pleocytosis with monocytic predominance. Cytology results were still negative for malignant cells. Given these inconclusive findings, a multidisciplinary discussion took place, leading to the decision for a lesional biopsy to better identify the etiology of his symptoms.

During the procedure, ultrasound was used to identify the cauda equina following intraoperative confirmation of the L3 level and subsequent removal of superior and inferior spinous processes, interspinous ligaments, and laminectomy. However, the nerve roots appeared adherent to each other and did not display the typical pattern observed in an axial view. Upon opening the dural layer, the thickened arachnoid mater below was incised to visualize the nerve roots. With gentle mobilization of the nerve roots, a firm, glassy lesion was encountered along the ventral aspect of the cauda equina, which was carefully biopsied (Fig. 2).

The intraoperative consultation was inconclusive for malignancy, but light microscopy examination of the neoplasm revealed a haphazard arrangement of spindled cells with rare mitoses and tumor-associated chronic inflammation in the absence of necrosis (Fig. 3). By immunohistochemistry, the neoplasm demonstrated patchy positivity for S100, SOX10, AE1/3, and glial fibrillary acidic protein (GFAP) but was negative for desmin, CD34, and smooth muscle actin, among other markers. H3 K27 trimethylation expression was retained in neoplastic cells. Ki-67 showed focal increases. NGS demonstrated a *TERT* promoter mutation (c.-146C > T) and a frameshift loss-of-function alteration of *NF1* (p.Y2285fs) in the absence of isocitrate dehydrogenase (*IDH*), *EGFR*, *PTEN*, or H3 K27 alterations. Methylation profiling performed at the National Institutes of Health classified the tumor as suggestive of GBM, IDH wild type, subclass

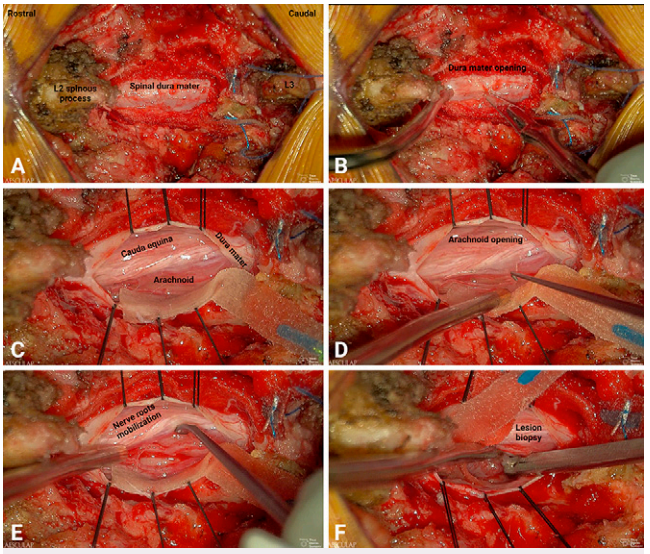

FIG. 2. Intraoperative exoscope images showcasing relevant anatomy of the approach (**A**–**D**), mobilization of atypical adherent cauda equina nerve roots (**E**), and subsequent isolation and biopsy of the indicated spinal cord lesion for diagnostic characterization (**F**).

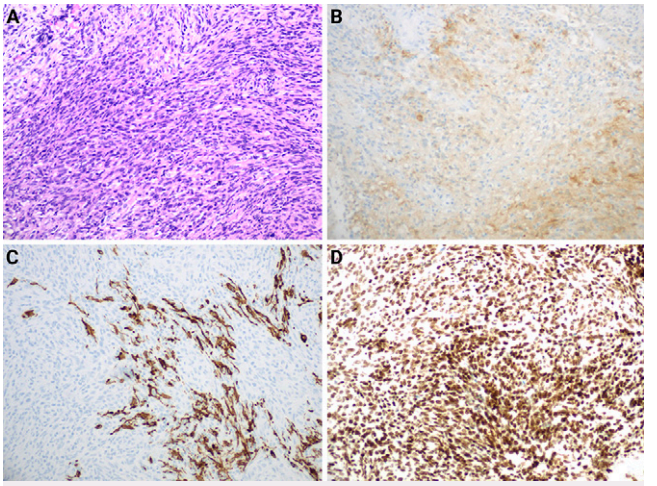

FIG. 3. Histopathology of the resected specimen revealed a spindled neoplasm with tumor-associated chronic inflammation in the absence of necrosis (**A**; hematoxylin and eosin) and patchy positivity for S100 (**B**) and GFAP (**C**). H3 K27 trimethylation was retained (**D**). Original magnification ×200 (**A–D**).

mesenchymal; however, the classification was below the established confidence score. Additionally, a +7/−10 chromosomal copy number signature was found. Integrating histological, immunohistochemical, and molecular results, an integrated diagnosis of GBM, IDH wild type was made (Fig. 4).

The patient was discharged for rehabilitation and was referred to oncology for further treatment. Unfortunately, the patient died several days later.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

Although the great majority of GBMs arise in supratentorial structures, occurrences of this tumor as a primary lesion in the infratentorial and spinal cord regions are rare.[14] Furthermore, the low incidence of intradural-extramedullary spinal cord tumors, particularly the rare and aggressive types, makes the diagnosis challenging because the disease responds poorly to therapy, and life expectancy is low.[15] In our patient, the rapidly progressive clinical presentation along with the diffuse changes on spinal cord imaging suggested a progressive myeloradiculitis syndrome with several potential differential diagnoses, including malignancy. However, it is worth noting that the inconclusive diagnostic studies and failure to respond to therapy ultimately led to a prompt tissue diagnosis. Nonetheless, despite the absence of biopsy for cranial nerve changes on brain MRI, such changes could potentially indicate an occurrence of GBM. Such presentations are exceedingly rare, with only a few cases reported in the literature.[16–22]

It remains uncertain whether the cranial nerve enhancements in our patient corresponded to leptomeningeal spread or a silent yet highly aggressive primary presentation of the tumor. In either scenario, this would be an exceptionally rare occurrence, and, to date, there are no reports of simultaneous spinal and peripheral nerve presentations of a primary spinal GBM. Additionally, the onset of spinal cord–related symptoms points toward a PSC-GBM, and the patient's

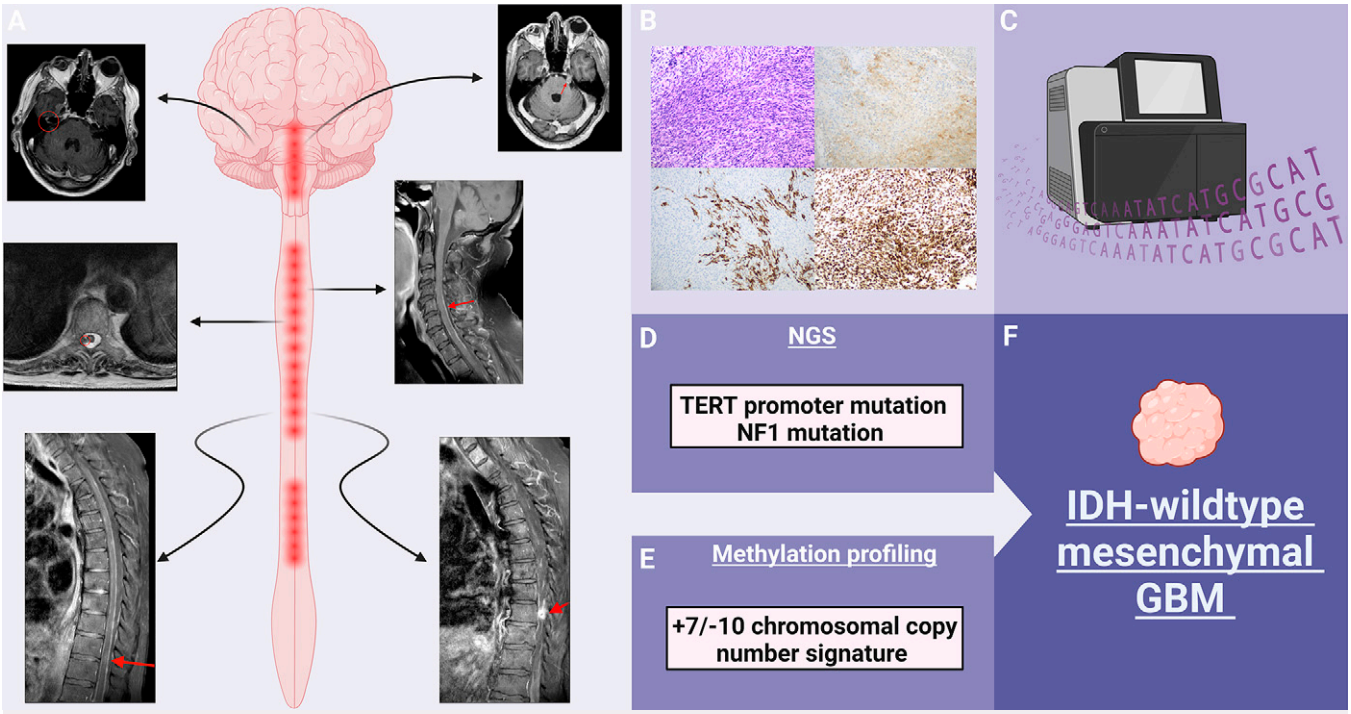

FIG. 4. Illustration of the integrated approach for diagnosing this PSC-GBM. Imaging findings (**A**), pathological and immunohistochemical analysis of the specimen (**B**), and molecular based methods using NGS and methylation profiling (**C**–**E**) made it possible to ultimately characterize this patient's spinal cord lesion as an IDH wild type, mesenchymal subtype GBM (**F**). Created with BioRender.com.

long-standing clinical history of lumbar and cervical pain could suggest a subclinical stage of this tumor, followed by a rapidly progressive stage. This progression is consistent with a similar report in the literature.[23]

Managing a patient with an extradural-intramedullary spinal cord tumor is centered on improving neurological function.[24] Consequently, the primary surgical goal is gross-total resection of the tumor, coupled with meticulous preservation of basal neurological function.[25] With this aim, the use of intraoperative monitoring, such as somatosensory evoked potentials and motor evoked potentials, is valuable. Maintaining the greatest possible number of bony structures and structural ligaments is also a crucial step for ensuring postoperative spinal stability and thus achieving better outcomes.[24] However, in this particular case, given the uncertainty surrounding the pathology and the diffuse multilevel changes observed on imaging, a lesional biopsy emerged as the best choice and proved to be valuable by giving a definitive diagnosis. Despite the bad outcome of the patient, this case showcased the impact of a timely tissue diagnosis. It has been well documented in the literature how rapid diagnoses can improve prognoses in patients with primary intradural spinal cord tumors.[26–31] Given the low incidence of this pathology, neglecting spinal cord GBM can undoubtedly delay a timely intervention. Additional studies are thus needed to explore alternative strategies and methodologies for achieving more prompt diagnoses in these patients.

The case is an illustrative example of integrated molecular diagnosis in the neuropathological evaluation of tumors. Although GFAP is commonly used for identifying glial differentiation, malignant peripheral nerve sheath tumors (MPNSTs) can express GFAP[32] as well as limited S100 and SOX10. Retained H3 K27 trimethylation has been reported in MPNSTs occurring in a spinal location.[33] Although *TERT* promoter mutations are commonly seen in IDH wild-type GBMs, they can also be encountered in many other neoplasms, including meningioma,[34] pleomorphic xanthoastrocytoma,[35] oligodendroglioma IDH-mutant and 1p/19q-codeleted,[36] melanoma,[37] and rare examples of MPNST.[38] Thus, the identification of a *TERT* promoter mutation alone is not diagnostic of GBM without accompanying evidence. The additional findings of a +7/−10 chromosomal signature, another common molecular alteration in GBM, and a methylation profile suggestive of GBM, IDH wild type, subclass mesenchymal were essential to making the integrated diagnosis of GBM in the histological and clinical context of this case, even though the methylation profiling classification of the tumor was below the established confidence interval. *NF1* mutations, one of which was documented in this case, are implicated in GBM acquiring a mesenchymal signature,[39] another supportive finding in the diagnosis of this malignant spindle cell neoplasm.

Of note, advances in sequencing technologies, including novel approaches such as liquid biopsy, may be valuable in aiding the diagnosis of complex clinical cases in the future. For example, a pilot study by Cheng et al.[40] assessed the utility of liquid biopsies in four patients with intramedullary tumors. Despite its small sample size, the study revealed that CSF-derived circulating tumor DNA could be a feasible means of molecular analysis of spinal cord tumors. It successfully identified key hotspot genetic alterations crucial for the molecular diagnosis and prognosis of the tumors. Notably, this method had a higher average mutant allele frequency than in tumor tissues, and its molecular findings were concordant with those from tissue samples.

In summary, we emphasize the critical significance of prompt tissue diagnosis in addressing a complex case of a rare PSC-GBM presenting with progressive weakness, urinary incontinence, a failure to respond to multiple treatments, and inconclusive diagnostic tests. Distinguishing signs of an aggressive spinal cord neoplasm in the absence of

a discernible primary location or evidence of other pathologies in the differential, such as infection or autoimmune disease, underscores the need for a swift tissue diagnosis. Integrated diagnoses that incorporate histological and molecular findings, such as information derived from NGS and methylation profiling, are crucial in cases of rare and histologically ambiguous neoplasms. To our knowledge, this case represents one of the rare instances where spinal GBM presents with multiple cranial nerve manifestations. This presentation raises the question whether it signifies a spread of the disease or origination from a true primary infratentorial source with an exceptionally rare spinal metastatic spread.

Lessons

We describe a case involving an atypical presentation of an intradural-extramedullary GBM with multiple cranial nerve effects in an elderly patient who experienced chronic but progressive neurological decline. In this case, an integrated diagnosis of GBM, IDH wild type, was made using NGS and methylation profiling results. We advocate for a prompt tissue diagnosis in uncertain cases where a spinal cord tumor is suspected on the basis of clinical symptoms and imaging findings. Similarly, the use of new molecular technologies is essential for diagnosis in complex cases. Lastly, we highlight the importance of considering rare yet aggressive primary tumors in the spinal cord, such as GBM, in the differential diagnosis for elderly patients with rapidly progressive neurological symptoms. A multimodal approach incorporating imaging and invasive but diagnostic procedures is necessary in handling such atypical cases.

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Author Contributions

Conception and design: Rodriguez. Acquisition of data: Rodriguez, Shelton, Nix, Gokden. Analysis and interpretation of data: Rodriguez, Shelton, Nix, Gokden. Drafting the article: Shelton, Mathews, Nix, Gokden. Critically revising the article: Rodriguez, Nix, Gokden. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Rodriguez. Administrative/technical/material support: Rodriguez, Aljiboori, Gokden. Study supervision: Rodriguez.

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