ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International

Editor-in-Chief: Nancy E. Epstein, MD, Clinical Professor of Neurological Surgery, School of Medicine, State U. of NY at Stony Brook.

SNI: Neuro-Oncology

Editor
Mitsutoshi Nakada, MD
Kanazawa University, Ishikawa, Japan

SNI
Open Access

Case Report

Oligodendroglioma with ganglioglioma-like maturation: the histopathological diagnostic challenge of a brain neoplasm with aberrant neuronal component – A case report and review of the literature

Gabriele Gaggero[1], Luca Carlin[2], Luca Valle[1], Giulia Gnocchi[3], Elisa Bennicelli[4], Pietro Fiaschi[5]

[1]IRCCS Ospedale Policlinico San Martino, Anatomic Pathology Unit, Genoa, Italy, [2]DISC, University of Genova, Genova, [3]Radiology Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, [4]Medical Oncology Unit, Ospedale Policlinico San Martino, [5]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal-Infant Sciences, University of Genoa, Genoa, Italy.

E-mail: *Gabriele Gaggero - gabriele.gaggero@hsanmartino.it; Luca Carlin - carlin.dla@hotmail.it; Luca Valle - valleluca9@gmail.com; Giulia Gnocchi - giulia.gnocchi@hotmail.it; Elisa Bennicelli - elisa.bennicelli@hsanmartino.it; Pietro Fiaschi - pf.pietrofiaschi@gmail.com

***Corresponding author:**
Gabriele Gaggero,
Anatomic Pathology Unit,
Ospedale Policlinico San
Martino, IRCCS, Genoa, Italy.

gabriele.gaggero@hsanmartino.it

Received : 29 August 2022
Accepted : 30 November 2022
Published : 23 December 2022

DOI
10.25259/SNI_792_2022

Quick Response Code:

ABSTRACT

Background: Oligodendroglioma with ganglioglioma-like maturation is a rare entity not included in the 2016 World Health Organization Classification of Tumors of the Central Nervous System. To date, only a few cases were described in the literature. We report a case of this tumor, along with a review of the previous case reports/series.

Case Description: A 63-year-old man with a left frontal mass and a 2-month history of seizures underwent surgical resection in our center. Grossly, the specimen appeared as a yellowish mass with prominent hemorrhagic component. Microscopically, the lesion was composed by small round cells often surrounded by a clear halo and, near the hemorrhagic area, by scattered large cuboidal cells with vesicular nuclei and prominent eosinophilic nucleoli. On immunohistochemical stains, both cells components tested positive for ATRX, p53, and GFAP; larger ganglion-like cells showed synaptophysin and chromogranin-A expression. IDH1 codon 132 mutation, 1p-19q-codeletion, and MGMT methylation were observed. Eventually, a diagnosis of oligodendroglioma (the WHO grade II) with ganglioglioma-like maturation was rendered. The patient received adjuvant chemotherapy and is currently alive and asymptomatic.

Conclusion: Recognition of ganglioglioma-like maturation in oligodendrogliomas may prevent undertreatment of these neoplasms. To this end, fluorescence *in situ* hybridization assays are crucial for defining the 1p-19q status.

Keywords: 1p-19q, Ganglioglioma-like maturation, Oligodendroglioma

INTRODUCTION

For the 1st time, the 2016 World Health Organization Classification of Tumors of the Central Nervous System (CNS) added molecular parameters to histological features to define many tumor entities. In fact, the diagnosis of oligodendroglioma and anaplastic oligodendroglioma requires the demonstration of both IDH1 or IDH2 mutation and codeletion of chromosomal arms 1p and 19q.[6]

Despite it represents a crucial innovation, this classification does not define a subgroup of oligodendrogliomas characterized by the presence of aberrant neuronal differentiation. These tumors were first described by Perry *et al*. in 2002 and 2010 and defined as "oligodendrogliomas with neurocytic differentiation" and "oligodendroglial neoplasms with ganglioglioma-like maturation."[9,10]

Knowing the existence of this, although very rare, histotype does not constitute merely a microscopic descriptive peculiarity, rather represents a crucial differential diagnostic crossroads between oligodendroglioma and ganglioglioma, with important clinical consequences: in fact, while oligodendroglioma (beyond the histological subtype) is still a diffuse glial neoplasm, ganglioglioma, on the other hand, represents an entity with extremely mild biological behavior.

More in detail

Gangliogliomas are rare slow-growing neuroepithelial tumors, composed by both neoplastic ganglion and glial cells, usually affecting children and young adults with a male predominance. They are preferentially located in the temporal lobe, but they can occur throughout all the CNS.[3] Most gangliogliomas are well-differentiated neoplasms, corresponding to the WHO grade I, in which the proportion of the two components varies considerably. Neuronal cells usually show dysplastic features, such as clustering, lack of cytoarchitectural organization, multinucleation, and peripheral aggregation of Nissl substance. They often show strong expression of chromogranin-A (usually absent or weak in normal neurons), CD34 (a stem cell epitope not expressed in normal brain and only rarely expressed by astrocytomas and oligodendrogliomas), and Neu-N (absent in neurons of adult brain): these immunohistochemical markers could be useful in distinguishing dysplastic ganglion cells from normal dysmorphic neurons entrapped in diffuse gliomas. The ganglioglioma glial component includes cell types usually resembling fibrillary astrocytoma and pilocytic astrocytoma, usually embedded in a fibrillary matrix with microcystic cavities and/or myxoid degeneration.[2] However, a pure oligodendroglial ganglioglioma was reported.[14] The proliferative activity of gangliogliomas is generally <2% as determined by investigations of Ki-67 immunolabeling.[5] Occasional mitoses and small foci of necrosis are compatible with the diagnosis of ganglioglioma, but neoplasms with overt malignant changes of the glial component could be classified as the WHO grade III. BRAF V600E mutation occurs approximately in 25% of gangliogliomas, whereas IDH mutation or combined loss of chromosomal arms 1p and 19q exclude the diagnosis, leading to an oligodendroglioma. Gangliogliomas prognosis is usually excellent, the recurrence rate after a complete resection is low and about the 80% of patients with chronic epilepsy have a complete and lasting seizure remission.[2,7]

On the other hand, oligodendrogliomas are usually diffusely infiltrating, low grade, and slow-growing gliomas with tumor cells resembling oligodendrocytes (monomorphic rounded nuclei with a surrounding artifactual halo giving the cells the so-called "fried egg" appearance).[1] These tumors are rare in pediatric age, usually affecting adults, and involving the cerebral hemispheres, frontal lobes being the most common location.[13] The new WHO 2016 classification requires both IDH1 (or IDH2) mutation and codeletion of chromosomal arms 1p and 19q to make this diagnosis. In case of absence of testing capabilities or if the genetic results are inconclusive, in presence of the typical histological features of oligodendroglioma, the diagnosis of oligodendroglioma NOS should be made.[6]

IDH-mutant and 1p/19q codeleted oligodendrogliomas typically show nuclear expression of ATRX (absent in most IDH-mutant diffuse astrocytomas) and no mutant-type p53 nuclear staining (often present in IDH-mutant astrocytomas). Ki-67 proliferation index is usually <5%. Nuclear atypia and occasional mitosis are compatible with the diagnosis of an oligodendroglioma (the WHO grade II tumor), but marked mitotic activity (at least six mitotic figures per high-power field), prominent microvascular proliferation, and spontaneous necrosis are indicators of anaplastic oligodendroglioma (corresponding to the WHO grade III).

In this differential clinical-diagnostic context, to the best of our knowledge, only few cases of oligodendroglioma with ganglioglioma-like maturation have been described.[4,8-12]

With the aim of collecting data to better characterize this rare entity, we present an oligodendroglioma displaying ganglion cells, including its histological and immunohistochemical findings and a review of the related literature.

CASE DESCRIPTION

A 63-year-old man presented to our hospital with a 2-month history of epileptic seizures. A head CT was performed revealing a left frontal large inhomogeneous isohypodense area, with tenuously hyperdense components and numerous focal calcium deposits, probably related to a productive lesion.

The MRI showed a large area of altered signal of uneven appearance with both cortical and white matter involvement, hyperintense on T1-weighted images, related to the known heteroplastic productive lesion. Within the lesion, small postcontrast agent hyperintense spots seemed to be appreciated. The characteristics of the MRI images in accordance with the CT images were suggestive of oligodendroglioma. No other lesions were found on whole body CT. Surgical removal of the lesion and pathological examination was performed.

The lesion appeared as a 5 cm coarse yellowish mass with a hemorrhagic component involving about half of the specimen.

Table 1: Clinical features in cases of oligodendroglioma with ganglioglioma-like maturation or neurocytic differentiation.

Case	Age	Sex	Site	Imaging features	Therapy	WHO	Patient status	Clinical follow-up	Recurrence after	Oligo component (FISH)	GGLF/NDF (FISH)
1[10]	43	M	L-FL	Min E	STR+RT	III	A	4 y	3 y	1p-deleted, 19q-deleted	1p-deleted, 19q-deleted
2[a][10]	34	M	L-FL	N/A	RT (TR) (TR) (TR)	III	A	13 y	4.3 y, 7.4 y and 8.5 y	1p-deleted, 19q-deleted	1p-deleted, 19q-deleted
3[10]	54	F	L-FL	Het E	STR+CT	III	A	4 m	/	1p-deleted, 19q-deleted	1p-deleted, 19q-deleted
4[10]	43	F	R-FL	Non E	STR (RT) (CT)	II	A	10 y	5 y and 9 y	1p-19q normal	1p-19q normal
5[9]	44	M	R-FL	Het E	STR+RT+CT	III	A	2.1 y	/	1p-deleted, 19q-deleted	1p-deleted, 19q-deleted
6[b][9]	58	M	L-TPL	Non E	STR+RT+CT (STR+CT) (CT)	III	D	7.5 y	4.4 y and 7 y	1p-deleted, 19q-deleted	Noninformative
7[9]	40	M	R-FPL	Het E	STR+CT	III	A	4.9 y	/	19q-deleted, 1p/19q LOH[c]	19q-deleted
8[9]	29	F	L-FL	Het E	STR (STR+CT)	III	A	3.5 y	2.2 y	1p-deleted, 19q-deleted	Noninformative
9[9]	55	M	R-FL	Het E	STR+RT	II	A	8 m	/	1p-deleted, 19q-normal	1p-deleted, 19q-normal
10[9]	63	F	L-FL	Min E	STR+RT+CT	III	A	1 m	/	1p-deleted, 19q-deleted	1p-deleted, 19q-deleted
11[9]	42	M	R-FL	Het E	STR	III	A	RD	/	Polysomies of 1 and 19	Polysomies of 1 and 19
12[12]	66	F	L-TL	Het E	R	III	N/A	N/A	N/A	1p/19q LOH	N/A
13[11]	40	M	R-IC	Het E	STR+RT+CT (STR+RT+CT)	III	A	1 y	1 y	1p-deleted, 19q-deleted`	1p-deleted, 19q-deleted
14[4]	46	F	R-FL	Non E	STR	II	A	1.3 y	/	1p-deleted, 19q-deleted	1p-deleted, 19q-deleted
15[8]	31	M	R-FL	N/A	TR+RT	II	A	2.5 y	/	1p-deleted, 19q-deleted	N/A
16 [our case]	63	M	L-FL	Het E	STR	II	A	2 m	/	1p-deleted, 19q-deleted	N/A

M: Male, F: female, R: Right, L: Left, FL: Frontal lobe, TPL: Temporoparietal lobe, FPL: Frontoparietal lobe, TL: Temporal lobe, IC: Insular cortex, Min E: Minimally enhancing, Het E: Heterogeneously enhancing, Non-E: Nonenhancing, STR: Subtotal resection, TR: Total resection, R: Resection (not specified if total/subtotal) , RT: Radiation therapy, CT: Chemotherapy, (): Therapy after recurrence, N/A: Not available, A: Alive, D: Dead, y: Years, m: Month, RD: Recently diagnosed, GGLF: Ganglioglioma-like foci, NDF: Neurocytic differentiation foci. [a]Case nr. 2 at first presented as anaplastic oligodendroglioma and then, on the second recurrence, as oligodendroglioma with neurocytic differentiation. [b]Due to poor specimen preservation, case nr. 6 could only be diagnosed as "diffuse glioma" not otherwise specified at first presentation. The tumor recurred as an anaplastic oligodendroglioma with focal ganglioglioma-like features. [c]Since chromosome 1p status was not informative by FISH in case nr. 7, loss of heterozygosity was investigated

After fixation in 10% buffered formalin, the entire surgical specimen was sampled according to standard procedures and embedded into paraffin. Serial 4-μm thick sections were stained with hematoxylin-eosin for conventional histology. Immunohistochemistry was performed on the paraffin sections with the following antibodies: synaptophysin (SP15, Ventana, Arizona, USA), Chromogranin A (LK2H10, Ventana, Arizona, USA), GFAP (EP672Y, Ventana, Arizona, USA), p53 (DO-7, Ventana, Arizona, USA), CD34 (QBEnd/10, Ventana, Arizona, USA), ATRX (D-5, Santa Cruz, Texas, USA), and Ki-67 (30-9, Ventana, Arizona, USA). The reactions were visualized using DAB detection.

Point mutations of IDH1 (codons 105/132), IDH2 (codons 140/172), and e BRAF (codon 600) were searched by real-time polymerase chain reaction. Hypermethylation of the MGMT promoter was verified by Pyrosequencing. The 1p/19q status was investigated with fluorescence *in situ* hybridization (FISH).

Microscopically, the lesion was composed by small round cells with slightly hyperchromatic nuclei often surrounded by a clear halo embedded in a fibrillary matrix. Near the degenerative hemorrhagic area, the lesion was hypercellular with scattered large and squared-shape cells, vesicular nuclei, and prominent eosinophilic nucleoli resembling ganglion cells. No anaplastic cells, mitoses, endothelial proliferation, or necrosis could be seen.

The lesion exhibited distinctive immunohistochemical profiles. Larger ganglion-like cells showed expression of synaptophysin and chromogranin-A, but no CD34 expression [Figure 1]. Both cells' components showed that expression of ATRX, p53, and GFAP was positive in almost all the lesion. Ki-67 labeling index was 1.1% in a hotspot of 4069 cells. IDH1 was mutated at codon 132 by DNA genotyping and 1p/19q codeletion was highlighted by FISH examination. MGMT gene was found methylated. Moreover, no BRAF V600E mutation in exon 15 by direct DNA sequencing could be detected.

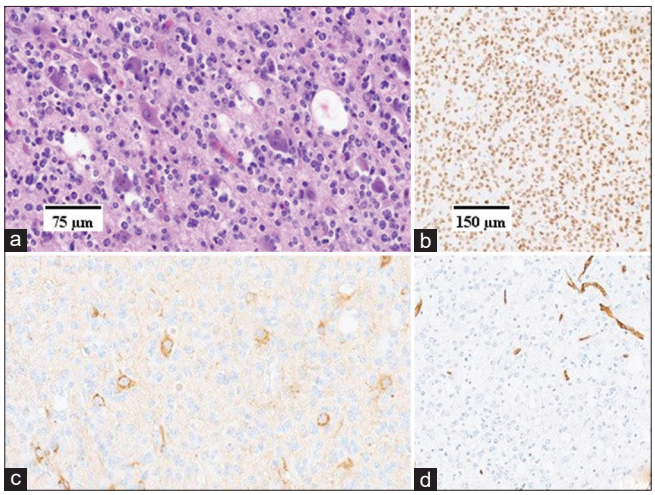

Figure 1: (a) Hematoxylin-Eosin: large neuronal cells can be seen between small round oligodendrocytes. (b) ATRX immunohistochemical staining: a diffuse staining is present in neoplastic cells. (c). Chromogranin immunohistochemical staining: An intense granular pattern is expressed in large neuronal cells. (d) CD34 immunohistochemical staining: neither small oligodendrocytes nor large neuronal cells expressed this marker. Scale bars: 75 μm (a-c); 150 μm (b and d).

Finally, the case was diagnosed as oligodendroglioma WHO grade II with ganglioglioma-like maturation, IDH1-mutated, and 1p/19q codeleted.

After 2 months from the surgery (subtotal resection of the tumor), the patient received chemotherapy for 7 months, due to an increasing of the residual lesion on RM and PET scans. The patient is currently alive and asymptomatic.

CONCLUSION

This case showed considerable diagnostic difficulties: in particular, the histopathological coexistence of glial cells with cytological similarities to oligodendrocytes, together with neuronal cells (ganglion-type), places oligodendroglioma, and ganglioglioma among the main differential diagnosis: two entities so similar histologically, as different in their molecular profile and respective clinical outcome since ganglioglioma usually has an indolent behavior compared with other neoplasms with diffuse glial component.

Immunophenotypic features (no expression of CD34 and expression of ATRX by ganglion-like cells) and molecular findings (IDH1 mutation and 1p/19q codeletion) lead us to conclude that our case was a rare example of oligodendroglioma with ganglioglioma-like maturation. Very few cases of this tumor to date have been described, and the characteristics of each are shown in Table 1. Our case, while morphologically overlapping with the others, shows only two differences from most of the others: the slightly older age of our patient in contrast to the mean age of other cases (45.9 years) and the lower WHO grade (II vs. III).

As previous authors have stated, recognition of ganglioglioma-like maturation in oligodendrogliomas may prevent misdiagnosis and undertreatment of these neoplasms.[9] To this end, FISH assays are crucial for defining the 1p/19q status, both in the oligodendroglial and the ganglioglioma-like components.[4,11] We hope that the findings we present could help raising information about this rare entity with aberrant neurocytic differentiation.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bailey P, Bucy PC. Oligodendrogliomas of the brain. J Pathol Bacteriol 1929;32:735-51.
2. Blümcke I, Wiestler OD. Gangliogliomas: An intriguing tumor entity associated with focal epilepsies. J Neuropathol Exp Neurol 2002;61:575-84.
3. Dudley RW, Torok MR, Gallegos DR, Mulcahy-Levy JM, Hoffman LM, Liu AK, *et al*. Pediatric low-grade ganglioglioma: Epidemiology, treatments, and outcome analysis on 348 children from the surveillance, epidemiology, and end results database. Neurosurgery 2015;76:313-20.
4. Hirose T, Nobusawa S, Nakazato Y, Sasaki A. A case of oligodendroglioma with prominent neuronal differentiation. Hum Pathol 2013;44:2353-9.
5. Hirose T, Scheithauer BW, Lopes MB, Gerber HA, Altermatt HJ, VandenBerg SR. Ganglioglioma: An ultrastructural and immunohistochemical study. Cancer 1997;79:989-1003.
6. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al*. The 2016 world health organization classification of tumors of the central nervous system: A summary. Acta Neuropathol 2016;131:803-20.
7. Luyken C, Blümcke I, Fimmers R, Urbach H, Wiestler OD, Schramm J. Supratentorial gangliogliomas: histopathologic grading and tumor recurrence in 184 patients with a median follow-up of 8 years. Cancer 2004;101:146-55.
8. Park JH, Cha YJ, Chang JH, Lee SK, Kim SH. A rare case of oligodendroglioma with gangliocytic differentiation in a 31-year-old male: Importance of genetic testing for IDH1/2. Brain Tumor Pathol 2020;37:95-9.
9. Perry A, Burton SS, Fuller GN, Robinson CA, Palmer CA, Resch L, *et al*. Oligodendroglial neoplasms with ganglioglioma-like maturation: A diagnostic pitfall. Acta Neuropathol 2010;120:237-52.
10. Perry A, Scheithauer BW, Macaulay RJ, Raffel C, Roth KA, Kros JM. Oligodendrogliomas with neurocytic differentiation. A report of 4 cases with diagnostic and histogenetic implications. J Neuropathol Exp Neurol 2002;61:947-55.
11. Tanaka Y, Nobusawa S, Yagi S, Ikota H, Yokoo H, Nakazato Y. Anaplastic oligodendroglioma with ganglioglioma-like maturation. Brain Tumor Pathol 2012;29:221-8.
12. Vajtai I, Arnold M, Vassella E. Oligodendroglioma with neurocytic differentiation and characteristic loss of heterozygosity on chromosomes 1p and 19q. Acta Neuropathol 2005;110:520-2.
13. Wesseling P, van den Bent M, Perry A. Oligodendroglioma: Pathology, molecular mechanisms and markers. Acta Neuropathol 2015;129:809-27.
14. Yamashita S, Yokogami K, Niibo T, Takeishi G, Ikeda T, Miyata S, *et al*. Oligodendroglial ganglioglioma. Brain Tumor Pathol 2011;28:311-6.

How to cite this article: Gaggero G, Carlin L, Valle L, Gnocchi G, Bennicelli E, Fiaschi P. Oligodendroglioma with ganglioglioma-like maturation: the histopathological diagnostic challenge of a brain neoplasm with aberrant neuronal component – A case report and review of the literature. Surg Neurol Int 2022;13:587.