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Case Report

From a dysembryoplastic neuroepithelial tumor to a glioblastoma multiforme: Pitfalls of initial diagnosis on biopsy material, a case report

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ABSTRACT

Background: Ganglioglioma (GG) and dysembryoplastic neuroepithelial tumor (DNET) belong to the group of low-grade epilepsy-associated tumors (LEAT) and are the most prevalent tumor types found in patients undergoing epilepsy surgery. Histopathological differentiation between GG and DNET can be difficult on biopsies due to limited tumor tissue.

Case Description: Here, we present a rare case where a low-grade tumor was initially classified as DNET, based on biopsy findings and unfortunately dedifferentiated within 10 years into a glioblastoma multiforme. After gross total resection, the initial tumor was reclassified as GG.

Conclusion: This case illustrates the diagnostic challenges of LEAT, especially on biopsy material. Therefore, we advocate to counsel for complete resection and histopathological diagnosis utilizing tumor markers to confirm the nature of the tumor and to advice type of follow-up and eventual concurrent treatment.

Keywords: Dysembryoplastic neuroepithelial tumor, Ganglioglioma, Glioblastoma, Low-grade epilepsy-associated tumor, Temporal lobe epilepsy

INTRODUCTION

Ganglioglioma (GG) comprises 0.93% of all primary central nervous system tumors, is frequently classified as WHO Grade I neoplasms, and belongs to the Low-grade epilepsy-associated tumor (LEAT) spectrum.[5,17,20] LEATs are frequently encountered in patients with chronic, drug-resistant epilepsy and form the second most common histopathological diagnosis after epilepsy surgery. In the group of LEATs, GG is the most prevalent, has a male preponderance, and is predominantly found in the temporal lobe.[3] These tumors rarely dedifferentiate although the probability varies among the LEAT subtypes. It is estimated that the lifetime risk of malignant transformation of a GG into a glioblastoma multiforme (GBM/WHO Grade IV) is around 3% and 12% to an anaplastic GG (WHO Grade III).[10,22] DNET (WHO Grade I) is the second most

prevalent tumor type after epilepsy surgery and approaches a 0% chance of dedifferentiation.[3,9,12] However, Heiland *et al.* presented a DNET showing its malignant potential.[7] The histopathological differentiation between GG and DNET after tumor biopsy is challenging due to the limited amount of available tissue.[1,18] Here, we describe a rare case of a GG which was diagnosed as a DNET after biopsy and reclassified as a dedifferentiated GG after gross-total resection 10 years later. This report provides insights in the challenges of tumor diagnosis, especially on limited material.

CASE DESCRIPTION

A 38-year-old Caucasian woman was admitted to our hospital in 2006 for focal epileptic seizures. Seizures consisted of paroxysmal contractions of the right shoulder without loss of consciousness at a frequency of 3 times/week. MRI-scan showed a non-enhancing, left-sided temporo-parieto-occipital tumor [Figures 1a and b]. Imaging findings were non-specific and could fit a low-grade glioma or other low-grade tumor. Tissue verification was advised by the multidisciplinary neuro-oncology board. As patient refused at that time a resection, a stereotactic biopsy of the tumor was performed, and histopathological examination of the limited tissue volume demonstrated a DNET. The epileptic seizures were treated with levetiracetam 500 mg twice daily and a wait-and-scan policy was advised.

For 8 years the seizures remained under control and the routine follow-up MRI-scan showed no signs of tumor progression. Shortly thereafter, the patient was admitted with agitation, dysphasia, and visual hallucinations in the right visual field. At admission, consciousness was intact and dysphasia, apraxia and a right-sided facial paresis was observed and levetiracetam was increased to 750 mg twice daily. An MRI-scan showed tumor growth, from 5.0 × 4.0 cm in 2006 to 7.6 × 5.8 cm in 2014. The tumor had solid and cystic components and did not enhance after gadolinium contrast. Mass effect was seen with slight displacement of the mesencephalon. The dysphasia and visual symptoms were interpreted as a combination of transient tumor (seizure) attacks and a mass effect on eloquent temporal neocortex and the optic radiation. The patient was scheduled for an awake craniotomy (Penfield procedure) but declined surgical treatment in the end. Ten years after the first admission, the MRI-scan showed further tumor progression with increased compression of the mesencephalon [Figures 1c and d]. Besides progression, a nodular region of enhancement developed within the lesion, suspect of a dedifferentiated glioma rather than a DNET. Despite the increased tumor size, the patient had unchanged dysphasia and dysarthria. This time, a gross-total resection of the tumor was performed. In the postoperative phase, the patient had slightly worsened dysarthria, probably due to edema, which ameliorated substantially at hospital discharge. A postoperative MRI-scan, within 72 h after surgery, showed slight residual pathological contrast enhancement at the resection margins, suggesting minimal rest tumor [Figures 1e and f]. Radiotherapy concurrent with temozolomide was started, according to the Stupp-protocol.[19] Concurrently, multiple cysts were found in the liver and kidneys suggestive for autosomal dominant polycystic kidney disease (ADPKD) and a mutation in the PKD2 gene was detected.

Control MRI-scan, 6-months after surgery showed decreased gliotic changes but also progression of both enhancing and non-enhancing nodular components with regions of increased perfusion ratios, indicative of further progression of dedifferentiated tumor components. One month after this MRI-scan, the patient presented on the ER with an acute visual aura, numbness in the right half of the face, weakness of the right arm, dysarthria, and dysphasia, and interpreted as postictal symptoms. Physical examination showed a latent paresis of the right arm and no further deficits. Subsequent MRI-scan showed further tumor progression [Figures 1g and h]. The following 2 years the patient was treated with chemotherapy using lomustine and radiotherapy but, unfortunately deceased in 2019. Due to the ADPKD and the subsequent liver-and kidney malfunction, the patient was excluded from clinical trials.

Histopathology

The biopsy showed brain tissue with increased cellularity, a variable distribution, and a remarkably perivascular pattern, suggestive for a low-grade primary brain tumor [Figure 2a]. In between, signs of fresh and older hemorrhages with hemosiderin-loaded macrophages and focal calcifications were seen. The tumor cells had round, slightly irregular nuclei with a changing chromatin pattern. There was some expression of glial fibrillary acidic protein (GFAP) and S100, the MIB-1 expression showed normal proliferation. The diagnosis DNET was favored by several neuropathologists at this time. Ten years later, the contrast enhancing parts in the temporal lobe showed a cell-rich, pleomorphic glioma with extensive necrosis and pathological endothelial proliferation [Figure 2b]. The tumor cells showed marked nuclear atypia with irregular nuclei, irregular chromatin pattern and an increase in mitotic figures. GFAP-immunoreactivity was strongly increased, which together with the other findings, lead to the diagnosis of a GBM. Molecular testing showed the absence of IDH1–and IDH-2 mutation. The MGMT promoter was not methylated, and further methylation diagnostics showed it to be of the mesenchymal subtype. Microscopic examination of the resected hippocampus showed a diffuse infiltrating tumor with variable cellularity and in some parts a nodular pattern [Figure 2c]. These cells showed partly an astrocytic and oligodendroglial phenotype

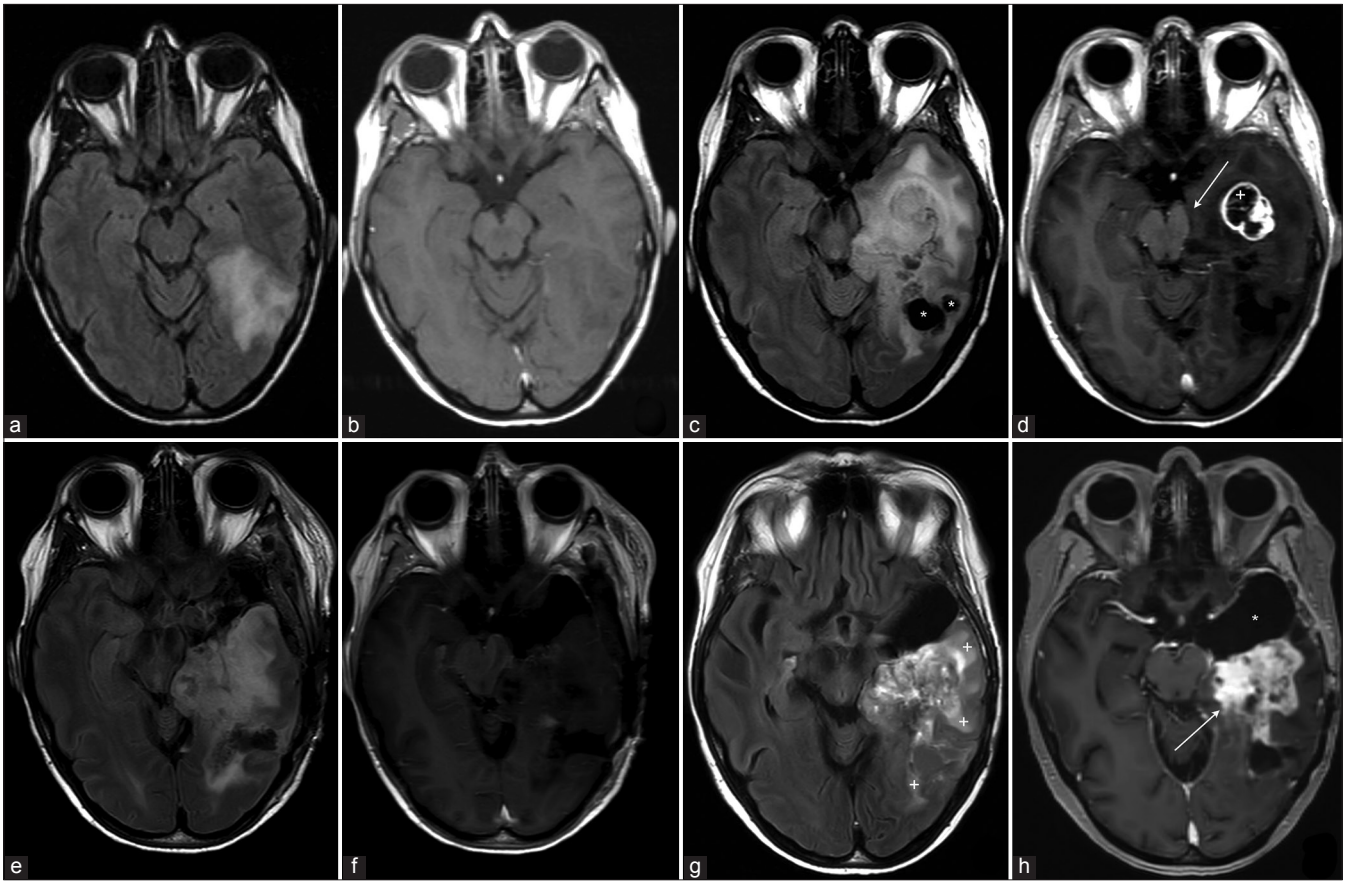

Figure 1: (a) Transverse FLAIR and (b) contrast-enhanced T1 at presentation show a non-enhancing T2-hyperintense mass in the left temporal lobe. These findings favor a low-grade tumor but are otherwise non-specific. (c) Transverse FLAIR and (d) contrast-enhanced T1 10 years after first presentation. There is evident progression of the mass, with cystic components (*) and a rim-enhancing component (+) in the anterior temporal lobe. Increase of transtentorial herniation with mass-effect on the brainstem (arrow). (e) Transverse Flair and (f) Contrast enhanced T1 Postoperative within 72 h shows slight residual pathological contrast enhancement at the resection margins, suggesting minimal rest tumor. (g) Transverse FLAIR and (h) contrast enhanced T1 13 years after first presentation. Despite anterior debulking (*marks the postoperative defect), there is evident progression of enhancing tumor (arrow) and surrounding edema (+).

with also the presence of glioneuronal nodules and atypical ganglion cells with increased immunoreactivity for GFAP. NeuN staining showed pre-existent hippocampus and significant loss in neuronal cell elements where the tumor infiltrated. There was no increase in proliferation and there was strong immunoreactivity for CD34 within the tumor with a typical nodular staining pattern with the presence of tumor satellites that are characteristically seen in GG. In some slides, the evolution of the glial component of this GG into a GBM could be clearly seen. In conclusion, the initial diagnosis of DNET was changed to a dedifferentiated GG after gross total resection which is supported by the CD34 immunoreactivity that was performed for this case report on the biopsy material.

DISCUSSION

This case report describes the complexity of the histopathological differentiation between tumors in the LEAT-spectrum, especially under the circumstances of limited tissue after tumor biopsy without resection. Besides, this report describes the urge of a correct diagnosis for the purpose of a meaningful prognostic patient counseling.

GG was first described by Perkins in 1926[13] and further elaborated by Cushing in 1927 and by Courville in 1930.[4] DNET was first reported in 1988 by Daumas-Duport *et al.* with a description of the clinical and pathological characteristics in 20 patients undergoing epilepsy surgery.[6]

The advent and application of different diagnostic tumor markers, such as CD34, have led to an increased recognition of these markers in the tumors of the LEAT spectrum. CD34 was first described in 1999 and in the LEAT spectrum 54/73 (74%) GG's and 4/23 (17%) DNET's showed immunoreactivity for this novel marker.[2] Qaddoumi *et al.*[15] showed that BRAF-alterations were present in 9/17 (53%) of the GG compared to 1/22 (2%) in the DNET-group, while FGFR1 alterations were found in 18/22 (82%) of DNETs and in none of the GGs. Similar results were found by

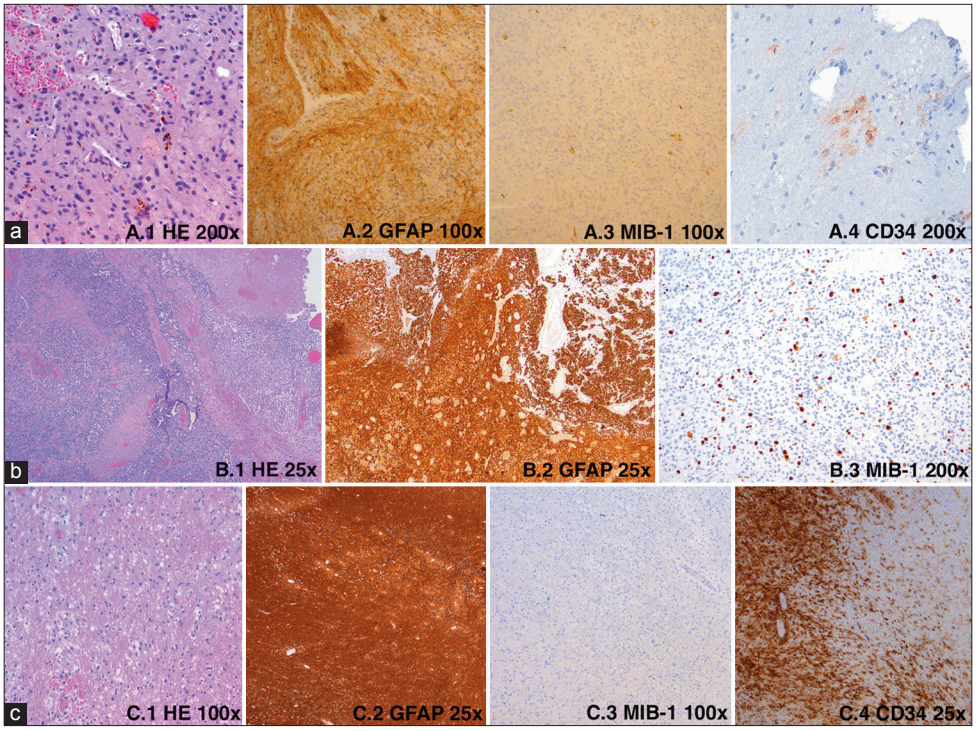

Figure 2: (a) First tumor biopsy HE-staining (1), GFAP staining (2), proliferation marker Mib1 (3) and later performed staining for CD34 (4), (b) high grade recurrence as GBM (resection) HE-staining (1), GFAP staining (2), proliferation marker Mib1 (3), (c) Resection of hippocampus (place of prior biopsy) with tumor in HE-staining (1), GFAP staining (2), staining for the proliferation marker Mib1 (3) and CD34 (4).

Rivera *et al.*[16] 25/43 (58%) confirmed that DNET tumors had a mutation in FGFR1 while BRAF V600E were absent. Besides molecular diagnostics, basic CT and advanced MRI techniques can help differentiate. Gadolinium contrast enhancements and calcifications are more common in GG than in DNETs on a CT scan. On advanced imaging, diffusion-weighted imaging ADC values will be higher in DNET. Detecting clusters composed of ganglio-like cells, granular bodies, and a perivascular lymphocytic cuff, although not pathognomonic, is supportive of the GG diagnosis.[11]

The importance of differentiating between these LEAT-spectrum tumors is the difference in prognosis between the tumor groups and the eventual postoperative follow-up. Due to the presence of a glial component in GG, these tumors can dedifferentiate into a high-grade glioma.[8,14,21] Transformation of GG is estimated at a lifetime risk of 12% and 3% to an anaplastic GG and GBM, respectively, while DNET approaches a 0% chance.[9,10,12,22]

In the presented case, the main difficulty was the amount of available tissue at initial diagnosis obtained after a biopsy. It is speculated that, at first presentation, histomorphological analysis of a larger tissue volume obtained after resection, together with the use of specific markers as mentioned above would have led to the correct GG diagnosis. In case, the amount of available tissue is sparse and specific tumor markers are absent, discriminating within the LEAT spectrum presents significant difficulties. As the current case illustrates, initial correct diagnosis is critically important to estimate the overall and progression-free survival and counsel the patient for prognosis and eventual treatment. In conclusion, in future cases of a suspected LEAT tumor the difficulty and chance of correct diagnosis and its implications using biopsy versus resection should be discussed. We advocate to counsel the patient in these cases for complete resection and the standard use of the above-mentioned tumor markers to confirm the exact nature of the tumor. This is necessary to advise the type of follow-up, decide on eventual concurrent treatment and to counsel the patient, when requested, with an estimation of the prognosis quoad vitam. In case of an unexpected tumor progression in a biopsy-diagnosed DNET, it is advisable to counsel the patient for a second look and gross-total resection.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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