



APC and EGFR Proteins Expression in Gliomas

Nahla E Abdelraheem^{1*}, Alsadig Gassoum², Sawsan Ahmed Hamed AL-Deaf³, Nihad Elsadig Babiker⁴, Lamyaa A Elhassan⁵, Mohamad Abdelrahman Arbab⁶ and Imad Fadl-Elmula⁷

¹Department of Histotechnology, National Center for Neurological Sciences (NCNS), Sudan

²Department of Immunology, National Center for Neurological Sciences (NCNS), Sudan

³CNS Surgeon, National Center for Neurological Sciences (NCNS), Sudan

⁴Department of Hematology, National Center for Neurological Sciences (NCNS), Sudan

⁵Department of Histopathology, National Center for Neurological Sciences (NCNS), Sudan

⁶Department of Surgery, University of Khartoum, Sudan

⁷Department of Cytogenetics, Assafa academy, Sudan

Abstract

Gliomas are the most common brain neoplasms in adults, accounting for about 70% of primary neoplasms of the Central Nervous System (CNS). Adenomatous Polyposis Coli (APC) is a tumor suppressor protein and one of the key players of the Wnt signaling pathway. Epidermal Growth Factor Receptor (EGFR) is an ErbB receptor with tyrosine kinase activity. EGFR over expression and activation can impact cancer cell survival, proliferation and invasion. The study was aimed to assess the possibility of using APC and EGFR proteins as markers for gliomas. Sixty-one tumor tissues were processed to obtain paraffin embedded blocks, 3 µm were cut and stained for APC and EGFR proteins immunohistochemistry. APC protein immunohistochemical staining showed cytoplasmic expression in 57.4% of the samples with over expression in 9.9%. EGFR protein immunohistochemical staining showed cytoplasmic expression in 31.1%, and membranous in 1.6% with over expression in 6.5% of the samples. APC was expressed mostly in astrocytoma I (19.7%), astrocytoma II (18%), ependymoma (1.6%) and Pleomorphic Xanthoastrocytoma (PXA) (1.6%) with over expression in Glioblastoma (GBM) (3%). EGFR was expressed in Astrocytoma I (9.8%) and astrocytoma II (14.8%) with over expression in of GBM (1.6%). Statistically there was no significant relationship between the Grades of gliomas and immune staining score of APC and EGFR proteins (P-value = 0.667 and 0.128, respectively). APC and EGFR proteins show both cytoplasmic and membranous expression in glioma and being over expressed in high grades of astrocytoma which suggests the possibility of using them as prognostic markers for astrocytoma.

Keywords: Gliomas; APC; EGFR; Immunohistochemistry

Introduction

Gliomas are the common brain tumor in adults, accounting for about 70% of primary neoplasms of the Central Nervous System (CNS). Glioblastoma (GBM) is the most popular glioma, accounting for approximately 70% of astrocytomas and 15% of all intracranial neoplasms. 90% of GBMs are classified as primary, affect mainly the older (mean age 62 years), have rapid progression (less than 3 months) and no evidence of previous clinical or histopathological precursor lesions [1]. Secondary GBMs are common in young individuals (average age 45 years) and progress slowly from a lower grade of diffuse astrocytoma, the two forms of GBM have worse prognosis. Histological analysis can only define the type of an astrocytic neoplasm and diagnostic difficulties may happen due to the diversity of the tumor, morphological similarity with other gliomas or partial sampling of the lesion. As a result, in recent decades, several studies have used molecular techniques aiming to define biomarkers with diagnostic and/or prognostic relevance, which allowed the identification of such markers and significantly increased the knowledge of the pathogenesis of gliomas, and identification of potential targets for new therapeutic approaches [1-3]. Epidermal Growth Factor Receptor (EGFR) is one of ErbB family receptors with tyrosine kinase activity [4,5]. EGFR is frequently over expressed or hyper-activated in human malignancies. Increased activation of EGFR can be both ligand-dependent and ligand-independent [6-8]. Mechanisms of increased activation include: Aberrant enhancement of ligand production; constitutive receptor activation by multiple exon deletion or missense mutations [9]; crosstalk with other receptors; increased receptor protein level through gene amplification; and malfunction in receptor degradation. EGFR over expression

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*Correspondence:

Nahla E Abdelraheem, Department of Histotechnology, National Center for Neurological Sciences (NCNS), Khartoum, PO. Box: 8204, Khartoum, Sudan,

E-mail: nahlaelrayah@gmail.com

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and activation have a significant impact on cancer cell hallmark traits, including increased cell survival, proliferation and invasion [10]. 90% of astrocytic tumors are associated with high protein levels of EGFR, indicating that alterations in transcription and translation of this gene might be involved in tumorigenesis. EGFR genetic alterations are common in primary GBMs. EGFR was found to be amplified in 40%, over expressed in 60%, and mutated in 20% to 30% of the patients [1]. Amplifications and rearrangements of EGFR are significantly related to high-grade gliomas, with a worse prognosis [11].

Adenomatous Polyposis Coli (APC) is a multiple role tumor suppressor. Besides its structural role in cellular architecture, the protein product of the APC gene is also one of the key players of the Wnt signaling pathway. Wnt proteins join to receptors on the cell surface, the signal is passed to beta-catenin, which gets in the nucleus to start transcription of Wnt target genes [12,13].

Despite the fact that the main signaling molecule of the pathway is beta-catenin, APC is an important component of the beta-catenin destruction machine heading to the proteasome and acts as a negative regulator of the Wnt pathway. When Wnt ligand is absent, beta-catenin binds to APC protein and is being destroyed. When APC become mutated, beta-catenin is stabilized, accumulates in the cytoplasm, and gets in the nucleus, where it binds to lymphoid enhancer factor-T cell factor, and start new gene expression programs [14]. It has been reported that genes and components of the Wnt signaling pathway are involved in brain neoplasms particularly those of epithelial origin [13]. The APC gene (chromosome 5q21) [15] is organized in 16 translated exons and encodes a 2843 amino acid protein that is expressed in specific epithelial and mesenchymal cells of several fetal and adult human tissues [16].

Our interest in studying the expression of APC came mainly from the findings that wild-type APC protein is expressed in the central nervous system [17,18] and significantly involved in the initiation of neuronal differentiation [19]. Also Wnt proteins regulate critical normal brain developmental processes [20-24], including cellular adhesion and synaptic rearrangements [25]. The Wnt pathway has repeatedly been involved in tumor genesis and lately in brain tumor genesis as well [26]. These findings guide us to focus our interest on the key player of the Wnt signaling, APC tumor suppressor protein. The majority of brain tumors originate sporadic unless those that are part of defined clinical syndromes. APC protein is significantly related to certain syndromes, such as Turcot's syndrome, which involves the development of primary brain tumors such as medulloblastomas and gliomas [27,28].

Material and Methods

This was a cross-sectional study based on clinical and histopathological analyses of surgical samples from patients with gliomas treated at the National Center for Neurological Sciences (NCNS) from January 2017 to December 2019. The study was approved by the Ethical Committee of the Center, age of evaluated patients ranged from less than 1 to 80 years old.

Immunohistochemical staining was performed in specimens obtained from the center. Sixty-one tumor tissues were fixed in 10% neutral buffered formalin and processed for paraffin embedding. 3 µm thick sections were stained using streptavidin-biotin peroxidase complex method. The sections were treated by the detection system containing the secondary antibody (Envision™ FlexLink System-HRP - Dako, cat# K8023), EGFR primary antibody (Thermo

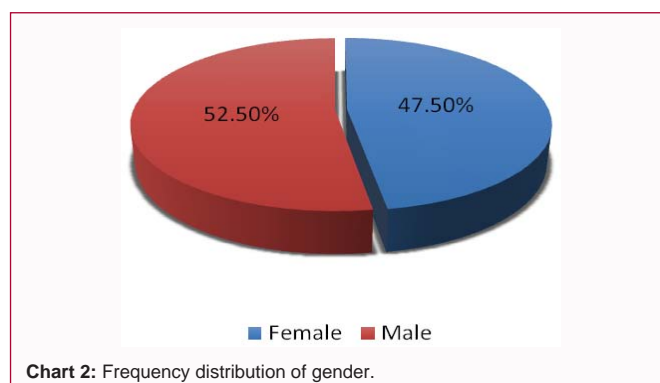
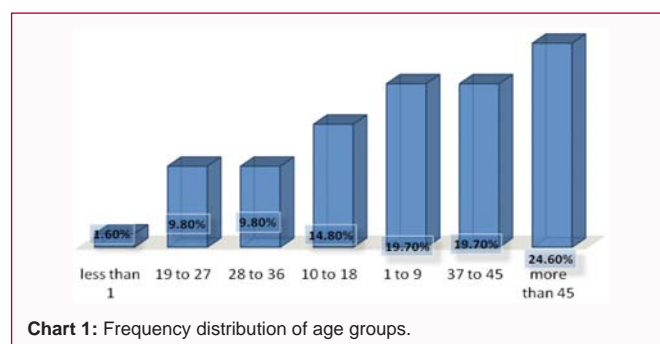
Scientific. Cat. #MS-378-R7) and APC primary antibody (rabbit polyclonal antibody; GeneTex Cat# GTX116009) which was diluted 1:500 subsequent the manufacturer's instructions. 3,3 Diamino-Benzidine (DAB) was the chromogen substrate. Positive and negative controls of the immunohistochemical reaction were used in all reactions. The immunostaining patterns for EGFR and APC were estimated considering, both cellular (cytoplasm and/or membrane). Ten high-power (40x) fields were selected randomly in each section, and the cells showing immune- positive staining were count to obtain a ratio of positive cells/total number of cells (%). The percentage obtained was expressed as scores; 1: 0% to 25%, 2: 26% to 50%, 3: 51% to 75%, and 4: 76% to 100%.

Statistical analysis: The distribution of patients' demographical and histopathological data was analyzed using chi square test. The relation between expression of APC and EGFR in different types of glioma was analyzed using fisher's exact test.

Results

The most affected age group was significantly the group more than 45 years old (24.6%) (Chart 1). Males represented 52.5% of the patients (ratio 1.1:1) (Chart 2). Most of the patients came from Algezira (23.0%), Khartoum (16.4%), and Gadarif (13.1%) (Chart 3) and descended from different races with the Afroasiatic being the predominant (96.7%). Most of the tumors (80%) were located in the supratentorial site of the brain (Chart 4). The most common type of glioma was significantly astrocytoma (96.7%) ($p=0.000$) (Chart 5) and the most frequent variant was significantly astrocytoma II (35.6%) followed by astrocytoma I (33.9%) and GBM (16.9%) ($p=0.000$) (Chart 6).

APC immunohistochemical staining showed positive cytoplasmic expression in 57.4% of the samples (Chart 7) (Figure 1), distributed to + (22, 62.9%) as the common score, ++ (7, 20%), +++ (4, 11.4%), and ++++ (2, 5.7%) as the lowest frequency, the distribution was significant ($P=0.000$), (Chart 8). EGFR immunohistochemical



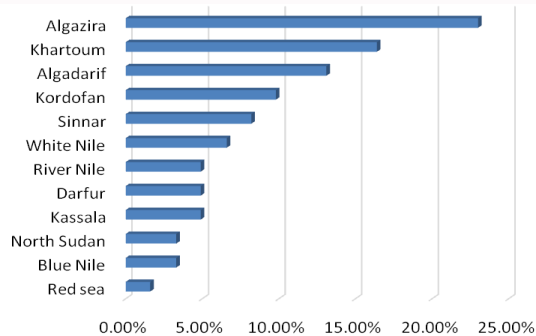


Chart 3: Frequency distribution of residence.

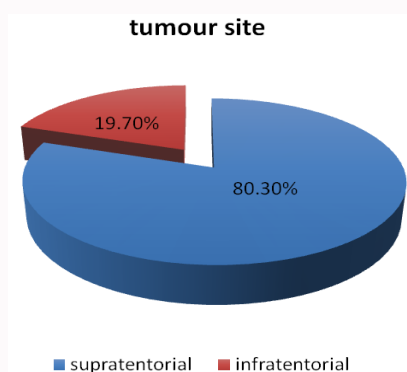


Chart 4: Frequency distribution of the tumour site.

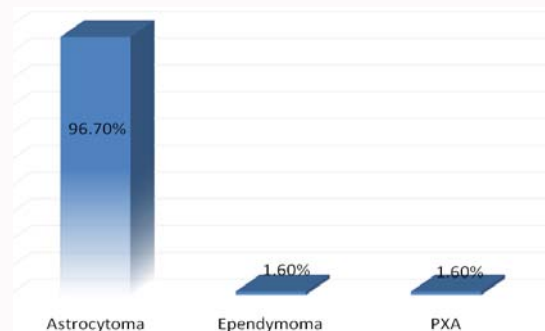


Chart 5: Frequency distribution of Gliomas types.

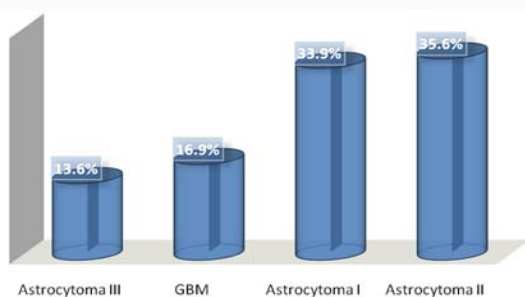


Chart 6: Frequency distribution of astrocytoma grades.

staining showed positive cytoplasmic expression in 31.1% of the samples (Chart 9, Figure 2) and membranous expression in 1.6% (Figure 3), distributed to + (78.9%) as the common score, ++ (15.8%), and ++++ (5.3%) as the lowest frequency and no patient achieved score +++, the distribution was significant ($P=0.000$) (Chart 10).

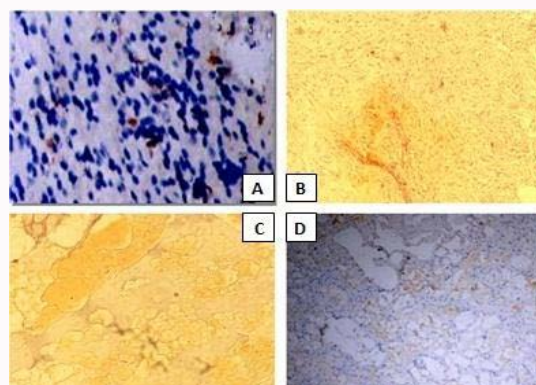


Figure 1: Cytoplasmic expression of APC protein in astrocytoma brown color indicates immune-positivity. Immune staining scores: A; score 1 (40x), B; score 2 (10x) C; score 3 (10x), D; score 4 (over expression) (10x)

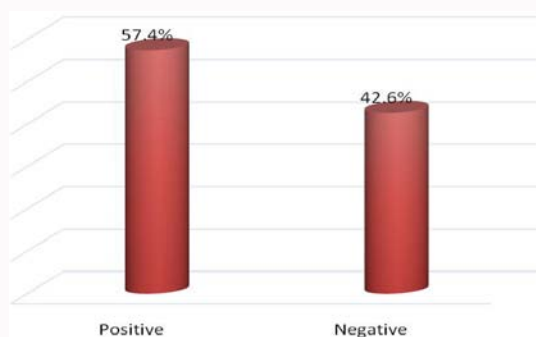


Chart 7: Frequency distribution of APC protein immune staining positivity.

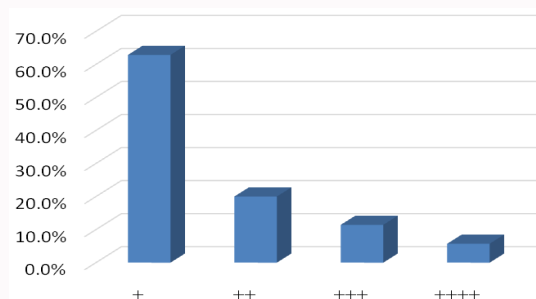


Chart 8: Frequency distribution of APC protein immune staining score. Immunohistochemical scores; +: 0% to 25% of tumor cells were positive, ++: 26% to 50% of tumor cells were positive; +++: 51% to 75% of tumor cells were positive; and ++++: 76% to 100% of tumor cells were positive.

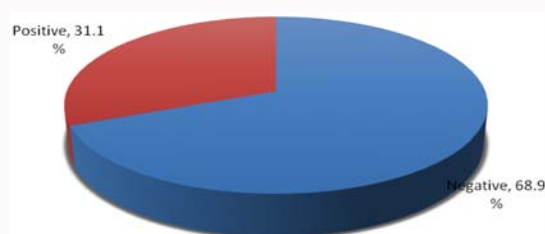


Chart 9: Frequency distribution of EGFR protein immune staining positivity.

Statistically there was no significant relation between the grades of Astrocytoma and immune staining score of APC and EGFR proteins ($P=0.667$ and 0.128 respectively) (Chart 11 and 12).

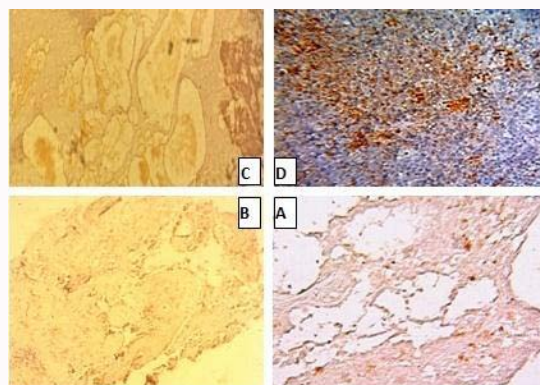


Figure 2: Cytoplasmic expression of EGFR protein in astrocytoma brown color indicates immune-positivity. Immune staining scores; A; score 1 (40x), B; score 2 (10x) C; score 3 (10x), D; score 4 (over expression) (10x)



Chart 10: Frequency distribution of EGFR protein immune staining score. Immunohistochemical scores; +: 0% to 25% of tumor cells were positive, ++: 26% to 50% of tumor cells were positive; +++: 51% to 75% of tumor cells were positive; and +++++: 76% to 100% of tumor cells were positive.

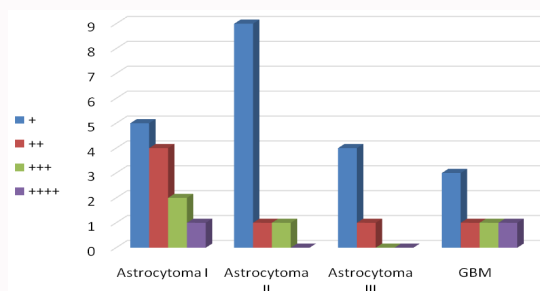


Chart 11: Crosstab of Grades of Astrocytoma and APC protein immune staining score.

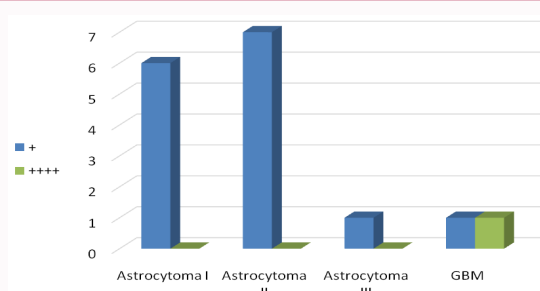


Chart 12: Crosstab of Grade of Astrocytoma and EGFR protein immune staining score.

Ependymoma was negative for both APC and EGFR proteins immune staining while xanthoastrocytoma showed positivity for

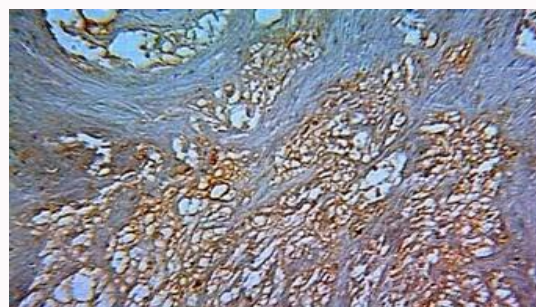


Figure 3: Membranous over expression (score 4) of EGFR protein in Glioblastoma (GBM), brown color indicates immune positivity, 10x.

APC protein immune staining.

Discussion

APC protein is expressed in the central nervous system [17,18] and is critically involved in the initiation of neuronal differentiation [19]. EGFR over expression and activation can significantly impact cancer cell's hallmark traits, such as increased cell survival, proliferation and invasion [10].

In the present study, the most affected age group was more than 45 years old (24.6%) which agrees with the fact that Cancer incidence generally increases with age [29] and also agrees with the finding of Mohammed Ahmed and Ali Bashir that incidence of brain tumors in Sudan increases following aging with peaking at 55 to 65 [30]. The present finding that males were more affected by gliomas than females is similar to Mohammed Ahmed and Ali Bashir finding [30]. Also, previous studies highlighted that: Brain tumors are so predominant among males with high incidents in developed countries (males, 5.8 and females, 4.1 per 100,000) than in less developed countries (males 3.0 and females 2.1 per 100,000) [31]. As well as stated by Mackinnny; where the male to female ratio was 1.5:1.0, the reason behind that may be due sexually dimorphic inactivation of the tumor suppressor retinoblastoma protein (known to reduce the risk for brain tumors) in males [32,33].

Most of the patients came from central Sudan: Gezira (23%) and Khartoum (16.4%) which might be due to easy access of patients at these areas to diagnostic facilities. Other areas are represented less commonly perhaps of undiagnosed tumor-related deaths (patients in extremely poor situations do not get diagnosed, simply because they do not have access to the modern diagnostic facilities). This finding is similar to that of previous study; the geographical distribution of BTs in different sectors of Sudan to some extend has a link with the risk factors and accordingly the center of Sudan and North of Sudan were the most endemic sectors by BTs relative to other sectors; which represented 45% and 35% respectively, then east and south of Sudan represented 12% and 8% respectively [30].

Most of the tumors (80%) were located in the supratentorial site of the brain, despite the fact that pathologies in the supratentorial areas remain silent for prolonged periods due to their slow growth and delayed presentation, but their earlier diagnosis is enhanced after utilization of MRI [34].

The expression of EGFR is important in molecular classification of astrocytic tumors and is considered as a prognostic marker with poor prognosis associated with increased level of EGFR in anaplastic astrocytomas and glioblastomas [35].

Most of the cases of astrocytoma I (70%) showed immune-negativity to EGFR and this is similar to previous studies which reported negative EGFR immune-staining in Grade I astrocytomas while EGFR positivity has been detected in Grade II, Grade III and Grade IV astrocytomas with increasing positivity in higher grades of astrocytomas [35].

The immunostaining positivity for EGFR was cytoplasmic and focally distributed, i.e., some areas of the lesion with strong or weaker labeling which may be due to technical pre-analytical issues like preservation and/or processing of the material. Also analytical issues such as exposure time to primary antibodies and lesion sampling may influence the variation in the staining pattern. With respect to the immunostaining pattern of EGFR that we observed it was assigned 4 (from 75% to 100% of the cells were positive) in 50% of positive cases of GBM, such range of percentage is closely similar to that described by Ishita et al., that 53.3% of GBM cases showed over expression of EGFR [36].

The present finding that EGFR was over expressed only in GBM is consistent with a previous finding of Montgomery and colleagues that over expression of EGFR contributes to the differentiation, proliferation, survival, migration and invasiveness of cancer cells and increases tumor angiogenesis [37].

Ependymoma revealed immune-negativity for EGFR which is contrary to previous finding that EGFR over expression was found in 30%/60% of ependymomas [37] and this might be due to the limited number of ependymoma cases (1.6%) in the study.

In spite of APC has been thought of primarily as a colon-specific tumor suppressor gene, its association with certain brain tumors and its expression in the CNS suggests that it performs important functions in these tissues also. Genes involved in formation and acquisitions of the full metastatic potential of specific tumors are not only those responsible for cell proliferation and survival, but also genes responsible for the control of cell adhesion and cell motility [38]. Perego et al. [39] demonstrated that disorganization of cadherin mediated junction, in which APC is included, is required to promote migration and invasiveness in glioblastoma cell lines.

Conclusion

APC and EGFR proteins show both cytoplasmic and membranous expression in glioma and being over expressed in high grade astrocytoma. APC and EGFR proteins' can be used as prognostic markers for astrocytoma.

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