

Glioblastoma with Primitive Neuroectodermal Tumor-Like Features: Case Report

Pirimitif Nöroektodermal Tümör Benzeri Özellikler Gösteren Glioblastom: Olgu Sunumu

ABSTRACT

Glioblastoma multiforme (GB) is the most aggressive, and the most frequent primary tumor of the brain in adults. Presence of less-differentiated areas which exhibit a small cell morphology and neural immunophenotype is quite uncommon in GBs. Tumor tissue which had been determined in the fronto-temporal region of a 61-year-old female patient and evaluated to be consistent with GB radiologically was subjected to total excision. Histopathological examination revealed two different components making up the tumor tissue. Using a morphological and immunophenotypic approach, the predominant component of the tumor was found to bear the properties of classic GB. The other component was composed of undifferentiated areas exhibiting small cell morphology and diffuse neuronal immunophenotype. The case was diagnosed as 'Glioblastoma with primitive neuroectodermal tumor-like component'. The patient who had been subjected to postoperative radiotherapy, showed no sign of recurrence during the follow-up examination performed on the 9th month. The histogenesis and prognostic significance of neuronal differentiation observed in glial tumors are not known yet. Inclusion of this component in pathological reports is important regarding formation of a database for future studies.

KEY WORDS: Astrocytoma, Glioblastoma, Immunohistochemistry, Neuronal phenotype, Synaptophysin

ÖZ

Glioblastom (GB) erişkinde en sık rastlanan ve en agresif seyirli primer beyin tümörüdür. GB' larda küçük hücre morfolojisine sahip ve nöral immünfenotip sergileyen az diferansiye alanların varlığı oldukça nadir görülmektedir. 61 yaşında kadın hastada, fronto-temporal bölgede saptanan ve radyolojik olarak GB ile uyumlu değerlendirilen tümör dokusu total olarak eksize edildi. Histopatolojik incelemede tümör dokusunun iki farklı komponentten oluştuğu görüldü. Tümörün hakim komponenti morfolojik ve immünfenotipik olarak klasik GB özelliklerini taşımaktaydı. Diğer komponent ise küçük hücre morfolojisinde, yaygın nöronal immünfenotip sergileyen indiferansiye alanlardan oluşmaktaydı. Olgu 'Primitif nöroektodermal tümör benzeri özellik gösteren GB' olarak tanı aldı. Operasyon sonrası radyoterapi uygulanan hastanın 9. ayda yapılan takibinde rekürrens saptanmadı. Glial tümörlerde görülen nöronal farklılaşmanın histogenezi ve prognostik önemi henüz bilinmemektedir. Patoloji raporlarında bu komponentin belirtilmesi ileri çalışmalara veri oluşturmak açısından önemlidir.

ANAHTAR SOZCÜKLER: Astrositom, Glioblastom, İmmünhistokimya, Nöral fenotip, Sinaptofizin

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INTRODUCTION

Glioblastoma (GB) constitutes 15-20% of intracranial malignancies and 50% of all glial tumors seen in adulthood. Histologically, GB is a highly cellular and mitotically active neoplasm. Microscopic appearance of the tumor shows variations both between cases and within the tumor itself. In addition to areas with obvious astrocytic differentiation, there are bizarre multinuclear cells and small undifferentiated cells with no astrocytic differentiation (1-3). Although lack of GFAP expression is often found in primitive small cell component in GB cases, these cells rarely exhibit a neuron-specific immunophenotype. In those cases, specific subtypes of glioneuronal tumors should be taken into account in the differential diagnosis (1-2, 4-12).

In our case report, a primary GB with widely dispersed small cell component and neuronal immune phenotype is presented in light of the literature.

CASE

Clinical history: A 61-year-old woman with a 1-month history of headache and drowsiness presented with a sudden onset of left facial paresis. Magnetic resonance (MRI) examination demonstrated a space-occupying mass lesion which was surrounded by a distinctive white matter edema and localized in the right frontoparietal region thereby extending to the corpus callosum and contralateral hemisphere while showing focal cystic necrotic foci and marked heterogeneous contrast enhancement following administration of intravenous contrast agent. Radiological results were evaluated as consistent with high-grade tumor (Figure 1A,B). At surgery, a nearly gross total resection was achieved. The patient who had been subjected to postoperative radiotherapy showed no sign of recurrence during the follow-up examination performed on the 9th month.

Pathology findings:

Histopathologically, tumor tissue was composed of two distinct components. In approximately 60% of the tumor, bizarre cells with abundant eosinophilic cytoplasm and atypical pleomorphic nuclei were dispersed in fine fibrillary stroma. High mitotic activity, microvascular proliferation and geographic necrosis with obvious nuclear palisading were observed in those areas (Figure 2. A,B). The second

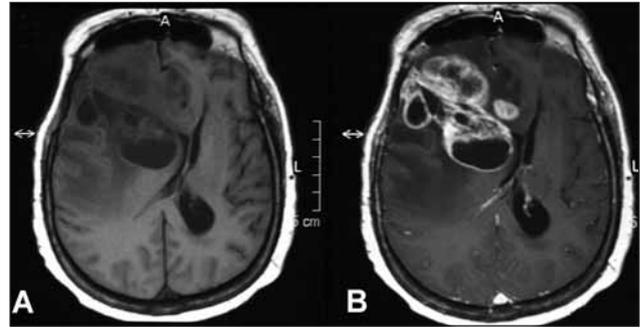


Figure 1: Axial T1-WI MRI (A) demonstrates a heterogeneous hypointense intraaxial lesion in the right frontotemporal lobe. Areas of cyst formation and infiltrative lesion with significant surrounding edema and mass effect. An axial postgadolinium T1-WI (B) image shows heterogeneous mass with irregular ring of enhancement and central necrosis along with surrounding signal abnormality which is probably associated with tumor extension and edema. Note the significant mass effect and midline shift.

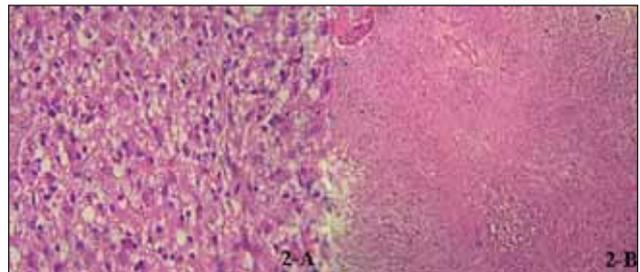


Figure 2: Histological appearance of typical areas of GBM, Hematoxylin-Eosin A: Neoplastic astrocytic cells exhibiting gemistocytic features in a fibrillary background (X100). B: Area of geographic necrosis (X40).

component of the tumor was highly cellular and minimal or no fibrillary material could be seen in the background. Tumor tissue consisted of small undifferentiated cells with scant cytoplasm and oval-round hyperchromatic nuclei in those areas. Undifferentiated cell groups were making pseudorosettes in some areas (Figure 3, A,B). True rosettes and ganglion-like cells were not observed.

Immunohistochemically, GFAP (Figure 4 A) and S-100 immunoreactivity was clearly seen in the areas with predominant astrocytic differentiation. Synaptophysin, NeuN, NFP or chromogranin positivity was not observed in these areas. The small cell undifferentiated component showed no GFAP or chromogranin immunopositivity. However, there was extensive and intense S-100, synaptophysin (Figure 4 B), NeuN (Figure 4 C) immunopositivity besides focal NFP (Figure 4 D) staining in these areas. The MIB-1 labeling index ranged from 10

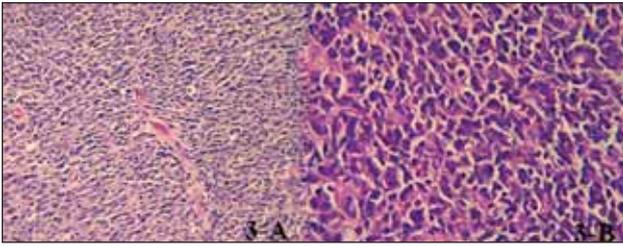


Figure 3: Photomicrographs demonstrating the component composed of primitive appearing small cells. Hematoxylin-Eosine. A: X40. B: X120.

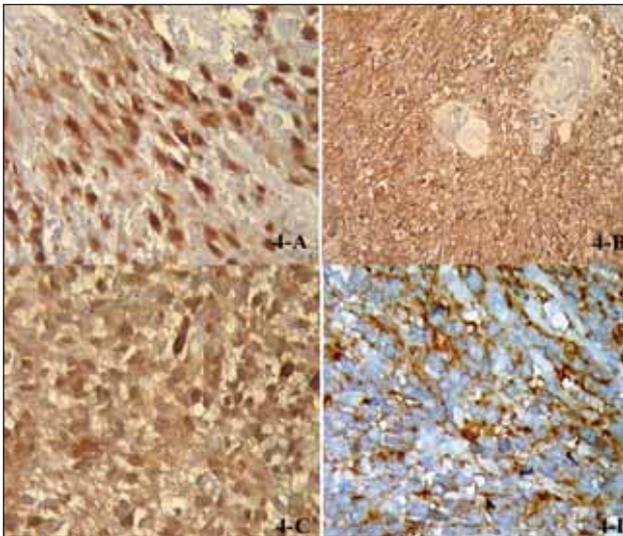


Figure 4: Immunophenotypes of typical GBM and small cell components, BSA-DAB. GFAP immunoreaction in typical GBM (A, X100). Synaptophysin (B, X100), NeuN (C, X100) and NFP (D, X120) immunoreaction in the small cell component.

(astrocytic component) to 65% (small cell undifferentiated component). The case was diagnosed histopathologically and immunohistochemically as 'Glioblastoma with primitive neuroectodermal tumor-like component (GB-PNET)'.

DISCUSSION

Small cell component with neuronal immunophenotype is a rare finding in GB. These 'undifferentiated' or 'embryonal' cells mostly do not give immunoreactivity to GFAP (1). Burger et al. reported that small cell-dominant glioblastomas are important components of primary glioblastomas and often show EGFR amplification (1). Varlet et al. suggested that tumors that could not be differentiated from classical GB morphologically, but demonstrating GFAP and NFP co-expression,

should be classified in the Malign Glioneuronal Tumors (MGNTs) group. These authors added that neuronal immunophenotypic cells mostly had small cell phenotype and their clinical behavior was different from classical GB (11).

Miller and Perry evaluated those tumors as a histological sub-group of GB and described them with the term GB-PNET.

As the clinical and histopathological properties of those tumors have been described only recently, the number of cases reported in the literature is limited. The largest series published on these tumors belong to Varlet et al (11). (n=40) and Perry et al. (12) (n=53). These studies highlighted the clinical, radiological, and histopathological differences of GB-PNET from classic GBs. They are encountered more commonly among adults and the occurrence of symptoms takes a considerably shorter duration (below 6 months in 85% of cases). 52.5% of tumors are localized in the temporal lobe, whereas they are rarely seen with an infratentorial localization. Radiologically, intratumoral hemorrhagia is observed in 15% of cases along the necrotic and cystic areas. The tumor demonstrates a significant mass effect and exhibits diffuse peritumoral edema. Having a well-circumscribed character facilitates the surgical excision. Compared with the classic GBs, those tumors exhibit a lower rate of local recurrence following total resection, whereas manifesting a more common metastatic spread. Standard protocols for radiotherapy and chemotherapy processes have not been identified yet. There are investigators who claim local cranio-spinal radiation therapy as an inadequate method for preventing the tumor from spreading, and mention chemotherapy as a more efficient therapeutic treatment.

Those tumors histomorphologically consist of undifferentiated cellular areas alongside classic GB areas. By evaluation of these fields, morphological (e.g. Homer-Wright rosettes) and immunohistochemical (e.g. Synaptophysin, Neu-N, NFP, neuron-specific enolase expressions) evidences of neuroblastic differentiation are obtained. No common agreement has been reached on the type of neuronal markers to be used in the diagnosis of such tumors. Synaptophysin and Neu-N are nonspecific markers which are employed in immunohistochemical detection of neuronal differentiation. Expression of those markers can be

found in many glial tumors (11-12). Therefore, morphological results should be supported with a comprehensive immunohisto-chemical analysis including neuronal markers while diagnosing GB-PNETs. Varlet et al (11) reported NFP positivity, particularly among mitotic active cells, as a diagnostic indicator.

The differential diagnosis of GB-PNETs includes other types of glioneuronal tumors (e.g. Papillary glioneuronal tumor, glioneuronal tumor with neurophil-like island), embryonal tumors (e.g. neuroblastoma, PNET) and metastatic neuroendocrine carcinomas (11,12). The patient's age, tumor localization, and radiological findings bear importance in the clinical differential diagnosis. Definitive diagnosis requires comprehensive histopathological and immunohistochemical examinations.

Cytological composition is not given in detail in pathology reports of GBs. However, when compared with classical GBs, GB-PNETs had a more aggressive course and post-operative survival was shorter on retrospective analyses. Besides, this component showed extensive invasion to surrounding tissues and metastases to subarachnoidal areas in autopsies when the whole brain was evaluated. A higher MIB-1 index in the small cell component may explain this aggressive behavior potential (4, 11-12).

Several theories have been proposed about the origins of tumors with more than one phenotypic component. According to the generally accepted opinion, those tumors develop from the same origin and show different differentiation patterns. New embryological data show that neuronal and glial cells of the central nervous system (CNS) are originated from the same stem cell (5-11). Singh et al found neural stem cell surface markers (CD113 and nestin) in stem cells isolated from human gliomas (7). These data support CNS tumors with neuronal and glial neoplastic cells may originate from the common stem cells. Studies have showed the presence of 'multipotential stem cells' in various parts of the brain, particularly in subcortical white matter (8-10). This finding explains the reason why GB-PNETs occur more often in superficial localizations and suggest that those tumors might be originating from the subcortical neural stem cells of the adult brain.

In our case, the tumor consisted of two different components which were histologically intermingled but easily perceptible. Atypical astrocytic cells were seen with abundant eosinophilic cytoplasm and large vesicular nuclei on fibrillary background in wide areas. Mitosis, microvascular proliferation and necrosis were also prominent in these areas. Immunohistochemically, GFAP positivity was found in astrocytic cells and fibrillary network. This supported the glial nature of the tumor. The second component showed a multifocal distribution and consisted of cellular areas of small cells with narrow cytoplasm and hyperchromatic nuclei. The cells in these areas were occasionally forming pseudo-rosettes and mitotic activity was high. Reactivity was not seen for GFAP, but was seen for neuronal markers (synaptophysin, NeuN, NFP and S-100) in these primitive cells. Since the glial component was dominant, it expressed both glial and neuronal markers immunohistochemically and the case was diagnosed as GB-PNET since specific histological findings of glioneuronal tumors (ganglion cell, true rosette formation) were not seen.

In conclusion, we present a primary GBM with small cell component exhibiting neuronal immunophenotype in this case report. A small cell primitive component can be observed, especially in primary GBs. These cells can give a positive reaction with neuronal markers and may lead to difficulties in histopathological differential diagnosis. Immunohistochemical and molecular genetic examinations supporting the histomorphological findings may contribute to the diagnosis. The prognostic significance of small cell component in GBs is not clear. However, it should be noted that these cells with a high proliferation rate may contribute to the aggressive behavior pattern of the tumor. Future studies in large series may provide reliable data on the origin and prognostic significance of this component.

REFERENCES

1. Burger PC, Pearl DK, Aldape K, Yates AJ, Scheithauer BW, Passe SM, Jenkins RB, James CD: Small cell architecture--a histological equivalent of EGFR amplification in glioblastoma multiforme? *J Neuropathol Exp Neurol* 60 (11):1099-1104, 2001
2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds): WHO Classification of tumours of the central nervous system. Lyon: IARC, 2007
3. Miller CR, Perry A: Glioblastoma. *Arch Pathol Lab Med* 131(3):397-406, 2007

4. Pinto LW, Chimelli L: Oligodendroglial and neuronal component in glioblastomas: Possible relation with prognosis. *Arq Neuropsiquiatr* 62 (4):1074-1078, 2004
5. Shibahara J, Fukayama M: Secondary glioblastoma with advanced neuronal immunophenotype. *Virchows Arch* 447 (3): 665-668, 2005
6. Shiras A, Bhosale A, Shepal V, Shukla R, Baburao VS, Prabhakara K, Shastry P: A unique model system for tumor progression in GBM comprising two developed human neuro-epithelial cell lines with differential transforming potential and coexpressing neuronal and glial markers. *Neoplasia* 5 (6): 520-532, 2003
7. Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, Squire J, Dirks PB: Identification of a cancer stem cell in human brain tumors. *Cancer Res* 15; 63 (18): 5821-5828, 2003
8. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkelman RM, Cusimano MD, Dirks PB: Identification of human brain tumour initiating cells. *Nature* 18; 432 (7015): 396-401, 2004
9. Singh SK, Dirks PB: Brain tumor stem cells: Identification and concepts. *Neurosurg Clin N Am* 18 (1): 31-38, 2007
10. Singh SK, Clarke ID, Hide T, Dirks PB: Cancer stem cells in nervous system tumors. *Oncogene* 20; 23 (43): 7267-7273, 2004
11. Varlet P, Soni D, Miquel C, Roux FX, Meder JF, Chneiweiss H, Dumas-Duport C: New variants of malignant glioneuronal tumors: a clinicopathological study of 40 cases. *Neurosurgery* 55 (6): 1377-1391, 2004
12. Perry A, Miller CR, Gujrati M, Scheithauer BW, Zambrano SC, Jost SC, et al: Malignant gliomas with primitive neuroectodermal tumor-like components: A clinicopathologic and genetic study of 53 cases. *Brain Pathol* 19 (1):81-90, 2008