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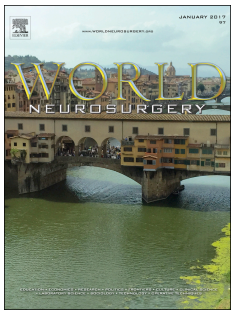

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Spinal metastasis of cerebral Glioblastoma (GBM) with genetic profile: case report and review of literature

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Key words: spinal GBM, drop metastasis of cerebral GBM, spinal metastasis

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Abstract

Spinal metastasis of cerebral glioblastoma (GBM) is very rare, with some reports suggesting a prevalence of 1-2%. (1) Herein, we present 2 unique cases of spinal metastasis of cerebral GBM, one of which was histologically proven to be a drop spinal GBM metastasis. The first case was a 25-year-old female who presented with a spinal intradural intramedullary spinal lesion a few months after resection of a left temporal lobe GBM (IDH wild type). The patient underwent surgical resection of the new lesion, and subsequent histopathological examination proved that the intramedullary spinal lesion was GBM. The patient experienced full recovery post operatively, and then a few months later, she presented again with widespread drop metastasis of the spinal cord. The second case is a middle-aged male with right temporal GBM who developed spinal metastasis 10 months after his diagnosis.

We are reporting these two cases due to the rarity of spinal metastasis in GBM. We reviewed the current literature and included genetic and molecular profiles in the discussion. Currently, there are no established treatment guidelines for GBM spinal metastasis. The Stupp protocol after initial brain surgery for GBM did not appear to have beneficial effects on prolonging survival in these patients with spinal metastasis. The goal of treatment was primarily to alleviate pain and neurological deficits with no effect on overall outcome. Prognosis following the diagnosis of spinal metastasis is poor.

Introduction

Glioblastoma is the most common brain tumor, accounting for approximately 16% of all brain tumors (primary and metastatic), and incidence is reported to be 3.2 per 100,000 per year. The median age for GBM is approximately 64 years old, and GBMs are considered Grade 4 according to the WHO classification of brain tumors (2,3). GBMs in younger patients usually exhibit IDH mutations (3). Spinal metastasis of cerebral GBM is very rare, and insufficient data exists to evaluate overall incidence and prevalence. Reports suggest prevalence to be 1-2% of all patients with cerebral GBM (1). Herein, we present 2 unique cases of metastatic spinal GBM, cautioning clinicians to pay close attention during follow up to patients within the first year after GBM diagnosis for any spinal symptoms or signs indicating drop metastasis.

Case Report 1

History

A 25-year-old female patient with a known case of cerebral glioblastoma, IDH wild type, was treated surgically. The first surgery was subtotal resection followed by a second surgery with gross total resection and subsequent radiotherapy and temozolomid. Six months later, she presented with a history of acute severe back pain for several weeks with exacerbation in the days prior to presentation associated with the inability to walk, heaviness in both lower limbs and the inability to pass urine or stool.

Clinical examination

The patient was fully conscious, alert, oriented, and moving all limbs with full power of all muscle groups. Hypertonia of bilateral lower limbs, exaggerated bilateral knees and ankles jerks (+3), bilateral clonus, and upgoing Babinski sign bilaterally were all observed.

An urgent MRI of the spine with contrast was performed (Figure 1) showing diffuse dural thecal sac enhancement with small nodular dural lesions, sized 0.15 x 0.7 cm (AP x Craniocaudal) at the level of T6 vertebra. Another dural enhancing lesion measuring 0.3 x 0.8 cm was observed at the lower T7 level on the right lateral aspect. A third, larger (1 x 1 x 1.9 cm) T2 isointense nodular enhancing lesion was noted, involving the thecal sac and infiltrating into the spinal cord to involve its posterior and mid portions, sparing only a small circumferential portion of the cord at anterior/lateral aspects in this location. There was extensive spinal cord edema throughout the thoracic cord, extending inferiorly to the conus medullaris and superiorly up to the C7 level. In the lumbar spine, there was a tiny nodular area of thecal sac enhancement at the right anterolateral aspect at upper L1 at the level of the conus medullaris, left posterior upper L2, upper L3, and mid posterior upper L5 levels (Image 1).

Given the history of primary glioblastoma, the most likely diagnosis was drop metastasis to the spine.

Surgical technique

T10 laminectomy with T9 laminotomy and excision of intradural/intramedullary metastatic spinal cord lesion was performed. Intraoperatively, ultrasound was used to localize the lesion. Then, durotomy was performed at the midline, and dural sutures were used for retraction of the dural edges. The spinal arachnoid layer was opened, and a whitish-grayish lesion attached to the spinal cord with a plane of demarcation was recognized. Bipolar and CAUSA were used for gradual debulking of the lesion until the normal spinal cord was recognized primarily at the caudal region. The lesion was hard in consistency and adherent to the spinal cord; therefore, complete resection of the remaining tumor capsule would have led to neurological deficits post operatively. In light of these findings, the lesion was debulked from the inside, and a small layer of adherent residual was left to avoid further neurological deficits in the patient.

Pathological examination (Figure 3 and 4)

Microscopic examination of the primary brain tumor, as well as the spine metastases, was the same, showing a high-grade glial neoplasm characterized by sheets and fascicles of polygonal as well as

spindle neoplastic astrocytes that appeared pleomorphic with hyperchromatic nuclei, numerous mitotic figures with abnormal shapes, and neovasculature and palisaded geographic necrosis (Figures 3 and 4). Molecular profiling of the tumor was performed, revealing tumor cells to be IDH-1 wild type, ATRX wild type, and exhibiting overexpression of p53 and a high Ki-67 index. The methylguanine-DNA methyltransferase (MGGMT) promoter was unmethylated. Neuro-oncology targeted next generation sequencing was performed to identify somatic mutations within 50 genes associated with tumors of the central nervous system and revealed mutations in the TERT and TP53 genes.

Postoperative course and follow up

Post operatively, the patient was started on 4 mg dexamethasone every 6 hours for 3 days and PCA fentanyl for pain control.

Postoperative day 1 MRI (Figure 2) showed the expected postoperative fluid and hemorrhagic changes noted during surgery, including debulking of a T9-10 spinal cord lesion measuring 6.4 x 5 x 14 mm compared to 10 x 10 x 19 mm. The residual showed similar signal characteristics and enhancement sparing with circumferential peripheral aspects of the cord. There was surrounding proximal and distal cord edema from T8 to T10 levels. Significant reduction in spinal cord edema, which was seen on the current exam, extending from T2 to T7 levels previously, was from C7 to the conus. Unchanged appearance and size of tiny nodule intrathecal deposits was observed at posterior T6, bilateral lower T7 (larger on the right), anterolateral L1, left posterior upper L2, upper L3, and mid posterior upper L5 levels.

On the days following surgery, postoperative incisional pain had improved, and the patient was able to ambulate independently. PCA fentanyl was stopped day 3 postop, and dexamethasone was tapered, with no urinary or bowel dysfunction. The patient was discharged on the fifth postop day.

Two weeks after surgery, the patient was started on local spine radiotherapy and was showing improvement in her pain and symptoms at the time. She was also referred for palliative and pain management services, as well as started on PRN morphine.

Two months after surgery, the patient presented with complaint of low back pain and left lower limb heaviness that had begun 10 days prior to complaint, with difficulty walking, 2 falls, and inability to pass urine, which began on the day of presentation. Upon examination, the patient was in severe pain, but right lower limb power was intact in all muscle groups. However, for the left lower limb, foot dorsiflexion and planter flexion were 2/5, knee extension and flexion were 2/5, and hip flexion and extension were 0/5. The patient was also experiencing decreased sensation of the left lower limb with no specific dermatomal distribution, and knee and ankle jerks of the left lower limbs were +1 and +3 for the right lower limb.

An urgent MRI of the spine (Figure 5) with performed, showing multiple intradural extramedullary lesions noted at the craniocervical junction, opposite C6-7 level, D5-6, D9-10, D11-through L2 multiple nodular matted lesions forming a large mass. In addition, along the cauda equina nerve

roots, there was no progression of previously surgically treated T9 lesion, but other small nodular lesions had grown significantly along with other new lesions, signifying spinal axis extensive drop metastasis. Given the extensiveness of the disease and the poor prognosis, the decision was made to perform palliative treatment and pain management, with continuation of spinal radiotherapy.

The patient died two months later.

Chemoradiotherapy regimen

The patient received adjuvant chemoradiotherapy after the surgical debulking of the second brain tumor (60 Gy in 30 fractions with temozolomide). After spinal cord tumor surgical resection, she received radiotherapy to the spine T8-T11 of 36 Gy in 12 fractions. Then, she experienced a recurrent left temporal tumor, so bevacizumab was administered on day 1, 14 and 28 every 6 weeks and carboplatin AUC for 5 days 1 and 28 every 6 weeks. She died 3 months after this.

Case report 2

History

A 49-year-old male with known diabetes mellitus, who was an ex-smoker presented to the emergency department with headache, nausea, and vomiting of acute onset. On clinical examination, he was alert oriented GCS 15 with no focal neurological deficits.

MRI (Figure 6) revealed a large ill-defined mass in the right temporal lobe with low signal in T1, high signal in T2 and heterogenous enhancement, denoting cytic/necrotic components with no diffusion restriction. The lesion was associated with significant vasogenic edema with mass effect and midline shift to the left side of 10 mm. MR brain perfusion showed elevated cerebral blood flow and cerebral blood volume primarily along the anteromedial component of the lesion. MR spectroscopy showed elevation of the choline peak with reduction in the N acetyl aspartate peak with some elevation of the lactate/lipid peaks.

A workup was performed, including CT of the chest, abdomen and pelvis, which did not identify any additional lesions. The patient underwent right pterional craniotomy for resection of mass lesion.

Pathological examination (Figure 7)

Microscopic examination of the primary and recurrent brain tumors showed a highly cellular glial neoplasm characterized by sheets of pleomorphic astrocytes with occasional multi nucleated tumor giant cells associated with numerous mitotic figures, including abnormal shapes along with neovasculature and extensive infarct-type necrosis as well as palisaded type geographic necrosis (Figure 7A). Molecular profiling of the tumor by IHC showed the tumor cells to be IDH1 wild type (Figures 7B), ATRX wild type with retained nuclear staining (Figures 7C), p53 overexpressing (Figure 7D) and having a high Ki-67 index (Figure 7E).

Postoperative course and follow up

Postoperative MRI of the brain showed gross total resection of the right temporal lesion. Post operatively, the patient received chemoradiotherapy as per the Stupp protocol.

Six months after surgery, a follow up MRI of the head showed an area of recurrence around the surgical cavity. The patient received surgery again for the recurrent GBM. Post operatively, the patient developed CSF collection in the scalp, so he underwent reoperation with duroplasty and a lumbar drain. The patient was discharged after resolution of CSF collection.

One month later, the patient presented with left side weakness, facial weakness, back pain and right shoulder pain for four days, and he complained of slipping after walking a short distance. Examination showed left facial palsy UMNL, left side weakness 4/5, hyperreflexia, +3, no Hoffman, Babinski downgoing bilateral, and intact sensations.

MRI of the whole spine (Figure 8) showed multiple intraspinal and intradural extramedullary enhancing lesions at the level of the C7 vertebra anteriorly, T1 and T2 posteriorly, in the lumbar spinal canal opposite L1, L2, L3 and L4, and in the distal portion of the thecal sac opposite S1 and S2 sacral segments. The largest mass was observed opposite the L2 vertebral level. The patient was discussed in a neuro-oncology multidisciplinary meeting, and the final plan was to forgo additional surgical intervention in favor of continuing chemoradiotherapy and supportive measures.

Chemoradiotherapy regimen

The patient received radiotherapy to the tumor bed and margins at 60 Gy in 30 fractions. The patient did not receive concurrent temozolamide chemotherapy because of increased LFT. After 1 month, he started the first cycle of temozolamide, and s/p 5 cycles, he experienced disease progression at the same previous tumor site. After his second surgery, he was started on systemic Avastin. After diagnosis of spinal mets, the patient was lost to follow up as he traveled to his home country.

Discussion

Epidemiology

Glioblastoma is the most common malignant neoplasm of the central nervous system. The most common location is supratentorial compartment. Local recurrence of the tumor after initial resection is the rule rather than exception. Thought it recurs at the margin of the resected cavity invariably, extracranial spread is very rare. The incidence of spinal metastasis of cerebral glioblastoma is approximately 1.1% in the published literature(6). An autopsy series reported an incidence of 25% in patients with cerebral GBM undergoing autopsy (1,7). Wright et al in their systematic review identified only 86 patients from 51 published articles, and out of those cases, there were only 22 patients reported from Asia. Here, we have presented two more cases Cerebral GBM metastasizing to spine and one of them is proven by histopathological examination (27).

There are 2 types of Glioblastoma metastasis to spinal cord: Malignant spinal cord compression metastasis (SCCM) (1) or Leptomeningeal disease (LMD)(4) To our knowledge, limited data available about actual percentage or number of GBM cases with SCCM. As well many research studies do not differentiate between SCCM and LMD. In a study conducted by Tinchon et al. on 9 patients diagnosed with supratentorial GBM with SCCM. Temporal lobe affection was found in 7 cases. Only 1 case was proven to be spinal GBM surgically, other cases diagnosed radiologically and clinically. In that case series, prevalence of SCCM was found to be 1% (1) metastasis of GBM was first described more than 70 years ago. (5) Stark et al reported GBM with SCCM in 1.1% in a cohort of 267 patients.(6) SCCM can be missed in final stages of disease and Although some autopsy series report 25%, autopsy studies not performed regularly. (1, 7).

Characteristics of primary brain lesion:

The patients with spinal metastasis from cerebral GBM are relatively young. Wright et al reported the mean age of the patient to be 46.78 years (95%CI= 43.71-49.85). The primary GBM were mostly supratentorial in location (96.43%) and unifocal (95.83). In patients who had information on extent of resection (n=57), 50.88% of the patients underwent gross total resection (27). Matsuda et al reviewed GBM in pineal region with leptomeningeal disease and spinal metastasis suggesting that spinal GBM occurs more frequently with pineal gland location(15). Both of our patients were also young (25 and 49 years of age). They both had unifocal supratentorial primaries located in the temporal lobe and had gross total resection of the primary lesion. Though it cannot be concluded, gross total resection does not appear to give protection against spinal metastasis.

Characteristics of spinal metastasis:

Most of the metastases are multifocal and thoracic spine is the most common level affected. Metastases from GBM are usually multiplanar, i.e., involving intramedullary, leptomeningeal and intradural extramedullary planes simultaneously. Wright et al described multifocal disease in 62.03% of the patients in their systematic review (27). Thoracic spine was the most common level affected (66.67%) followed by lumbar (44.93%) and cervical (34.78%). Leptomeningeal disease was present in 53.45% of the patients, intramedullary disease in 53.23% and intradural extramedullary disease in 47.14%. Our first case had multifocal disease involving multiple spinal levels and the patient had leptomeningeal and intradural extramedullary lesions. Our second case had lumbar disease in intradural extramedullary plane.

Neck pain or back pain and neurological deficits are the most common presenting symptoms. Approximately 86% of the patients described by Wright et al in their systematic review had weakness of limbs and approximately 80% had bowel/bladder dysfunction. The mean time between diagnosis of the primary brain GBM and spinal metastasis was 13.54 months (95%CI = 10.84–16.25). Both of our cases presented with back pain and neurological deficits. The time between primary GBM and diagnosis of spinal metastasis in the 1st case was 6 month and in the 2nd case was 9 months.

Genetics:

Glioblastoma can be classified into IDH mutant and wild type on a molecular basis. IDH wild type tumors are common in older patients and possess a worse prognosis. In contrast, IDH mutant tumors are common in younger patients and possess better prognosis. Patients who experience

spinal metastases are younger (mean age 46.78). Both of our cases were young and had the following genetic profiles:

First case: MGMT promoter methylation absent, IDH-1 wild type

Second case: IDH 1 wild type

-ATRX expression was retained

-p53 was overexpressed

It has been suggested that certain genetic profiles might predispose patients to developing spinal metastasis, and more research needs to be done to explore the interaction between age and genetic profile and aggressiveness in tumors (14). According to a systemic literature review on spinal metastasis by Wright et al, IDH status and MGMT methylation status were reported in only 4 patients of 86 included in their paper, which indicate that additional genetic studies need to be done for these patients, including for research purposes (27).

Treatment and outcome

There are no established guidelines for treatment of spinal metastasis from cerebral glioblastoma. Stupp et al reported improved survival at 2 years (26.5%) in response to radiotherapy plus concomitant adjuvant temozolomide compared to radiotherapy alone (10.4%) (28). However, in their systematic review, Wright et al were unable to validate the beneficial effect of the Stupp protocol. Patients who had undergone the Stupp regimen for primary GBM had a median survival of 10.5 months, while those who were not treated according to the Stupp protocol had a median survival of 15 months. From the current literature, it can be inferred that the Stupp protocol does not appear to convey a survival benefit in the subset of patients who experience spinal metastasis (27,28).

Some studies recommend specific radiotherapy schedules, including 30 Gy (12) and 21 Gy (10). In these two studies, the authors suggest that treatment was only for pain relief and neurologic deficits but exerted no effect on overall outcome. In a study by Tichon et al, different local radiation doses were given to 5 patients in combination with different chemotherapeutic agents with poor outcome or no benefit observed (1).

After diagnosis of spinal metastasis, chemoradiotherapy is the primary method of treatment. Surgery can be done for focal lesions, but chemoradiotherapy is the only option for patients with diffuse or leptomeningeal disease (1). The first patient in our report underwent surgery followed by radiotherapy, and the second patient underwent palliative chemoradiotherapy only.

The mean time between diagnosis of spinal GBM metastasis and death was 3.72 months (95%CI: 2.59-4.85), and the median was 2.8 months in Wright et al's systematic review (27). Patients with only leptomeningeal metastasis had a worse median survival (2.5 months) than those with pure intramedullary disease (4.0 months) or pure intradural extramedullary disease (7.0 months). One of our patients died after 4 months of surgical intervention, and the other was lost to follow up due to traveling abroad.

Conclusions

Spinal metastasis of cerebral glioblastoma is rare. It is more common in younger patients and is usually multifocal with tumors harboring wild-type IDH glioblastoma. Thoracic spine is the most common level affected followed by lumbar and cervical regions. Currently, there are no established treatment guidelines available. The Stupp protocol after initial brain surgery does not appear to have a beneficial effect on prolonging survival in these patients. The treatment goal is primarily to alleviate pain and neurologic deficits with no effect on overall outcome. Prognosis following the diagnosis of spinal metastasis is poor. Certain genetic profiles might predispose patients to develop spinal metastasis, and more research is needed to further explore these genetic profiles and to develop targeted therapies for these patients (1-28).

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Table of data of our 2 cases

Patient number	Age/ Sex	Location of primary GBM	Location of spinal metastasis	symptoms	signs	Surgery for spinal metastasis	CRT*	prognosis
1	25 YO Female	Left temporal	Mainly T9-10 with other lesions T2,T6, L1,2,3	Back pain, heaviness both LL, inability to pass urine, stool	Hypertonia, hyperreflexia with clonus, positive Babinski	Yes	Local spine radiotherapy,bevacizumab, carboplatin AUC	Died after 4 months of surgery
2	49 YO Male	Right temporal	Mainly L2	Back pain, right shoulder pain, slipping during walking	Hyperreflexia +# with left side weakness 4/5	No	Palliative therapy	Lost follow up (travel)

*** CRT chemoradiotherapy**

Summary of reported cases with genetics from literature review:

Author and year	**Genetic profile of reported cases spinal GBM**	**Involved brain region**
Schwartz et al 2018 . (14)	**IDH wild type** **(MGMT) promoter methylation negative** high focal Ki-67 proliferation index	**Right temporal lobe**
Tai et al. 2015. (23)	**IDH Mutant type absent** **(MGMT) promoter methylation negative**	**Corpus callosum and right frontal lobe**
Our 1st case	**MGMT promoter Methylation: Absent., IDH-1 wild-type**	**Left temporal**
Our 2nd case	**IDH 1 wild-type,** **-ATRX expression is retained.** **-p53 is overexpressed.**	**Right temporal**

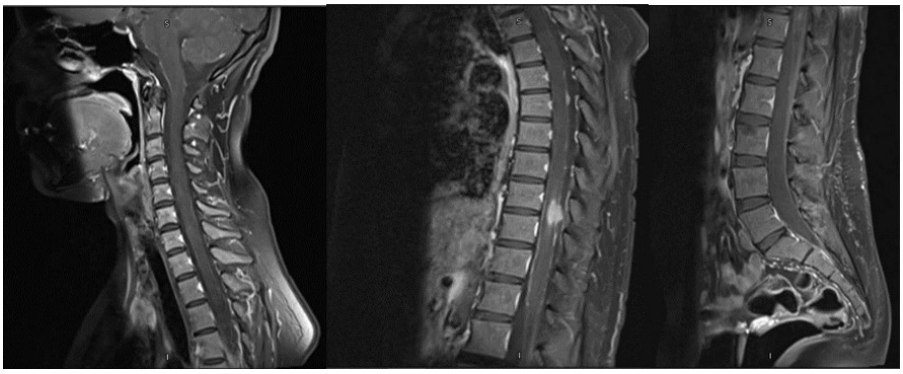

Figure 1a MRI spine T1 with contrast sagittal cervical, thoracic and lumbar spine

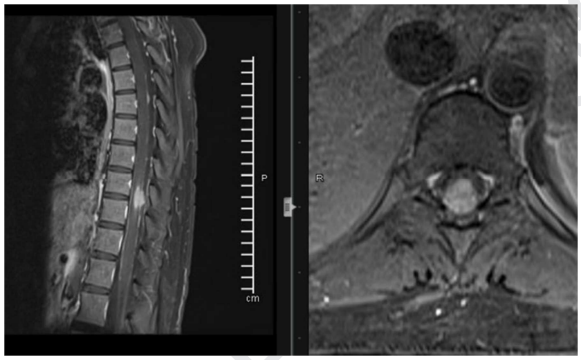

Figure 1b MRI thoracic spine T1 with contrast Axial Cut, sagittal cuts

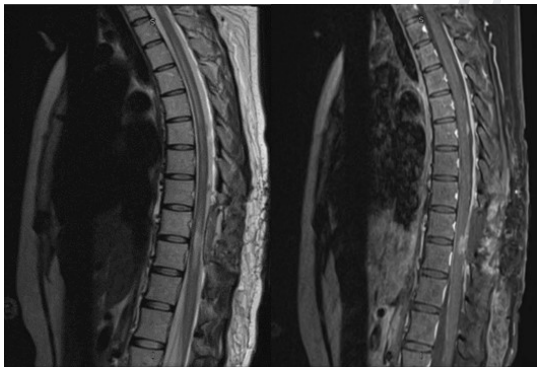

Figure 2a: MRI thoracic spine with contrast sagittal T1 on the right , T2 on the left

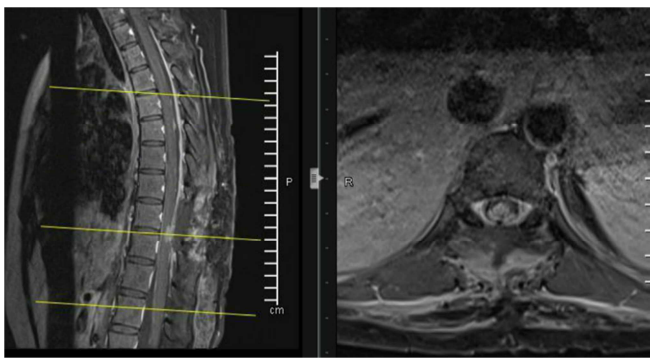

Figure 2b: MRI thoracic spine T1 with contrast Axial Cut, sagittal cuts

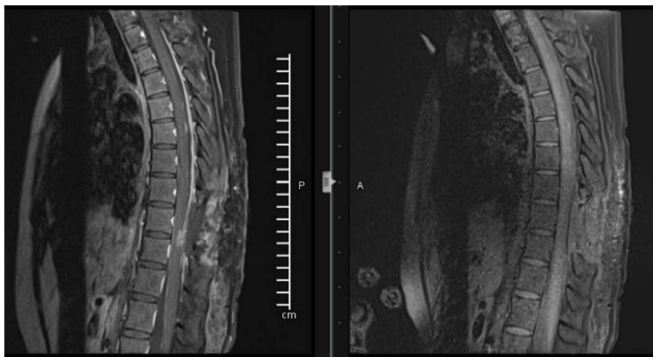

Figure 2c: MRI thoracic spine with contrast T1 without contrast on the right and T1 with contrast on the left sagittal cuts

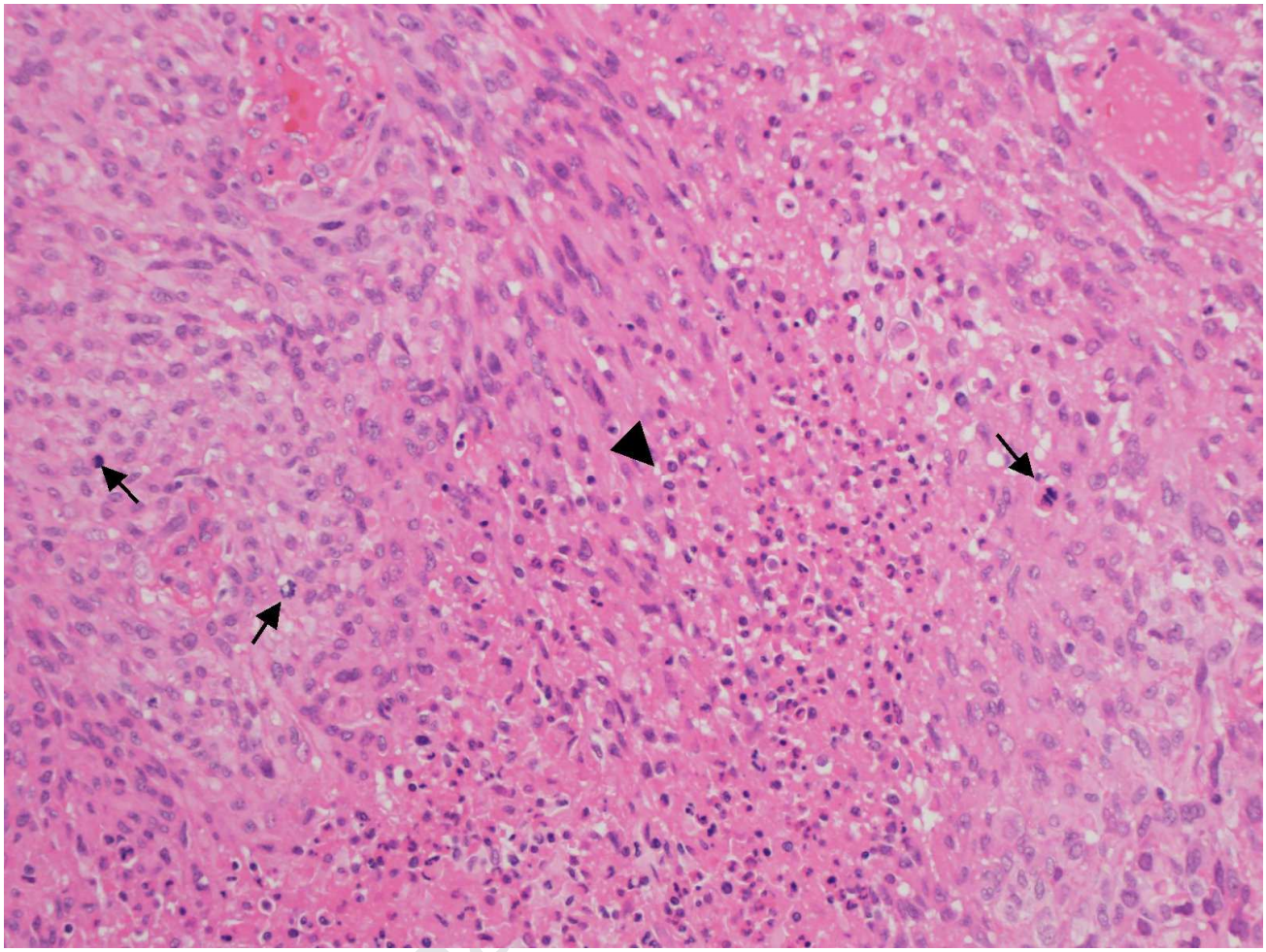

Figure 3: Photomicrograph of the brain tumor showing high grade glial tumor with numerous mitosis (arrows) and central necrosis (arrowhead) (H&E ×200).

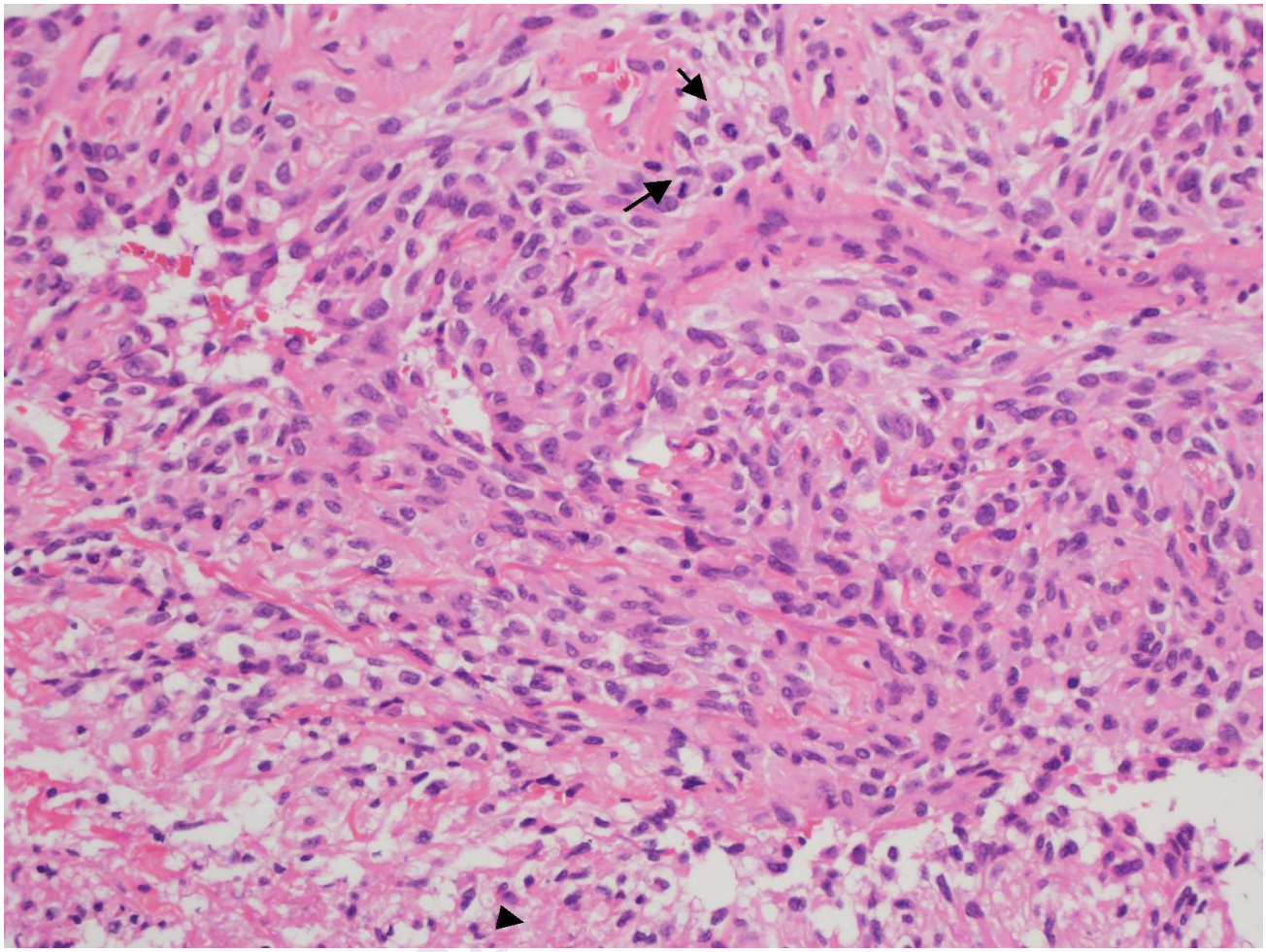

Figure 4: Photomicrograph of the spinal metastasis showing similar features to the brain tumor with numerous mitoses (arrows) and necrosis (arrow head) (H& E ×200).

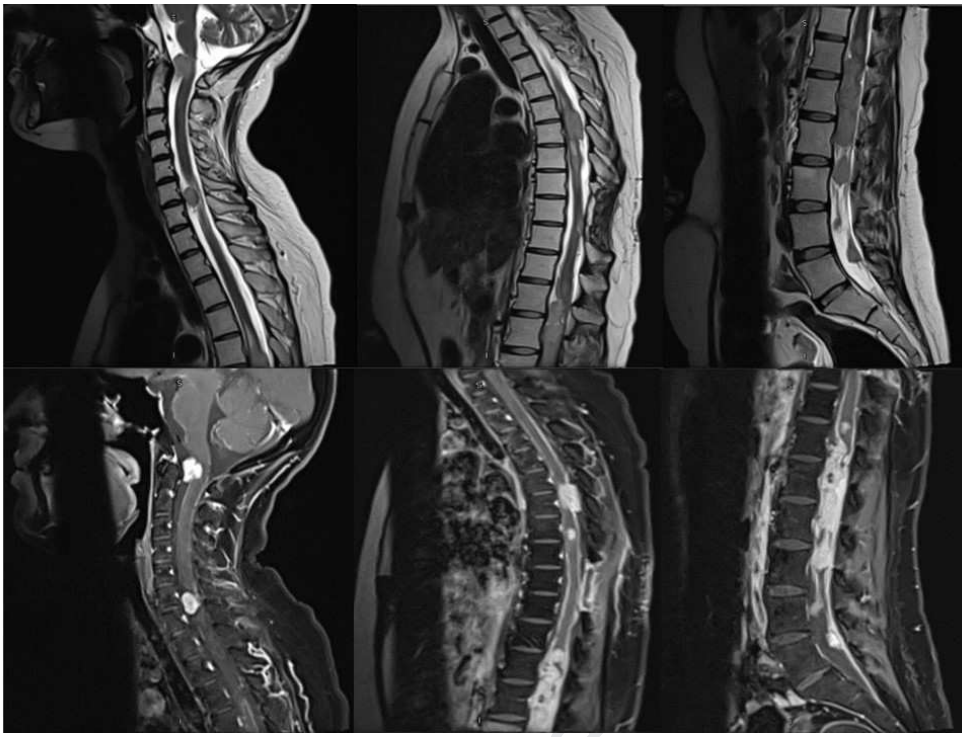

Figure 5: MRI whole spine with contrast upper row T2 sagittal cervical , thoracic, lumbar, lower row T1 with contrast cervical, thoracic, lumbar

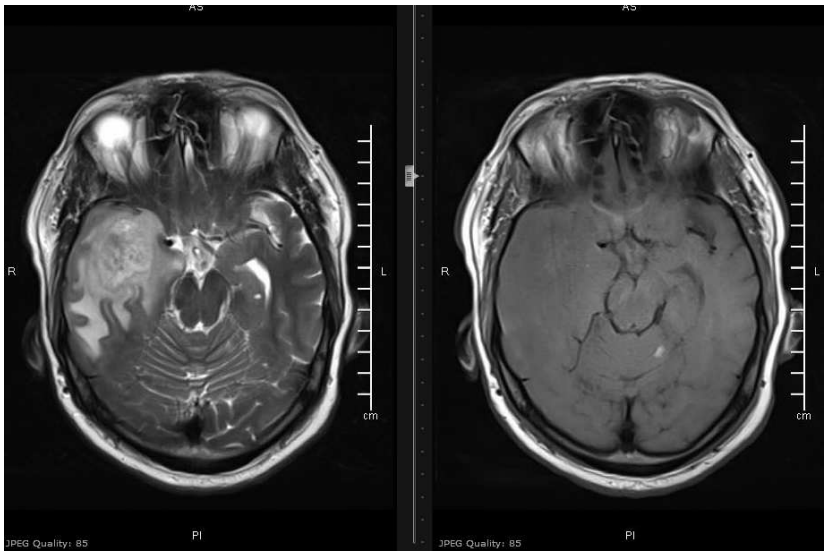

Figure 6a MRI Head T1 on right side, T2 left side

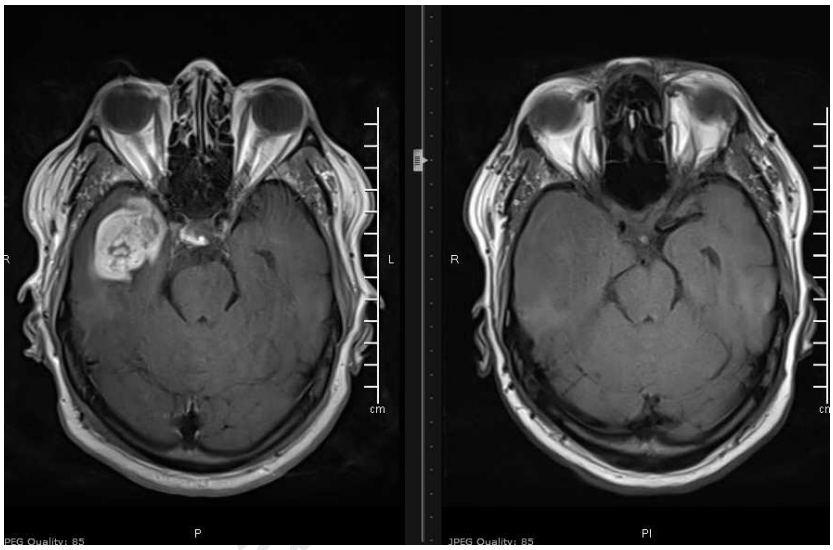

Figure 6b:MRI T1 axial right side, T1 with gadolinium enhanced contrast on left side

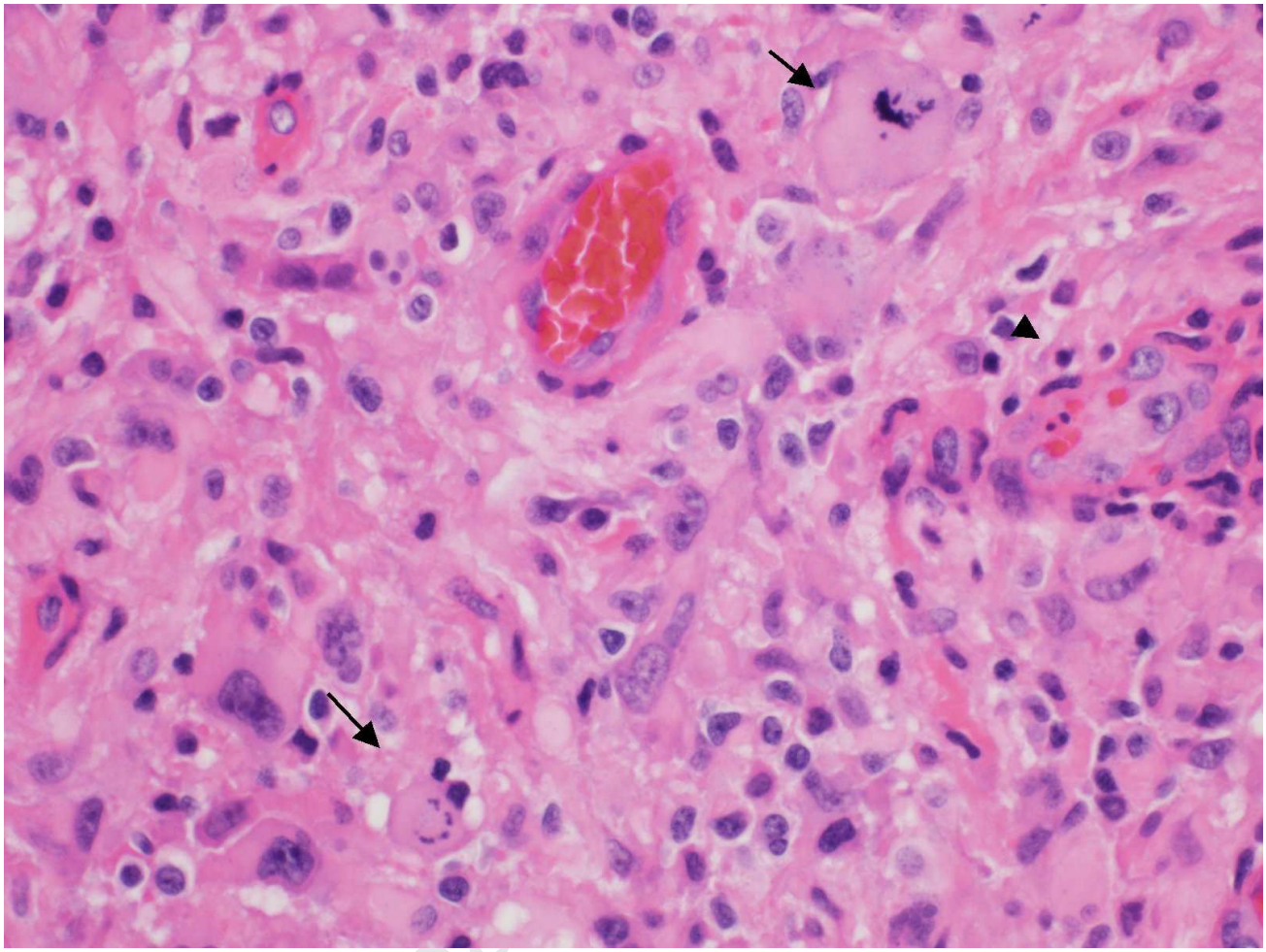

Figure 7A: Microscopic examination showing glial tumor with numerous mitotic figures (arrows) and neo-vasculature (arrowhead) (H&E ×200).

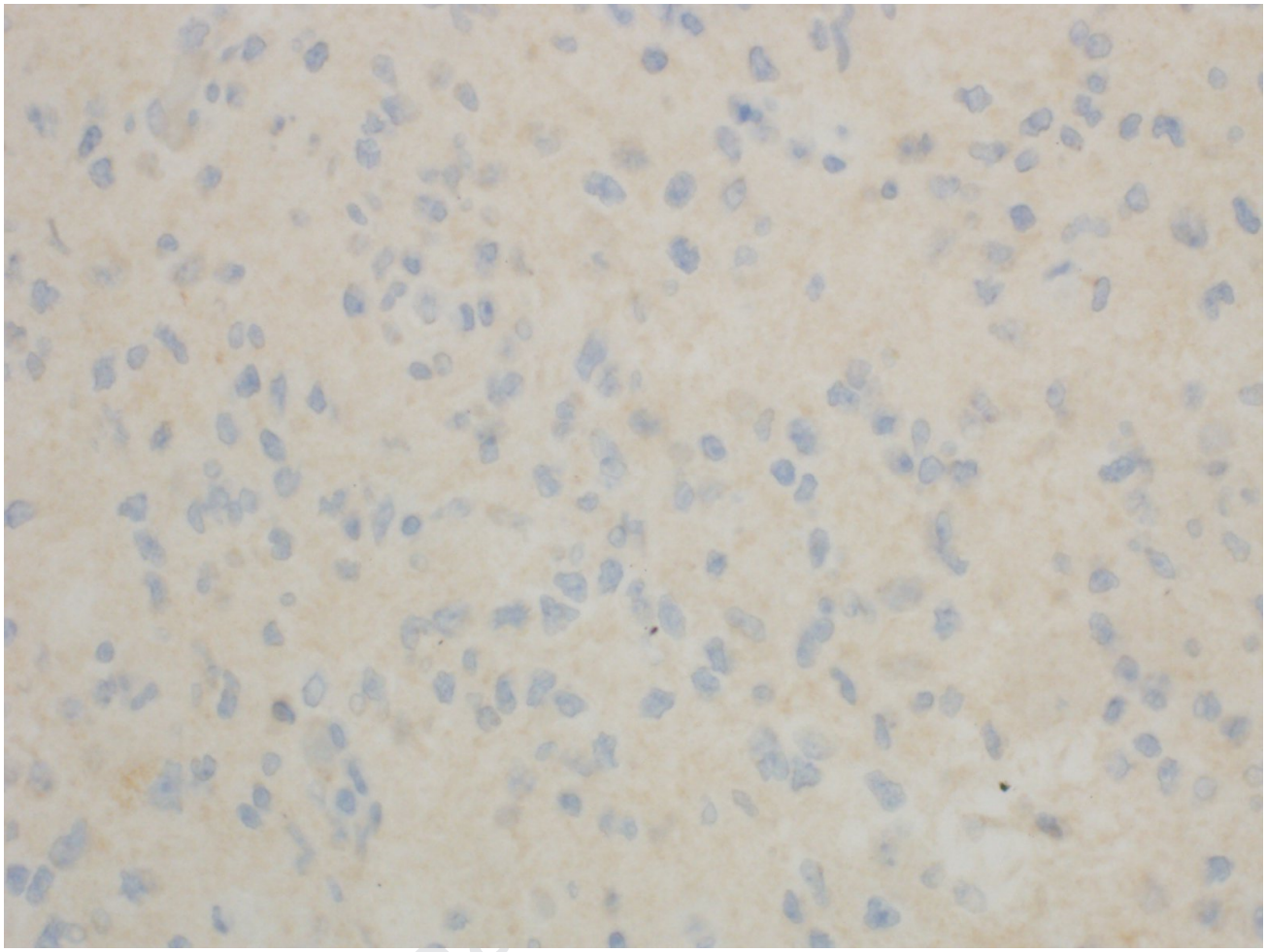

Figure 7B: IDH-1 is negative (wild-type) (Immunohistochemistry ×400).

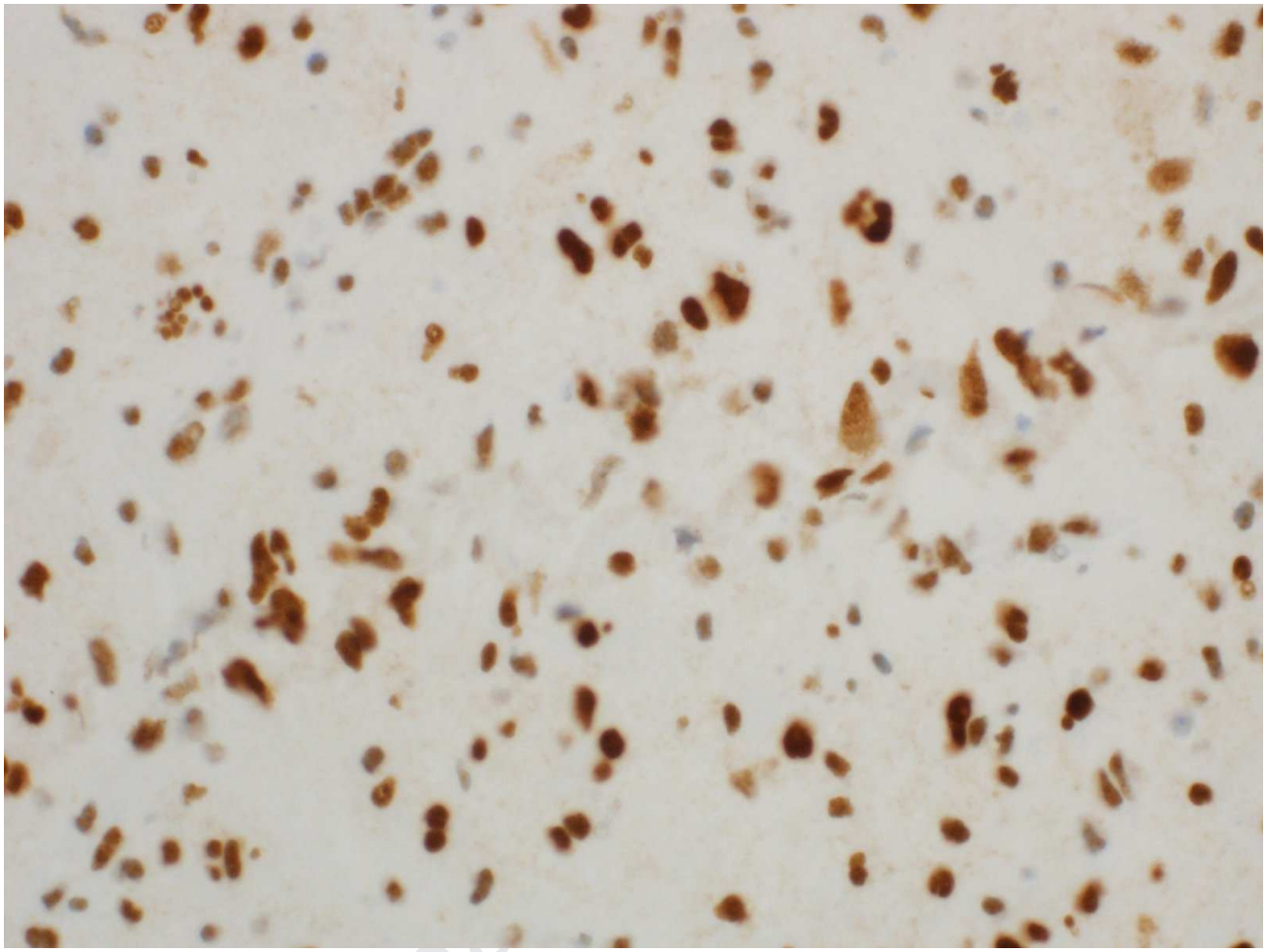

Figure 7C: ATRX is overexpressed (Immunohistochemistry ×400).

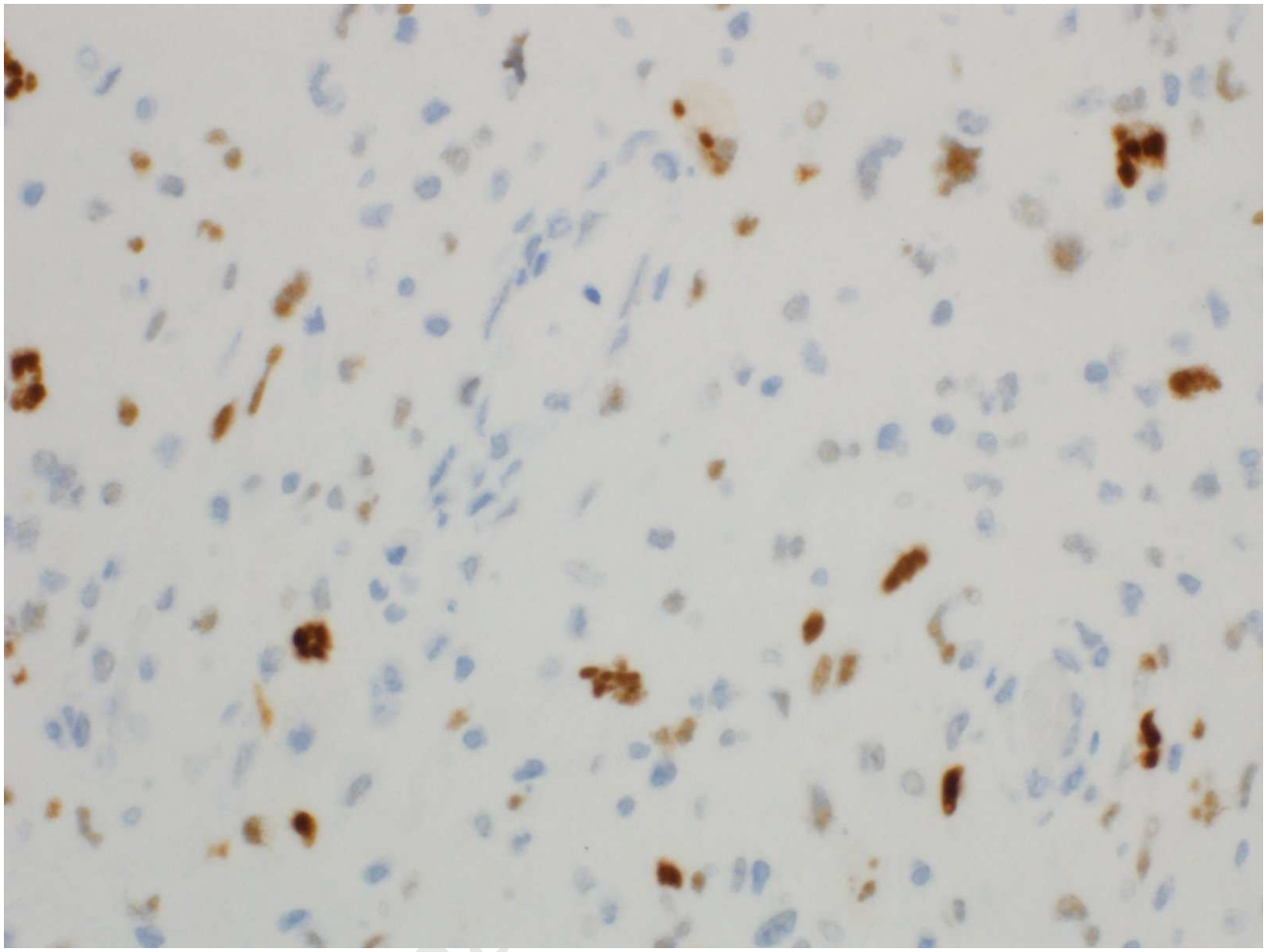

Figure 7D: p53 is overexpressed (Immunohistochemistry ×400).

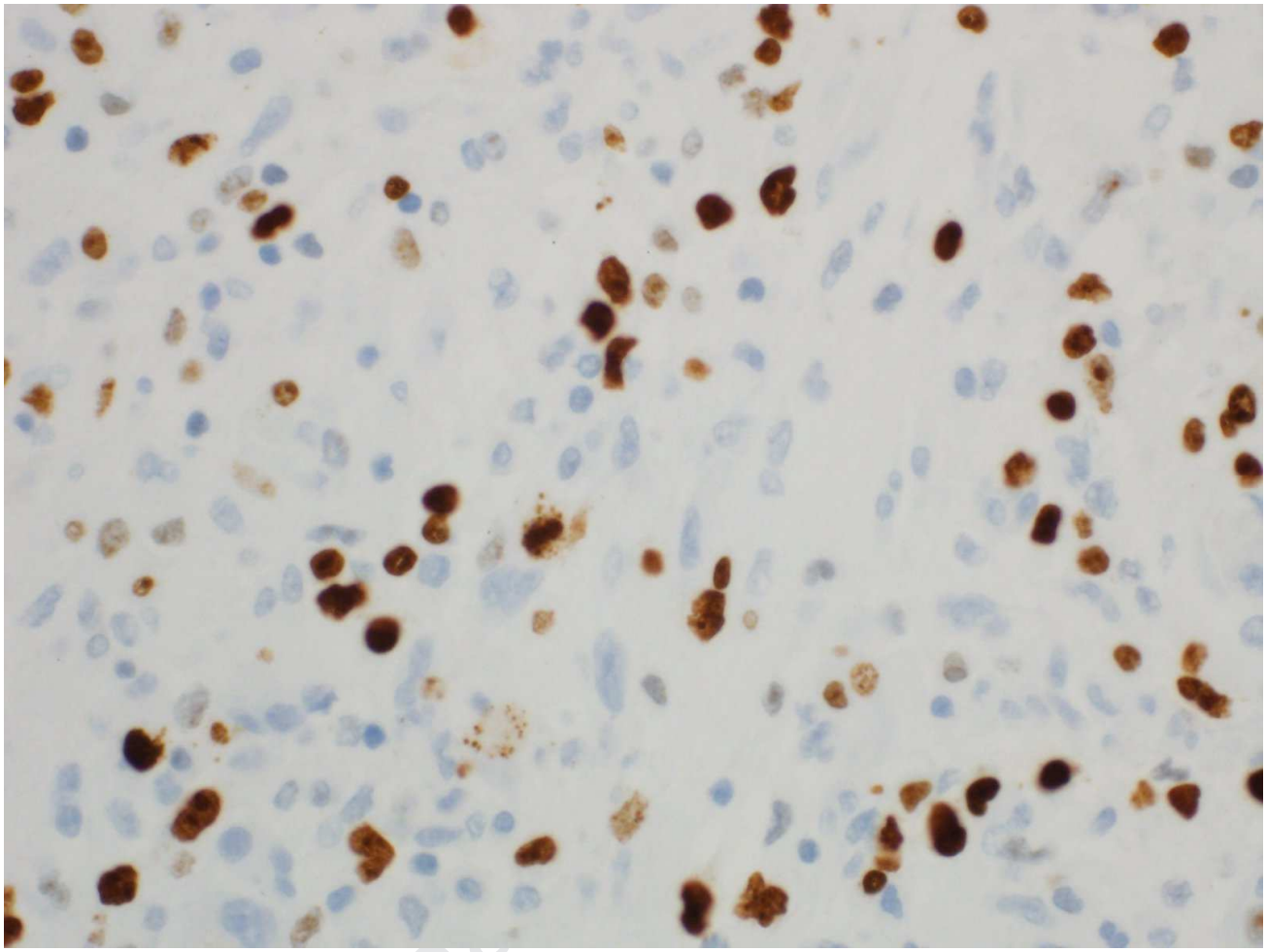

Figure 7E: Ki-67 index is elevated (20%)(Immunohistochemistry ×400).

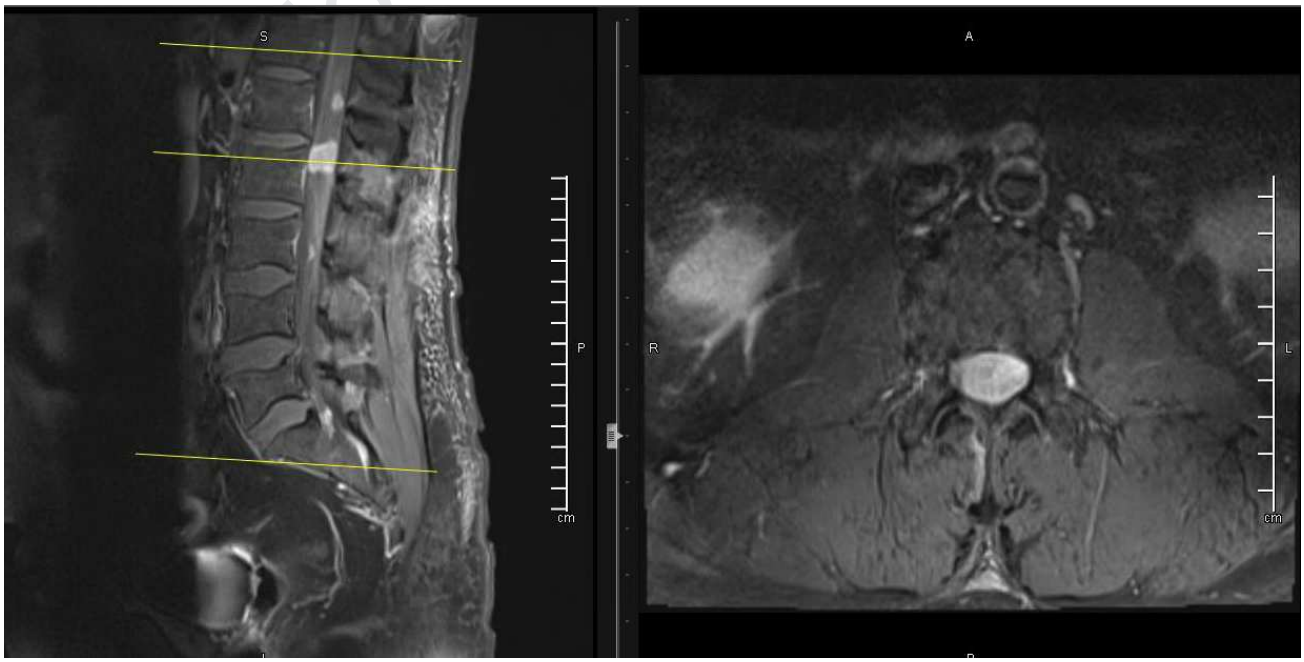

Figure 8a: MRI T1 with gadolinium enhancement sagittal and axial Lumbar level showing multiple intradural , intraspinal metastasis with largest one at level of L2

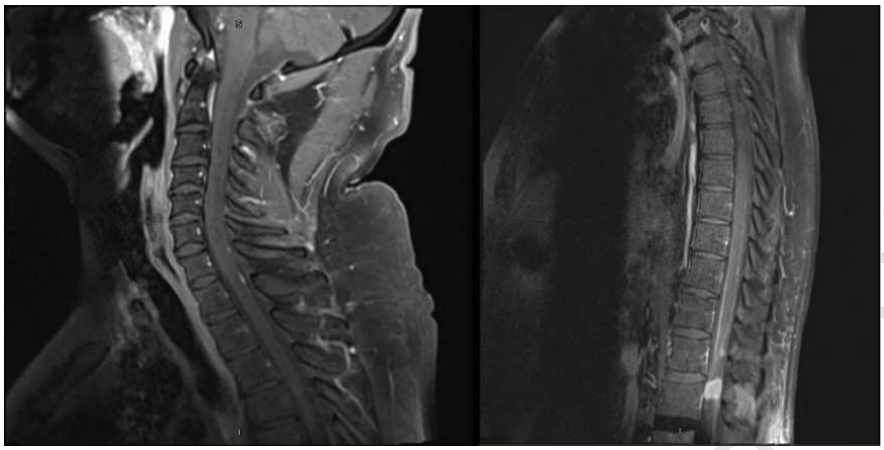

Figure 8b: MRI T1 with gadolinium enhancement sagittal cervical left side, thoracic right side showing again multiple intadural, intraspinal drop metastasis

Glioblastoma (GBM)

Magnetic resonance imaging (MRI)

No conflict of interest