Case Report

Gliosarcoma with primitive neuroectodermal, osseous, cartilage and adipocyte differentiation: a case report

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Abstract: We describe a rare case of gliosarcoma with primitive neuroectodermal, osseous, cartilage and adipocyte differentiation. A 57-year-old man experienced a month history of headache, nausea and vomiting. Worse yet, the headache has become more severe for the past 6 days. Magnetic resonance (MR) images disclosed a lesion with operative indications located in the right frontal lobe. Then the tumor was macroscopically totally removed. Histologically, the tumor showed two kinds of components. One kind of the tumor cells appeared typical astrocytic tumor cells with anaplastic appearance. The other kind of the tumor cells appeared sheets of small round hyperchromatic cells, which presented a kind of pancreatic neuroendocrine tumor (PNET)-like structure. These sheets of small round cells were surrounded by a large number of relative-sparse-spindle cells. Multiple separate distinct areas of adipose tissue, osteoid matrix laid down and cartilage tissue were also identified. Immunohistochemically, a portion of typical astrocytic tumor cells and some small round hyperchromatic cells showed GFAP positivity. Small round hyperchromatic cells were positive for S-100, Fli-1, Nestin, MAP-2 and Syn. A large amount of relative sparse spindle cells (sarcomatous areas) were positive for vimentin. In addition, reticulin staining demonstrated expression of reticular fibers in relative-sparse-spindle cells areas but not in the astrocytic tumor cells and small round hyperchromatic cells areas. Molecular cytogenetic analyses demonstrated PTEN allele loss and no evidence of amplification of EGFR in both the astrocytic tumor cells, PNET-like structure and sparse spindle cells areas. These data suggest that this tumor was a gliosarcoma with primitive neuroectodermal, osseous, cartilage and adipocyte differentiation. To our knowledge, this is a rare gliosarcoma, reporting our additional new case would add to the better understanding of this tumor.

Keywords: Gliosarcoma, osseous, cartilage, adipocyte, FISH, PNET

Introduction

Gliosarcoma (GS) is a primary central nervous system neoplasm composed of both malignant glial and sarcomatous components. While GS belongs to World Health Organization (WHO) grade IV neoplasm the occurrence of osseous, cartilage and adipocyte elements is an exceedingly rare case. The histogenesis and histology of GS was highly controversial. Recent studies have supported the contention that both elements of this biphasic neoplasm may arise from a single progenitor clone rather than from separate clones. Both glial and mesenchymal elements may be derived from a common neoplastic neuroectodermal progenitor cell [1-3]. We therefore present the clinical, light microscopic, immunohistochemical and molecular findings of this rare gliosarcoma with primitive neuroectodermal, osseous, cartilage and adipocyte differentiation.

Case report

A 57-year-old man presented with a month history of headache, nausea and vomiting and the headache has worsened for the past 6 days. Magnetic resonance (MR) images disclosed a lesion in the right frontal lobe. T2 weighted axial MR imaging of the brain revealed a large heterogeneous mass lesion in the right frontal lobe with wide peri-tumoral oedema. The tumor had complex solid areas with associated mass effect and midline shift (Figure 1B). MR images
showed hypointense on T1-weighted MR images and enhancement on T1 gadolinium (Gd) image (Figure 1A, 1C). No attachment to the overlying skull bones or meninges was apparent.

The tumor was microscopically totally removed and subjected to histopathological examination. Afterwards the patient received radiotherapy and chemotherapy during the next following months. Up to now, he has not showed any symptom or sign of recurrence, with a survival time of more than 11 months.

Microscopically, the tumor was texture medium, dark-red mass, rubbery tissue with associated chondro-osseous portions, measured 6.5 cm × 5 cm × 4.5 cm in size. After formalin fixation, 4-μ-thick paraffin sections were stained routinely with HE and reticulin. Immunohistochemical (IHC) staining was performed with monoclonal antibodies against GFAP (1:500), Fli-1 (1:400), vimentin (1:50), MAP-2 (1:500), nestin (1:300), synaptophysin (Syn, 1:300), EMA (1:250) S-100 (1:300), pan-cytokeratin (1:250), desmin (1:300), TP53 (1:300) and MIB-1 respectively. All antibodies were purchased from DAKO, Denmark. In addition, positive and negative controls were also included and evaluated appropriately for each procedure. In addition, reticular fiber staining were also performed.

Histologically, there was significant heterogeneity among the sections of formalin fixed paraffin embedded tumor tissue. One kind of the tumor appeared typical astrocytic tumor cells with anaplastic appearance, high mitotic index, focal complex microvascular proliferation and geographic foci of necrosis (Figure 2A, 2B). Occasional prominent nucleoli and multinucleated giant cells were present (Figure 2C). The other kind appeared sheets of small round hyperchromatic cells with minimal cytoplasm and numerous mitoses oval (Figure 2D, 2E), which presents sort of PNET-like structure (2F), but was devoid of reticulin fibers. These cells were predominately arranged in sheets and nests, surrounded by relative sparse spindle cells. The spindle cells areas (sarcomatous) were with a large amount of thin reticulin fibers. Multiple separate distinct areas of adipose tissue (Figure 2G) osteoid matrix laid down (Figure 2H) and cartilage (Figure 2I) tissue were also identified. Their overall portion in the tumor tissue was less than 5%. These areas were surrounded by spindle cells (sarcomatous areas).

IHC staining demonstrated cytoplasmic expression of GFAP in the typical astrocytic tumor cells portion and some small round hyperchromatic cells portion (Figure 3A), but not in the relative-sparse-spindle cells areas. The astrocytic tumor cells portion and small round hyperchromatic cells portion were devoid of reticulin fibers (Figure 3B). The small round hyperchromatic cells portion was immune-positive for S-100 (Figure 3C), Fli-1 (Figure 3D), MAP-2, Syn and Nestin. In addition, focal expression of EMA and pan-cytokeratin was also observed. No expression of pan-cytokeratin, desmin or glial markers was seen in spindle cells area. The spindled cells area (sarcomatous) was positive for vimentin (Figure 3E), with a large
amount of thin reticulin fibers (Figure 3F). Both typical astrocytic tumor cells and small round hyperchromatic cells components exhibited a highly elevated MIB-1 proliferation rate up to 50%. The spindled component also exhibited a highly elevated MIB-1 proliferation rate up to 30%. More than 60% of p53-positive tumor cells were seen in both areas of astrocytic tumor cells and small round hyperchromatic cells. The p53-positive tumor cells were also seen in spindle cells areas. The adipose tissue and cartilage were strongly positive for S-100.

Dual-color Fluorescence in situ hybridization (FISH) was performed using LSI PTEN/CEP10 Dual Color Probe (Vysis/Abbott Molecular) for losses of PTEN. The EGFR gene copy number was determined by FISH using the LSI EGFR SpectrumOrange/CEP7 Spectrum-Green Probe (Vysis/Abbott Molecular). Fluorescent signals were visualized and quantitated under fluorescence microscope. A minimum of 100 non-overlapping intact nuclei were assessed by hybridization. At least 30% or more increase in nuclei number is necessary for a signal to be scored as a deletion. Amplification of EGFR was defined as ratio of EGFR signal to CEP7 signal greater than or equal to two. Percentage of the cells showing deletion and amplification was estimated separately and independently for two component parts of this tumor.

FISH was performed utilizing probes against CEP7, EGFR, CEP10 and PTEN. There was evidence of polysomies (gains) of chromosomes 7 consistent with an overall state of polyploidy/aneuploidy (Figure 4). Additionally, there was evidence of chromosome 10q deletion (Figure 5). No EGFR gene amplifications were found.

Figure 2. A. Photomicrograph showing neoplastic astrocytes with nuclear pleomorphism and microvascular proliferation (H&E ×200). B. Focus areas of necrosis (H&E ×100). C. Multinucleated giant cells were present (H&E stain ×200). D, E. Primitive component with sheets of small round hyperchromatic cells with minimal cytoplasm and numerous mitoses (H&E stain ×100, ×200). F. Homer-Wright rosettes within the primitive component (H&E, ×400). G. Areas of adipose tissue (H&E ×200). H, I. Osteoid matrix laid down and cartilage structures were also identified (H&E ×200, ×200).
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Discussion

GSs are primary central nervous system neoplasms composed of both malignant glial and sarcomatous components. Their histogenesis and histology have been highly controversial. It was first proposed by Feigin and Gross that the sarcomatous component arises from proliferating tumor cells [4]. However, it has been shown that the EGFR gene, which is involved in cell proliferation control and amplification, occurs in approximately 40% of all glioblastomas with predominance for primary glioblastomas. Its expression seems to be mutually exclusive from mutations in the TP53 tumor suppressor gene [5]. In contrast EGFR expression is not common in gliosarcomas, whereas mutations in the TP53 and PTEN genes are predominantly observed [2]. Bier nat et al. first proposed the monoclonal theory in GS, and his study demonstrated identical p53 mutations in both tumor areas (gliomatous and sarcomatous areas) [6]. Subsequently, many studies found both components in GS shared the similar genetic characteristics by comparative genomic hybridization, FISH, cytogenetic analysis and microsatellite analysis [7]. Recent comparative genomic hybridization studies have also shown similar genetic alterations in both components, which strongly support the interpretation that both elements are derived from a common neuroectodermal progenitor [1-3]. The molecular genetic analyses displaying identical mutations in the PTEN and p53 genes favored a monoclonal origin [2, 6]. In our case, the mutations in PTEN and p53 genes were used to help diagnostic requirements. In this case the mutations in PTEN and p53 genes were found, but No EGFR gene amplifications were found. Immunohistochemical stains also help to delineate the biphasic nature of GS better. GFAP stains the glial component, whereas vimentin positivity is diagnostic for the spindled cells component (sarcomatous component).

In this case, the tumor presented the primitive neuroectodermal, osseous, cartilage and adipocye elements primitive neuroectodermal all in one case of GS. Only few cases of gliosarcoma with cartilage or chondroid differentiation have been reported in literature so far [8-10]. Cases of GS with PNET reported were even much less [11]. Some reports found that the presence of a PNET-like component in GS may reflect the capability of neuroectodermal progenitor cells to differentiate along multiple lines.
or may reflect a clonal proliferation of the stem/progenitor cell itself. Recent data showed that a cancer stem cell can be isolated even from conventional glioblastomas [1], which would be consistent with the latter hypothesis.

Some reports suggested the osseous component in GS may be unequivocally malignant [8-10]. It was demonstrated that neoplastic astrocytes are capable of differentiating into cartilage through mucopolysaccharide deposition, which can evolve to form a chondroid matrix [12, 13]. In our case there was dominant morphological evidence of glioblastoma with PNET differentiation, with relatively sparse spindle cell (sarcomatous component) transformation. There were also focal area of adipocyte tissues, area with osteoid matrix laid down and chondroid metaplasia areas. And the focal cartilaginous components were completely surrounded by sarcomatous neoplastic tissue. The chondroid metaplasia areas and adipocyte tissues present had focal S-100 positivity.

It was considered the malignant potential of the tumor, the patient underwent radiotherapy and chemotherapy with temozolomide as adjuvant treatment. He has remained free of recurrence for 11 months. We believe that this combination therapy is presently reasonable and appropriate.

In conclusion, we experienced a very rare GS case associated with a primitive neuroepithelial component, osseous, cartilage and adipocyte differentiation. It is possible that the primitive neuroectodermal component seen in this tumor either reflects the capacity of the neoplasmic neuroectodermal progenitor cell or may represent a clonal proliferation of the progenitor cell itself. Generally speaking, it is possible that patients with PNET-like component may require altered, more aggressive treatment regimens. However, follow-up of additional cases is needed to definitely determine whether the presence of this component significantly alters the already aggressive biology of GS in general. Reporting additional cases would be of great help in better understanding of the pathogenesis, clinical course and outcome of GS.

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Disclosure of conflict of interest

None.

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