



# Oligodendroglioma with Anaplastic Features, Case Report and Review of the Literature

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## Abstract

Anaplastic oligodendrogliomas (AOD) are rare brain tumors with variable overall survival accounting for approximately 1.3% to 4.4% of brain tumors and about 5% to 10% of the gliocytomas. Anaplastic oligodendrogliomas, or grade III oligodendrogliomas, describe rare primary malignant brain tumors with exceedingly variable overall prognosis. Gliomas originate from neural stem cells or glial progenitor cells that develop or maintain glial characteristics. These tumors occur most frequently in males during the 5th and 6th decade of life often presenting with new onset seizures. The WHO grading system distinguishes two histopathologic grades of Oligodendrogliomas: grade II (low-grade) and grade III (anaplastic oligodendroglioma or AOD). Here we present a case of anaplastic oligodendrogliomas and review the literature.

**Keywords:** Oligodendrogliomas, Anaplastic, Grade, Molecular, benign

## ABBREVIATION

**AOD:** Anaplastic oligodendrogliomas, **LOH:** loss of heterozygosity, **WHO:** World Health Organization, **LGGs:** low-grade gliomas, **PFS:** progression-free survival, **OS:** overall survival, **pODG:** pediatric oligodendrogliomas,

## INTRODUCTION

Anaplastic oligodendrogliomas (AOD), or grade III oligodendrogliomas, describe rare primary malignant brain tumors with exceedingly variable overall prognosis (1,2). Oligodendrogliomas represent approximately 1.3% to 4.4% of brain tumors and about 5% to 10% of the gliocytomas (3). Gliomas originate from neural stem cells or glial progenitor cells that develop or maintain glial characteristics (4). Studies showed that the most common location for primary oligodendrogliomas occurs within the frontal lobes of the cerebral hemispheres (5). Structural imaging reveals two main key features of oligodendrogliomas: calcification and cortical-subcortical location. When found infratentorial or in deep nuclei, oligodendroglial tumors historically represent a more aggressive phenotype (6).

Oligodendrogliomas occur most frequently in males during

the 5<sup>th</sup> and 6<sup>th</sup> decade of life often presenting with new onset seizures (4). AOD almost exclusively presents as a single lesion. Although several case reports of multifocal AOD, leptomeningeal spread, and extraneural metastases exist. These cases are rare and potentially reflect the natural course of a glioma with prolonged survival (5, 6). Patients experiencing generalized tonic-clonic seizures frequently exhibited the greatest lesion load in mesial frontal regions such as the cortex connected to the genu of the corpus callosum. While patients with partial seizures experienced oligodendrogliomas more caudo-laterally in orbitofrontal and temporal lobes, sparing cortex connected to the genu. These findings indicate that the genu of the corpus callosum serves as a major pathway for seizure generalization (4, 7).

Researchers identified that loss of heterozygosity (LOH) of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q, 1p19q LOH) in tumor tissue represents a somatic genetic finding common to oligodendrogliomas (8, 9). The co-deletion of chromosomal arms 1p and 19q serves diagnostic importance as well as provides prognostic and predictive relevance (10). The current standard therapy of oligodendrogliomas includes neurosurgery with radiation and chemotherapy (11-13).

## CASE PRESENTATION

A 40-year-old man presented with severe headache, visual disturbance and generalized epileptic seizures. No significant medical history was identified. MRI with gadolinium was performed and a single frontal lobe mass was identified. T1 images demonstrated mixed hypointense and hyperintense mass. T2 images revealed a hyperintense mass with mild surrounding edema. Enhancement was noted with contrast administration. Intratumoral calcification was also noted.

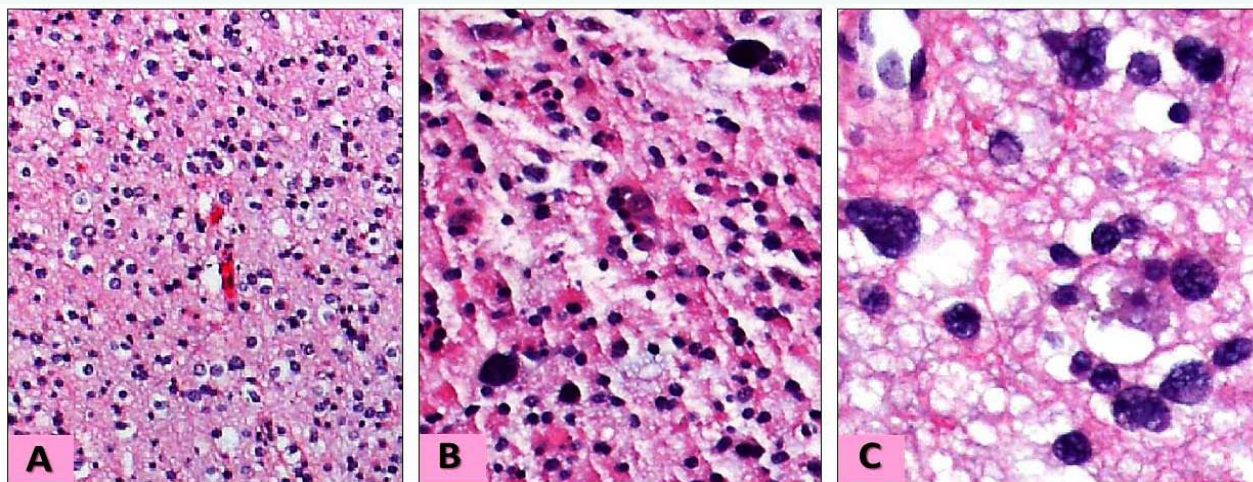
Stereotactic biopsy was obtained, the tumor showed diffuse infiltration with moderate cellularity (**Figure 1A**). Branching small, chicken wire-like blood vessels and fried egg-like cells, with clear cytoplasm and well-defined cell border characteristic of oligodendroglioma were noted (**Figure**

**Submitted:** 31 March, 2021 | **Accepted:** 28 April, 2021 | **Published:** 30 April, 2021

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**Citation:** Mahmoudzadeh S, Parrill A, Tsao T, Eaton K, Sheplay K, et al. (2021) Oligodendroglioma with Anaplastic Features, Case Report and Review of the Literature. SM J Neurol Neurosci 7: 5.



**Figure 1** Pathologic examination of the tumor.

**1A:** The tumor shows diffuse infiltration with moderate cellularity (H&E stain X20). **1B:** Branching small, chicken wire-like blood vessels and fried egg-like cells, with clear cytoplasm and well-defined cell border characteristic of oligodendroglioma were noted (H&E stain X40). **1C:** Many areas showed increased nuclear pleomorphism and vascular proliferation (H&E stain X60)

**1B).** Many areas showed increased nuclear pleomorphism and vascular proliferation (**Figure 1C**). Some foci showed sheets of pleomorphic oligodendrocytes with hyperchromatic nuclei, clear to eosinophilic cytoplasm, increased mitotic activity (>6 mitotic figures/10 HPF), and necrosis. Sheets of minigemistocytes and lymphocytic infiltrate were also identified. The tumor morphologic features were consistent with anaplastic oligodendrogliomas grade III. FISH analysis failed to demonstrate 1p36 or 19q13 deletions. Extra signals of 1 and 19 chromosomes were observed suggestive of Trisomy/tetrasomy.

The patient received aggressive multimodal treatment including surgical resection, radiotherapy, and chemotherapy (combination chemotherapy with packed cell volume “PCV” administered every 6 weeks for a total of 6 cycles). The patient was followed with regular MRI scans at 3 months initially and then every 6 months. Despite prolonged response, the patient experienced disease relapse and ultimately expired of progressive disease 18 months later.

## DISCUSSION

The World Health Organization (WHO) classification divides astrocytoma into four grades (I–IV), separated according to the glial type from which they arise, astrocytoma or oligodendroglioma (14, 15). The WHO classifies diffuse low-grade gliomas (LGGs) as grade II astrocytomas, oligodendrogliomas, and oligoastrocytomas (14–17). Clinicians often classify low-grade gliomas as benign neoplasm, disregarding their association with neurological morbidity and mortality and potential for anaplastic transformation (15, 18). Unfortunately, lack of sufficient data results in unclear optimum management of this tumor and individual clinical judgement with subsequent debate currently drives the decision-making process (15, 19).

Anaplastic oligodendroglial tumors frequently present with additional genetic aberrations, in particular 9p LOH and/

or deletion of the *CDKN2A* gene (p16), *PIK3CA* mutations, and polysomies (4, 20, 21). Some studies suggest shortened recurrence free survival times or poorer prognosis in patients who developed oligodendroglial tumors with polysomy of 1p and 19q (4, 22, 23). The finding of 1p19q LOH in a glial neoplasm shows predictive value of tumor chemosensitivity and prolonged patient survival (24–27). When defined by strict histological criteria or a unanimous diagnosis by four neuropathologists, 1p19q LOH occurred in over 85% of oligodendrogliomas (8, 27, 28). IDH1 mutations occur mainly in low-grade gliomas (astrocytomas and oligodendrogliomas) and retain during tumour progression. This mutation helps distinguish low-grade gliomas from other tumour entities where the mutation is absent or uncommon. The presence of an IDH1 mutation also impacts prognosis, with a median survival of 3.8 years for patients with mutated IDH1, versus 1.1 years for patients with wild-type IDH (15, 29). One study evaluated prognostic factors of AOD including surgical, radiographic, and histopathologic analysis of 95 patients diagnosed with AOD for 20 years. They measured progression-free survival (PFS) and overall survival (OS). The researchers performed subgroup analyses in isocitrate dehydrogenase (*IDH1/2*)-mutant and 1p/19q-codeleted patients. The median PFS and OS lengths were 24.7 months and 50.8 months respectively. Patients with the *IDH1/2*-mutant and 1p/19q-codeletion yielded median PFS and OS lengths of 54.2 and 57.8 months, respectively. This study concluded that young age, frontal lobe involvement, weak enhancement, gross total resection, low Ki-67 index, 1p/19q-codeletion, and *IDH1/2* mutations yielded favorable outcomes (30).

Another study evaluated the overall survival (OS) in pediatric oligodendrogliomas (pODG) and found a mean of 199.6 months. Furthermore, the study concluded that pODG presented with smaller size and lower grade than similar adult tumors. Location, size, grade, use of radiotherapy, and extent of resection



represented significant prognostic factors with size and grade displaying stronger prognostic factors in children than adults. pODG is less frequently developed in the frontal lobe compared to adult tumors; however, the tumor more commonly occurred in the temporal lobe and extracortical regions. The study determined no significant difference in outcome between children with high-grade tumors and adults with high-grade tumors (31).

Low-grade oligodendrogliomas display round and uniform nuclei with crisp nuclear membranes, delicate chromatin and small-to-inconspicuous nucleoli. In anaplastic examples, despite maintaining an overall sense of regularity and nuclear roundness, cells frequently show enlarged and epithelioid cell structure with nuclei that often exhibit increased size and pleomorphism, vesicular chromatin pattern, and prominent nucleoli (4, 32, 33). However, the histopathological classification of diffuse glioma remains a subject of criticism and suffers from considerable interobserver variability. In fact, tumors with a similar microscopic appearance may present with significantly different clinical outcomes (34). Roughly only 30% of oligodendroglial tumors display anaplastic characteristics histologically. These findings include: nuclear atypia, increased cellularity, increased proliferation activity, and increased cell mitosis (13, 14).

Neurosurgery is instrumental for tumor removal and acquisition of neoplastic tissue in order to make a definitive diagnosis. Sophisticated diagnostic preoperative and perioperative methods, magnetic resonance imaging (MRI), use of 5-aminolevulinic acid, MRI tractography, perioperative ultrasound and MRI, awake surgical method, hybrid positron emission tomography (PET) and computed tomography (CT)) and navigated microsurgical techniques serve as integral parts of surgical treatment (12, 13). Non-contrast CT showed coarse calcifications in 90% of oligodendrogliomas (10). Confirming the extent of tumor resection requires a postoperative MRI with 24-72 hours following surgery. Additionally, clinicians reserve targeted-biopsy of the tumor when resection is impossible (13, 35, 36). Patients evaluated early on with modern technology such as 3-D ultrasound, intraoperative MRI, or mapping techniques often achieve safe resections, reducing overall neurological deterioration (18, 37). In AOD patients with LOH at 1p19q, MR single-photon emission computed tomography (SPECT) shows increased thallium-201 uptake irrespective of grade (38).

Researchers retrospectively reviewed Serial MRIs of 27 patients with untreated WHO grade II oligodendrogliomas or mixed gliomas. They examined the kinetics of tumor growth and anaplastic transformation and noticed that untreated low-grade oligodendrogliomas or mixed gliomas grow continuously during their premalignant phase. Analysis of the mean tumor diameters over time showed constant growth while linear regression found an average slope of 4.1mm per year with a relatively narrow range (Mandonnet, 2003). Due to the slow and often constant growth rate in LGGs (18, 39), reduction of tumor cells capable of undergoing malignant transformation via early resection may provide improved mortality. These researchers found a significant difference in low-grade glioma patients with improved overall survival, and a survival advantage that

increased with time in patients with early surgical dissection as opposed to those with biopsy and watchful waiting strategy (18). Additional favorable prognostic factors include young age, good overall medical condition (Karnofsky score), larger extent of tumor resection and combined oncological treatment (13, 40).

Uncontrolled trials found that patients with chemotherapy sensitive recurrent AOD and anaplastic oligoastrocytoma (AOA) responded to procarbazine, lomustine, and vincristine (PCV) in 60% to 70% of cases (16, 41). Triple combination chemotherapy of procarbazine, lomustine and vincristine (PCV) or temozolomide represents the mainstay of treatment (11-13). In fact, oligodendrogliomas with the 1p/19q co-deletion demonstrate response to early chemotherapy with procarbazine, lomustine and vincristine (1, 2). However, clinical trials illustrate variably prognoses of patients with AOA and low concordance rates in diagnosis of classical AOD. Additionally, clinicians hold ongoing discussions about whether following the removal of AOA with resultant necrotic grade III glioblastoma merits a separate diagnosis (14, 32, 42-46).

AODs are rare brain tumors with variable overall survival. Combined chemotherapy, radiation and neurosurgery are necessary to reduce disease progression and recurrence. We present this case to highlight the spectrum of presentation of this rare tumor and molecular changes. And review the literature to discuss the most recent treatment modalities.

## ACKNOWLEDGMENT

Special thanks to Titilopemi Odunlami, Mohamed El-Jammali, and Fareshta Shafaq, MD candidates, American University of the Caribbean for their assistance in reviewing the final manuscript

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