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Clinico-pathological features and molecular background of oligodendrogliomas. A single centre retrospective study

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ABSTRACT

Background: Diffuse gliomas are the most frequent primary central nervous system (CNS) neoplasms, originating from the parenchyma itself, oligodendrogliomas accounting for approximately 10% of cerebral gliomas. For the past 20 years, the study of genetic/molecular mechanisms of glioma genesis and progression has gradually come into focus. However, the biological and clinical significance of these mutations are still to be completely characterized. The purpose of this article is to describe our clinical experience with oligodendrogliomas and to review the current literature, in order to better describe the characteristics of the molecular/genetic oligodendroglioma subgroups.

Methods: We performed a single-institution retrospective study that included 66 patients with oligodendrogliomas operated in our department between January 2011 and December 2018.

Results: Our study included 26 female patients (39%) and 40 male patients (59%). The mean age at presentation was 39.9-year-old (range 26-59-year-old). The tumours were located predominantly in the right hemisphere (53%), the majority being situated in the frontal lobe (59%). 64% of the patients had signs of mass effect on the imaging studies, 13% presented with brain herniation syndromes, and 16% of the surgically treated patients had a relapse with regrowth and malignant transformation of the tumour. The most common complaint that the patients had at admission was a headache. Seizures were the second most common symptom that determined the patients to seek medical attention.

Conclusion: The expanding knowledge regarding the genetic alterations of oligodendroglial tumours could lead to significant changes in treatment strategies. However, the utility of each particular marker in planning the treatment has yet to be

Keywords

oligodendrogliomas,
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established. Emerging data will, most likely, improve outcome prediction and adjuvant therapy strategies by identifying the patients most likely to benefit from a particular treatment.

INTRODUCTION

Diffuse gliomas are the most frequent primary central nervous system (CNS) neoplasms, originating from the parenchyma [1]. About 75% of gliomas in adults are astrocytic, two-thirds being glioblastomas, the most malignant form. Oligodendroglial tumors account for than 10% of the gliomas [2]. For the largest part of the last century, the diagnosis of oligodendrogliomas has been based on histopathological aspects alone. For the past 20 years, the study of genetic/molecular mechanisms of glioma genesis and progression has gradually come into focus. The 2021 World Health Organization (WHO) Classification of Tumors of the CNS includes molecular features for diagnosis and further classification of oligodendroglioma into IDH-mutant and 1p/19q-codeleted [3]. The biological and clinical significance of these mutations are still to be completely characterized. The purpose of this article is to describe our clinical experience with oligodendrogliomas and to review the current literature, in order to better describe the characteristics of the molecular/genetic oligodendroglioma subgroups.

MATERIALS AND METHODS

We performed a single institution retrospective study that included the patients of the 4th Clinical Department of Neurosurgery of the Bagdasar-Arseni Clinical Emergency Hospital.

We retrospectively reviewed the case files of 66 patients with oligodendrogliomas operated in our department between January 2011 and December 2018. We only included patients operated for oligodendrogliomas with a positive anathomopathological examination for a "classical" oligodendroglioma. Exclusion criteria were diagnosis of primary glioblastoma, oligoastrocitoma with important oligodendroglial compound or patients with a high suspicion for oligodendroglioma, that refused surgery or biopsy for diagnosis. Data were obtained by studying patient files.

RESULTS

Our study included 26 female patients (39%) and 40 male patients (59%). The mean age at presentation

was 39.9year-old (range 26-59year-old). The tumors were located predominantly in the right hemisphere (53%), the majority being situated in the frontal lobe (59%). 64% of the patients had signs of mass effect on the imaging studies, 13% presenting with brain herniation syndromes (Figure 1).

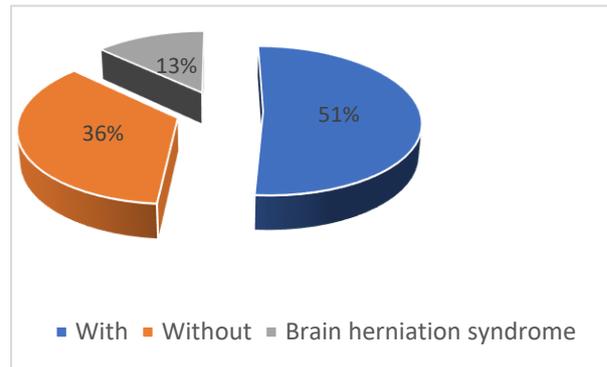


Figure 1. Distribution of patients based on the presence/absence of mass effect on imaging studies.

16 % of the surgical treated patients had a relapse with regrowth and malignant transformation of the tumor (Figure 2).

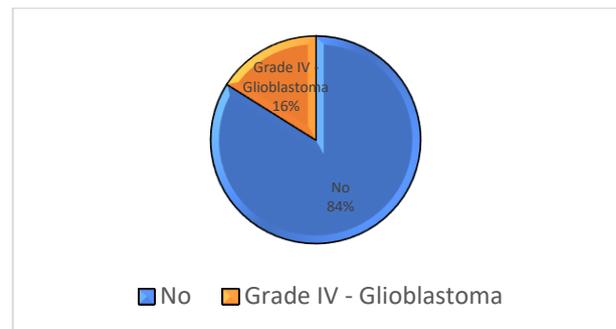
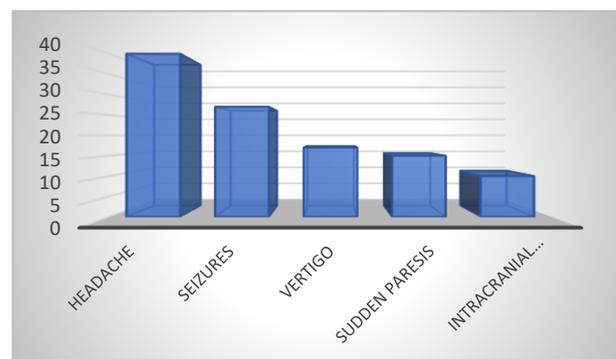


Figure 2. Distribution of the patients based on the presence/absence of relapse with malignant transformation.

Figure 3. Distribution of the patients based on the clinical symptoms at admission.



The most common complaint that the patients had at admission was headache. Seizures were the second most common symptom that determined the patients to seek medical attention (Figure 3).

ILLUSTRATIVE CASE

A 30-year-old male with no significant medical history was referred to our clinic for intense

headache, progressively worsened during the month prior to admission. Clinical examination showed no neurological deficit. Gadolinium-enhanced MRI scan revealed a right fronto-temporal tumor, measuring 9.5 cm in diameter, compressing the adjacent structures and producing mass effect on the right lateral ventricle (Figure 4).

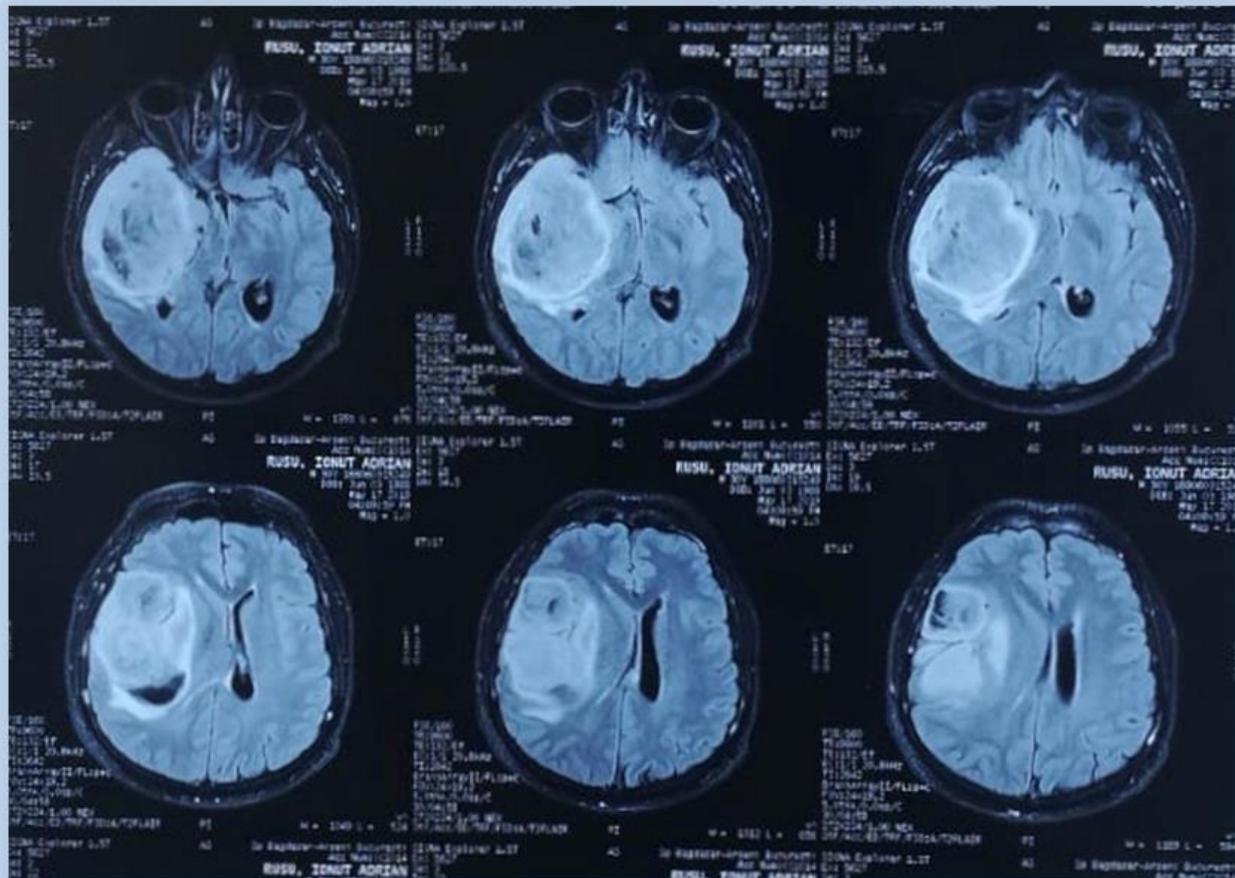


Figure 4. Gadolinium enhanced MRI scan, axial section, showing a right fronto-temporal tumour, measuring 9.5 cm in diameter, compressing the adjacent structures with inhomogenous enhancement.

Figure 5. Intraoperative aspect showing the yellow-grey tumour.

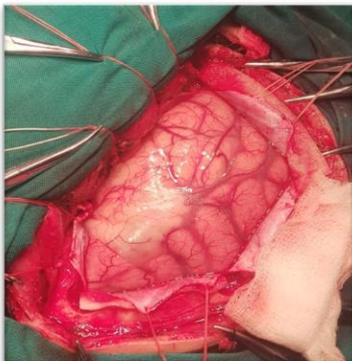
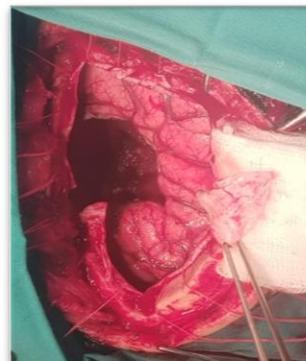


Figure 6. Intraoperative aspect showing the resection cavity.



We performed a gross total resection through a pterional approach (Figure 5, Figure 6). The patient was discharged 7 days later, with no postoperative neurological deficits. Control CT scan showed a gross total resection of the tumor (Figure 7).

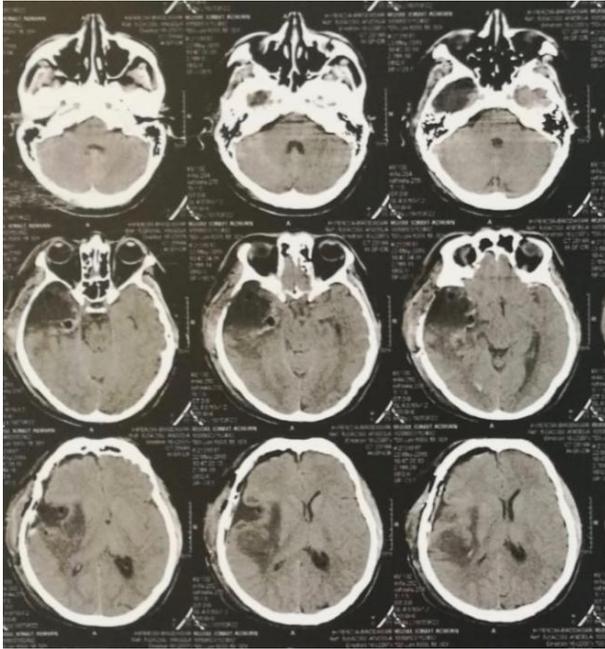


Figure 7. Postoperative CT scan showing the resection cavity.

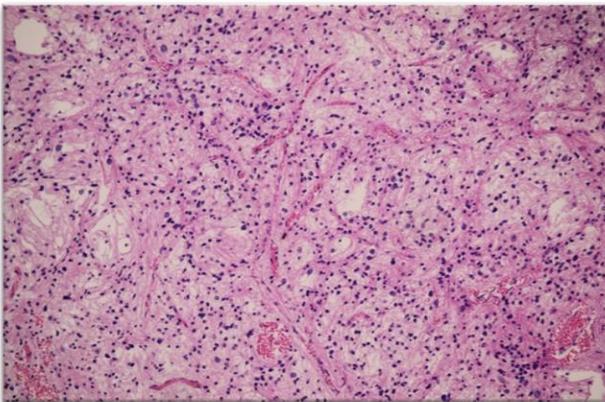


Figure 8. Histopathological specimen showing arciform vascularization.

Histopathological examination showed arciform vascularization (Figure 8), “boiled egg cells” (Figure 9) and high fibrillarity (Figure 10).

MLPA analysis of the tumor sample identified a codeletion of 1p19q and a c.395G>A (p.R132H) mutation in the exon 4 of IDH1 gene. The analysis was negative for mutations of exons 11 and 15 of

BRAF gene, EGFRvIII, MGMT promoter methylation and TERT promoter mutation.

The patient had a favorable evolution, with no neurological deficits and was discharged in the seventh postoperative day.

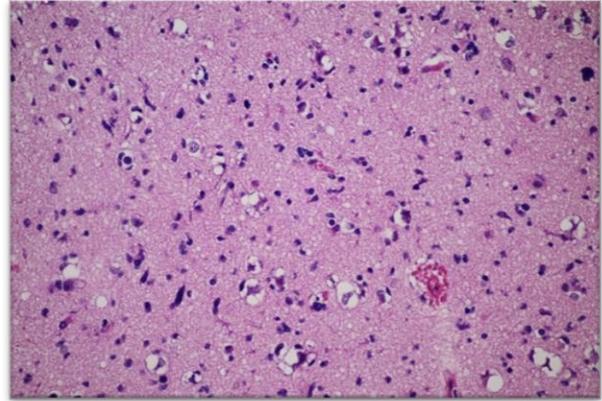


Figure 9. Histopathological specimen showing “boiled egg cells” aspect.

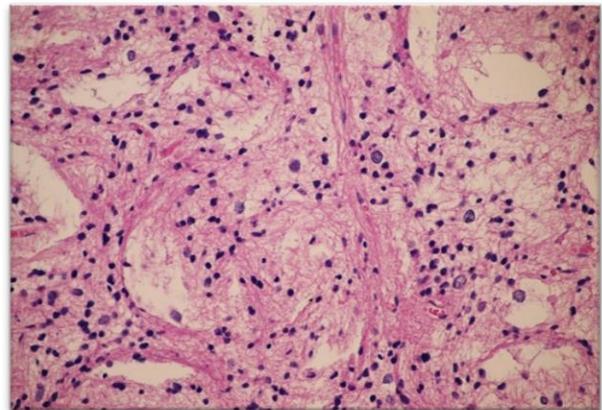


Figure 10. Histopathological specimen showing high fibrillarity.

DISCUSSION

Under the generic term “oligodendroglioma” is a heterogenous group of tumors, with a variable response to adjuvant therapy. This variance highlights the need for markers that can guide the clinical decision-making. Codeletion of 1p19q occurs in 50 to 76% of oligodendrogliomas [4] [5]. EORTC 26951 and RTOG 9402 studies proved that combining radiation therapy with procarbazine, vincristine and lomustine chemotherapy protocol drastically increased overall survival in 1p19q codeleted anaplastic oligodendroglioma patients compared to radiotherapy alone [6] [7]. The EORTC 26951 trial investigated the adding of six cycles of standard procarbazine, vincristine and lomustine to

radiation therapy of 59.4 Gy in 33 fractions in anaplastic oligodendroglioma patients and reported a significant difference in overall survival [7] [8]. Patients with 1p19q codeleted oligodendrogliomas benefitted more from the addition of chemotherapy to radiotherapy, the risk reduction in patients with non-codeleted tumors being significantly lower [7]. Regarding both trials, it is also notable the fact that patients with 1p19q codeleted oligodendrogliomas who were treated with adjuvant radiotherapy alone initially, had a lower survival rate at progression, despite being administered a heightened chemotherapy regimen [4] [7]. The CODEL trial has been designed to compare administration of adjuvant therapy consisting of either radiotherapy alone, temozolomide alone or radiotherapy combined with temozolomide. The analysis from the initial study design showed that temozolomide-alone patients experienced a significantly shorter progression free survival, compared to either one of the radiotherapy arms [9]. The study has been subsequently redesigned to compare radiotherapy combined with procarbazine, lomustine and vincristine to radiotherapy and temozolomide regimens and is still ongoing.

Mutations of IDH1 and IDH2 seem to occur in about 70% of oligodendroglioma tumors, mainly affecting amino acid 132 of IDH1 or IDH2 [10] [11]. IDH1 is known to function as a tumor suppressor, its mutational inactivation leading to tumorigenesis, partially through the induction of the HIF-1 pathway [12] [13]. IDH mutations have been reported in several studies to produce a favorable prognostic impact [7] [10] [14]. However, despite the more favorable prognosis of patients with oligodendrogliomas harboring IDH mutations, it hasn't been proven yet that the treatment strategy should be changed regarding the IDH status.

CONCLUSION

The expanding knowledge regarding the genetic alterations of oligodendroglial tumors could lead to significant changes in treatment strategies. However, the utility of each particular marker in planning the treatment has yet to be established. Emerging data will, most likely, improve outcome prediction and adjuvant therapy strategies through identifying the patients most likely to benefit from a particular treatment.