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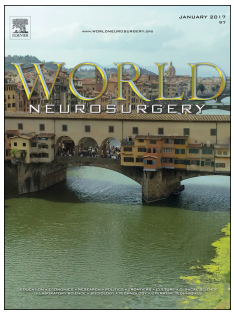

Spinal drop metastasis of Glioblastoma - Two Case Reports, Clinicopathological features, Current Modalities of Evaluation and Treatment with a Review of literature.

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TITLE PAGE

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SHORT TITLE: Spinal drop metastasis of Glioblastoma – Two case reports

Key words: Glioblastoma, leptomeningeal spread, Spinal glioblastoma metastasis, Type1a nodular LM, Type 1b diffuse LM, Cyber knife for metastatic spinal glioblastoma, Proton beam therapy for metastatic spinal glioblastoma

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Spinal drop metastasis of Glioblastoma Two Case Reports, Clinicopathological features, Current Modalities of Evaluation and Treatment with a Review of literature.

BACKGROUND: Glioblastomas (WHO Grade IV), are aggressive primary neoplasms of the central nervous system. Spinal metastasis occurs supposedly in 2 to 5% of patients. This may be only the tip of iceberg as most succumb to the disease before clinical detection and few documented cases are reported.

CASE DESCRIPTION: A 45-year-old male presented with history of diplopia and gait disturbance. MRI revealed a Left Cerebellar space occupying lesion. The histopathology was consistent with Glioblastoma. He underwent adjuvant chemoradiation. A year later he presented with seizures, worsening headache, neck stiffness and low back pain. Imaging showed metastasis to the S1/S2 region of the spinal canal.

A 29-year-old male presented with episodic headaches associated with nausea, vomiting, neck stiffness and imbalance while walking. CT scan brain showed a hypodense lesion involving the left midbrain, pons and left middle cerebellar peduncle causing fourth ventricular pressure with obstructive hydrocephalus. A navigation guided biopsy of the brainstem lesion confirmed the diagnosis of Glioblastoma WHO Grade IV, IDH 1 (R132 H) and H3K27M negative. IDH gene sequencing was suggested. He was referred for chemoradiation .During treatment he worsened neurologically and developed axial neck and back pain. Neuraxis screening showed disseminated leptomeningeal spread, which was confirmed on dural biopsy.

CONCLUSION: Spinal and dural metastasis should always be suspected in patients with Glioblastoma with signs and symptoms not explained by primary lesion. A regular protocol with post-contrast MRI before and after initial surgery, is mandatory to detect spinal metastasis before they become clinically apparent thereby improving the prognosis and quality of life in patients.

Spinal drop metastasis of Glioblastoma - Two Case Reports, Clinicopathological features, Current Modalities of Evaluation and Treatment with a Review of literature.

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Abstract

We present two cases of glioblastoma with leptomeningeal metastasis to the spinal canal that was detected on post-contrast MRI, at an early stage, even before development of significant clinical deterioration. Both patients who had infratentorial glioblastoma(cerebellar and brain stem) developed head ache and meningeal signs post procedure. Contrast enhanced MRI screening of the neuraxis revealed leptomeningeal spread. One patient with an intradural nodular lesion refused excision biopsy and opted for cyberknife therapy. The second patient who underwent navigation guided biopsy, had a more fulminant clinical course. 3T MRI screening

with contrast revealed the leptomeningeal glioblastoma which was confirmed by biopsy. Both patients had hydrocephalus. Clinicopathological features, current investigation and treatment guidelines followed at our institution are discussed. Cyberknife, Proton Beam and conventional neurosurgical strategies have been reviewed.

KEY WORDS

Glioblastoma, leptomeningeal spread, Spinal glioblastoma metastasis,Type1a nodular LM, Type 1b diffuse LM, Cyberknife for metastatic spinal glioblastoma, Proton beam therapy for metastatic spinal glioblastoma.

Introduction

Glioblastoma, is the commonest and most aggressive primary malignancy of the central nervous system in adults[1].This grade IV glioma is seen in age group of 40 to 60 years[2]. The heterogeneity and variability in the outcome of these lesions is attributed to the histopathological presence of both neoplastic and stromal cells[2]. The outcome of brainstem gliomas, is worse in comparison[2].Leptomeningeal metastasis in autopsy studies have been reported to be up to 20-25% with mean survival of 3-4 months[3,4].The current standardized treatment involves maximal, yet safe, surgical resection of the tumour with post-operative adjuvant chemoradiotherapy[5]. Despite the best possible multimodal treatment, prognosis is poor and over 75% of patients succumb within 18 months of diagnosis[6].Spinal metastasis that is symptomatic and macroscopically evident occurs only in about 2 to 5% of patients[2,4]. The known incidence is low because patients succumb to the disease even before the manifestation of clinical symptoms[6]. While the metastasis of glioblastoma to the spinal cord has been increasingly noted in recent years, there are only few well-documented cases in the literature[6] . With an intention to document this perhaps not so rare complication of glioblastoma, we present two cases of glioblastoma who presented with symptoms of headache and meningeal signs. One had a nodular type drop metastasis at S1/S2 level, and the second with diffuse leptomeningeal metastasis of glioblastoma. The value of early detection through magnetic resonance imaging with gadolinium enhancement allowed for an early diagnosis.

These two cases highlight the importance of regular follow-up contrast enhanced MRI scans of the brain and spine for early detection of a possible metastasis before it becomes clinically significant[7,8,9] for institution of appropriate treatment of the dissemination which can lead to improvement in prognosis as well as the quality of life. Current treatment guidelines followed at our institution are discussed. Both being infratentorial lesions is interesting and further highlights the indication of spine imaging in these circumstances.

Case Reports

Case I.

CASE -1 A 45-year-old man underwent a neuronavigation guided left suboccipital craniotomy and gross total excision of cerebellar tumour at another centre. Histopathological analysis of the tumour showed a cellular neoplasm arranged in sheets and composed of neoplastic astrocytes with moderate to markedly pleomorphic vesicular nuclei, few with nucleoli and scant cytoplasm against a fibrillary background. Occasional tumour giant cells were seen. Brisk mitosis and microvascular proliferation was noted (Fig-1). A diagnosis of Glioblastoma – (WHO Grade IV) was rendered. Although Immunohistochemistry was suggested for categorization, the patient refused further work up. Standard adjuvant radiotherapy (60 Gy/ 10 fractions) was given for 5 days per week over 6 weeks. Concurrent chemotherapy with Temozolamide at a dose of 100 mg/day, 7 days per week from the first to the last day of the radiotherapy, was also given. Following the chemo-radiation, patient was continued on Temozolamide for 6 months at the dose of 250 mg/day over the first 5 days of every 28-days cycle. He also received Nimotumab (200mg) injections every 15 days, over the same period. Repeated follow-up MRI brain scans revealed a stable residual left cerebellar lesion. 6 months after completion of the chemoradiation, the residual lesion measured 1.9 x 1.8x 1.3 cm. On completion of the 6^{th} cycle of Temozolamide and 12^{th} cycle of Nimotumab, there was temporary intentional interruption of treatment for 2 months before he received another 2 cycles of Temozolamide.

A year later following treatment, patient presented with seizures, worsening headache, neck stiffness associated with a new onset of low back pain. Metastasis to the S1/S2

region of the spinal canal was detected with a residual tumour at primary site, in a post-gadolinium MRI scan (Fig -2) which was confirmed by a PET-CT scan.

He was offered excision biopsy of the spinal lesion and follow up of the early hydrocephalus but he refused surgery. He was referred for Cyberknife with a radiation dose of 35 Gray/10 Fractions for 2 weeks (5 days per week) for both the residual lesion and the drop metastasis. Patient was continued on chemotherapy but succumbed after 5 months of detection of spinal drop metastasis .

CASE –II . A young 29-year-old man presented with severe episodic headaches associated with nausea and vomiting of one-month duration with neck stiffness and imbalance while walking of 15 days duration. CT scan brain showed a hypodense lesion in the brainstem with sparse patchy enhancement involving the left midbrain, left pons and the left middle cerebellar peduncle causing fourth ventricular pressure with obstructive hydrocephalus.MRI showed significant diffusion restriction and raised perfusion-suggesting a high-grade lesion (Fig-3). He underwent an Endoscopic third ventriculostomy followed by a frameless navigation guided biopsy of the brainstem lesion. Histopathology showed a glial neoplasm showing diffusely infiltrating astrocytic cells displaying round to oval nuclei showing hyperchromasia in a fibrillary background(Fig-4a). Occasional mitosis of 1–2/10 high power fields along with focal endothelial proliferation was evident(Fig-4b). Immunohistochemistry revealed the tumour to be negative for IDH1(R132H) with ATRX showing loss of expression. p53 failed to exhibit nuclear positivity and H3K27M was negative. Ki67 proliferation index was 5%. A diagnosis of Glioblastoma,IDH1(R132H) negative, H3K27M,WHO Grade IV was made. IDH gene sequencing was suggested. He was referred for chemoradiation following the tumour board discussion. He was initially started with focal conformal radiation by image guided intensity modulated radiotherapy with concurrent oral capsule Temozolomide (100 mg daily) as per the standard protocol. While undergoing the therapy when he had received 19.8 Gy/11 fractions he began to worsen neurologically becoming drowsy and developed axial neck and back pain. His neuraxis screening showed disseminated spinal and intracranial leptomeningeal spread of lesion (Fig-3). He then underwent a D7-D8 laminectomy and biopsy confirmed the leptomeningeal spread (Fig-4c&d). He was

advised intrathecal methotrexate as a salvage therapy along with radiation and chemotherapy.

Discussion

Glioblastoma is the most common malignant brain tumour in adults[2,5]. Glioblastoma, recurs locally and spreads along glial tracts (corpus callosum, optic radiation, anterior commissure ,fornix) or through the CSF dissemination[10,6].Earlier literature doubted and under reported metastasis of glioblastoma[6]. Rudolph Virchow characterised it in 1863 and in 1928 Davis described metastatic spread of glioblastoma using the older histological diagnosis of spongioblastoma multiforme[11]. In 1931, Cairns and Russell reported that glioblastoma can metastasize along the cerebrospinal fluid (CSF) pathways to the spinal cord[12] . Saito et al. have reported intracranial metastases to be commoner than spinal dissemination with an incidence of 25% and 8.8% respectively[13].

Clinical course of glioblastoma is fulminant with a dismal prognosis despite all advances in surgery, technology and adjuvant therapy[1,2,5,].The reported metastasis in incidence is 2 to 5%[1,2,14].This is probably only the tip of iceberg as life span after diagnosis is very short[1,15].Erlich et al reported that spinal leptomeningeal metastasis in glioblastoma was common at autopsy[15].The rate of detection will increase significantly as contrast MRI screening of neuraxis becomes routine and primary treatment continues to prolong disease free periods[1,7,9,15].The leptomeningeal spread of medulloblastomas, ependymomas, diffuse pontine gliomas, pilocytic astrocytomas, brain metastasis, and other systemic malignancies is well recognised[16,17,18,19,20,21].Choroid plexus carcinomas have a reported 45% leptomeningeal dissemination at diagnosis and are associated with a poor prognosis[22] . Rare lesions like solitary fibrous tumours and rhabdoid meningiomas have been reported to spread via CSF pathways[23,24].

Spinal metastases may be a very small undetected seeding or large one causing symptoms[4,25] . These are seldom detected clinically when glioblastoma is seemingly under control[6]. The average age of patients developing clinically significant

metastasis is 41.2 years, our first case was 45 years old and the second was 29. In a study involving 267 glioblastoma patients, Stark et al. found that only 1.1% developed spinal drop metastases 5, 8 and 11 months following craniotomy[26] . The lag between diagnosis of the primary lesion to symptomatic spread ranges from 1 month to 2 years[27]. In our first patient, the delay between initial diagnosis and early symptomatic manifestation of the metastatic lesions was 12 months.

Three basic types of dissemination are seen 1)Diffuse leptomeningeal spread 2)Plaque like deposits due to the invasion of the Virchow -Robin spaces 3)Nodular formation. Bordignon et al proposed a classification system (**Table -1**) of malignant glioma dissemination based on pathophysiological mechanisms and MRI patterns of spread[27].In this report both cases were leptomeningeal Type 1.Case I was type -1a (nodular) and Case II was Type1b (diffuse).

CLINICOPATHOLOGICAL CORRELATES

Multiple factors predispose to metastasis of glioblastoma . Direct cellular extension, lymphatic, haematogenous and CSF dissemination are possible[6]Indirect factor like immunosuppression due to chemoradiation are involved[23,28,29].Drop metastasis may develop during surgery or at the time of recurrence[6]. Direct CSF extension is by invasion of the basement membrane and the choroid plexus[10]. The spread to the third, lateral and fourth ventricles by opening into the ventricular system while resection can cause CSF dissemination[27]. Ependymal fissuring secondary to hydrocephalus, tumour fragmentation within the CSF spaces and ependymal invasion are other risk factors for CSF dissemination[12].Posterior fossa lesions have a very high incidence of leptomeningeal spread when compared to supratentorial glioblastoma 60% vs 15 to 20% [4,15,21]. This was also reported by Salazar and Rubin who described incidence of hemispheric glioblastoma and posterior fossa tumours metastases as 6% and 60% respectively[30].Both our cases being infratentorial (Case-I Cerebellar and Case -II Brainstem) is interesting and hence spine imaging could be more indicated in these locations. A study of supratentorial gliomas in children by Grabb et al., showed statistically increased incidence of CSF dissemination with

ventricular entry, multiple resections and male sex[31] . A ventriculoperitoneal shunt can cause peritoneal spread.

Genetic signature analysis of glioblastoma has been proposed for stratification into different subgroups with prognostic and survival variation[32].Glioblastoma with primitive neuronal components has a high dissemination rate of up to 40%[33,34].Perry et al reported that the primitive component of MG-PNET is emergent within a secondary glioblastoma which has metaplasia of tumour stem cell/progenitor cell clone. Anaplasia is represented by N-myc ,C-myc amplification. These tumours have a higher tendency to seed CSF[34]. Leptomeningeal spreading tendency of glioblastoma may have other markers too. Onda et al proposed that glioblastomas which were immunohistochemically poorly differentiated and GFAP negative spread by CSF dissemination and the GFAP positive ones spread locally[3].According to Arita et al the biological characteristics suitable for leptomeningeal spread seen in 14% of tumours was acquired and the disseminated lesions on immunohistochemistry expressed less GFAP[4].Katsuoshi et al[23]postulated that an increase of MIB-1labelling index from 1% - 13%led to CSF dissemination in their patient with a fibrous tumor. Buhl et al hypothesized extensive tumour cell perivascular cuffing in two patients with multifocal glioblastoma with spinal drop metastasis to be the cause of widespread dissemination[35].Hsu et al reported an intramedullary T11-L1 metastasis from a supratentorial glioblastoma which had progressed to a gliosarcoma. Gliosarcomas are known to metastasize but the seeding in that case occurred prior to transformation[36].

The CSF dissemination of the glioblastoma can occur to all regions of the spine, spinal cord, nerve roots and leptomeninges[37,38,39,40].The commonest sites of spinal metastasis are at the lower thoracic, upper lumbar and lumbosacral regions including cauda equina and thecal sac due to the gravity[41,42]. Systemic metastasis outside the central nervous system may occur to the scalp, orbit, paranasal sinus, cervical lymph nodes, vertebral body, liver, spleen and peritoneum. The spinal cord is an uncommon site of metastasis[25].

The clinical diagnosis is possible with awareness of possibility of metastases, careful neurological examination and a postcontrast neuraxis screening[6,7,9,25,28].There are two different patterns of clinical presentation: (a) Early (metastasis at

diagnosis)[43,44,45] and (b) Late (Initial local Glioblastoma with subsequent metastasis)[25] . Our first case presented after an year and the second case had early metastasis. General signs of leptomeningeal spread are headaches, nausea, vomiting, diplopia, cerebellar dysfunction, back pain and leg weakness[7].The lack of early signs of spinal metastasis as seen in both our cases is attributed to the infiltration rather than destruction of nerve roots by tumour cells [40]. Clinically axial back pain, neck pain and interscapular pain with radiculopathy, myelopathy are seen. Progressive paraparesis or quadriparesis, bowel, bladder and sexual dysfunction can occur[39,42,46,47]. Presentation may be acute or progressive[47,42] . Acute onset of weakness may occur due to vertebral collapse after a metastatic spread[46] . Metastasis could be intramedullary or extramedullary, although intramedullary metastasis is less common[39]. Symptomatic metastases are usually detected after a lag following the treatment rather than at the diagnosis of the primary, with the median occurrence being 14.1 months[25,40].

Patients may have specific symptoms of primary lesion eg. diagnostic dyspraxia due to posterior corpus callosal glioblastoma with splenial involvement and multiple nerve root involvement due to leptomeningeal spread[43] . The other presentations have been, radicular pain[42], acute tetraplegia, cardiac arrest[47], SAH[38], high lumbar disc herniation like symptoms[41], vertebral collapse with quadriparesis[46],intramedullary deposits[39], epidural[37] and extracranial metastasis [48,49].

Vertosick in a clinical review of 11 patients reported metastasis was more common in younger age group and in patients with extended survival[40]. Paediatric cases have a more aggressive course[44,50,51].Kanai et al reported fulminant progression of clinical and radiological primary and spinal metastasis with the latter having a more rapid growth in a 4 year old girl[44] .

In a meta-analyses of 35 reported cases, Shahideh et al found 10 months median time from primary lesion and 3 months from spinal metastasis to death[52].Patients who had only a biopsy, had a shorter time to develop spinal metastasis like seen in our second case. The time interval of 14.1 months was seen between initial diagnosis and discovery of metastatic spread. Overall survival was for only 2.8 months[40].

Lumbar puncture and subsequent CSF cytology is not very sensitive in detecting spinal dissemination. False negative is seen in 14% of patients even after 3 consecutive samples[7]. A high specificity of (> 95%) has been reported but with less than 50% sensitivity[53]. CSF flow cytometry and testing for matrix metalloproteinases, cathepsins, chemokines CXCL8 ,CCLI8 and VEGF levels may have a role[53].(CT) myelography used commonly in pre MRI era may be required rarely in cases where MRI cannot be done . CT may show nonspecific cord thickening in the cervical and thoracic region and nodularity of nerve roots and thecal sac at the lumbar region[40,54].Spinal screening MRI with contrast enhancement has replaced the CT myelography. Initial reports established the role of the MRI in the detection of metastatic seeding[9,55].In a large cohort of patients with leptomeningeal spread of malignancy MRI has demonstrated more sensitivity than the gold standard CSF cytology[7].Currently, based upon our experience for all glioblastoma at the posterior fossa and those at the supratentorial region with ependymal spread, gadolinium contrast enhanced fat saturated T1 weighted sagittal (either thin 2D or 3D) spine imaging is recommended. Pre contrast fat saturated sagittal T1 weighted sequences and sagittal fat saturated T2-weighted sequences, with axial contrast images at regions of interest, can be added to the protocol.Recommendations have not been validated but post contrast sagittal Volumetric 3D T1 imaging with isotropic 1 mm voxels, which will permit reformatting in all three 3 planes, is probably the best sequence to identify leptomeningeal metastasis[7,56].Sagittal T1 post-contrast MRI screening was the imaging modality that managed to identify the metastatic lesions in our patients. Diffuse leptomeningeal enhancement can rarely be caused by venous stasis secondary to hydrocephalus and infectious causes[57].MRI findings may be detected in only 50%(70-80%) of patients with neoplastic meningitis. Serial follow up MRI every 3-6 months and other modalities of investigation may be required[53].Gururangan et al in a series of diffuse pontine gliomas demonstrated the use of MR spectroscopy and FDG-PET in evaluation of neuraxis metastasis[18].Chamberlain et al proposed a three element consensus for response assessment in neurooncology RANO workup group which includes a standardised neurological examination,CSF cytology, flow cytometry and radiographic evaluation.MR spectroscopy, MR perfusion and PET use is undefined[58]. In current practice, leptomeningeal spread is often made without CSF analysis, using MRI contrast imaging and is reported to have a sensitivity and

specificity of approximately 75%, while CSF analyses at first instance have sensitivity of only 55%.

Both our cases were diagnosed by MRI post contrast neuraxis screening and were offered surgery for histological confirmation. Case I was asymptomatic of his nodular leptomeningeal spread and PET showed both the recurrence and spinal deposit. He opted for direct cyberknife treatment. Case-II underwent a laminectomy and biopsy confirmation of the leptomeningeal spread.

The possibility of neuraxis dissemination and its prevention and treatment is well established in CNS tumours like medulloblastomas, ependymomas, pilocytic astrocytomas, brain metastasis and diffuse pontine gliomas[16,17,18,19,20,21].Glioblastoma treatment is currently after the guidelines by Stupp et al and includes maximal safe surgical excision followed by radiotherapy and adjuvant chemotherapy[5]. Treatment options for glioblastoma metastasis are undefined and palliative [25,45,52,59,60,61,62]. Surgery ,chemotherapy, radiation and combination therapies are used in tackling neuraxis metastasis[16,25] .Surgical decompression may be used for large metastatic deposits, progressive myelopathy, radiculopathy and also for cytoreduction and biopsy[39,51,52].Pathological spine fracture causing instability myelopathy or radiculopathy will require instrumented fusion, local radiotherapy and adjuvant therapy[46].Due to the diffuse nature of the metastasis, surgery other than for histopathological confirmation may not always be indicated[61]. Hamilton et al in a intramedullary thoracic metastasis could document leptomeningeal spread by staining the arachnoid biopsied for GFAP[39].For those not amenable to surgery, radiotherapy (with a total dose of 25 to 40 Gy), intravenous/ intrathecal chemotherapy, corticosteroids and pain medication have been used. Intravenous or intrathecal chemotherapy is less common. Atalakis et al.,indicate that preventive CSF dissemination protocols should be adopted in glioblastoma initial management. They have suggested stereotactic biopsy with cranial irradiation and delayed resection as well as the use of intrathecal radiolabelled monoclonal antibody as appropriate options[42] . Radiotherapy of the craniospinal axis has also been proposed[15]. External beam radiotherapy (EBRT) is the commonest choice of modality for palliation. This helps relieve pain but does not improve any neurological deficits. Once there is a leptomeningeal spread including spinal deposits, the intent is palliative and hence a

few fractions of high-precision radiation such as delivered by cyber knife is a reasonable one. Most of the guidelines are flexible in this regard and leave the final decision at the discretion of the treating physician. Imaging with clear cut evidence of a spinal deposit even without any definite histological confirmation is also well accepted. Our first patient was given Cyberknife treatment. A study by Lipani et al., found that Cyberknife stereotactic radiosurgery and hypofractionated radiotherapy compared favourably to historic data using focal External beam radiation therapy , although they cautioned that larger scaled analysis were needed to prove the effectiveness[63] . Proton beam therapy confers even more precision and fall off the doses rapidly with significant preservation of normal tissues. Charged ions can tailor precise tumour targeting without spill over and this can be combined with temozolomide and Bevacizumab[64]. However in a palliative situation, it is probably not indicated and employed in view of the resources involved (both complex planning/delivery as well as logistics). It may be considered though in a re-irradiation setting or if we have to deliver craniospinal irradiation (CSI), where it is unequivocally superior dosimetrically to any conventional photon technique. Proton of-course is the treatment of choice in any CSI such as in medulloblastomas, germ cell tumours or sometimes in ependymomas. Temozolomide an oral second generation alkylating agent is well tolerated and has been proved to increase progression free survival rates in patients with glioblastoma[5,65] .Nandipati et al[66] demonstrated sustained radiological and clinical improvement by temozolamide in leptomeningeal metastasis of glioblastoma . Bevacizumab, is a humanised monoclonal antibody that inhibits VEGF and reduces the CSF VEGF levels. The drug is reported to act by normalising tumour vascularisation and also improving the penetration of temozolamide into CSF. It has been used with advantage with temozolamide in leptomeningeal metastasis of glioblastoma[67,68].Fiorentino et al., did not show any durable improvement on adding bevacizumab for intramedullary and leptomeningeal metastatic glioblastoma[69].

Currently, patients who receive treatment are those presented with clinically significant signs and symptoms and radiological evidence. In our patients, we managed to identify the lesion before significant symptoms appeared. This then raises the question of whether a routine contrast MRI screening should be carried out for spinal metastasis and whether subsequent early management would be beneficial.

While early treatment may prevent progression of disease, in literature there is lack of evidence on potential benefit weighted against the potential morbidity of the treatment[7]. Probably in some variants of glioblastoma with an increased proclivity to metastasize along CSF pathways aggressive management strategies including platinum based chemotherapy may be tried[34].Unfortunately, the prognosis for spinal glioblastoma metastasis is dismal and the outcome is fatal[5,16,60,61]. Survival from diagnosis to death ranges from 2 to 20 months(mean of 2 to 3 months) only[43]. Younger patients with spinal metastasis of glioblastoma have been reported to have marginally better outcomes[46]. Liu et al. found that younger age, coexistence of primary tumor, early metastasis, glioma leptomeningeal seeding and the nodal sub-type on MRI were poor prognostic factors[16]. Biswas et al reported a dismal prognosis in a 7 year old child with giant cell Glioblastoma with spinal and leptomeningeal metastasis[70].The increasing frequency of diagnosis is attributable to better and more sensitive imaging (3T MRI). Larger numbers of Glioblastoma survivors today are due to the surgical and technological advances like5-ALA, fluorescein guided resections, awake-craniotomy, neurophysiological monitoring, intraoperative MRI, per-operative ultrasound and better adjuvant therapy. It is reasonable to believe that with increasing survival rates of the glioblastoma patients, late-onset metastasis will be diagnosed with greater frequency[2,59].

Conclusion

These two case reports are being published to increase our clinical suspicion and therapeutic effectiveness by an early detection and treatment, thereby improving patient outcomes in this dismal disease. Spinal metastasis, a possible delayed complication of glioblastoma is on the increase due to continued advancements in treatment of primary intracranial lesions, better survival rates, knowledge of this entity, early and precise diagnosis[7,15,59].There is a significant unmet need for the evaluation, treatment and improving the dismal response of leptomeningeal metastasis[58].Prevention as well as treatment of spinal metastasis of intracranial glioblastoma requires heightened clinical and radiological scrutiny[15].In every patient

with a history of intracranial glioblastoma presenting with signs and symptoms that are not explained by the primary lesion, spinal and dural metastasis should always be suspected. This may mandate a CSF evaluation, MRI contrast screening of neuraxis and dural or lesion biopsy and resection as required. A regular protocol of imaging with post-contrast MRI both before and after initial surgery, should be undertaken to identify spinal metastasis even before they become clinically apparent. Earlier diagnosis of dissemination picked up by periodic post-operative contrast MRIs at regular intervals can lead to improvements in prognosis as well as quality of life in patients[15,56,66,69,68,71].

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Table .1

Instituto de Neurologia de Curitiba Classification.

TYPE -1 LEPTOMENINGEAL

Type -1a Nodular

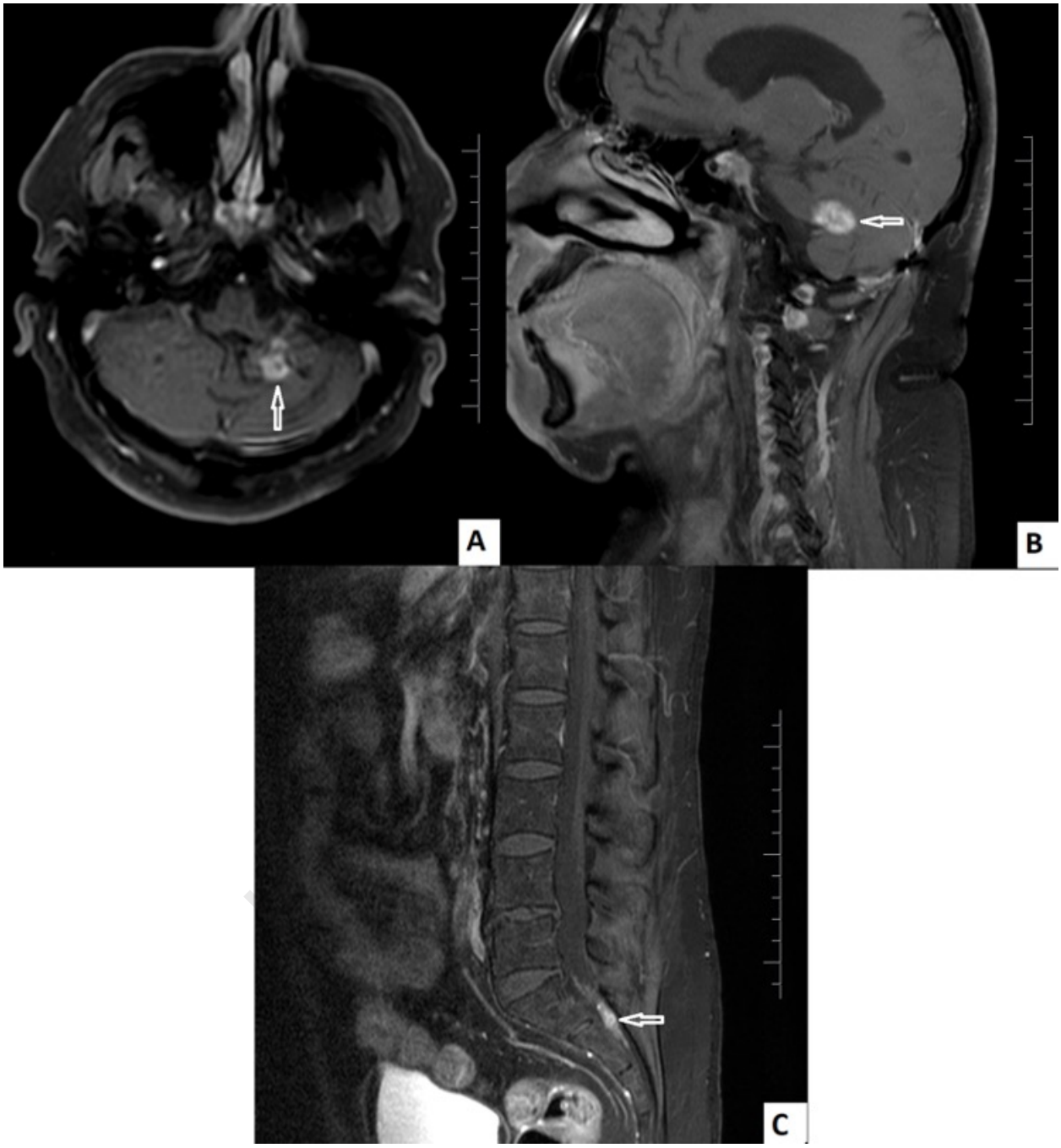
Type -1b. Diffuse

TYPE-11 SUBEPENDYMAL

TYPE-111 SATELLITE

TYPE -1V MIXED (Combination of two or more types)

Bordignon KC, Neto MC, Ramina R, de Meneses MS, Zazula AD, de Almeida LG. Patterns of neuraxis dissemination of gliomas: suggestion of a classification based on magnetic resonance imaging findings. Surg Neurol. 2006; 65(5):472-477.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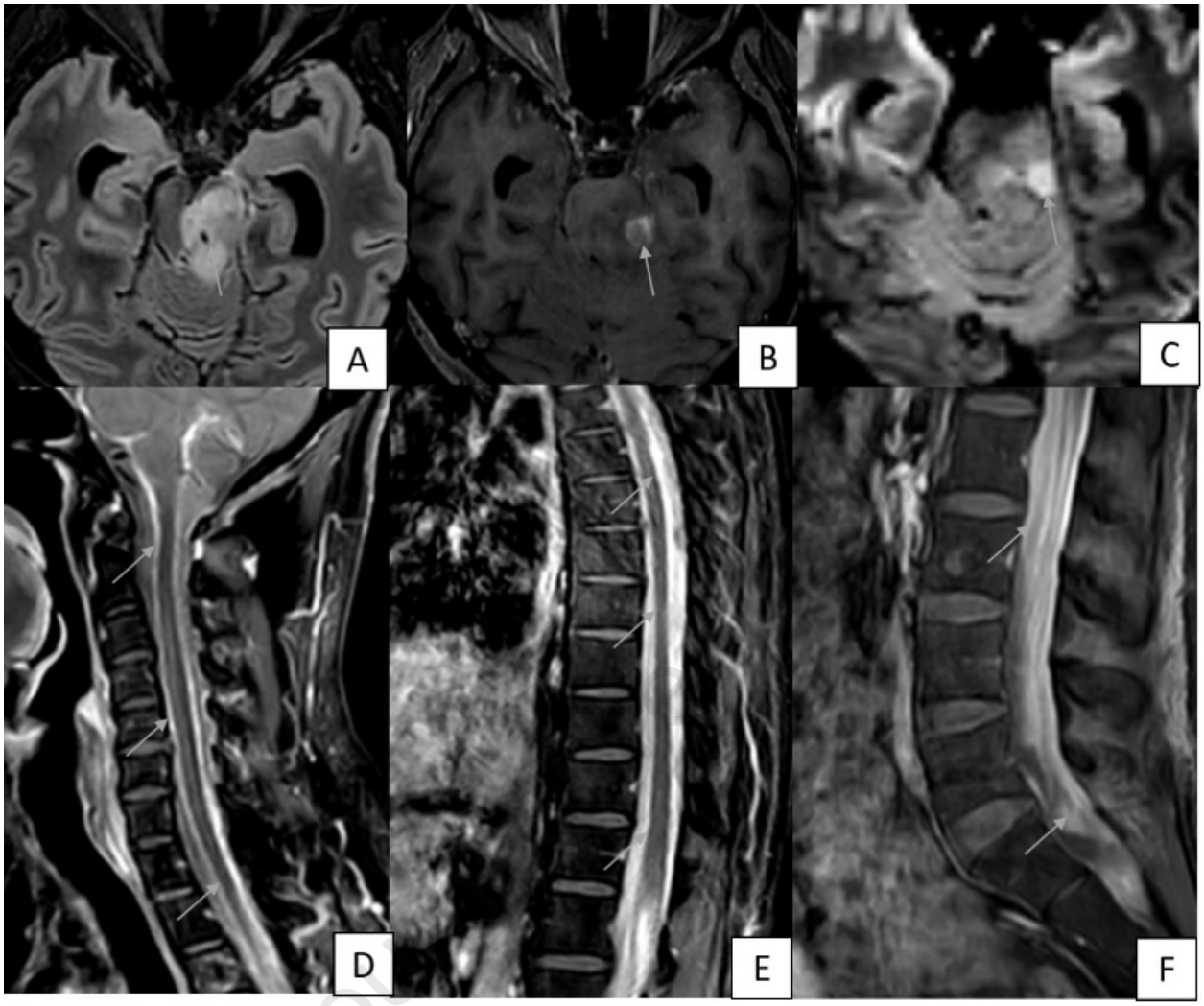
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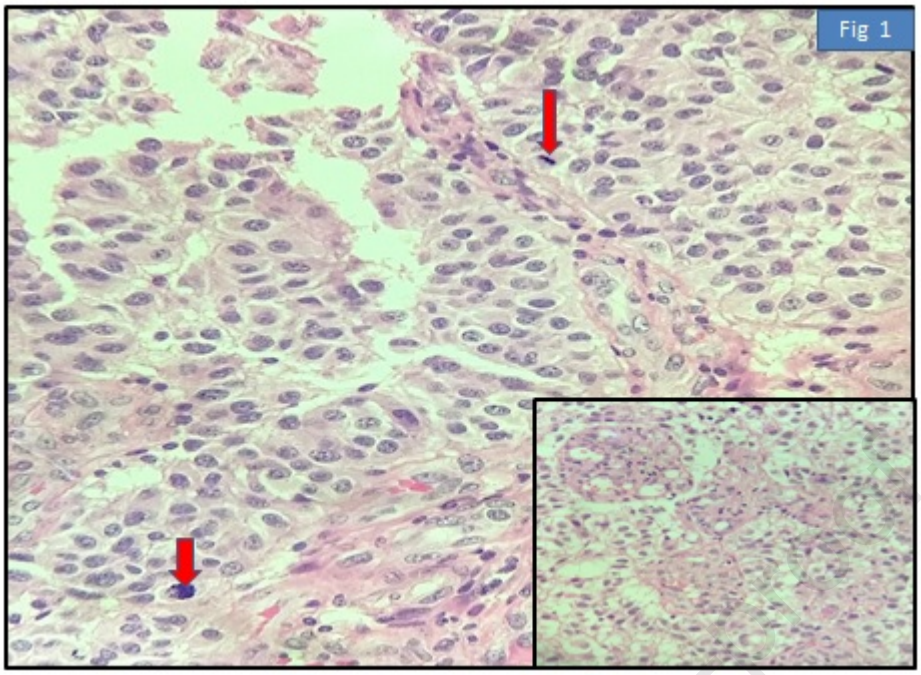

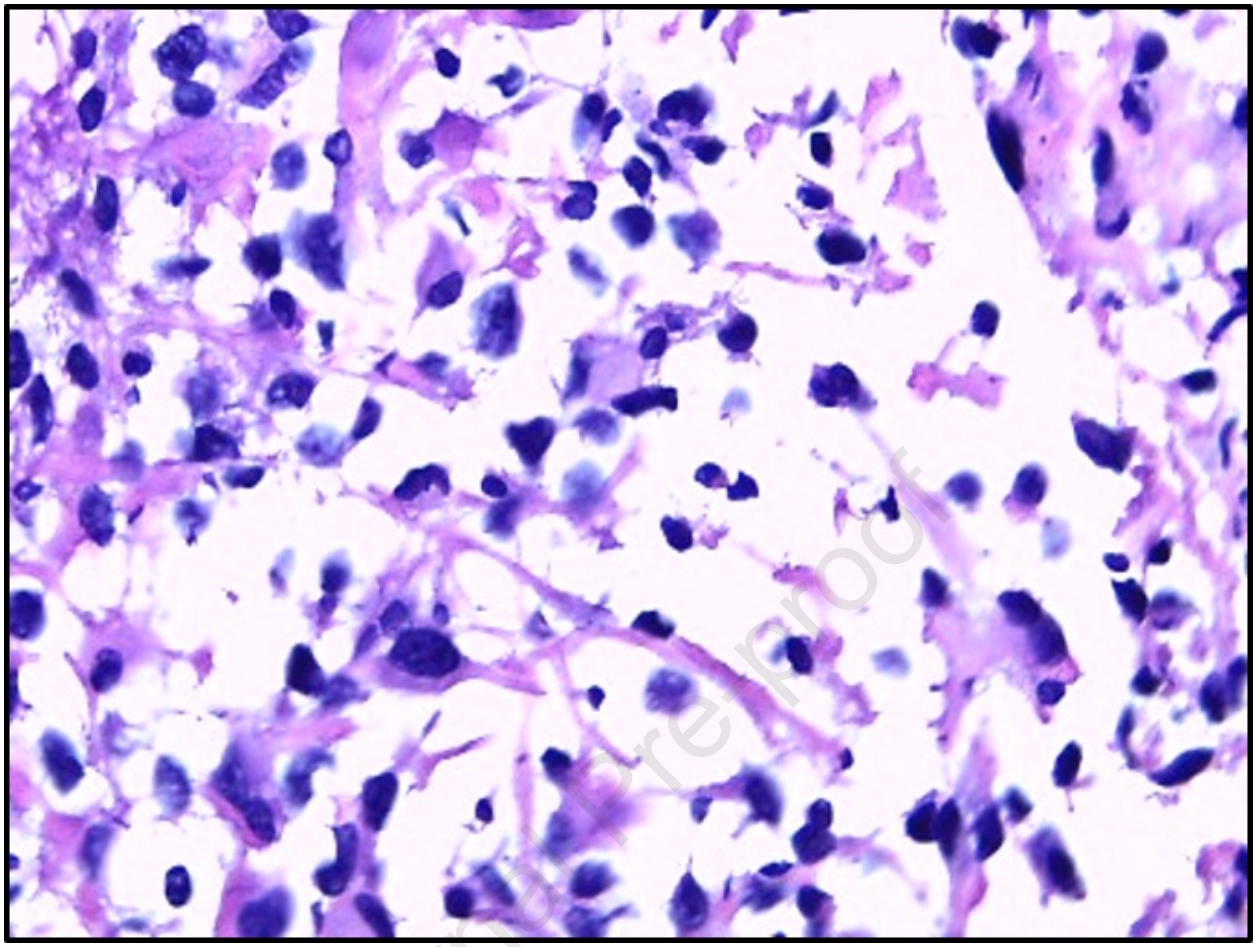

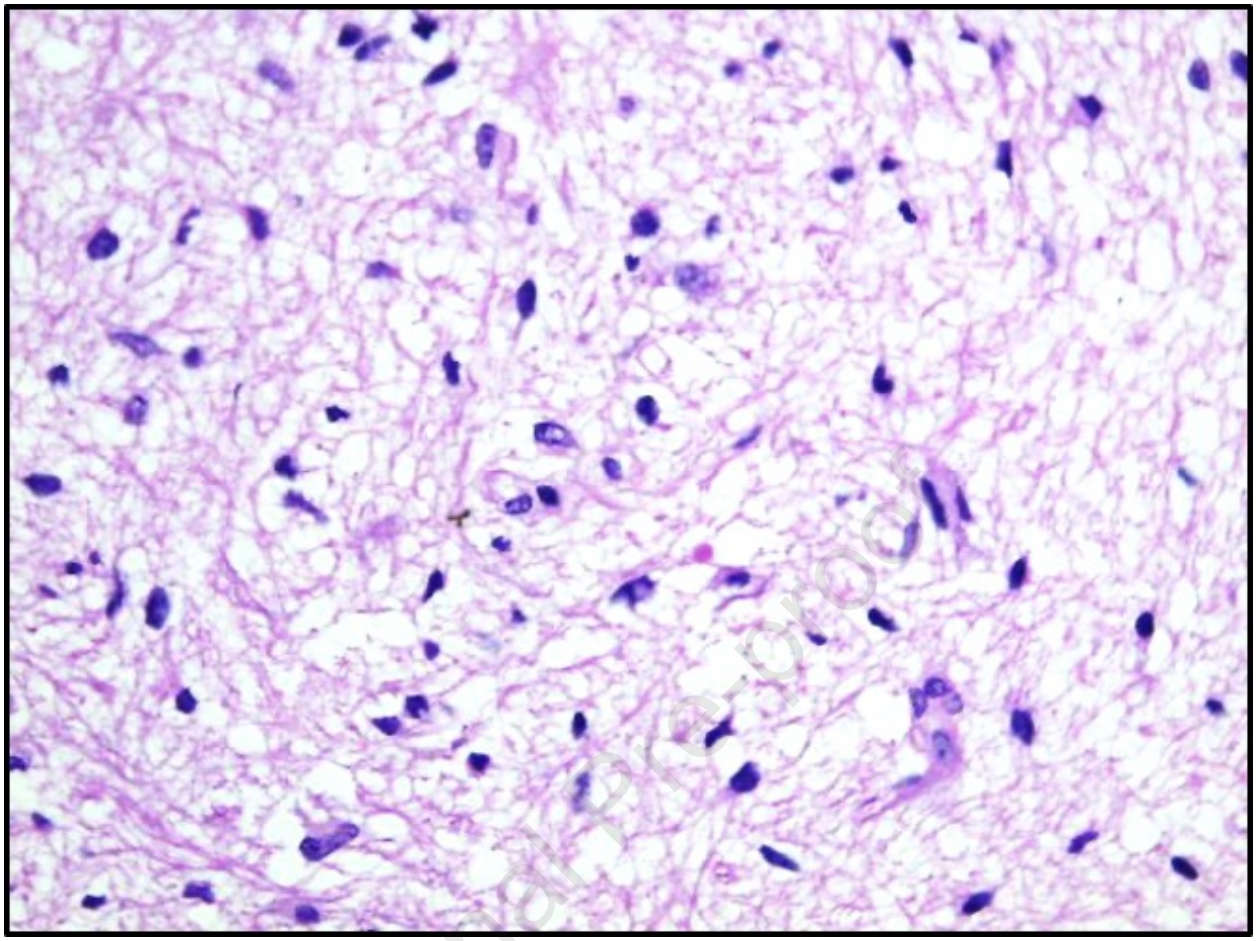

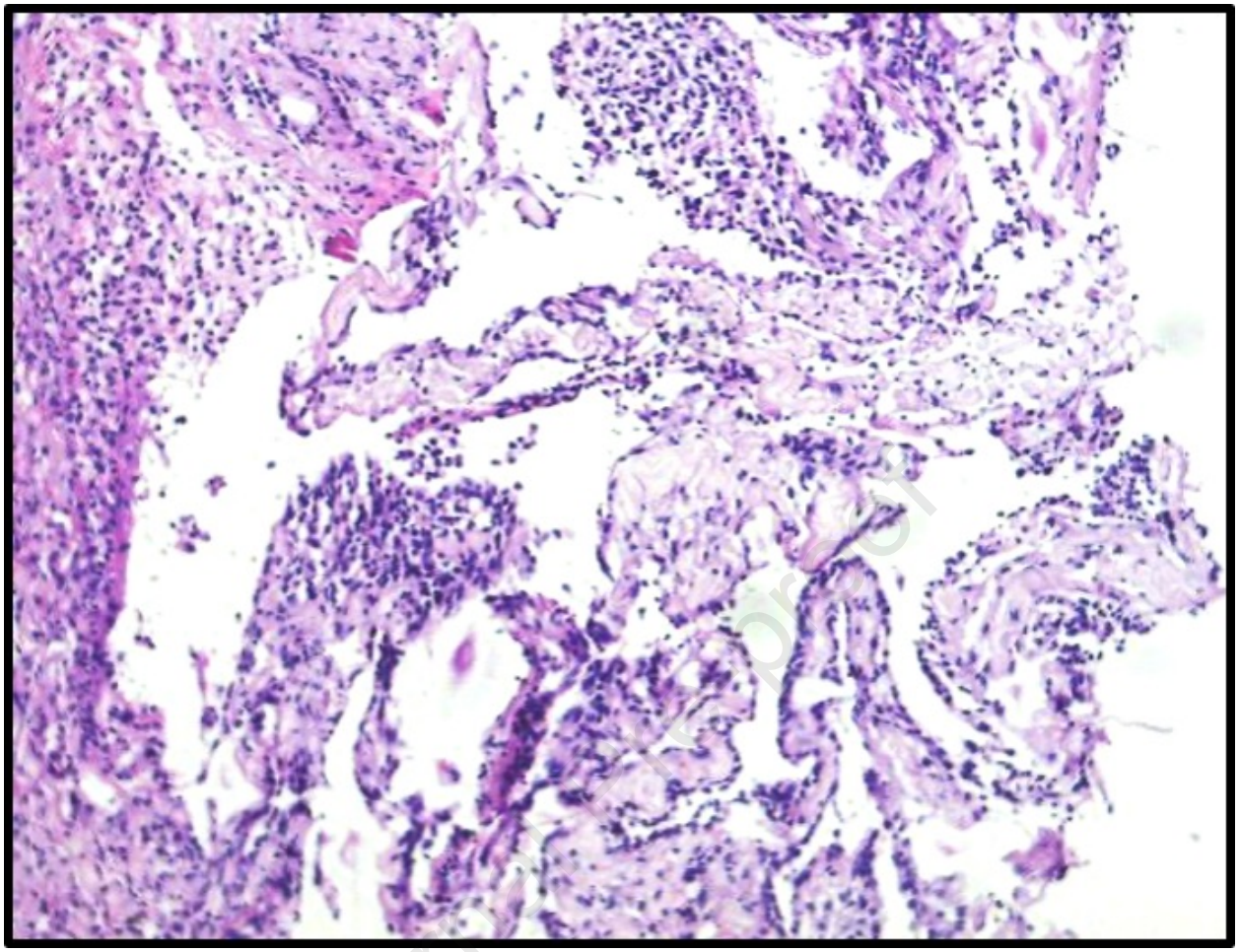

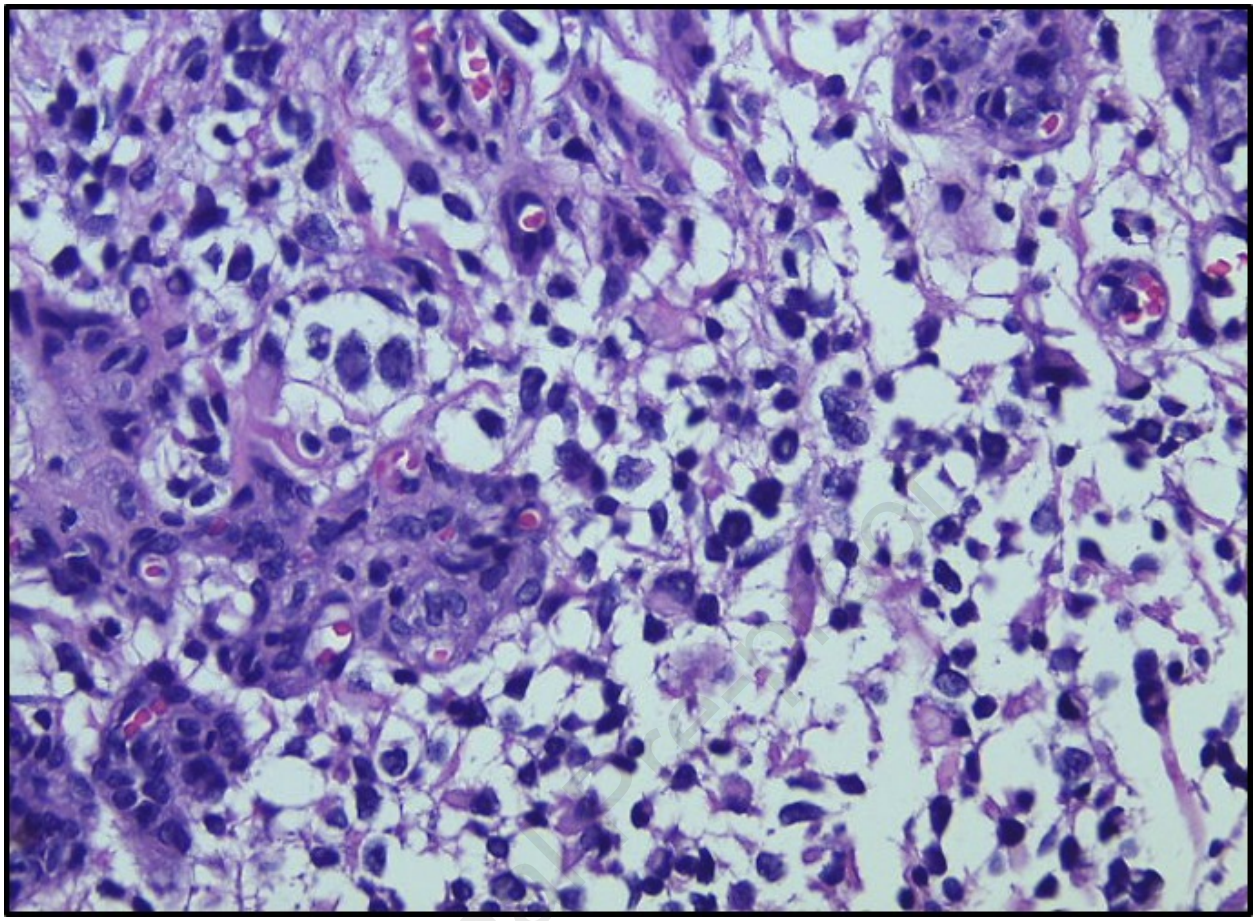

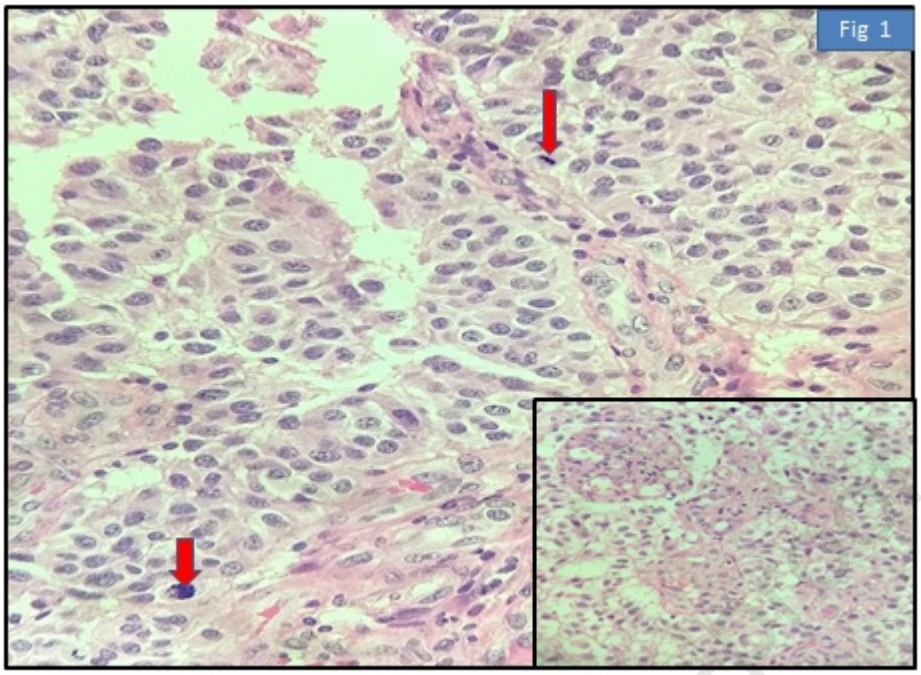

LEGENDS

FIG-1.(CASE-1) Microphotograph showing a cellular glial neoplasm arranged in sheets and showing neoplastic astrocytes with moderately pleomorphic vesicular nuclei, prominent nucleoli arranged in sheets in a fibrillary background. Foci of mitosis (depicted by an arrow) and endothelial proliferation is noted (inset) [H&E 40x]

FIG-2.(CASE-1) Post contrast T1 fat suppressed sequence of brain shows a nodular enhancing lesion in left cerebellum, consistent with residual tumor (A and B, arrows). Post contrast T1 fat suppressed image of lumbo-sacral spine shows enhancing nodular lesion in sacral spinal canal at S1/2 level (C, arrow), suggesting drop metastasis.

FIG-3.(CASE-2)

In MRI brain of this patient, a diffuse T2 FLAIR hyper intense lesion was seen at the mid brain, extending to pons and thalamus, with aqueduct narrowing and obstructive hydrocephalus. T2 FLAIR hypo intense biopsy site was seen (A, arrow). An area of contrast enhancement (B, arrow) and restricted diffusion (C, arrow) seen at the lateral aspect of the lesion. On post contrast spine screening, diffuse leptomeningeal contrast enhancement (D-cervical, E-dorsal, F- lumbosacral regions) seen suggesting drop metastasis.

FIG-4 (HISTOPATHOLOGY)

a : Microphotograph of the brain stem lesion showing a high grade glial neoplasm of astrocytic lineage with increased cellularity and showing marked anisonucleosis with hyperchromasia in a fibrillary background (H&E 40x)

b: Photomicrograph of the brain stem lesion showing atypical mitosis (depicted by an arrow) and inset showing endothelial proliferation (H&E 20X)

c: Microphotograph of the dural biopsy showing leptomeninges with infiltration by tumor (H&E 10X)

d: Photomicrograph of the dural biopsy with a high grade hypercellular astrocytic neoplasm with endothelial proliferation (H&E 20X)

ABBREVIATION LIST

MRI : Magnetic Resonance Imaging

3T : 3 Tesla

CT : Computerized Tomography

LM : Leptomeningeal

WHO : World Health Organization

PET - CT : Positron Emission Tomography and Computerized Tomography

Gy : Gray

ETV : Endoscopic Third Ventriculostomy

IHC : Immunohistochemistry

IDH : Isocitrate Dehydrogenase

ATRX : Alpha Thalassemia Retardation X

GFAP : Glial Fibrillary Acidic Protein

PNET : Primitive Neuroectodermal tumor

SAH : Subrachnoid haemorrhage

VGEF : Vascular endothelial growth factor.

CSF : Cerebrospinal fluid

DISCLOSURE – CONFLICT OF INTEREST

We the authors of the manuscript titled titled “Spinal drop metastasis of Glioblastoma - Two Case Reports, Clinicopathological features, Current Modalities of Evaluation and Treatment with a Review of literature ”which is being submitted to World Journal of Neurosurgery as a case report do hereby state that there is no Declaration/Disclosure of Conflict of interest

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