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GRANULAR CELL ASTROCYTOMA: AN UNUSUAL CASE AND REVIEW OF THE LITERATURE

Pathology

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ABSTRACT

We present a case of a 51-year-old woman with no significant medical history who presented with seizures and weakness in the left extremities. Imaging revealed a well-defined mass in the right temporoparietal junction. She underwent an emergency craniotomy, and entire mass was removed. Microscopic examination revealed a granular cell astrocytoma with focal anaplastic changes. Immunohistochemical staining showed GFAP (+), EMA (+), CD68(+), S100(+), CD34(+), synaptophysin (-) and NFP that supported the infiltrative nature of tumor. Ki-67 proliferative index was 30%. Mitotic index was 2-3/HPF. No adjuvant therapy was administered. In the follow-up period a tumor mass was resident in the right frontal lobe, which was evaluated as a residual tumor. The patient underwent a second craniotomy and was started on a chemo-and radiotherapy.

KEYWORDS

Granular Cell Astrocytoma, Immunohistochemistry, Temporoparietal Junction

INTRODUCTION:

Granular Cell Astrocytoma (GCA) was previously reported as a granular cell tumor of the central nervous system (CNS) for the first time in 1972 (1). In 2002, the disease was named GCA and described as infiltrative gliomas with granular cells (2).

GCAs are a rare variant of glial tumors that presents with an aggressive clinic and poor prognosis. The most common symptoms such as headache, vomiting, and seizures are due to the mass effect. Although some case reports demonstrated unusual locations, GCAs are most commonly seen in cerebral hemispheres (3).

Histopathological diagnosis is the most challenging aspect. There is a risk of misinterpretation of the pathology as a lesion infiltrated by macrophages due to the morphology which resembles macrophages. They are distinguished by the expression of macrophage markers (CD68 and CD163) and Glial fibrillary acidic protein (GFAP). CD68 and GFAP are positive in these tumors, but CD163 expression is not observed (2, 4). This case report demonstrates our histopathological approach to this rare pathology.

Case Report:

A 51-year-old woman with no significant medical history was admitted to our hospital with complaints of new-onset seizures, weakness in the left extremities, and dysphagia. She was conscious and cooperative on admission. On physical examination, her light reflexes were normal, and she did not have anisocoria. She had left facial asymmetry and hemiparesis. On magnetic resonance imaging (MRI) and computed tomography (CT) a mass with well-defined borders was seen on the temporoparietal lobe (Figure 1A). The patient was then taken into emergency craniotomy and the entire tumor mass was removed and sent for a pathological evaluation.

Pathologic Findings:

The tumor was hypercellular and had extensive microvascular proliferation (Figure 2A, B, C). It contained eccentric and hyperchromatic nuclei with periodic Acid-Schiff (PAS) (-) granules. No necrosis was observed. The nuclei found in cell cytoplasm were also non-reactive for May Grünwald-Giemsa and Grocott stains, as well as PAS stain.

Immunohistochemical Findings:

An extended glial immunopanel was applied (Table 1). The tumor cells are GFAP (+) (Fig. 3A), epidermal growth factor receptor (EGFR) (+) (Fig. 3B), oligodendroglia lineage marker (OLIG2) (Fig 3C), CD68(+) (Fig. 3D), and p53 (Fig.3E) (+). Ki67 labelling index was calculated as 80% by digital assisted computerized quantification. (Fig. 3F) Also IDH1 (p132) was non-reactive (not shown). Therefore, it was interpreted as a high-grade astrocytic neoplasm (WHO Grade 3). The tumor also showed an infiltrative pattern by neurofilament protein (NFP). CD34 (+) (20%: microvascular proliferation) was another indicator of a high-grade glioma.

Clinical Treatment and Follow-Up:

No adjuvant therapy was administered to the patient after the operation. 40 days post-operation a 45x38 mm tumor mass on the patient's right frontal lobe was considered as a residual tumor mass (Figure 1B). The mass was hyperintense on T1A, hypointense on T2A, and FLAIR MRIs. Her light reflexes were normal, and her pupils were normoisocoric. She did not have any motor or sensory deficits. Babinski's reflex was negative bilaterally. She underwent a second craniotomy to remove the tumor. Her post-op MRI showed no residual tumor mass (Figure 1C). Her left-hand motor strength was 4/5, left elbow flexion was 4/5, left shoulder abduction was 3/5, and left lower extremity was strength 4/5 on discharge. She also had facial asymmetry. She was later put on a radiotherapy and chemotherapy regime consisting of 8 cycles of temozolomide and 2 cycles of lomustine.

Discussion and Review of the Literature:

GCAs are usually located in the suprasellar region. The most involved parts are the frontal, parietal, and temporal lobes (5). There are also case reports demonstrating GCAs in uncommon localizations, such as the pineal gland and cerebellum (6, 7). 73 cases, including our case, have been reported (Table 2). The most commonly involved part is the Parietal lobe (31,5%). It is followed by Frontal lobe (32,5%), Temporal lobe (32,5%), Occipital lobe (21,9%), Corpus Callosum (8,2%), Pineal gland (4,1%), Basal ganglia (2,7%), Brain stem (1,4%), Cerebellum (1,4%), Spine (1,4%) and Periventricular area (1,4%). Invasion of more than one part was reported in most of the cases.

GCAs have been most commonly seen in the fifth decade of life and has a male predominance. Out of 73 patients, 27 were female and 56 were male. The age of diagnosis ranges from 9 to 83. Median diagnosis age of these patients is 58 years, and the mean diagnosis age is 56 years.

Surgery and adjuvant chemo-and radiotherapy has been the choice of treatment for most of the clinicians. Although the patients were treated with a multimodality strategy, the outcome is poor. 43 of 73 patients were followed until they die. The mean survival time of these patients was 9.56 months. The reason of poor outcome is not well established. There are some genetical differences demonstrated between GCAs and typical infiltrating astrocytomas. Allelic losses at chromosome segments 9p and 10q are more in GCAs. The rate of these losses is high even in low grade pathologies. This feature may explain the aggressive behavior (8).

Histopathology has the greatest role in the diagnosis. A clinical series revealed that these tumors were immunohistochemically OLIG2, GFAP, and CD68 (+) and IDH (–) (4). 69 of 73 patient's sections were

stained with PAS and 68 were positive. 5 were stained with OLIG 2 and, they were positive. 58 patient's sections were stained with GFAP and 56 were positive .45 were stained with CD68 and 33 of them were positive. IDH1 was stained in 10 sections and they were negative.

Cytogenetic investigations illustrated monosomy 10 in 6 of 6 patients. Deletion of 13q and 14 was also reported in some patients. Next-generation sequencing tests demonstrated mutations in PTEN/PIK3 genes, NF1, TP53, PALB2, STAG2, AR, and EGFR in different ratios. CDKN2A/B deletion and TERTC228T mutations were also identified in a group of patients. No mutations regarding IDH1, IDH2, CIC, FUBP1, H3F3A, BRAF, and ATRX genes were observed. Demonstration of no correlation between the aggressive behavior of the malignancy and the grade or extent of the granular cell morphology was another important conclusion (4).

Atypical enhancement patterns and areas of diffusion restriction are findings of primary CNS lymphomas which led to the misdiagnosis of a GCA previously (9). GCA's imaging properties depend on the grade of the tumor. Contrast enhancement with central necrosis and peritumoral edema was reported in high-grade tumors (Grades 3 and 4). Hyperintense lesions without contrast enhancement was demonstrated on T2-weighted MRI images of grade 2 tumors (2).

Rosai-Dorfman disease (RDD) and Erdheim-Chester disease (ECD) are considered in the differential diagnosis. CNS involvement of RDD is seen in fewer than 5% of cases. Due to the atypical clinic and radiological features, the most accurate diagnostic method is histopathological examination. RDD's pathognomic cytological feature is the massive expansion of the sinusoids by large histiocytes with large vesicular nuclei and aberrant pale eosinophilic cytoplasm with ill-defined borders. Demonstrating the absence of emperipolesis, a phenomenon, where erythrocytes and lymphocytes are observed in histiocytes, in the S100 positive histiocytes is enough for exclusion of RDD in similar cases (10,11).

ECD is characterized by infiltration of organs by xanthomatous histiocytes, Touton giant cells, lymphocytes, and scattered plasma cells with surrounding fibrosis. Staining of these histiocytes are positive for CD68, CD163, Factor XIIIa and negative for CD1a and Langerin. Emperipolesis and S100 positivity are rarely seen in ECD. Due to the CD68 positivity and CD1a negativity in the current case, ECD is a possibility. Even though BRAFV600 and INI1 stainings are absent, demonstration of GFAP and OLIG2 positivity supports the diagnosis of GCA. In addition to that F13a negativity, absence of toutan giant cells, xanthomatous features and lack of other organ system involvement symptoms are against the ECD diagnosis. On the other hand, CD1a negativity excludes Langerhans Cell Histiocytosis diagnosis (11).

CONCLUSION:

The most challenging aspect regarding the approach to GCA is the diagnosis of the pathology. The aforementioned article includes universal information on GCAs and our process of investigation. We strongly believe that our experience will provide useful information for physicians dealing with GCAs.

Table 1: Immunohistochemical panel

Monoclonal Antibody	Reactivity	Cell Type	Location	Dilution	Company
S100	+	Neoplastic cells	Nuclear, Cytoplasmic	Ready-to-use	Genemed
GFAP	+	Neoplastic cells	Cytoplasmic	Ready-to-use	Genemed
EMA	+ (80%)	Neoplastic cells	Paranuclear dot-like	Ready-to-use	Thermo
IDH1	-	No reactivity	Cytoplasmic	1/15	Dianova
EGFR	+ (100%)	No reactivity	Mem branous	1/50	Cell Marque
OLIG2	+ (60-80%)	No reactivity	Nuclear	1/100	Cell Marque
CD34	+ (20%)	Endotheliu m	Cytoplasmic	Ready-to-use	Thermo
Ki-67	30%	Neoplastic cells	Nuclear	Ready-to-use	Dako
p53	50%	Neoplastic cells	Nuclear	Ready-to-use	Genemed
Cd68	+ (Score 4)	Macrophages in germinal centers, microglial cells	Cytoplasmic	Ready-to-use	Dako
CD1a	-	Langerhans cells, Thymocytes	Membranous, Cytoplasmic	Ready-to-use	Dako
F13a	-	Plasma cells	Cytoplasmic	1/120	Medaysis
CD79a	-	Plasma cells, B-cells	Cytoplasmic	Ready-to-use	Dako
CD138	+(Score 2)	Plasma cells, Endothelial cells	Membrane	Ready-to-use	Dako

Table 2: Features of previously published cases of GCA

Year	Reference	Location	Age/Sex	Treatment	OLIG2	GFAP	Cd68	IDH1	PAS	Survival (months)
1973	Markesbery et al (1)	P	58/M	STR+RT	N/A	N/A	N/A	N/A	+	17
1975	Ule et al (12)	O-C-Brain stem	55/M	-	N/A	N/A	N/A	N/A	+	6
1978	Pialat et al (13)	P-O	61/M	STR	N/A	N/A	N/A	N/A	+	4
1980	Pasquier et al (14)	T-P-O	64/F	TR	N/A	N/A	N/A	N/A	+	8
1981	Sakurama et al (15)	Fr-BG	50/M	STR+RT	N/A	N/A	N/A	N/A	+	12
		Fr-T-P	37/M	STR+RT	N/A	N/A	N/A	N/A	+	24
1982	Lechevalier et al (16)	P-O	62/M	STR+RT	N/A	+	N/A	N/A	+	alive
1985	Hori et al (17)	3rd Ventricle	56/F	TR	N/A	N/A	N/A	N/A	+	0.25
1986	Dickson et al (18)	Fr	27/F	STR+RT	N/A	+	N/A	N/A	+	alive
	Kornfeld et al (19)	T-P	49/M	-	N/A	N/A	N/A	N/A	+	8
		Fr-P	46/M	STR+RT	N/A	N/A	N/A	N/A	+	2
1987	Conzen et al (20)	T-P	71/F	STR+RT	N/A	+	N/A	N/A	+	N/A
1989	Kawano et al (21)	T	62/M	STR+RT+CT	N/A	+	N/A	N/A	+	9
1990	Nakamura et al (22)	C	41/M	STR+RT+CT	N/A	+	N/A	N/A	+	16
	Claassen et al (23)	P-O	50/M	STR+RT	N/A	N/A	N/A	N/A	+	alive
	Gambini et al (24)	Fr	46/F	STR+RT	N/A	N/A	N/A	N/A	+	6
1991	Harris et al (25)	O	65/M	B+RT	N/A	+	N/A	N/A	+	12
1992	Albuquerque et al (26)	Fr-T-P	62/F	STR	N/A	+	N/A	N/A	+	5

	Snipes et al (27)	PG	25/F	STR+RT	N/A	+	N/A	N/A	+	alive
		PG	36/M	STR+RT	N/A	+	N/A	N/A	+	alive
1993	Melaragno et al (28)	T	60/M	B+RT	N/A	+	N/A	N/A	N/A	alive
1996	Geddes et al (29)	O	57/F	TR	N/A	+	-	N/A	+	12
		P-O	64/M	STR+RT	N/A	+	-	N/A	+	8
		T-P	55/F	TR+RT	N/A	+	-	N/A	+	8
		P	65/M	B+RT	N/A	+	-	N/A	+	4
		Fr	66/F	B+RT	N/A	+	-	N/A	+	alive
2000	Chorny et al (30)	Fr-P-C	78/M	TR+RT+CT	N/A	N/A	+	N/A	+	7
		Fr-P-O	83/F	B+RT	N/A	N/A	-	N/A	+	3
		T-P	66/F	STR+RT+CT	N/A	N/A	-	N/A	+	25
2002	Brat et al (2)	P	49/F	TR+RT	22:N/A	1: N/A 19:+2: -	5: N/A 15: +2: -	22:N/A	22:+	51
		P-O	69/M	TR+RT						3
		T	59/M	STR						1
		P	47/M	STR+RT						11
		P	29/M	STR+RT						3
		T	72/M	STR+RT						10
		P	45/M	STR+RT						12
		Fr-P	49/M	STR						1
		T	60/M	STR+RT+CT						5
		C-Fr	44/M	-						N/A
		O	52/M	STR+RT						12
		T	62/M	-						N/A
		C-Fr	55/F	STR+RT+CT						7
		Fr	70/F	STR+RT						9
		Fr	66/F	TR+RT						5
		O	56/M	-						N/A
		Fr-P	75/F	STR+RT						11
		Fr-P	75/M	STR+RT						1
		Fr	68/M	TR						9
		T	54/M	-						N/A
		P	72/M	STR						9
		T	47/M	ST+RT+CT						7
2006	Saad et al (7)	Cerebellum	9/Fe	-	N/A	+	+	N/A	+	0.5
2007	Shin et al (31)	T	28/F	TR	N/A	+	N/A	N/A	+	10
	Rodriguez y Baena (32)	Spine	48/F	TR+RT	N/A	+	+	N/A	+	alive
	Kinjo et al (33)	Fr	68/M	STR	N/A	+	-	N/A	+	6
2008	Lee et al (34)	O	47/M	B+RT	N/A	+	+	N/A	+	alive
	Wierzba-Bobrowicz et al (35)	P	59/M	TR	N/A	+	+	N/A	+	N/A
2010	Schittenhelm et al (37)	T-O	69/F	TR+RT	N/A	+	+	-	+	5
2011	Arvanitis et al (36)	Fr	66/F	-	N/A	+	-	N/A	+	N/A
2012	Kim et al (38)	Fr	75/M	B	N/A	+	+	N/A	+	N/A
	Ishii et al (39)	T	56/F	STR+RT+CT	+	+	+	-	+	12
2013	George et al (40)	T	76/M	STR	N/A	+	+	-	+	N/A
2013	Joo et al (43)	Fr-T	55/F	TR+RT+CT	N/A	+	+	-	+	18
2014	Campbell et al (42)	T	58/M	B	N/A	+	+	N/A	N/A	6
	Yao et al (44)	Fr	52/F	TR+RT+CT	N/A	+	+	N/A	+	N/A
2015	Voellger et al (45)	P-O	64/F	B+RT	N/A	+	+	-	+	13
	Imitola et al (41)	Peri ventricular	51/M	TR+RT+CT	N/A	+	N/A	-	N/A	3
	El Asri et al (6)	PG	16/M	STR	N/A	+	+	N/A	+	alive
2016	Caporalini et al (46)	P-O	54/M	TR+RT+CT	N/A	+	-	N/A	+	alive
2021	Hussain et al (47)	C-F-BG	59/M	STR+RT	+	+	+	-	N/A	N/A
	Homma et al (48)	T-P	64/M	STR+RT+CT	+	+	+	-	+	alive
2023	Batool et al (49)	P	64/M	TR+RT	+	+	+	-	+	N/A
	Current case	T-P	51/F	TR+RT+CT	+	+	+	-	-	N/A

Abbreviations:

Fr: Frontal lobe, T: Temporal lobe, P: Parietal lobe, O: Occiptal lobe, C: Corpus Callosum, BG: Basal ganglia, PG: Pineal Gland, F: Female, M: Male, STR: Subtotal resection, TR: Total resection, B: Biopsy, RT: Radiotherapy, CT: Chemotherapy, N/A: Not available

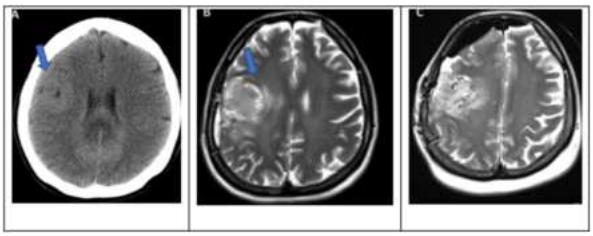

Figure 1: A)Pre-op CT image taken on 16.10.2018 demonstrates the lesion on temporoparietal lobe B) Pre-op MRI image taken on 21.11.2018 demonstrates the residual malignancy area C) Post-op MRI image taken on 30.11.2018 does not illustrate any abnormality.

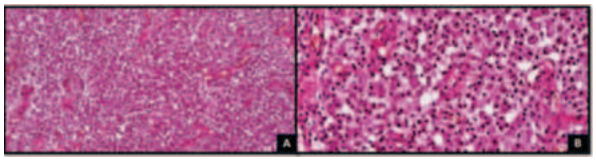

Figure 2: A) Hypercellular tumor composed of monotonous cells unaccompanied with necrosis and microvascular proliferation. (HE, x100, original magnification) B) Highpower field reveals tumor cell with granular cytoplasms.(H&E, x800 original magnification)

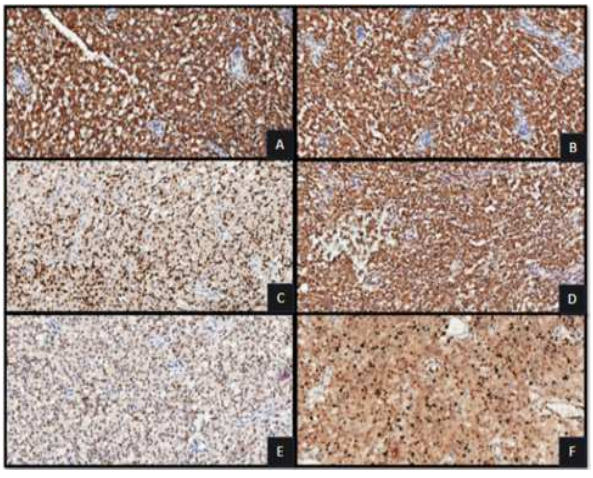

Figure 3:A) GFAP: Tumor cells are immnureactive to GFAP (GFAP, x400, Streptavidine biotinylated complement) B) Diffuse and strong reactivity to EGFR (EFGR, x400, Streptavidine biotinylated complement) C) Diffuse and strong nuclear reactivity to Olig2 (Olig2, x400, Streptavidine biotinylated complement)D) Diffuse and strong reactivity to CD68 (CD68 x400, Streptavidine biotinylated complement) E) Almost half of tumor cells bear nuclear oncoprotein p53 (p53, x400, Streptavidine biotinylated complement) 3F) Ki-67labeling index calculated 80% (MIB-1 x400, digital assisted computerized quantification, Streptavidine biotinylated complement

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