WITHDRAWN: A Histopathology Model of Astrocytoma

Alireza Arabestanino
alirezaarabestanino@gmail.com

Harvard University

Arman Ai
Tehran University of Medical Sciences

Hastin Jalali
Tehran University of Medical Sciences

Research Article

Keywords: Astrocytoma, Neoplastic, anaplastic astrocytoma, glioblastoma

Posted Date: November 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1091746/v1

Additional Declarations: No competing interests reported.

EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Neoplastic transformation occurs in all glial cell types of the human nervous system, producing a wide variety of clinic-pathological entities and morphological variants. As the molecular events responsible for astrocytoma formation and progression are being clarified, it is becoming possible to correlate these alterations with the specific histopathological and biological features of astrocytoma, anaplastic astrocytoma and glioblastoma multiforme. Diagnosis, treatment, and prognostication in brain stem astrocytoma's have been hindered by the occurrence in the same site of two distinct pathological entities-fibrillary and pilocytic astrocytoma. The small size of the specimens from this region adds an additional confounding factor in tumor classification. Nevertheless, histological assignment to either of these two prognostically different categories is often possible, especially if the importance of this distinction is recognized. In the face of a nonspecific histological diagnosis, e.g. "low-grade astrocytoma', certain radiographic and clinical features may, in combination with the pathological findings, be useful in tumor subclassification.

Introduction

1.1 Epidemiology: The astrocytoma's are the commonest form of gliomas and primary tumor's of the brain in man. Tumorigenesis is a multi-step process in which cells become immortalized, proliferate, invade and modulate their environment. Over the past few years, molecular biological studies have provided insights into the basic mechanisms underlying such tumorigenic processes in a variety of tumors, including the common diffuse, fibrillary astrocyte. The epidermal growth factor receptor (EGFR), as well as the platelet-derived growth factor (PDGF) and its receptors, have been implicated as oncogenes and genes on chromosomes lp, 9p, 10, l2p, 13q, 17p, 19q and 22q as tumor suppressors. The World Health Organization (WHO) has recently published current criteria for classification and malignancy grading of all brain tumor's. The WHO malignancy grading has been shown to correlate to the biological behavior of the individual types tumor's, and ranges from malignancy grade I (the least biologically aggressive) to grade IV (the most malignant). Some tumor types have only one grade others up to four.

TABLE 1. Comparison of the World Health Organization (WHO) and St. Anne/Mayo grading system for astrocytoma's

WHO Grade	WHO designation	St. Anne/Mayo	Histopathology	Associated genetic alterations
I	Pilocytic astrocytoma	Pilocytic astrocytoma	Bipolar, piloid cells, Rosenthal fibers, Eosinophilic granular bodies	Accumulation of P53 (>50%) Deletion of 17q/NF1 (<20%)
II	Low grade astrocytoma	Astrocytoma Grade 1 and 2	Neuroplastic fibrillary, or gemistocysitc astrocytes; nuclear atypia	P53 accumulation (>40%), p53 mutation (>25%), LOH 17p (>20%)
III	Anaplastic astrocytoma	Astrocytoma Grade 3	Neuroplastic fibrillary, or gemistocysitc astrocytes; nuclear atypia, mitotic activity	P53 accumulation (>50%), p53 mutation (>30%), LOH 10 (15%) 19q (40%)
IV	Glioblastoma multiforme	Astrocytoma Grade 4	Cellular anaplasia, nuclear atypia, mitoses, vascular proliferation, necrosis	P53 accumulation (40%), p53 mutation (>25%), LOH 10 (>60%), 17p (25%), 19q (24%), p16 deletion (>60%), EGF-R (>30%) and CDK4 (>70%) amplification

Modified from P. Kleihues, P.C Burger, and B.W. Scheithauer, Brain Pathol. 3:255-268(1993).

The terminology used in this paper will correspond to the most recent WHO report. Astrocytic tumor's constitute 65–70% of all gliomas and are malignancy graded on the basis of histological features into grades I–IV. The pilocytic astrocytoma's (malignancy grade I) are the least malignant, occur mainly in children, only very rarely progress to more malignant tumor's and have generally a good prognosis. Consequently they will not be discussed further in this text. In contrast, the adult diffuse astrocytic tumor's frequently show malignant progression. The adult diffuse astrocytoma's include the astrocytoma's (malignancy grade II), the anaplastic astrocytoma's (malignancy grade III) and the glioblastomas (malignancy grade IV), and these will be the main focus of this text. The average survival of patients with an astrocytoma (malignancy grade II) is around 7 years, while patients with anaplastic astrocytoma's have a median survival half that time. Glioblastoma patients have a very poor prognosis with average survival reported between 9 and 11 months despite modern therapy. Grade II tumor's have a peak incidence between 25 and 50, while the glioblastomas have a peak incidence between 45 and 70 years. Glioblastomas are the most common form and are divided into those that develop from a previously diagnosed astrocytoma or anaplastic astrocytoma (secondary glioblastomas) and those that appear to develop de novo – that is with no evidence of there having been an earlier tumor of lesser malignancy grade. There are clinical and molecular data to support the hypothesis that these tumor's may develop in different ways.

In this prospective, we develop a Histopathological model which summarizes known molecular genetic abnormalities and relates these to key histological and biological phenomena that characterize human astrocytoma's.

Biological And Histopathological Of Astrocytoma

The malignancy stages of astrocytic tumors are displayed graphically in Figure 1. Tumors of the cerebral hemispheres of young adults and on computerized tomographic (CT) scans which appear as ill-defined, non-enhancing masses are diagnosed as low grade astrocytoma's. At the microscopic level, tumors with these radiographic features show normal brain infiltrated with dispersed small astrocytic cell with somewhat enlarged and irregular nuclei, although the cell density may not be markedly different from normal tissue (Fig. 1). Cells from some of these tumors have been shown to have some cytogenetic abnormalities, usually numerical changes of chromosomes 7, 10, 22, and Y. Some astrocytoma's remain dormant, some enlarge slowly, and some progress to medium or high grade tumors. As can be seen in Fig. 1, these progressing tumors acquire distinct phenotypic features. For example, the higher stage recurrent tumor in the case shown in became enlarged and enhanced on CT. As well, progression is marked morphologically by increased cellularity, nuclear pleomorphism, and endothelial proliferation; and, in glioblastoma, the most malignant stage of the disease, necrosis (Fig. 1). Cells from tumors with either medium or high grade histology have shown some consistent cytogenetic aberrations including loss of chromosome 10, gains of chromosome 7, various aberrations of chromosomes 9 and 22, and double minute chromosomes. Although some late stage tumors have clearly evolved from less malignant precursors, a large number seem to arise de novo. Whether de novo glioblastomas have evolved differently, or just more rapidly and sub clinically, is debatable. Further, there is a curious relationship between age, tumor stage, and clinical behavior of astrocytic tumors. As a general rule, astrocytic tumors increase in frequency with advancing age, the proportion of malignant to benign tumors increases, and tumors of any stage tend to behave more aggressively in older patients. The basis for this relationship is unclear.

2.1. ASTROCMOMA GENETICS: The assumption that astrocytoma's arise from astrocytes is supported by two observations. First, astrocytoma cells have the morphologic characteristics of astrocytes and express the astrocyte marker, glial fibrillary acidic protein (GFAP). Second, mature astrocytes appear to retain the ability to divide, a feature characteristic of cells capable of neoplastic changes. On the other hand, these correlations have limitations especially when one considers mixed gliomas, tumors with more than one differentiated element. One hypothesis is that astrocytoma's arise from initiated periventricular stem cells and that further genetic damage to these pluripotent precursors gives the tumors their individual peculiarities. This argument is particularly relevant when considering the relationship of the relatively less differentiated glioblastomas to other members of the pathway To date, evidence for the progressive nature of astrocytic malignancy has relied solely on the clinical and morphological analyses exemplified in. One of the cardinal features of advanced malignancy, the wide regional heterogeneity of cell types (both in terms of differentiation of the cells and their degrees of anaplasia) seems to suggest an ongoing evolution of cellular populations. Though apparently clonal, tumors appear to acquire divergent genetic characteristics through this evolution, resulting in genotypically and phenotypically diverse populations in the same tumor. In order to address some of these aspects of astrocytoma biology and to determine the underlying basis for progression of these tumors, we have undertaken a genetic lineage analysis. We have taken advantage of the wealth of information indicating the involvement of two classes of genetic aberrations in growth dysregulation and other phenotypes in the malignant cell. On one hand, the overexpression and genetic rearrangement of cellular or viral alleles of proto-oncogenes has been shown to occur with genetically dominant effects on the acquisition of malignant characteristics. On the other hand, the loss of alleles of genes presumably responsible for the maintenance of the normal growth state has also been shown to occur in tumors, relative to constitutional genotypes. Thus, the malignant phenotype appears to be the result of a combination and accumulation of events which act at loci controlling both the positive and negative regulation of cell growth. The clues we have followed in mapping these loci have come, in the main, from cytogenetics. For example, the previously mentioned presence of double minute chromosomes and polysomy of chromosome 7 accomplishes genomic amplification of the epidermal growth factor receptor (EGFR) gene which is located on chromosome 7q. The incidence of EGFR amplification in gliomas is in the range of 40% E131, and is exclusive to the more malignant stages. The aforementioned aberrations of chromosome 9p appear to result in deletions of the interferon (IFN) 01 and p loci and these aberrations include most of the malignancy stages. The observation of numerical changes of chromosomes 10 and 17 in glioblastoma has been refined and extended through the comparison of alleles at loci on these chromosomes in normal and tumor tissues of the various stages. These latter analyses showed that loss of alleles caused mainly by mitotic recombination of chromosome 17 homologues occurred in the low, medium, and high grade tumors. Point mutations of the p53 gene (located on chromosome 17p) have been detected in glioblastomas and are now being analyzed in lower grade tumors as well. Allelic comparisons of chromosome 10 loci have shown a nearly obligate loss of one entire homologue in glioblastomas but not in lower stage tumors. Examples of the data supporting each of these inferences of genetic change are shown in. Although the functional influence of these changes on the attainment of malignancy is yet subject to experimental testing, they can be used to make several inferences about the process. Excepting alterations of chromosome 17p, these abnormalities have been restricted to glioblastoma and anaplastic astrocytoma, representatives of the malignant end of the spectrum. These data when combined with the biological evidence for malignant progression of fibrillary astrocytoma's suggest that losses of genetic information for chromosome 10, deletion of the IFN loci, and other less frequent events are likely to be more closely related to tumor progression than initiation.

Clinical Signs And Symptoms

Signs & Symptoms of grade I and grade II astrocytoma's are subtle because the brain is able to temporarily adapt to the presence of a slow-growing tumor. Symptoms of grade III and grade IV astrocytoma's may be sudden and debilitating. Symptoms can result from increased pressure within the brain and may include headaches, vision changes and nausea or vomiting. Symptoms may also occur based on the location of the tumor due to interference with normal brain function and include focal seizures, difficulty with speaking, loss of balance and weakness, paralysis or loss of sensation of one side of the body. Fatigue and depression are common in individuals with an astrocytoma. Desmoplastic infantile astrocytoma (DIA) is a very rare grade I astrocytoma. This tumor tends to occur the cerebral hemispheres and is usually diagnosed in children less than two years of age. Symptoms may include an increased head size, bulging soft spots (fontanelles) in the skull, eyes that focus downward and seizures. A related tumor, desmoplastic infantile ganglioglioma, is a mixed astrocytic and neuronal tumor, but is otherwise similar to DIA. Subependymal giant cell astrocytoma occurs in the ventricles of the brain and is almost always associated with a genetic condition called tuberous sclerosis. Other rare neuroepithelial tumors include pleomorphic xanthoastrocytoma (PXA) and ganglioglioma (a mixed glial-neuronal tumor).

Astrocytic Tumors

Astrocytoma's are defined as tumors composed predominantly of neoplastic astrocytes. If not further specified, the term applies to diffusely infiltrative neoplasms which, according to their biologic behavior, are subdivided into low grade astrocytoma (WHO Grade II), anaplastic astrocytoma (WHO Grade III), and glioblastoma multiforme (WHO Grade IV). A distinctly different entity is the pilocytic astrocytoma which is decidedly different in terms of its location, age distribution, biologic behavior, and genetic basis.

4.1.1 Pilocytic Astrocytoma (malignancy grade I): This is the most frequent brain tumor in childhood, with a peak incidence between the age of 8 to 13 years. In contrast to diffuse astrocytic tumors, the pilocytic astrocytoma is a more circumscribed, slowly growing lesion which very rarely undergoes progression to anaplasia. It therefore corresponds to WHO grade I. Pilocytic astrocytoma's are typically located in midline structures, e.g., the optic nerve, the third ventricle, the thalamus, the median temporal lobe, the brain stem, and the cerebellum. Location in the cerebral hemispheres is much less common. Total surgical resection is difficult in some locations but relatively easy in others, such as the cerebellum. Subtotal resection is often followed by slow recurrence but some lesions remain stable over a course of several years. Macroscopically, the pilocytic astrocytoma is homogeneous, with occasional cysts and well circumscribed borders. It is histologically characterized by bipolar, fusiform, or "poloid cells with dense fibrillation. Particularly common is a biphasic pattern in which pilocytic areas are intimately associated with a loosely structured microcystic component. Hyperchromatic, bizarre nuclei, glomerid vascular proliferation, and invasion of the leptomeninges are common but do not sei malignancy. Elongated eosinophilic, club-shaped structures (Rosenthal fibers), and eosinophilic intracytoplasmic protein droplets ("granular bodies") are histopathological hallmarks of this neoplasm. Glial fibrillary acidic protein (GFAP) expression is always demonstrable, although to a varying degree. The histogenesis of pilocytic astrocytoma's has remained enigmatic. Its morphological characteristics and predilection for certain brain areas of children and adolescents may reflect an origin from a distinct precursor cell, but no such cell type has been identified to date. More likely is the possibility, that pilocytic astrocytoma's do not have a distinct cell of origin but that their biological and morphological features reflect the acquisition of genetic alterations different from those of other gliomas. This explanation is supported by the observation that pilocytic astrocytoma's, especially in the optic nerve, frequently occur in association with neurofibromatosis von Recklinghausen (NF1 syndrome) and that some sporadic pilocytic astrocytoma's show loss of genetic material from chromosome 17q, the region in which the NF1 gene is located.

4.1.2 Astrocytoma's (malignancy grade II): WHO Grade II Molecular genetic events. The formation of WHO grade I1 astrocytoma's is associated with at least three alterations: inactivation of the pS3 tumor suppressor gene, activation of the PDGF system, and loss of a tumor suppressor gene on chromosome 22q. The pS3 gene on chromosome 17p encodes the p53 protein, which has an integral role in a number of cellular processes, including apoptosis, cell cycle arrest, response to DNA damage and angiogenesis. Inactivation of pS3, usually with mutation of one copy and chromosomal loss of the remaining allele, occurs in approximately one-third of astrocytoma's, anaplastic astrocytoma's and glioblastoma multiforme (GBM). These mutations are primarily missense mutations and target the evolutionarily-conserved domains in exons 5, 7 and 8. Particular hot spots for mutations include codons 175, 248 and 273, in which C to T transitions are most likely the result of spontaneous deamination of 5-methylcytosine residues. These mutations affect p53 residues that are crucial for DNA binding, presumably leading to loss of p53-mediated transcriptional activity. The MDM2 and p14ARF genes have been studied in small numbers of these tumors and no abnormalities have been reported. Recent studies of the TP53 related gene, P73, have not identified any mutations. Other findings considered significant include overexpression of the PDGFRA gene. Loss of alleles from 6q, 10p, 13q, and 22q occur in some astrocytoma's. There is no evidence to suggest that there is mutation of the single retained tumor suppressor gene RB1 allele at 13q14.2 or the NF2 tumor suppressor gene on 22q. Deletion mapping of chromosomes 6 and 10 shows losses on 6q and the distal end of 10p in a significant number of astrocytoma's. The potential tumor suppressor genes in all of these regions remain unknown. There are no consistently reported amplified genes or regions of the genome reported in astrocytoma's. The changes found in the astrocytoma's form the baseline for progression in the adult diffuse astrocytic tumor series. Epigenetic changes such as hypermethylation of tumor suppressor gene promoters may also play an important role in transcriptional silencing of important cancer genes and the development of astrocytoma's. This has not been studied in any detail as yet.

4.1.3 Anaplastic (Malignant) astrocytoma's (malignancy grade III): An astrocytoma with focal or diffuse anaplasia, e.g., a tendency to increased cellularity, pleomorphism, and nuclear atypia. In contrast to grade I1 astrocytoma's it displays mitotic activity. Anaplastic astrocytoma's may arise from low-grade astrocytoma's but are also frequently diagnosed at first biopsy, without indication of a less malignant precursor lesion. The fraction of tumor cells with immunoreactivity for GFAP varies. Anaplastic astrocytoma's show an inherent and often rapid tendency to progress to glioblastoma. The numbers of cases of anaplastic astrocytoma's studied is also limited. There are also some practical problems in studying a series of anaplastic astrocytoma's. In sparsely sampled tumor's the diagnosis can only indicate a minimum malignancy grade – there could be regions fulfilling the criteria for glioblastoma elsewhere. Thus in a series of anaplastic astrocytoma's there may be some glioblastomas while there will be no anaplastic astrocytoma's in a glioblastoma series as once the criteria for glioblastoma are fulfilled the tumor cannot be classified as anything other than a glioblastoma. However, this applies only to a clinical diagnosis that is always based on the worst findings in a tumor. Naturally in a tumor that is progressing from one malignancy grade to another there will remain tumor cell populations of the lesser malignancy grade that might be included in a sample molecular analysis. Thus the findings have to be interpreted with care and relatively large series are necessary to enable a correct interpretation of the findings. Cytogenetics, comparative genomic hybridization and molecular genetic techniques all show that the losses of alleles on 6q, 10p, 13q, 17p and 22q, as seen in the astrocytoma malignancy grade II and they occur at similar or higher frequencies in the anaplastic astrocytoma's. Mutations of the TP53 gene also occur at approximately the same frequency. Thus in the anaplastic astrocytoma's the p53 pathway is also non-functional and in the majority of cases (approximately 67%) and this is due to mutations of the TP53 gene. With the sole exception of losses of alleles on 19q (targeted gene(s) unknown) there are no conclusively demonstrated abnormalities specific to this malignancy grade. Around 20% of anaplastic astrocytoma's show similar genetic abnormalities to those found in glioblastomas and discussed below.

4.1.4 Glioblastomas (malignancy grade IV): This is the most frequent and malignant brain tumor and typically affects adults, with a peak incidence between 45 and 60 years. The clinical history is usually short (less than 3 months) unless the neoplasms has developed from low grade or anaplastic astrocytoma (secondary glioblastoma). Patients typically present with nonspecific neurological symptoms, such as headache and personality changes, or with rapid development of life threatening intracranial pressure. After incomplete surgical resection and radiotherapy, the mean survival time is in the range of 6-9 months. The histological criteria for glioblastomas are well defined and these tumor's if adequately sampled, are generally easy to differentiate from the astrocytoma's of lower malignancy grade. Despite this, glioblastomas developing from tumor's of lesser malignancy grade (secondary glioblastomas) may retain in the primary tumor populations of cells that represent the different stages that the tumor went through during its progression. Secondary glioblastomas have only been studied in relatively small numbers for a myriad of reasons. However, the high frequency de novo glioblastomas has permitted their study in considerable numbers. Glioblastomas show the greatest numbers of genetic abnormalities among the astrocytic tumor's and clear patterns of abnormality in these tumor's are emerging. In addition to the targeting of the p53 pathway as is seen in the astrocytoma's and anaplastic astrocytoma's, the mechanisms controlling cellular entry into the S-phase of the cell cycle are also rendered inoperative. In contrast to the astrocytoma's and anaplastic astrocytoma's, the glioblastomas abrogate the p53 pathway in different ways. Some have no wild-type TP53 gene, as found in the astrocytoma's of lower malignancy grade (approximately 37%), but note that this inci- dance is much lower. Others have wild-type TP53 genes but mutate genes coding for proteins that control cellular levels of p53. The mutations found lead to the rapid brake-down of the wild-type protein resulting in a cell with little or no wild-type p53.

Clinical Management And Therapy

The use of molecular findings in providing useful prognostic information in astrocytic tumor's has yet to be realized. There have been many studies providing results that are frequently difficult to interpret. The age of the patient at diagnosis and the histopathological information still provide the most useful data.

We should not be disheartened by this as our understanding of the workings of the normal and malignant cell are as yet rudimentary. Many of the molecular and genetic findings outlined above have also resulted in attempts to experimentally design therapies to block or reinstate the cellular mechanisms activated or deranged by the mutations observed. Some have even got to the stage of phase I and II trials. While many have built on careful observation of human tumor tissue and extensive experimental manipulation in laboratory tests no clear therapeutic breakthrough has yet occurred. However, we can expect that the more we understand the complex mechanisms of the normal cell as well as the aberrations that occur in the malignant cell we will be able to find ways of specifically treating malignant disease, leaving the normal surrounding brain less, if not entirely, undamaged.

Summary

Although the model presented here is undoubtedly very simple, it is a simple and logical model of the formation and histopathology of emerging astrocytoma's. Some histological and pathological signs of astrocytoma's can be partially explained molecularly-biologically. Pathological changes can also be caused by a number of biological and genetic pathways. So far, many studies have shown little correlation between biological and genetic parameters and patient prognosis, but there is no clear association with tumor behavior. However, the ability of molecular and pathological research to evaluate biological events in human astrocytoma's increases the likelihood that a new approach to diagnosis and treatment based on understanding biological phenomena will emerge.

References

TEXTBOOKS

- Vassall E. Essential Guide to Brain Tumors. Darby, PA: Diane Publishing Company; 2005.
- Asher A, Burger PC, et al. A Primer of Brain Tumors: A Patient's Reference Manual, 8th Edition. Des Plains, Il: The American Brain Tumor Association; 2004.

1. Kleihues, P., Burger, P.C., and Scheithauer, B.W. (1993b) Histological Typing of Tumours of the Central Nervous System: World Health Organization International Histological Classification of Tumours. Springer, Berlin.
2. Kraus, J.A., Koopmann, J., Kaskel, P., Maintz, D., Brandner, S., Schramm, J., Louis, D.N., Wiestler, O.D., and von Deimling, A. (1995) Shared allelic losses on chromosomes lp and 19q suggest a common origin of oligodendroglioma and oligoastrocytoma. J. Neuropathol. Exp. Neurol., 54:91-95.
3. Haddad, S.F., Moore, S.A., Schelper, R.L., Goeken, J.A. (1992)Vascular smooth muscle hyperplasia underlies the formation of glomeruloid vascular structures of glioblastoma multiforme. J. Neuropathol. Exp. Neurol., 51:48&?-492.
4. Bigner, S., Johnson, W. (1994) Cytopathology of the Central Nervous System. Edward Arnold, London.

5. Burger, P.C., Scheithauer, B.W., and Vogel, F.S. (1991) Surgical Pathology of the Nervous System and its Coverings. Churchill Living stone, London.
6. Burger, P.C., and Scheithauer, B.W. (1994)Atlas of Tumor Pathology: Tumors of the Central Nervous Svstem. Armed Forces Institute of Pathology, Washington, D.C.
7. Schiffer, D. (1993) Bruin Tumors. Pathology and Its Biological Correlates. Springer-Verlag, Berlin.
8. Kraus, J.A., Koopmann, J., Kaskel, P., Maintz, D., Brandner, S., Schramm, J., Louis, D.N., Wiestler, O.D., and von Deimling, A. (1995) Shared allelic losses on chromosomes lp and 19q suggest a common origin of oligodendroglioma and oligoastrocytoma. J. Neuropathol. Exp. Neurol., 54:91-95.
9. von Deimling, A., Krone, W., and Menon, A.G. (1995) Neurofibromatosis type 1: Pathology, clinical features, and molecular genetics. Brain Pathol., 5:153-162.
10. P. Kleihues, International Agency for Research on Cancer(1995) Histopathology, Classification, and Grading of Gliomas, 150, Cours Albert-Thomas, 69372 Lyon, Cedex 08
11. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Di- agnosed in the United States in (2012). Ref Type: Report
12. Scheithauer, B. W, Hawkins, C, & Tihan, T. VandenBerg SR, Burger PC. Pilocytic as- trocytoma. In: David N.Louis, Hiroko Ohgaki, Otmar D.Wiestler, eds. WHO Classifi- cation of tumours of the central nervous system. Lyon: IARC, (2007). , 2007, 14-21.
13. Louis, D. N, Reifenberger, G, Brat, D. J, & Ellison, D. W. Tumours: introduction and neuroepithelial tumours. In: Seth Love, David N.Louis, David W.Ellison, eds. Green- field´s Neuropathology. London: Hodder Arnold, (2008). , 2008, 1855-60.
14. Koeller, K. K, & Rushing, E. J. From the archives of the AFIP: pilocytic astrocytoma: radiologic-pathologic correlation. Radiographics (2004). , 24, 1693-708.
15. Abdollahzadeh, M, Hoffman, H. J, Blazer, S. I, et al. Benign cerebellar astrocytoma in childhood: experience at the Hospital for Sick Children 1980-1992. Childs Nerv Syst (1994). , 10, 380-3.
16. Aldape, K, Simmons, M. L, & Davis, R. L. Discrepancies in diagnoses of neuroepithe- lial neoplasms: The San Francisco Bay Area Adult Glioma Study. Cancer (2000). , 2342-9.
17. Reardon DA, Rich JN, Friedman HS, Bigner DD. Recent advances in the treatment of malignant astrocytoma. J Clin Oncol. 2006;24(8):1253-65.
18. Jennings MT, Ivengar S. Pharmacotherapy of malignant astrocytomas of children and adults: current strategies and future trends. CNS Drugs. 2001;15(9):719-43.
19. Davis FG, McCarthy BJ. Epidemiology of brain tumors. Curr Opin Neurol. 2000;13(6):635-640.
20. Louis DN (1994) The p53 gene and protein in human brain tumors. J Neuropathol Exp Neurol53: 11-21.
21. Cho Y, Gorina S, Jeffrey PD, Pavletich NP (1994) Crystal structure of a p53 tumor suppressor-DNA complex. urderstandirg tumorigenic mutations Science 265: 346- 355.
22. Jung J-M. Bruner JM, RLar, S, Lang'ord LA, Kyri:s s AP, Kobayashi T, ievin VA, Zharg W (1995) 1rc:eased levels of ~~IWAF~IC~O~ ir i-uman krair: tumcrs. Oncogene 1 I. 28.

23. David N. Louis, Molecular Neuro-Oncology Laboratory, CNY6. Massachusetts General Hospital, 149 Thirteenth St.. Charlestown, MA 02129, USA.
24. . Nowell PC: Science 194:23, 1976.
25. Knudson AG: Annu Rev Genet 20:231,1986.
26. Bigner SH, Mark J, Mahaley MS, Bigner DD: Hereditas 101:103, 1984.
27. Winger MJ, MacDonald DR, Cairncross JG: J Neurosurg 71:487,1989.
28. Cairncross JG: J Neuro Oncol5:99,1987.
29. Rubinstein U, Herman MM, Vandenberg SR: In Rosenblum M (ed): “Brain Tumor Biology.” Basel; New York: Karger, 1984, pp 32-48.
30. Varmus HE: Annu Rev Genet 18:553,1984.
31. Nordenskjold M, Cavenee W: In DeVita Jr. V, Hellman S, Rosenberg SA (eds): “Important Advances in Oncology 1988.” Philadelphia: Lippincott, 1988, pp 83.
32. Humphrey PA, Wong AJ, Vogelstein B, Friedman HS, Werner MH, Bigner DD, Bigner SH: Cancer Res 48: 2231,1988.
33. Nigro JM, Baker SJ, Preisinger AC, Jessup JM, Hostetter R, Cleary K, Bigner SH, Davidson N, Baylin S, Devilee P, Glover T, Collins FS, Weston A, Modali R, Harris CC, Vogelstein B: Nature (Lond.) 342:705, 1989.
34. es CD, Carlbom E, Dumanski JP, Hansen M, Nordenskjold M, Collins VP, Cavenee WK: Cancer Res 48:5546, 1988.
35. Miyakoshi J, Dobler KD, Allalunis-Turner J, McKean JD, Petruk K, Allen PB, Aronyk KN, Weir B, Huyser Wierenga D, Fulton D, Urtasun RC, Day RS 111: Cancer Res 50:278, 1990.
36. James CD, Carlbom E, Nordenskjold M, Collins VP, Cavenee WK: Proc Natl Acad Sci (USA) 86:2858, 1989.
37. C.D. James, E. Carlbom, J.P. Dumanski, M. Hansen, M. Nordenskjold, V.P. Collins, W.K. Cavenee, Clonal genomic alterations in glioma malignancy stages, Cancer Res. 48 (1988) 5546–5551.
38. J.R. Simpson, J. Horton, C. Scott, W.J. Curran, P. Rubin, J. Fischbach, S. Isaacson, M. Rotman, S.O. Asbell, J.S. Nelson, A.S. Weinstein, Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials, Int. J. Radiat. Oncol. Biol. Phys. 26 (1993) 239–244.
39. B.M. McCormack, D.C. Miller, G.N. Budzilovich, G.J. Voorhees, J. Ransohoff, Treatment and survival of low-grade astrocytoma in adults – 1977–1988, Neurosurgery 31 (1992) 636– 642.
40. M.J. Winger, D.R. Macdonald, J.G. Cairncross, Supratentorial anaplastic gliomas in adults. The prognostic importance of extent of resection and prior low-grade glioma, J. Neurosurg. 71 (1989) 487–493.
41. P. Kleihues, W.K. Cavenee (Eds.), World Health Organization Classification of Tumours World Health Organization Classification of Tumours, Vol. 1, IARC Press, Lyon, 2000.

42. K. Ichimura, M.B. Bolin, H.M. Goike, E.E. Schmidt, A. Moshref, V.P. Collins, Deregulation of the p14ARF/MDM2/ p53 pathway is a prerequisite for human astrocytic gliomas with G1-S transition control gene abnormalities, Cancer Res. 60 (2000) 417–424.
43. A.J. Ekstrand, N. Sugawa, C.D. James, V.P. Collins, Amplified and rearranged epidermal growth factor receptor genes in human glioblastomas reveal deletions of sequences encoding 6 V.P. Collins / Cancer Letters 188 (2002) 1–7 portions of the N- and/or C-terminal tails, Proc. Natl. Acad. Sci. USA 89 (1992) 4309–4313.
44. K. Mishima, T.G. Johns, R.B. Luwor, A.M. Scott, E. Stockert, A.A. Jungbluth, X.D. Ji, P. Suvarna, J.R. Voland, L.J. Old, H.J. Huang, W.K. Cavenee, Growth suppression of intracranial xenografted glioblastomas overexpressing mutant epidermal growth factor receptors by systemic administration of monoclonal antibody (mAb) 806, a novel monoclonal antibody directed to the receptor, Cancer Res. 61 (2001) 5349–5354.
45. I.A. Lorimer, C.J. Wikstrand, S.K. Batra, D.D. Bigner, I. Pastan, Immunotoxins that target an oncogenic mutant epidermal growth factor receptor expressed in human tumors, Clin. Cancer Res. 1 (1995) 859–864.
46. A.J. Ekstrand, N. Longo, M.L. Hamid, J.J. Olson, L. Liu, V.P. Collins, C.D. James, Functional characterization of an EGF receptor with a truncated extracellular domain expressed in glioblastomas with EGFR gene amplification, Oncogene 9 (1994) 2313–2320.
47. R. Nishikawa, X.D. Ji, R.C. Harmon, C.S. Lazar, G.N. Gill, W.K. Cavenee, H.J. Huang, A mutant epidermal growth factor receptor common in human glioma confers enhanced tumor igenicity, Proc. Natl. Acad. Sci. USA 91 (1994) 7727–7731
48. N. Sugawa, A.J. Ekstrand, C.D. James, V.P. Collins, Identical splicing of aberrant epidermal growth factor receptor transcripts from amplified rearranged genes in human glioblastomas, Proc. Natl. Acad. Sci. USA 87 (1990) 8602–8606.
49. P.A. Humphrey, A.J. Wong, B. Vogelstein, M.R. Zalutsky, G.N. Fuller, G.E. Archer, H.S. Friedman, M.M. Kwatra, S.H. Bigner, D.D. Bigner, Anti-synthetic peptide antibody reacting at the fusion junction of deletion-mutant epidermal growth factor receptors in human glioblastoma, Proc. Natl. Acad. Sci. USA 87 (1990) 4207–4211.
50. Y. Sonoda, T. Ozawa, K.D. Aldape, D.F. Deen, M.S. Berger, R.O. Pieper, Akt pathway activation converts anaplastic astrocytoma to glioblastoma multiforme in a human astrocyte model of glioma, Cancer Res. 61 (2001) 6674–6678.
51. W. Zundel, C. Schindler, D. Haas-Kogan, A. Koong, F. Kaper, E. Chen, A.R. Gottschalk, H.E. Ryan, R.S. Johnson, A.B. Jefferson, D. Stokoe, A.J. Giaccia, Loss of PTEN facilitates HIF-1-mediated gene expression, Genes Dev. 14 (2000) 391– 396.
52. M.P. Myers, I. Pass, I.H. Batty, J. Van der Kaay, J.P. Stolarov, B.A. Hemmings, M.H. Wigler, C.P. Downes, N.K. Tonks, The lipid phosphatase activity of PTEN is critical for its tumor suppressor function, Proc. Natl. Acad. Sci. USA 95 (1998) 13513–13518.

53. M.P. Myers, J.P. Stolarov, C. Eng, J. Li, S.I. Wang, M.H. Wigler, R. Parsons, N.K. Tonks, P-TEN, the tumor suppressor from human chromosome 10q23, is a dual-specificity phosphatase, Proc. Natl. Acad. Sci. USA 94 (1997) 9052–9057.
54. F.B. Furnari, H.J. Huang, W.K. Cavenee, The phosphoinositol phosphatase activity of PTEN mediates a serum- sensitive G1 growth arrest in glioma cells, Cancer Res. 58 (1998) 5002– 5008.
55. E. Schmidt, K. Ichimura, H.M. Goike, A. Moshref, L. Liu, V.P. Collins, Mutational profile of the PTEN/MMAC1 gene in primary human astrocytic tumors and xenografts, J. Neuropathol. Exp. Neurol. 58 (1999) 1170–1183.
56. P.A. Steck, M.A. Pershouse, S.A. Jasser, W.K.A. Yung, H. Lin, A.H. Ligon, L.A. Langford, M.L. Baumgard, T. Hattier, T. Davis, C. Frye, R. Hu, B. Swedlund, D.H.F. Teng, S.V. Tavtigian, Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers, Nat. Genet. 15 (1997) 356–362.
57. J. Li, C. Yen, D. Liaw, K. Podsypanina, S. Bose, S.I. Wang, J. Puc, C. Miliaresis, L. Rodgers, R. McCombie, S.H. Bigner, B.C. Giovanella, M. Ittmann, B. Tycko, H. Hibshoosh, M.H. Wigler, R. Parsons, PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer, Science 275 (1997) 1943–1947.
58. M.E. Alonso, M.J. Bello, J. Lomas, P. Gonzalez-Gomez, D. Arjona, J.M. De Campos, M. Gutierrez, A. Isla, J. Vaquero, J.A. Rey, Absence of mutation of the p73 gene in astrocytic neoplasms, Int. J. Oncol. 19 (2001) 609–612.
59. H. Huang, S. Colella, M. Kurrer, Y. Yonekawa, P. Kleihues, H. Ohgaki, Gene expression profiling of low-grade diffuse astrocytomas by cDNA arrays, Cancer Res. 60 (2000) 6868– 6874.
60. B. Westermark, H. Carlhendrik, M. Nister, Platelet-derived growth factor in human glioma, Glia 15 (1995) 257–263.
61. K. Ichimura, E.E. Schmidt, H.M. Goike, V.P. Collins, Human glioblastomas with no alterations of the CDKN2A (p16INK4A, MTS1) and CDK4 genes have frequent mutations of the retinoblastoma gene, Oncogene 13 (1996) 1065– 1072.
62. K. Hoang-Xuan, P. Merel, F. Vega, J.P. Hugot, P. Cornu, J.Y. Delattre, M. Poisson, G. Thomas, O. Delattre, Analysis of the NF2 tumor-suppressor gene and of chromosome 22 deletions in gliomas, Int. J. Cancer 60 (1995) 478–481.
63. Y. Ino, J.S. Silver, L. Blazejewski, R. Nishikawa, M. Matsutani, A. von Deimling, D.N. Louis, Common regions of deletion on chromosome 22q12.3–q13.1 and 22q13.2 in human astrocytomas appear related to malignancy grade [In Process Citation]. J. Neuropathol. Exp. Neurol. 58 (1999) 881–885.
64. A. Miyakawa, K. Ichimura, E. Schmidt, S. Varmeh-Ziaie, V.P. Collins, Multiple deleted regions on the long arm of chromosome 6 in astrocytic tumours, Br. J. Cancer 82 (2000) 543–549.
65. K. Ichimura, E.E. Schmidt, A. Miyakawa, H.M. Goike, V.P. Collins, Distinct patterns of deletion on 10p and 10q suggest involvement of multiple tumor suppressor genes in the development of astrocytic gliomas of different malignancy grades, Genes Chromosomes Cancer 22 (1998) 9–15.

66. G. Reifenberger, L. Liu, K. Ichimura, E.E. Schmidt, V.P. Collins, Amplification and overexpression of the MDM2 V.P. Collins / Cancer Letters 188 (2002) 1–7 5 gene in a subset of human malignant gliomas without p53 mutations, Cancer Res. 53 (1993) 2736–2739.
67. G. Reifenberger, J. Reifenberger, K. Ichimura, V.P. Collins, Amplification at 12q13–14 in human malignant gliomas is frequently accompanied by loss of heterozygosity at loci proximal and distal to the amplification site, Cancer Res. 55 (1995) 731–734.
68. A.J. Ekstrand, C.D. James, W.K. Cavenee, B. Seliger, R.F. Pettersson, V.P. Collins, Genes for epidermal growth factor receptor, transforming growth factor alpha, and epidermal growth factor and their expression in human gliomas in vivo, Cancer Res. 51 (1991) 2164–2172.
69. J.F. Costello, C. Plass, W.K. Cavenee, Aberrant methylation of genes in low-grade astrocytomas, Brain Tumor Pathol. 17 (2000) 49–56.
70. E.E. Schmidt, K. Ichimura, K.R. Messerle, H.M. Goike, V.P. Collins, Infrequent methylation of CDKN2A(MTS1/p16) and rare mutation of both CDKN2A and CDKN2B(MTS2/p15) in primary astrocytic tumor's, Br. J. Cancer 75 (1997) 2–8.
71. W. Biernat, Y. Tohma, Y. Yonekawa, P. Kleihues, H. Ohgaki, Alterations of cell cycle regulatory genes in primary (de novo) and secondary glioblastomas, Acta Neuropathol. (Berl.) 94 (1997) 303–309.
72. J. Roth, M. Dobbelstein, D.A. Freedman, T. Shenk, A.J. Levine, Nucleo-cytoplasmic shuttling of the hdm2 oncoprotein regulates the levels of the p53 protein via a pathway used by the human immunodeficiency virus rev protein, EMBO J. 17 (1998) 554–564.
73. R. Honda, H. Tanaka, H. Yasuda, Oncoprotein MDM2 is a ubiquitin ligase E3 for tumor suppressor p53, FEBS Lett. 420 (1997) 25–27.
74. J.Y. Wang, E.S. Knudsen, P.J. Welch, The retinoblastoma tumor suppressor protein, Adv. Cancer Res. 64 (1994) 25–85.
75. M. Nakamura, Y. Yonekawa, P. Kleihues, H. Ohgaki, Promoter hypermethylation of the RB1 gene in glioblastomas, Lab. Invest. 81 (2001) 77–82.

Charts

Charts 1-2 are in the supplementary files section.

Figures

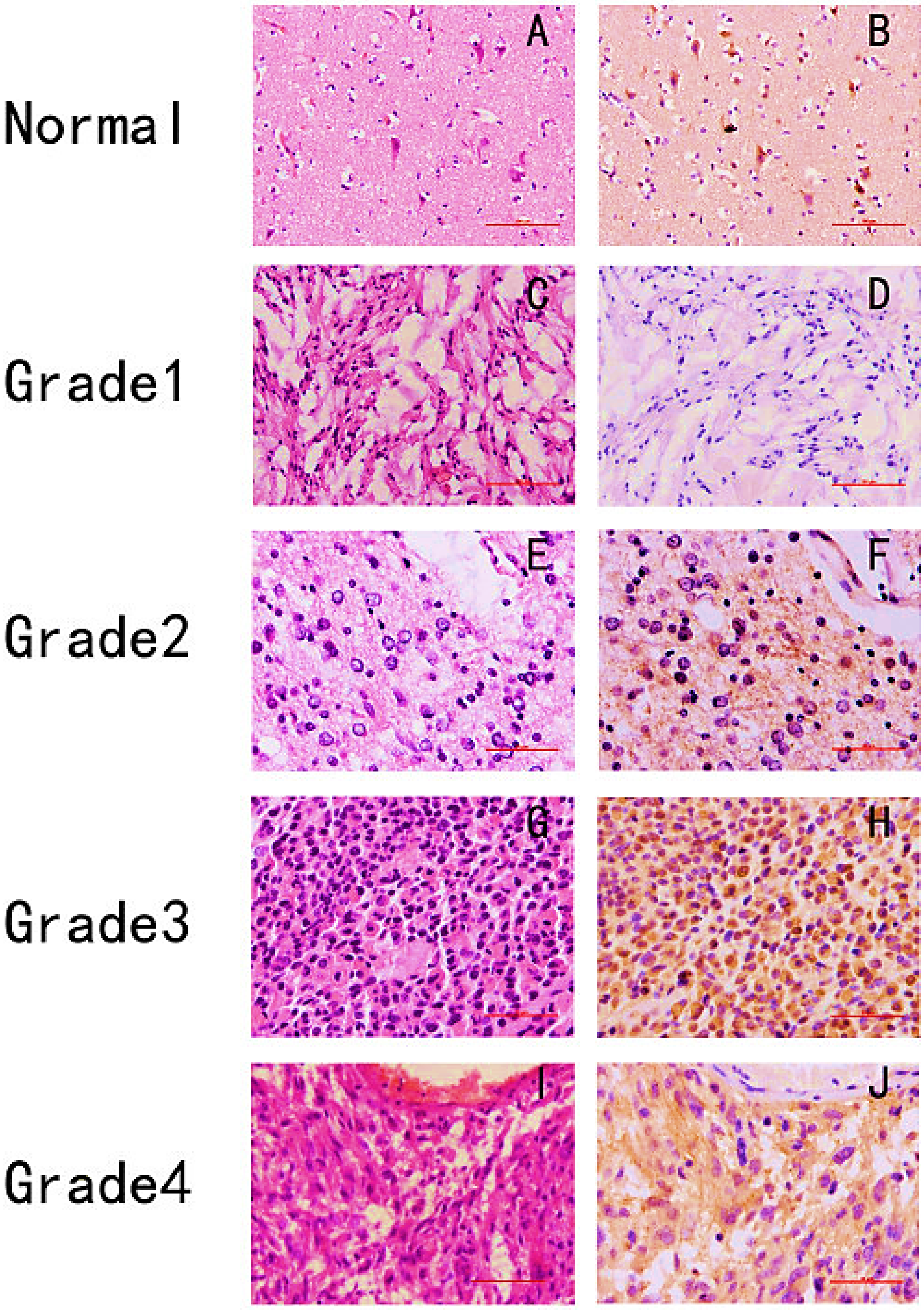

Figure 1

Histologic features of the stages of astrocytoma progression-astrocytoma with relatively normal looking cells , anaplastic astrocytoma with prominent nuclear pleomorphism, and glioblastoma with more extensive pleomorphic, vascular proliferation, and necrosis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- floatimage1.png
- floatimage3.png