Epithelioid glioblastoma

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Epithelioid glioblastoma is a variant of glioblastoma (along with gliosarcoma and giant cell glioblastoma) added to the World Health Organization Classification of Tumors of the Central Nervous System 2016 [1].

Whether or not epithelioid glioblastomas are distinct from rhabdoid glioblastomas is at present unclear, however, the latter term should be avoided and is not recognised in the current World Health Organization Classification of Tumors of the Central Nervous System [2] [3].

It is important to note that true epithelial differentiation of glioblastomas (typically squamous) is very rarely seen in adults but is distinct from epithelioid glioblastoma [4].

Epidemiology

Unlike run-of-the-mill glioblastomas that are usually encountered in older adults, epithelioid glioblastomas have a predilection for young adults and children [5].

Pathology

Epithelioid glioblastoma are WHO grade IV tumours [6]. Interestingly, they sometimes co-exist with pleomorphic xanthoastrocytomas, however, their exact relationship is at present unclear [7].

Microscopic appearance

These tumors are heterogeneous with large epithelioid cells that have abundant eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli. These cells are reminiscent of melanoma

cells. Rhabdoid cells are also sometimes encountered [8].

Immunophenotype

Immunohistochemistry demonstrates a mixture of astrocytic and epithelial markers [9]:

vimentin: positive

S100: positive

GFAP: positive but patchy

EMA: variable

cytokeratins: variable

Genetics

Approximately 50% of cases of epithelioid glioblastoma have BRAF V600E mutations [10] [11] [12].

Radiographic features

Epithelioid glioblastomas most frequently present as diencephalic or less frequently superficial cerebral hemispheric masses [13] [14].

Haemorrhage and leptomeningeal seeding are probably fairly common at the time of diagnosis [15].

These tumours are indistinguishable for glioblastoma on imaging, with enhancement, necrosis and diffusion restriction present in the vast majority of tumours.

Differential diagnosis

In children the main differential is atypical teratoid / rhabdoid tumour (AT/RT), distinguished by universal lack of INI1 expression in AT/RT [16].

Treatment

Particularly in younger glioma patients and in patients with an epithelioid glioblastoma, screening for the V600E mutation of the BRAF gene appears to be promising, since in these cases targeted therapy with BRAF inhibitors seems to be a valuable salvage treatment option [17].

Outcome

Epithelioid glioblastomas are aggressive tumours with poor prognosis, even worse than ordinary glioblastomas [18].

In one series the median survival was only 169 days [19].

These tumours also sometimes demonstrate systemic metastases, a very uncommon occurrence for other primary brain tumours [20].

Case series

Four consecutive patients aged 16-48 years were diagnosed with epithelioid/rhabdoid GBM by pathological and immunohistochemical analysis at Yamaguchi University Hospital from 2006 to 2012. Two of these patients had relatively long-term survival (19 and 23 months after diagnosis). Two cases had a BRAF V600E mutation, whereas no ATRX mutation was present in any cases. All patients suffered leptomeningeal and/or spinal dissemination that worsened their prognosis. These results illustrate the need for a new therapeutic approach, such as molecular targeted drug therapy like BRAF inhibition, in addition to standard chemoradiotherapy for typical GBM [21].

A few case series in adults have described the characteristics of epithelioid glioblastoma (e-GB), one of the rarest variants of this cancer.

Epithelioid glioblastoma (eGBM) and pleomorphic xanthoastrocytoma (PXA) with anaplastically transformed foci (ePXA) show overlapping features. Eleven eGBMs and 5 ePXAs were reviewed and studied immunohistochemically. Fluorescence in situ hybridization for EGFR amplification, PTEN deletion and ODZ3 deletion was also performed, with Ilumina 450 methylome analysis obtained in five cases. The average age for eGBM was 30.9 (range 2-79) years, including five pediatric cases and a M : F ratio of 4.5. The ePXA patients had a M : F ratio of 4 and averaged 21.2 (range 10-38) years in age, including two pediatric cases. Six eGBMs and two ePXAs recurred (median recurrence interval of 12 and 3.3 months, respectively). All tumors were composed of solid sheets of loosely cohesive, “melanoma-like” cells with only limited infiltration. ePXAs showed lower grade foci with classic features of PXA. Both tumor types showed focal expression of epithelial and glial markers, retained INI1 and BRG1 expression, occasional CD34 positivity, and lack of mutant IDH1 (R132H) immunoreactivity. BRAF V600E mutation was present in four eGBMs and four ePXAs. ODZ3 deletion was detected in seven eGBMs and two ePXAs. EGFR amplification was absent. Methylome analysis showed that one ePXA and one eGBM clustered with PXAs, one eGBM clustered with low-grade gliomas, and two eGBMs clustered with pediatric-type glioblastomas. Common histologic, immunohistochemical, molecular and clinical features found in eGBM and ePXA suggest that they are closely related or the same entity. If the latter is true, the nomenclature and WHO grading remains to be resolved [22].

Review of clinical characteristics and therapy, imaging studies and histology was performed in patients younger than 22 years with e-GB seen over 15 years. Sequencing of hotspot mutations and fluorescence in situ hybridization of relevant genes were undertaken.

Median age at diagnosis of six patients was 7.6 years. Tumours originated in the cerebral cortex (n = 2) or diencephalon (n = 4). Three patients presented with acute, massive haemorrhage and three had leptomeningeal dissemination at diagnosis. Paediatric e-GB had the typical histological characteristics seen in adult tumours. Universal immunoreactivity for INI1 and lack of diverse protein expression were seen in all cases. One tumour had a chromosome 22q loss. Three tumours (50%) harboured a BRAF: p.V600E. One thalamic tumour had an H3F3A p.K27M. All patients received radiation therapy with (n = 3) or without chemotherapy (n = 3). All patients experienced tumour progression with a median survival of 169 days. One patient with nonmetastatic disease had early leptomeningeal progression. Two patients had symptomatic tumour spread outside the central nervous system (CNS) through a ventriculoperitoneal shunt. One additional patient had widespread metastases outside the CNS identified at autopsy.

Paediatric e-GBs are rare cancers with an aggressive behaviour that share histological and genetic characteristics with their adult counterparts. BRAF inhibition is a potential treatment for these tumours [23)].

see Intraventricular epithelioid glioblastoma.

Case reports

A 67-year-old man with a prior history of mycosis fungoides, a common form of cutaneous T-cell lymphoma, presented with memory loss and impaired peripheral vision. Two discrete brain lesions highly suspicious for metastases were identified by magnetic resonance imaging (MRI).

INTERVENTION: The patient underwent two separate craniotomies; both lesions were successfully resected in toto with an excellent post-surgical outcome.

CONCLUSION: Epithelioid glioblastoma is one of the rarest morphologic subtypes of glioblastoma. Here we describe the first case to our knowledge of multifocal epithelioid glioblastoma that convincingly mimicked a secondary metastatic process. Multifocal epithelioid glioblastoma should be included in the differential diagnosis of patients who present with multiple discrete brain lesions. An attempt at gross total resection is recommended when anatomically feasible for definitive histopathological diagnosis and to improve progression free survival of patients who present with similarly ambiguous and potentially misleading multiple lesions [24)].

A 43-year-old woman who had undergone breast cancer surgery 1 year previously complained of headache and nausea. Her brain computed tomography (CT) scan and magnetic resonance imaging (MRI) showed a well-circumscribed, heterogeneously enhanced tumor in the right thalamus. She underwent gross total resection of the tumor followed by radiochemotherapy, and her clinical course was uneventful after surgery. Histological examination revealed a moderate number of tumor cells with fine bipolar processes in a mucoid matrix, which suggested pilocytic astrocytoma. The tumor was associated with microvascular proliferation but did not show significant mitosis or necrosis. In some areas, it had an epithelioid appearance, with ribbon-like, cribriform, and pseudoglandular patterns involving cuboid-shaped cells showing nuclear atypia and mitotic figures. Immunohistochemically, the

tumor cells were positive for glial fibrillary acidic protein (GFAP) and vimentin in the area resembling pilocytic astrocytoma, but in the epithelioid area they were negative for GFAP and vimentin as well as for breast cancer markers, including AE1/AE3. The proliferating potential, represented by the MIB-1 labeling index, was high (82.5%) in the area of epithelioid appearance, compared to only 3% in the area of pilocytic astrocytoma-like appearance. As a rare histoarchitectural variant of glioblastoma, the epithelioid pattern may represent a very primitive tumor cell phenotype. Typically, this pattern is characterized by well-circumscribed masses, although its clinical significance is unknown [25].

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