Original Article

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Spinal metastases of Intracranial Glioblastoma – Can Immunohistochemical Features Explain the Mechanism of Spread?

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Abstract

We report the case of a 34 year old male patient with acute onset and rapidly progressive paraplegia caused by leptomeningeal metastases of an intracranial Glioblastoma Multiforme (GBM), as an illustrative example to enumerate the clinical features and explain the mechanism of spread on the basis of the immunohistochemistry (IHC) of both the primary and secondary tumours. The biopsies of the primary intracranial and the secondary spinal leptomeningeal lesions were subjected to IHC analysis for Glial Fibrillary Acidic Protein (GFAP). Also, 98 additional cases of intracranial GBM with symptomatic leptomeningeal and intramedullary spinal metastases, obtained by review of the literature, are presented here. Mean interval between the identification of spinal metastases and death was 4.5 months. Location of the symptomatic spinal metastases was more frequently leptomeningeal than intramedullary. The case presented in this case report showed high and prominent GFAP expression in both the primary intracranial and secondary leptomeningeal lesions. This runs contrary to the hypothesis proposed by Onda et al and supported by Arita et al. This finding is important as further prospective studies are needed before the pathomechanisms of spinal seeding can be explained on the basis of the tumour's IHC characteristics alone.

Keywords: Glioblastoma Multiforme; Spinal Metastases; Leptomeningeal Spread; GFAP Expression.

General Considerations

Glioblastoma multiforme (GBM) is the most common primary malignant intracranial tumour in adults. It commonly occurs in the supratentorial brain, with infratentorial location of primary GBM being very rare [21]. Spinal location of primary GBM is even more rare [12].

Spinal metastases, both leptomeningeal and intramedullary, occur in one out of five GBM patients, as revealed by autopsy studies [11,8,10,18,2,3]. Spinal metastases are also diagnosed by staging exams preceding radiotherapy. Survival of patients with symptomatic spinal metastases is short, despite available chemotherapy and radiotherapy of the neuraxis. But early identification and treatment of spinal metastases might improve the quality of life during the period of survival [17].

Assessment of risk of spinal metastases in an intracranial GBM is still very unclear. CSF cytology has very low sensitivity [1]. But assessing the degree of astrocytic cell differentiation in GBM through the GFAP expression in the intracranial tumour has been suggested as a dependable means of predicting dissemination via cerebrospinal fluid (CSF) [2].

The case reported in this article is that of a 34 year old male with acute onset and rapid progression of paraplegia caused by leptomeningeal seeding of a primary intracranial GBM. Analysis of literature relating to GFAP expression in the primary as well as the metastatic lesions has given the general idea that leptomeningeal spread occurs in tumours showing low GFAP expression in both the primary and metastatic leptomeningeal lesions, while local recurrence and intramedullary metastasis occur in tumours showing prominent GFAP expression in the primary as well as secondary lesions (local recurrence and intramedullary metastases). But the case reported in this article showed prominent GFAP expression in both the primary intracranial and secondary leptomeningeal lesions, contradicting the general postulations.

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Material and Methods

Literature search and review were done on www.pubmed.org. The search words were "Glioblastoma spinal metastases". The search generated 98 reports. All reports of adult patients older than 16 years, with intracranial GBM with metastases to the spinal cord (leptomeningeal and intramedullary), were included in the review. Other reports were excluded. Primary spinal gliomas were not included.

Histological diagnosis of GBM was made on the basis of hypercellularity, nuclear pleomorphism, high mitotic activity, prominent neovascularisation and necrosis. Tissue samples of both the intracranial and spinal lesions in our case were subjected to immunohistochemical analysis with special reference to GFAP expression in terms of high or low expression.

GFAP expression is a reflection of the degree of astrocytic differentiation with high expression signifying good astrocytic differentiation, and low expression signifying poor astrocytic differentiation.

Analysis of Data

The literature search revealed 27 cases that met our criteria. Mean age at the time of initial diagnosis of the intracranial GBM was 45.1 years. The salient features of the analysis are given in Table 1.

The common complaints were neck and back pain, weakness of limbs and sphincteric dysfunction occurring, respectively, in 17, 16 and 10 instances.

20 cases received spinal irradiation after the diagnosis of spinal metastases, 4 cases underwent decompressive laminectomy alone and 3 cases underwent tumour resection. Five cases were untreated.

Illustrative Case Report

We present a 34 year old male patient who presented with head ache and vomiting caused by a right parieto occipital space occupying lesion. Magnetic Resonance Imaging (MRI) of the brain (Figure 1) revealed a irregular rim enhancing hypo to

Table 1: Salient features of analysis of data

Age at diagnosis	45.1 years
Male: female ratio	2:1
Mean interval between primary intracranial and secondary spinal lesions	13 months
Mean survival from initial diagnosis of Intracranial GBM	18.1 months
Average survival after diagnosis of spinal metastases	4.9 months
Location of spinal metastases	Leptomeningeal: 63.1%, Intramedullary: 36.9%

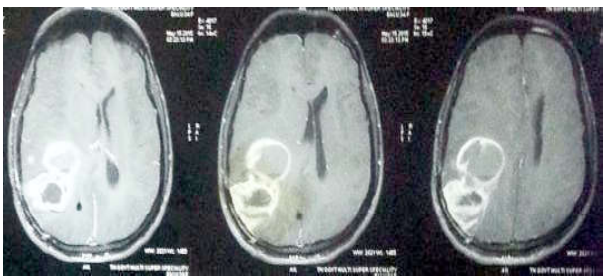

Fig. 1: MRI (T1 weighted with contrast) of Brain showing the primary Intracranial GBM

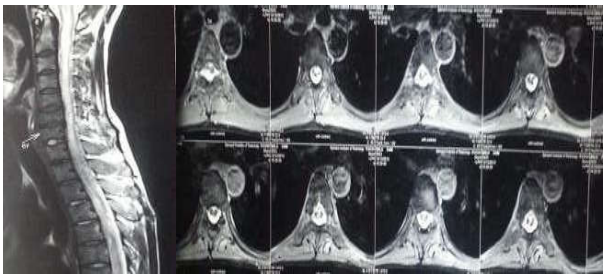

Fig. 3 & 4: MRI (with contrast) of spine showing diffuse leptomeningeal seeding and syringomyelia.

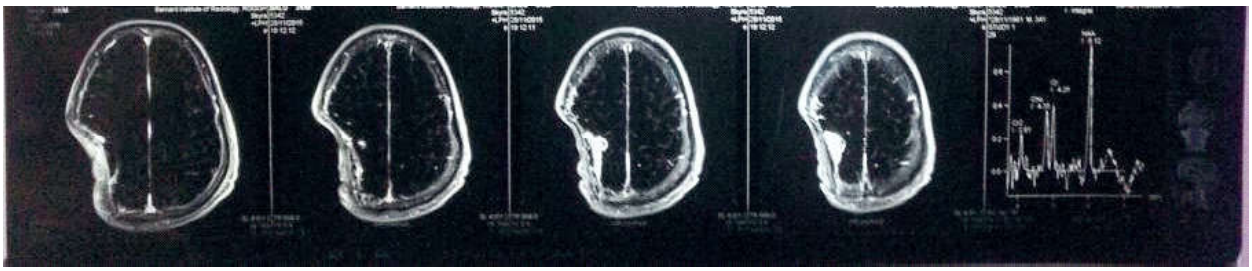

Fig. 2: Magnetic Resonance Spectroscopy of Brain at the time of presentation with spinal leptomeningeal metastases showing no local recurrence with only a NAA peak seen

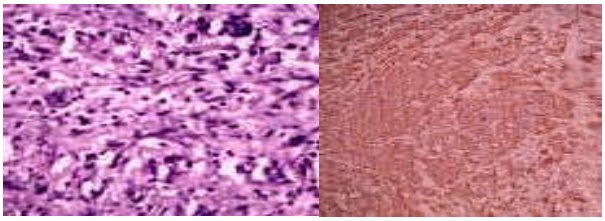

Fig. 5 & 6: Microphotograph of the HPE (figure 5) & IHC (figure 6) for GFAP of the primary intracranial lesion showing intense positivity (redness).

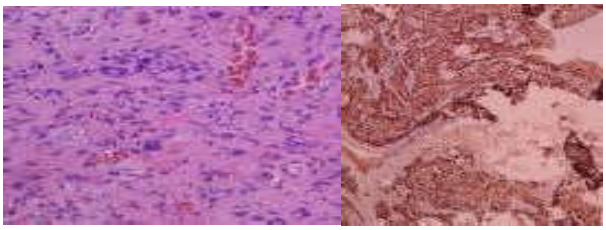

Fig. 7 & 8: Microphotograph of the HPE (Figure 7) and IHC for GFAP (figure 8) of the leptomeningeal deposits showing intense positivity

isointense lesion which was resected gross totally. He was apparently relieved of his symptoms. The resected tissue turned out to be a GBM (Figure 5) for which he received radiotherapy (60Gy), five days a week for six weeks and concurrent oral temozolamide (100mg/m^2) on all days of radiotherapy. This was followed by adjuvant chemotherapy with oral temozolamide (250mg/m^2) for five days every four weeks for six cycles. Six months after the operation, when he was receiving the fifth cycle of adjuvant chemotherapy, the patient developed acute onset of quadriparesis and urinary retention which progressed to paraplegia in one day. MRI and MR Spectroscopy of the brain showed no local recurrence (Figure 2). MRI of the spine showed extensive leptomeningeal deposits from the cervicomedullary junction to the lumbar region and a syringomyelia from C2 to C7 (Figures 3 & 4). Extensive cervicodorsal decompressive laminectomy and excision of leptomeningeal deposits was done. Histopathological examination of the leptomeningeal deposits revealed them to be GBM (WHO Grade IV) (Figure 7). Tissue samples from both the intracranial primary and the spinal secondary leptomeningeal lesions showed intense and high GFAP expression of 80% (Figures 6 & 8). The patient was then referred for radiotherapy of the spine. The patient expired 3 months after the diagnosis of the spinal leptomeningeal metastases.

Discussion

Autopsy studies show the incidence of spinal metastases of intracranial GBM to be around 20%, with the majority remaining asymptomatic[2]. In another study, the incidence of symptomatic spinal metastases was about 2% [3]. As most patients with GBM do not survive long enough for small spinal seedings of tumours to grow large enough to cause symptoms, instances of symptomatic spinal metastases are not commonly reported. In support of this notion, the review of literature revealed an average interval of 13 months between the initial diagnosis of intracranial GBM and the diagnosis of spinal symptomatic metastases, a latency period that parallels the median survival for most patients aggressively treated for an intracranial GBM. Staging and surveillance imaging of the spine is also not routine. Therefore, post-mortem findings of spinal seeding are much higher than the incidence of symptomatic spinal metastases.

In patients with symptomatic spinal metastases, the mean age at diagnosis of the primary Intracranial GBM is 45 years [8,18]. Our patient was only 32. This is significantly younger than the age at presentation of primary GBM which is over 50 years [13,14,19].

Opening or contact with CSF pathways was not shown to be factors required for CSF seeding [7]. But symptomatic leptomeningeal metastases were far more frequent than intramedullary seeding.

In the illustrative case reported in this article, tissue samples were obtained from both the intracranial and spinal leptomeningeal lesions and then subjected to both histopathological and immunohistochemical analysis. This has been reported only once in the literature reviewed by us [20].

Onda et al observed and hypothesised that intracranial GBM with low or negative GFAP expression show marked CSF/ leptomeningeal dissemination but little local infiltration and the reverse for tumours with high or prominent GFAP expression [2].

Arita et al studied 157 patients with intracranial GBM with leptomeningeal deposits and found low GFAP expression in leptomeningeal lesions than in the primary intracranial tumours [8].

Maslehaty et al reported a case of primary intracranial GBM with both leptomeningeal and intramedullary metastases. The intracranial and spinal intramedullary lesions showed GFAP expression as opposed to the leptomeningeal lesions which had no GFAP expression [20].

These studies agreed on the hypothesis that primary intracranial GBM showing low or negative GFAP expression (poorly differentiated astrocytic glioma cells) may have much higher disposition to disseminate via CSF pathways and cause leptomeningeal deposits, whereas highly

differentiated astrocytic tumours showing high/ prominent GFAP expression show more infiltrative behaviour causing local recurrence and intramedullary spinal metastases.

But, the illustrative case reported in this article, showed prominent GFAP expression in both the primary intracranial tumour and in the leptomeningeal deposits. Moreover, there was neither a local recurrence at the site of the primary tumour nor a spinal intramedullary deposit, as would be expected in cases with high GFAP expression. This runs contrary to the hypotheses proposed by Onda et al and Arita et al.

Whether there are more than one subtype of GFAP (as yet undiscovered), or whether younger age (as in our patient) plays a modifying role in the spread of the disease remains to be seen. Our patient survived only for 9 months after his initial presentation with an intracranial GBM, which is much shorter than the mean of 18 months. Again, whether GBM tends to have a more aggressive course in younger patients is not clear. Till such time as these things become clear, the mode of spread and location of spinal metastases of primary intracranial GBM cannot be predicted on the basis of GFAP expression alone.

Conclusion

The illustrative case reported by us in this article does not agree with the hypothesis that intracranial GBM with low/ no GFAP expression lead to leptomeningeal metastases and those with high GFAP expression lead to local recurrence and intramedullary spinal metastases. The pathomechanisms of spinal metastases in primary intracranial GBM need further studies before generalisations can be made on the basis of only the immunohistochemical characteristics of the primary and secondary lesions. All patients with intracranial GBM must be followed more closely for the early diagnosis of spinal metastases which are occurring with increasing frequency with more effective treatment and control of the primary intracranial lesion. Leptomeningeal deposits cause widespread & catastrophic disabilities & morbidities when compared to intramedullary deposits. If there was a way to predict whether Leptomeningeal or Intramedullary deposits would occur (if at all they are going to occur), based on the Immunohistochemical characteristics of primary tumour, it will go a long way in improving the quality of life while the patient is alive, by expectation & early recognition of leptomeningeal vs Intramedullary deposits. This will aid in earlier institution of adjuvant therapies. This would ultimately mean a longer life with acceptable quality for these relatively young patients who are stricken with an invariably fatal disease.

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