Brain Pathology 7: 785-798 (1997)

Classification and Grading of Low-Grade Astrocytic Tumors in Children

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This article reviews current perspectives in the classification and grading of astrocytomas in children and calls attention to several histologically distinct groups of low-grade tumors that characteristically arise during childhood. Recognition of these tumors and the range of histological features that they may exhibit is essential for making rational assessments regarding their expected behavior and, more importantly, for guiding therapeutic intervention. For example, pleomorphic xanthoastrocytoma, which may exhibit "anaplastic" features, generally carries a relatively favorable prognosis and should not be classified with other high-grade gliomas, such as anaplastic astrocytoma and glioblastoma multiforme. Similarly, the finding of anaplastic features, such as vascular proliferation or necrosis, in pilocytic astrocytomas does not automatically portend the unfavorable prognosis that such features would imply for "diffuse" astrocytomas. Increased appreciation of the morphological diversity of astrocytomas in children should help to improve the management of children with low-grade astrocytic tumors by avoiding potentially dangerous overtreatment of otherwise indolent lesions.

Introduction

Astrocytic tumors are the most common primary brain tumors in children. They account for 30-40% of all the central nervous system neoplasms depending upon the neuroaxial compartment affected (8).

According to the 1993 WHO classification (61), astrocytic tumors fall into two major groups. The first and numerically most common is represented by the spectrum of ordinary, diffuse astrocytomas. They show a tendency towards progressive anaplastic transformation and occur in different grades (II to IV), equating with astrocytoma (A), anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM). Such tumors exhibit considerable cytologic variation. The second group is somewhat heterogeneous and includes pilocytic astrocytoma (PA), pleomorphic xanthoastrocytoma (PXA) and subependymal giant cell astrocytoma (SEGA), three distinct clinicopathological entities generally associated with a favorable prognosis.

The 1993 WHO classification and grading scheme for astrocytic tumors is summarized in Table 1. For the sake of completeness and clarity, the WHO grading system, which is coded by Roman numerals, is compared with the St. Anne-Mayo grading scheme. The latter is a simple and widely applied method designed and validated (27) for the grading of ordinary, diffuse astrocytomas alone.

In adults, astrocytic tumors of the diffuse or ordinary type, particularly high grade forms (AA and GBM), are the most frequently occurring group. In contrast, the majority of childhood lesions are of the pilocytic type (36). Only in the cerebral hemispheres and the brain stem do diffuse astrocytomas outnumber the pilocytic lesions. Regardless of site, a clear distinction must be drawn between these two types of tumors, given their very different clinicopathological features and prognoses. Whereas diffuse astrocytomas, particularly low grade examples, are very ill-defined, solid, and non-contrast enhancing, pilocytic tumors are often cystic, relatively circumscribed, and show considerable contrast enhancement. As a rule, diffuse astrocytomas are widely infiltrative of parenchyma and, when low grade, consist of cells with little accompanying cytoplasm. In contrast, pilocytic tumors are relatively solid, show limited tissue infiltration, and feature a broad cytologic spectrum as well as the formation of microcysts, Rosenthal fibers and eosinophilic granular bodies.

In adults, low-grade diffuse astrocytomas show a marked tendency to anaplastic transformation, many eventuating in GBM (66). In contrast, both diffuse and pilocytic astrocytomas in the pediatric age group are relatively slow-growing, and even diffuse astrocytomas are associated with a relatively favorable prognosis. As we will discuss, based upon available literature, it is difficult to fully understand the natural history of diffuse astrocytomas and to determine their incidence of anaplastic transformation (28,29,92). Diffuse astrocytomas of childhood, like their adult counterparts, do show a limited tendency to anaplastic transformation, but its incidence remains to be determined. In rare cases, even pilocytic astrocy-

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Comparison of the World Health Organization (WHO) and St. Anne/Mayo Classification and Grading Systems for Astrocytomas

WHO Designation (variants)	WHO Grade	St. Anne/Mayo Grade
Astrocytoma (fibrillary, protoplastic, gemistocytic)	II	1 and 2
Anaplastic Astrocytoma	III	3
Glioblastoma Multiforme (giant cell, gliosarcoma)	IV	4
Pilocytic Astrocytoma	I*	Not Applicable
Pleomorphic Xanthoastrocytoma	II*	Not Applicable
Subependymal Giant Cell Astrocytoma	I	Not Applicable

*Malignant transformation occurs rarely in these two tumors, in which case the tumors are categorized as anaplastic (pilocytic), astrocytoma (grade III), or pleomorphic xanthoastrocytoma with progression to anaplastic astrocytoma (grade III) or to glioblastoma (grade IV).

Table 1.

tomas follow this course, although in most reported instances, radiation treatment is thought to have played a role in such progression (115).

Pleomorphic xanthoastrocytoma (PXA) is a distinct astrocytic neoplasm and represents a new addition to the 1993 WHO classification (61). It affects primarily children and young adults and exhibits characteristic clinical and radiological presentation. Despite a generally favorable prognosis, PXA differs from other astrocytoma in showing a minor tendency towards anaplastic transformation. The precise incidence and the histopathology underlying PXA progression towards malignancy remains a topic of debate.

Last among astrocytic tumors is the subependymal giant cell astrocytoma (SEGA), a relatively benign tumor with distinctive histological features and a capacity to express glioneuronal characteristics (44,68). Practically limited to the tuberous sclerosis complex, this tumor arises in the lateral ventricle and typically obstructs the foramen of Monro. Histological malignancy is uncommonly encountered and does not affect the very favorable prognosis of this tumor (107).

To avoid confusion of these very different glioma categories, it is of paramount importance that the pathologist be aware not only of the morphologic diversity of astrocytic tumors, but of their characteristic clinical and radiological presentations. It must also be emphasized that the histological parameters so useful in grading diffuse astrocytomas (atypia, mitoses, endothelial proliferation and necrosis) are not of the same ominous significance when seen in other astrocytoma variants (19,27,61). Failure to correctly subclassify an astrocytic tumor type may therefore result in gross overgrading and in damaging overtreatment of relatively indolent neoplasms.

The present work is a clinicopathological review of different astrocytic neoplasms and includes a discussion of the criteria used in their classification. The discussion of grading will focus on its applications to diffuse astrocytomas and will concentrate upon the histological features of anaplastic transformation, a process that appears to occur uncommonly among diffuse astrocytomas in children. The significance of the finding of histological features of malignancy in favorable prognostic variants of astrocytoma is also discussed.

Low Grade (Grade II) Astrocytoma

As generally applied, the term "low grade astrocytoma" refers to the WHO grade II astrocytoma, the low grade end of the spectrum of ordinary or diffuse astrocytic tumors (Figure 1). Such tumors are uncommon in children, representing 14% of all brain tumors in one series (8). They may occur at any site but favor the cerebral hemispheres where they outnumber pilocytic astrocytomas. Among astrocytic tumors, the frequency of diffuse astrocytomas and the proportion of low (grade II) versus high grade (grades III and IV) examples differ in children as compared to adults. In children, diffuse astrocytomas represent less than 50% of all astrocytic tumors, the majority of these (63%) being low grade. In adults, by comparison, the majority of astrocytic tumors are of the diffuse type, few being low grade (14-25%) (8,27,59,97).

Astrocytomas of WHO grade II are tumors composed predominantly of well-differentiated neoplastic astrocytes (61) (Figure 1). They are grossly ill-defined and microscopically show a diffusely infiltrating pattern of growth within brain parenchyma. The morphology of their constituent cells varies (18). The most frequent cytologic variant is composed of fibrillary astrocytes with elongated, atypical nuclei and scant cytoplasm. The other major variant, the

gemistocytic astrocytoma, features large cells with eccentric nuclei and plump eosinophilic cytoplasm. Only when cellularity is appreciable does GFAP highlight the numerous fibrillary processes in the first variety, whereas the ample cytoplasm and the less abundant, stocky processes of gemistocytes are always immunoreactive. Mitotic activity is (by definition) absent. For practical purposes, WHO grade II astrocytoma corresponds to grade 2 astrocytomas of the St. Anne-Mayo scheme due to the fact that St. Anne-Mayo grade 1 lesions are extremely rare (27).

A detailed discussion of the St. Anne-Mayo scheme is beyond the scope of this article. Thus, the reader is referred to the original article describing the method (27). Briefly, the St. Anne-Mayo scheme is based upon scoring the presence or absence of four prognostic indicators. Clearly defined, these include atypia, mitoses, endothelial proliferation and necrosis. At present, the St. Anne-Mayo scheme is the only grading method that has been validated with respect to interobserver reproducibility and the prognostic significance of its parameters. Several studies of diffuse astrocytic tumors in adults have confirmed its utility. However, the method has not been applied systematically to large series of pediatric tumors. The 1993 WHO grading scheme, a modification of the St. Anne-Mayo method, adopts its criteria but forgoes scoring. Instead, it simply defines the grades, predicting grade 2 upon the presence of nuclear atypia, grade 3 upon the additional finding of mitoses, and grade 4 upon the presence of endothelial proliferation or necrosis as well.

Low-grade diffuse astrocytomas in children generally appear to carry an excellent long-term prognosis. Indeed, 20 low-grade diffuse astrocytomas in a series of 71 patients with low-grade gliomas, including pilocytic astrocytomas, oligodendroglioma and oligoastrocytomas, were associated with an overall survival of 82% at 10 years and a progression-free survival of 76% (92). This observation is perhaps not surprising because even in series consisting largely of adults, age has been found to be a very significant and independent prognostic indicator (27). The excellent prognosis recently reported by Piepmeier et al (91) in their series of 55 patients with supratentorial low-grade diffuse astrocytomas, many associated with chronic seizures, may also be largely explained by young patient age.

These above-noted figures differ markedly from the reported <20% ten-year survival rate of adults with grade 2 diffuse astrocytoma (27). Tumor progression with low- to high-grade transformation appears to be chiefly responsible for this unfavorable outcome. Such transition is not uncommon in adult patients. In a large series of 461 adults with supratentorial "low grade astrocytomas," biopsies at recurrence or autopsy showed 39 of 78 (49%) to have undergone high-grade transformation (66). By contrast, the malignant transformation of low-grade diffuse astrocytomas is a relatively rare event in children and is generally the subject of case reports.

It is difficult to study the natural history of low-grade diffuse astrocytomas and their incidence of malignant progression for the following reasons: the relative infrequency of this type of tumor; the lack of large, well-studied series; the frequent failure of many authors to clearly distinguish pilocytic from diffuse astrocytomas of low grade; the fact that biopsy confirmations of tumor progression are uncom-

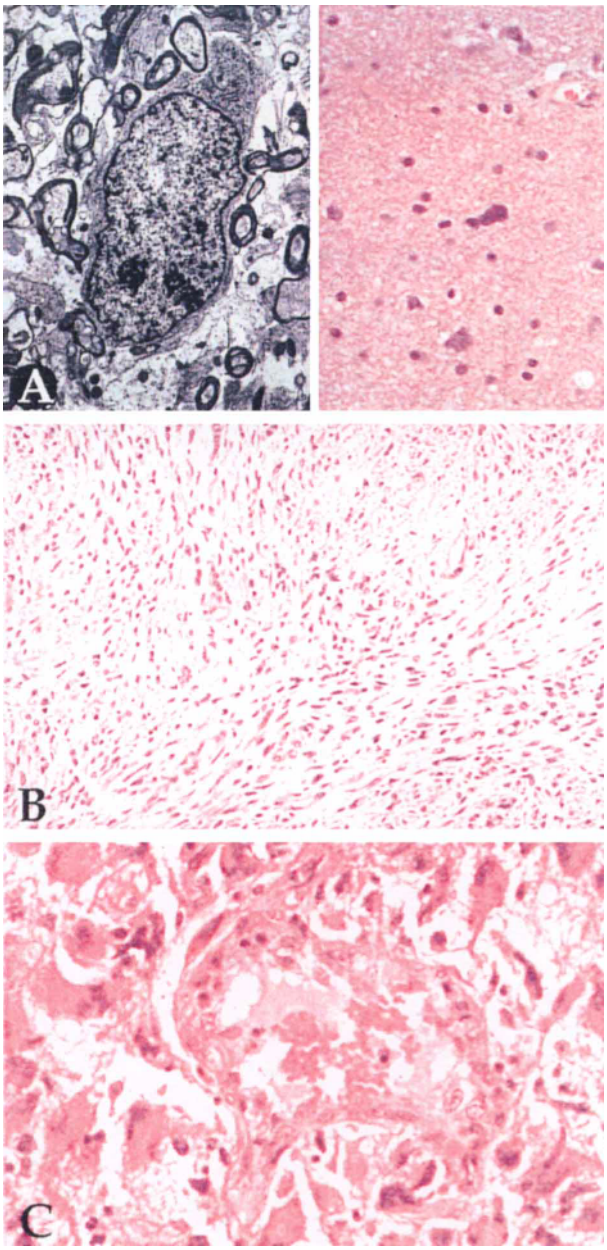

Figure 1. Diffuse astrocytic tumors. The infiltrative, hypocellular portion of this astrocytoma features neoplastic cells with nuclear abnormalities including hyperchromasia (**A, left**) but no appreciable cytoplasm ("naked nuclei"). At the ultrastructural level, such cells often lack filaments and show no specific differentiation (**A, right**). In tumors of higher cellularity, cells typically form cytoplasmic processes and acquire distinctive pink cytoplasm (**B**). With transition to grade 4 malignancy (glioblastoma), endothelial proliferation is commonly seen and consists of apparent multilayering of endothelial cells (**C**). Such vessels differ significantly from the glomeruloid vasculature so commonly seen in pilocytic astrocytomas. (See **Figure 2B**.)

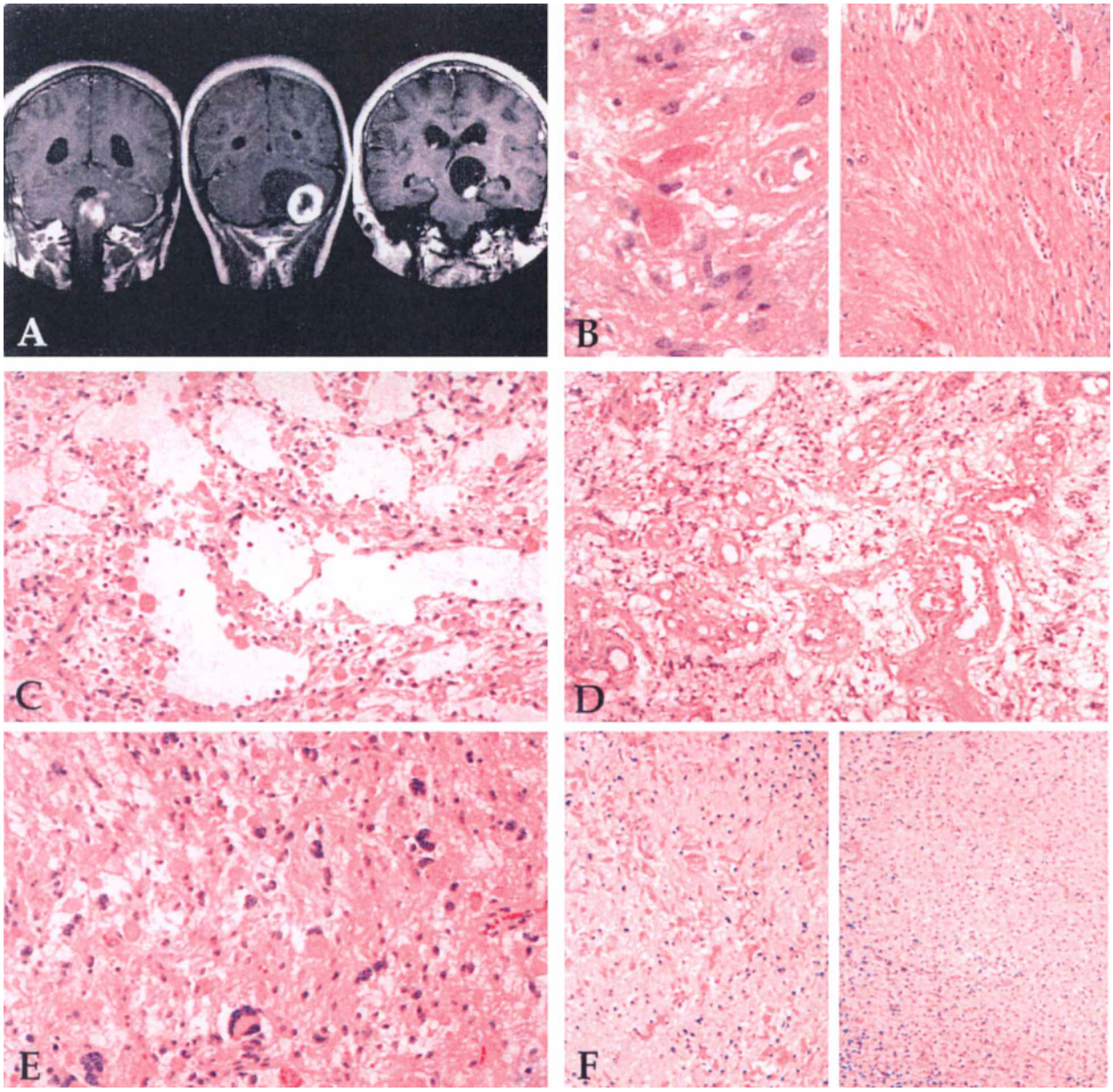

Figure 2. Pilocytic astrocytoma. Solid and/or cystic as well as generally discrete, pilocytic astrocytomas are typically contrast-enhancing tumors. Three examples are shown on an MRI scan affecting the cerebrum, cerebellum, and brain stem (**A**). Histologically their patterns vary from compact (**B**) to microcystic (**C**) and feature Rosenthal fiber (**B**) or granular body formation (**C**), respectively. Glomeruloid vasculature is commonly seen (**D**), as is degenerative nuclear atypia (**E**) and the formation of giant cells with peripheral nuclei ("pennies on a plate") (**E, bottom**). The uncommon "diffuse variant" of pilocytic astrocytoma (**F, left**) may simulate diffuse fibrillary astrocytoma, but the relative lack of nuclear atypia and the focal finding of a more typical pilocytic pattern (**F, right**) confirms the diagnosis.

monly obtained. In the pediatric study of Pollack et al (92), only in 8 of the 13 patients clinically exhibiting progression of disease were the histopathological features of the recurrence examined, and in 5 of these 8, the appearance of the lesion was similar to that of the initial resection. In the 3 remaining cases, only 1 of which was identified as a diffuse astrocytoma at first resection, there was bonafide progression to anaplastic astrocytoma. This patient had received radiation therapy. Only by including 3 patients who died from progression of disease without undergoing a second resection or autopsy as well as 2 patients still alive with progression, but without histopathological confirmation, could the authors estimate an incidence of malignant progression of 11.4% for the overall series, which included pilocytic and diffuse astrocytomas, oligodendrogliomas and oligoastrocytomas. In a series of 50 high-grade malignant astrocytomas in children, tumors arose at the sites of previously diagnosed low-grade diffuse astrocytomas in only three cases; in another 5 cases, it was thought in retrospect that a low-grade tumor

may have undergone high-grade evolution. Based on this assumption, the incidence of malignant transformation in this series would be 16 %, a figure still much lower than is reported in adults (28). Lastly, in the series of Dirks et al (29), of the 6 reported cases of low-grade astrocytomas with anaplastic transformation, only one tumor, a thalamic lesion, was with certainty a low-grade diffuse astrocytoma at first diagnosis. Thus, information regarding the natural history of diffuse astrocytomas in childhood remains limited. The study of a larger series of cases with strictly defined classifications and grading criteria will be necessary in order to clarify these issues.

Pilocytic Astrocytoma

Pilocytic astrocytomas are the most frequently occurring astrocytic tumors in children (Figure 2) (8). Although they show a distinct predilection for certain sites, such as the cerebellum (33,37,41,102), optic pathway (15,46,75,113) and the hypothalamic-third ventricular region (47)—hence the synonyms "cerebellar astrocytoma," "optic glioma," etc.—pilocytic astrocytomas may occur at any level of the neuraxis, including the cerebral hemispheres (43,45,74,85) and spinal cord (76,98). The incidence of this tumor, its histopathological features and the clinical implications of diagnosis are often underappreciated by clinicians, radiologists and pathologists. This is mainly due to the common, imprecise use of a wide variety of terms that are not all synonyms. Specifically, it is often assumed that low-grade fibrillary and pilocytic astrocytomas equate with "low-grade" astrocytoma. Since this unqualified term engenders confusion and promotes misdiagnosis, it should be judiciously avoided. The pilocytic astrocytoma is a well-defined histopathological entity and should be viewed as separate and distinct from diffuse astrocytomas of the ordinary type. These tumors differ markedly in their clinicopathological features and in their potential for malignant transformation. According to the 1979 and 1993 WHO classifications (61,128), the use of the term "astrocytoma" without further qualifiers applies exclusively to low-grade tumors of the diffuse variety (grade II astrocytoma). The unqualified term "astrocytoma" should not, therefore, be used as a synonym for pilocytic astrocytomas or other "low-grade" (grades I and II) tumors in the WHO scheme, including pleomorphic xanthoastrocytomas (PXA) or subependymal giant cell astrocytomas (SEGA). Wishing not to invite interpretative error, we further discourage the use of the unqualified term "astrocytoma" without such descriptors as "diffuse" or "fibrillary" to clearly indicate diffusely infiltrative lesions.

Distinguishing between diffuse and pilocytic astrocytomas may at times be extremely difficult on histological grounds alone. This is especially true when only a small specimen is available, as in spinal cord biopsies (76). As a rule, the rather characteristic clinical and neuroradiological features of pilocytic tumors greatly facilitate their diagnoses. However, in cases wherein this collective data is insufficient to discriminate between these two lesions, a diagnosis of "astrocytoma, subtype and grade indeterminate" is preferable to the frankly misleading term "low-grade" astrocytoma. In such instances, obtaining a more generous specimen or adopting a clinical approach of "watchful waiting" usually resolves the dilemma.

The histology of pilocytic astrocytomas is very distinctive (18,19) (Figure 2). Most are biphasic in pattern and consist of a variable admixture of loosely textured microcystic tissue composed of stellate, rather afibrillar astrocytes and of compact tissue, which is composed of elongated (piloid) astrocytes with conspicuous cytoplasmic fibrillation. The proportion of the two components is highly variable. A minority of tumors consist mostly of either microcystic or compact piloid tissues. Eosinophilic granular bodies and Rosenthal fibers are almost invariably present; the former predominate in the microcystic areas and the latter in solid, compact tissue. Neoplastic nuclei usually have uniform, delicate chromatin and show little variation in size and shape. Degenerative, nuclear changes such as pleomorphism and cytoplasmic pseudoinclusion formation may, however, be marked.

Multinucleated giant cells with peripherally situated nuclei, an arrangement likened to "pennies on a plate", are also common. Mitoses are generally rare or absent. We recently reviewed a series of 131 pilocytic astrocytomas, 94 (72%) of which were from patients less than 18 years of age, and found mitoses in 42 (32%). In 23 cases, despite a careful search of all available slides, only a solitary mitosis was found. In 17 cases, the mitotic index was 1 or 2 per 10 HPF (x 40); in 2 cases, the index was 3 and 4 per 10 HPF respectively (unpublished data). The MIB-1 labeling index was generally low (mean 1.1, SD ± 0.9, range 0 to 3.4) (35). Vascular hyalinization as well as vascular proliferation in the form of glomeruloid structures are commonly seen; only a small minority of tumors show endothelial proliferation defined as apparent multilayering of endothelial cells. In our series, endothelial proliferation was encountered in 23 of the 131 cases (18%). In addition, necrosis (without pseudopalisading) was present in 10 (8%). None of these features, mitoses, endothelial proliferation or necrosis, were statistically associated with survival. Our findings suggest that these histological parameters, so significant in the grading of diffuse astrocytomas, cannot be made the basis of a stringent grading scheme for pilocytic astrocytomas. However, the significance of these features, when markedly expressed, (eg. high mitotic indices), still remains to be determined. Although pilocytic astrocytomas are indolent tumors generally associated with an excellent prognosis, a number of clinically malignant astrocytomas of the pilocytic type have been reported. These include tumors appearing frankly anaplastic (115) as well as rare examples showing aggressive local behavior and leptomeningeal seeding despite lack of anaplastic features (9,106).

Pilocytic astrocytomas of the optic nerve and/or chiasm typically occur in children (15,18,19). Only a small percentage of cases are associated with neurofibromatosis type I, a condition that predisposes to bilateral tumors (18). The great majority of optic

pathway gliomas that occur in children probably represent pilocytic astrocytomas, since diffuse or fibrillary astrocytomas are said to be very uncommon at this site. In many studies of optic nerve and chiasmal gliomas, the noncommittal term "low-grade astrocytoma" was indiscriminately applied to both pilocytic and diffuse astrocytomas (7,30,83,99,113,124,125). The only thing that is clear from various series is that high-grade diffuse astrocytomas are very uncommon. Of these, most affect young adults rather than children and are not limited to the optic nerve but rather involve the chiasm or optic tract as well (49,109). Of gliomas of the optic pathway, those limited to the optic nerve often remain static for years and are controlled by partial resection alone (99,113). In some instances, however, an aggressive and unpredictable course has been reported (46,53). Since most reported series made no critical distinction between pilocytic and diffuse low-grade astrocytomas, and since a significant number of "optic gliomas" were presumptively treated by radiation without histological confirmation, it is difficult to establish the real incidence of diffuse astrocytomas at this site and to study the biology of transformation to anaplastic astrocytoma or glioblastoma. In some cases, it is clear that anaplasia supervenes after an initial confirmed diagnosis of pilocytic astrocytoma (29). It remains to be determined, therefore, whether malignant transformation of a pilocytic tumor occurs with any real frequency or whether a particular tumor is instead developing a high-grade, radiation-induced glioma.

As may be inferred from reviewing Cushing's original description of a series of cerebellar astrocytomas (26), astrocytic tumors of the cerebellum occurring in children are almost exclusively pilocytic. We recently had the opportunity to review our previously published institutional experience with cerebellar astrocytic tumors, a series of 132 patients of all ages (43). Among the 105 patients whose slides were available for review, 69 were less than 18 years of age at diagnosis. Of these, 67 (97%) had pilocytic astrocytomas; only two tumors were diffuse astrocytomas, both of grade 4 (GBM). Pilocytic astrocytomas of the cerebellum are usually discrete, cystic, and contrast-enhancing. Given the high frequency with which a gross total removal is achieved (1,33,43,102), prognosis is generally excellent. Faced with a generous surgical specimen, the histological diagnosis usually poses no problem. More of a challenge is the recognition of what has been termed the "diffuse variant of pilocytic astrocytoma," a tumor less circumscribed than more typical pilocytic astrocytomas (37,43). Although it mimics diffuse astrocytomas of the ordinary type in terms of its infiltration pattern, the variant differs in its cytologic uniformity, relative or utter lack of atypia, and the presence of at least a focal, obvious pilocytic pattern. This form of pilocytic astrocytoma represents 15% of cerebellar examples and does not significantly differ in its prognosis (43,86). Another point worth noting is that although neuroimaging suggests that pilocytic tumors are discrete masses, one systematic histological study showed them to be variously infiltrative of surrounding parenchyma (22). Pilocytic astrocytomas can also be deeply situated, occurring at such sites as the thalamus, hypothalamus and third ventricular area (11,47). In these locations they often form partly intraventricular masses and may not be amenable to resection. Such lesions require hard choices regarding the advantages and disadvantages of aggressive surgical therapy, a factor strongly influencing prognosis at these sites (47).

Although in the cerebral hemispheres and brainstem diffuse astrocytomas far outnumber pilocytic examples, the importance of recognizing the latter at these sites cannot be overemphasized. The two lesions exhibit very different biological behaviors (2,3,31,58,74,85). In a recent review of brain stem astrocytomas operated at Johns Hopkins Hospital between the years 1980 and 1995, Burger et al (17) found that survival among 12 patients with pilocytic astrocytomas was 90% both at five and ten years. By contrast, none of the 7 patients with diffuse astrocytomas, including three grade II, one grade III and three grade IV lesions, experienced more than a two-year postoperative survival (median, 8.1 months) (17). A distinct subgroup of tumors may be represented by a reported series of children with focal midbrain tumors confined to the tectal plate or tegmentum (118). Despite extension upward to the thalamus and/or downward to the pons, they had a relatively favorable outcome. Although all were said to be low-grade, non-pilocytic astrocytomas (i.e., tumors of the diffuse type), their neuroradiological descriptions, specifically the displacing, noninvasive nature of these tumors and their defined edges, solid consistency, and intense, uniform contrast enhancement, all argue in favor of a pilocytic diagnosis. Unfortunately, no histological illustrations were provided.

Primary spinal cord tumors in children are very rare. Most are astrocytomas (81) and include both the diffuse low-grade and pilocytic varieties. The reported frequencies in children for these varieties were 33% and 36%, respectively, in two recent series in which a critical distinction of these two tumor types was adopted (76, 98). In the 79-patient-study by Minehan et al. (76) which included 14 patients below age 20, histological type appeared to be the most significant prognostic indicator; the 10-year survival of pilocytic tumors was 81% whereas it was 15% for diffuse astrocytomas of all grades. By comparison, in the series by Rossitch et al. (98), all tumors, including eight diffuse and four pilocytic astrocytomas, lacked mitoses, vascular proliferation or necrosis, and were associated with prolonged postoperative survival in most cases. Rossitch et al. (98) suggested that MRI scanning with contrast may aid in the distinction of pilocytic and fibrillary diffuse astrocytomas of the spinal cord.

Also of note is the recent report by Constantini et al (25) of a series of 27 patients with spinal cord tumors, all occurring in patients below age 3 years; no pilocytic astrocytomas were said to be found. We believe that the lack of pilocytic astrocytomas is a reflection of the authors' overly restrictive requirement that a definite biphasic pattern consisting of both loose, spongy and densely compacted area elements signifies a diagnosis of pilocytic astrocytoma.

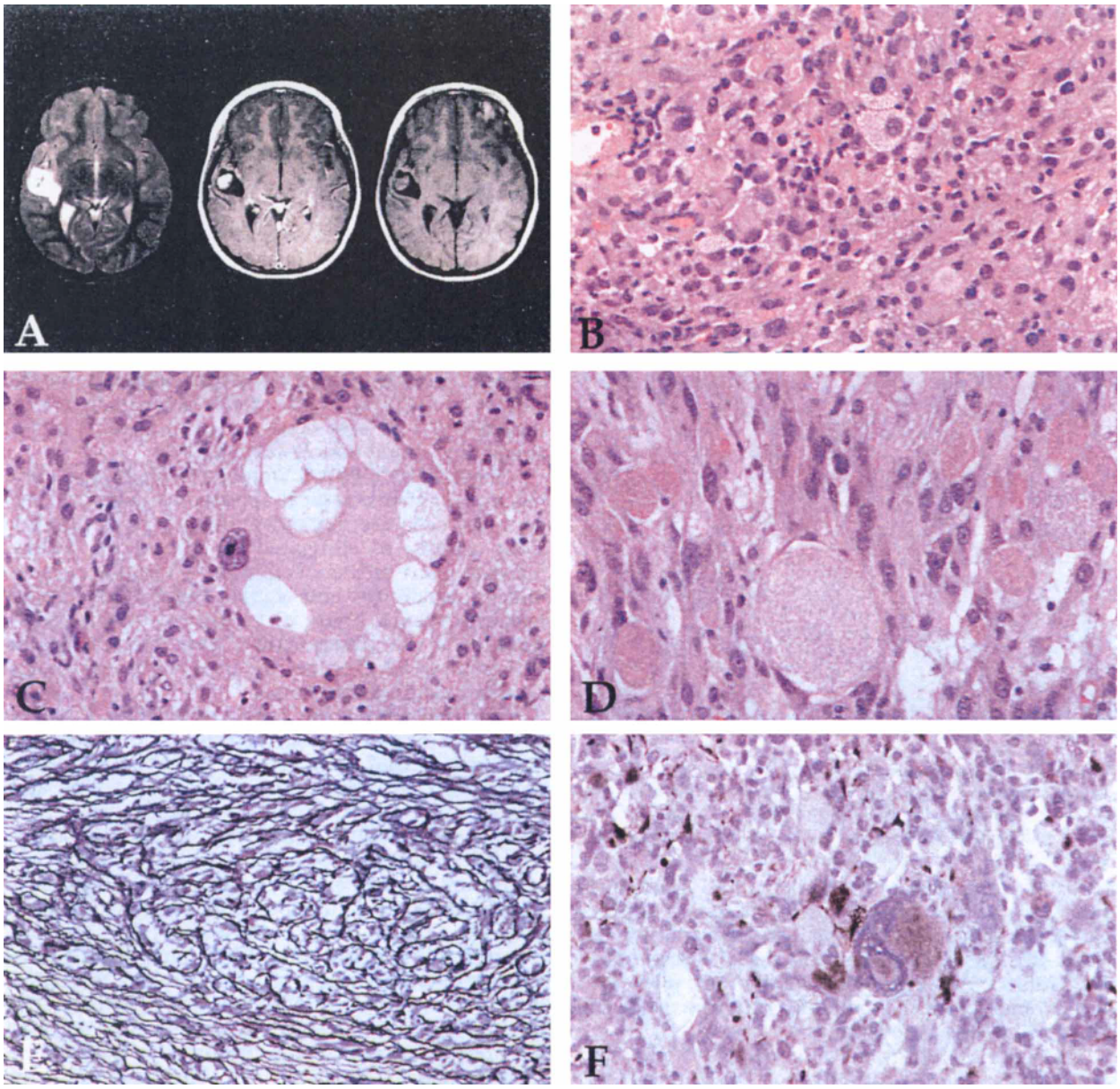

Figure 3. Pleomorphic xanthoastrocytoma (PXA). This superficially situated tumor, here illustrated in an MRI sequence, often shows a cyst-mural nodule architecture (**A**). *Distinctive microscopic features include marked cytologic atypia in the face of little or no mitotic* activity (**B**), lipidization of tumor giant cells (a feature that may be inconspicuous; **C**) and the finding of granular bodies ranging from small, coarse and eosinophilic to large, delicate and pale (**D**). The pattern of reticulin staining in solid, often superficial portions of these tumors varies from inter and pericellular to perilobular (**E**). Immunostaining for GFAP is often non-uniform (**F**).

Their radiological findings of contrast enhancement in more than 90% of the cases studied with gadolinium are difficult to reconcile with their findings of 12 low-grade diffuse astrocytomas out of 27 cases (including three high-grade diffuse astrocytomas, eight gangliogliomas and other miscellaneous lesions). Low-grade diffuse astrocytomas are typically non-enhancing tumors.

The significance of "atypical" features in pilocytic astrocytomas was recently discussed by Tomlinson et al. in a paper also reporting upon the occurrence of histological malignancy in cerebellar examples (115). Six patients with atypical cerebellar astrocytomas, defined by the presence of mitotic activity (<1 per 10 250x fields) and endothelial proliferation but lacking necrosis, were treated with subtotal (2) or total (4) surgical resections; all were alive at a mean follow-up of 19.8 years (range 13 to 24). In addition, four tumors with frankly malignant features, including brisk mitotic activity (at least one per 250x field), endothelial proliferation and necrosis, were also reported. Of these, two occurred as primary tumors without a prior history of radiation therapy. Together with other previously reported cases (10,57,110), these two tumors represent rare examples of spontaneously occurring malignant pilocytic astrocytomas.

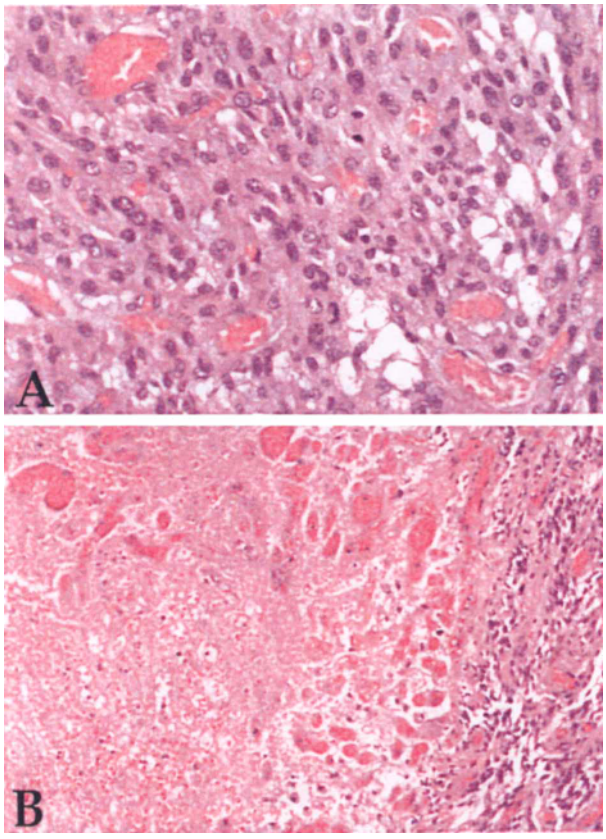

Figure 4. Malignant pleomorphic xanthoastrocytoma (PXA). Anaplastic transformation in a PXA is usually heralded by an increase in mitotic activity and a shift to smaller, epithelioid cells of more uniform size (**A**). Necrosis is a less constant feature (**B**).

It is of note that one of the patients in Tomlinson's study (115) with a histologically malignant tumor treated with surgery alone remained alive and well at 5 years. It is therefore conceivable that the postoperative course of histologically malignant pilocytic astrocytomas is not as generally dismal as that of high-grade diffuse astrocytomas.

The majority of histologically malignant pilocytic astrocytomas occur in patients who have undergone radiation therapy for otherwise typical pilocytic astrocytomas (5,10,16,20,29,62,77,79,87,96,103,104, 105,110,115,117,122,123). The latency interval to malignant transformation reportedly varies from 2 to 52 years following treatment. The biological behavior of these tumors is often aggressive, leading to a fatal outcome in a short time (29). The alternative possibility that radiation causes an intermediate or high-grade astrocytoma at the site of a previously treated astrocytoma must also be considered. Their occurrence in the field of irradiation and the long latency periods reported would also be consistent with postradiation neoplasia.

After meningiomas and sarcomas, astrocytomas are the third most common tumors reported to occur after irradiation of glial and non-glial tumors of the CNS (12,80,108,119). Post-radiation gliomas have also been reported following treatment of craniopharyngioma (69), paraganglioma (94), medulloblastoma (23,63,90,101) or systemic malignancy, e.g., leukemia and lymphoma (72). It remains to be determined whether or not children are more susceptible to the development of radiation-induced tumors than are adults.

Pleomorphic Xanthoastrocytoma

This unique tumor was first recognized in 1979 by Kepes and coworkers who reported a series of 12 cases, emphasizing the relatively favorable prognosis of a tumor frequently mistaken for glioblastoma or giant cell sarcoma of the brain (55). Now a well-recognized clinicopathological entity, PXA is the most recent addition to the 1993 WHO classification of astrocytic tumors (61). It is typically associated with seizures, affects primarily young patients, arises almost exclusively in the cerebral hemispheres, is superficially situated and typically appears as an enhancing, mural nodule within a cyst.

Histologically, PXA is architecturally complex but has a distinct histological appearance (Figure 3). Its compact cells are markedly pleomorphic, ranging from spindly to elongated to epithelioid. Multinucleate giant cells are common. A variable number of cells, usually few and of giant proportion, contain intracytoplasmic lipids, as confirmed by Oil Red O stain, or at the ultrastructural level. These range in size from small droplets to larger vacuoles—hence the term xanthoastrocytoma.

Scattered among the astrocytic cells are a highly variable number of eosinophilic granular bodies, either coarse and bright red or delicate and pale in appearance. In typical PXAs, mitoses are rare, and necrosis, as well as endothelial proliferation, are absent. As previously noted, most PXAs are hemispheric, arise in the temporal lobe, and grow superficially in intimate association with the leptomeninges. The formation of an underlying cyst is common. It is the superficial, typically leptomeningeal, portion of the PXA tumor that features a dense intercellular reticulin network due to pericellular basement membrane deposition. Prior to the immunohistochemistry era, it was this particular feature that prompted the notion that PXA was of mesenchymal derivation (54). The true nature of PXA became apparent with the finding of glial fibrillary acidic protein reactivity within tumor cells (57). In addition to the superficial nodular component, virtually all PXA show some degree of parenchymal infiltration, often no more than is evident in pilocytic tumors.

Since the first description of PXA, approximately 90 cases have been reported, two thirds occurring in patients less than 18 years of age (4,32,34,40,48,50, 52,55,57,64,65,67,70,71,78,82,88,89,93,100,111,112, 114,121,126,127). All series have confirmed the overall favorable clinical prognosis of this lesion (84). Nonetheless, PXA may recur, and a significant proportion may demonstrate aggressive clinical behavior leading to the patient's demise (84). Such an aggressive course is usually associated with anaplastic transformation (high mitotic activity and/or necrosis) as confirmed by biopsies of recurrent lesions or at autopsy (Figure 4). At present, there are no minimal

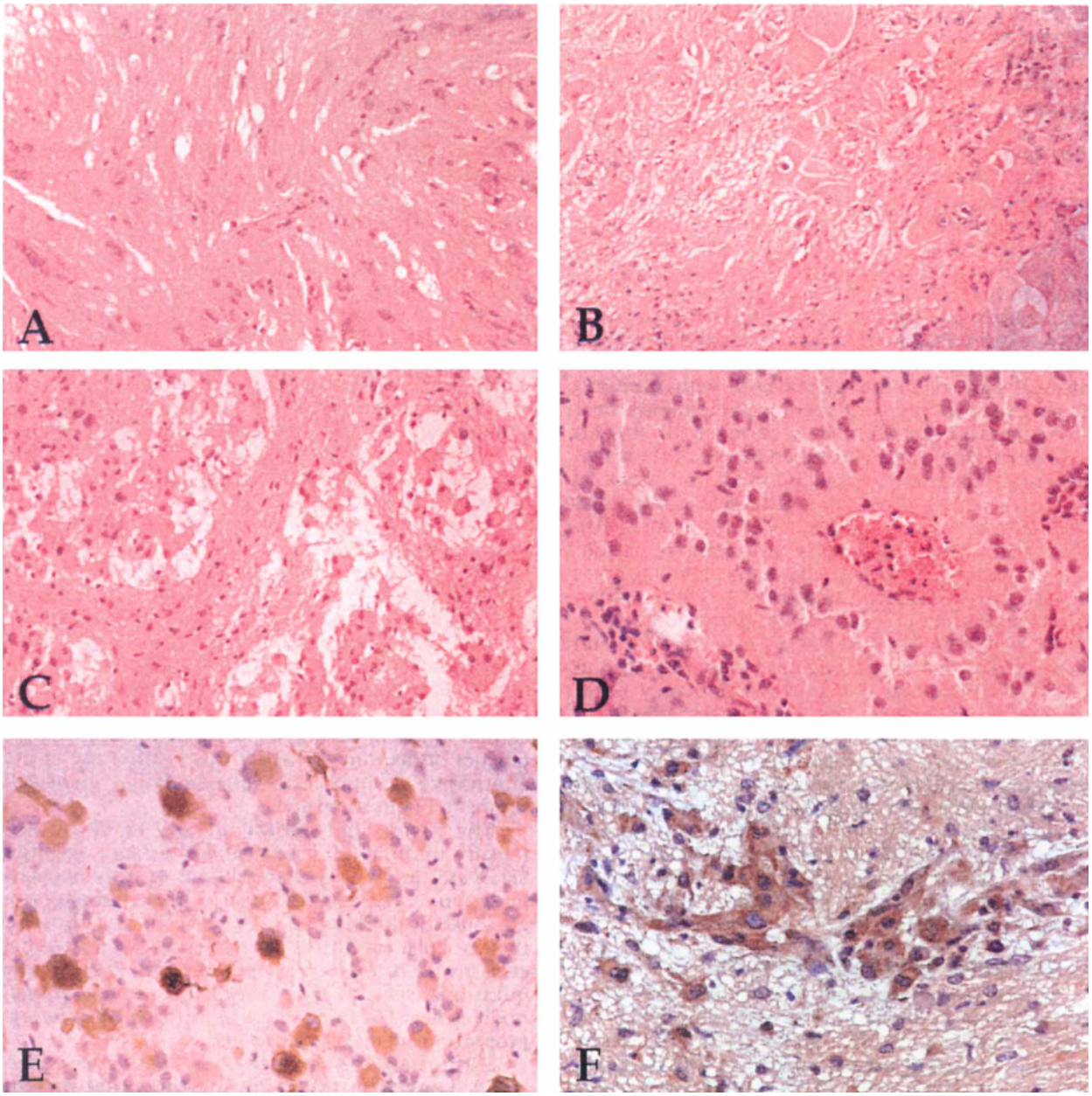

Figure 5. Subependymal giant cell astrocytoma (SEGA). Cytologic variation is typical of SEGA and ranges from spindled (**A**) and epithelioid cells (**B**) to occasional giant cells resembling neurons (**C**). Sweeping of cells about vessels is common (**A**), but well formed perivascular pseudorosettes are less frequently seen (**D**). The expression of neuronal markers or of neurotransmitters, here illustrated by immunostaining for class III (-tubulin (**E**) and somatostatin (**F**), is also frequent.

histopathological criteria predictive of recurrence or indicative of anaplastic transformation. Anaplastic lesions often appear in small series or as single case reports with limited clinical and follow-up information; in addition, detailed descriptions of histological features that might be of prognostic significance are lacking. It is therefore difficult to draw conclusions on the basis of published data. A critical review of published cases can be summarized as follows: of the 45 patients below age 18 at diagnosis and on whom clinical follow-up was available (78% of the reported cases), 10 had died of tumor progression. In 6 cases, the tumor progressed or recurred within 6 months of the original diagnosis, and survival was 4-12 months (34,40,57,88,121). In yet another patient the tumor recurred at 15 months and proved fatal 24 months after the initial diagnosis (52). This subset of patients had, therefore, experienced an aggressive, monophasic malignant course from the time of diagnosis to death. Three of the originally resected tumors featured necrosis, and four exhibited mitotic activity which was not quantified. One patient in whom the tumor recurred six years after diagnosis died six months later; histological signs of anaplasia were only noted in the recurrence (57). One other patient underwent three surgical resections before dying of a

recurrent tumor 25 years after the original diagnosis; the specimens demonstrated progressive anaplasia (55). Lastly, one patient, in which the tumor recurred nine years after the first diagnosis, died in the postoperative period (111).

Among 12 patients alive at the time of publication, tumors had recurred after a mean interval of five years (median 3.5 ; SD ± 5) after diagnosis. As compared to the patients who did not experience a recurrence and in whom histological data were available (n=16), tumoral mitotic activity was observed in five of 12 cases (versus 12 of 16), but necrosis was absent in both groups. Only in four cases with recurrent tumors was sufficient (greater than one year) postoperative follow-up available (range of 1.5 - 8 years). Although in two of these cases there were histological signs of tumor progression, with appropriate surgical and adjuvant therapy the patients were alive 3 and 6 years after the recurrence (4, 70). An accurate mitotic count performed in one of these two patients demonstrated focally up to four mitoses x 10 HPF in the original resection specimen and ranged between 0 and 32 x 10 HPF in the recurrence (70). Despite recurrence with anaplastic transformation, such PXAs should not be regarded as glioblastomas because the clinical evolution of PXAs with anaplastic transformation is usually not as precipitous.

We have recently reviewed 59 cases of PXAs and carefully recorded in the original biopsy or resection specimens histological features which may be of prognostic significance. Our data suggest that accurate mitotic count may be useful in identifying those tumors that have an increased probability of recurrence and anaplastic transformation. Necrosis is also associated with high frequencies of recurrence and mortality, but it may be too infrequent a finding (13%) to be relied on as the only predictor. Since PXA is a slowly growing tumor, our findings will need to be confirmed with more cases and longer follow-up (unpublished data).

Subependymal Giant Cell Astrocytoma

Subependymal giant cell astrocytoma (SEGA) is a tumor practically limited in its occurrence to the setting of tuberous sclerosis complex (TSC) (107). Those rare cases ostensibly unassociated with TSC are subjudice in that only a few had long follow-up or were subjected to clinical scrutiny, thus, an association with TSC could not be entirely excluded (14,42). Lastly, reduced penetrance of the various traits of TSC could also account for some apparently "primary" tumors (24,39). Although SEGAs are the most common tumors of the TSC, other neoplasms, including hemangioma, neurilemmoma, ependymoma and spongioblastoma, have been reported (13,51, 73,95,116). Subependymal giant cell astrocytomas are usually situated within the lateral ventricle and overlie the head of the caudate nucleus, where they often obstruct the foramina of Monro (60,107). They arise from histologically similar subependymal nodules located on the wall of the lateral ventricles of affected patients. By convention, nodules which grow larger than one cm or to the point where they become symptomatic are considered subependymal giant cell astrocytomas. The tumors are circumscribed and, frequently, calcified. They are composed of large astrocytic-appearing cells with abundant eosinophilic cytoplasm (Figure 5). These vary in size and shape, from epithelioid to spindle or giant cell (6), and frequently aggregate in clusters or arrange around vessels. Nucleoli may be prominent; mitoses are usually rare (61). In a recent retrospective review of 345 patients with tuberous sclerosis, Shepherd et al. (107) found 21 cases of subependymal giant cell astrocytoma (6.1%). In this study, as in the study by Chow et al. (21), atypia and mitoses were not uncommon. In one case, the mitotic activity was brisk (>5 mitoses per 10 HPF), and necrosis was present. The authors did not find any correlation between the histological features and clinical course or survival.

The immunophenotype of SEGA is complex. Its cells show not only variable GFAP staining and widespread S100 protein immunoreactivity but frequently express neuronal markers, thus bringing into question the very nature of the neoplasm. Such neuron-associated markers include neurofilament protein epitopes (33%), class III β-tubulin (83%), calbindin (67%), and neurotransmitter substances (metenkephalin, 5-hydroxytryptamine, β-endorphin, neuropeptide Y somatostatin, etc.) (44, 68) (Figure 5e & 5f). Based upon these findings and such ultrastructural features as stacks of rough endoplasmic reticulum and microtubules, one can conclude that SEGA cells, despite their largely astrocytic phenotype, exhibit biochemical and some ultrastructural characteristics of neurons. Whether this justifies use of the alternative designation "subependymal giant-cell tumor" remains unsettled.

The nature and natural history of SEGA also remains uncertain. It is unclear, for instance, whether SEGA are simply large hamartomas or truly neoplastic lesions. Even less is known of their ultimate origin, specifically how and if their cells and those of their nodular precursors are related to the primordial cells involved in cerebral development. Even simple questions, such as why only those subependymal nodules near the foramen of Monro grow to tumoral proportions, remain unanswered.

Fortunately, the behavior of SEGA is better understood. Long-term follow-up indicates that patient survival is very favorable. In one recent series it approached 80 % at both 5 and 10 years (107). It is of note that of the 7 deaths reported in this series, 4 were due to treatment complications rather than to the direct effects of the tumor. Spontaneous intratumoral hemorrhage is also occasionally the basis of a patient's demise. By comparison, the survival of a group of patients with diffuse astrocytoma exhibiting giant cell components, 85 % of which were of grade 4 (glioblastoma), was less than 10 % (107).

References

1. Abdollahzadeh M, Hoffman HJ, Blazer S, Becker LE, Humphreys RP, Drake JM, Rutka JT (1994) Benign cerebellar astrocytoma in childhood: experience at the Hospital for Sick Children 1980-1992. *Childs Nerv Syst* 10: 380-3

2. Afra D, Muller W, Slowik F, Firching R (1986) Supratentorial lobar pilocytic astrocytomas: report of 45 operated cases, including 9 recurrences. *Acta Neurochir (Wien)* 81: 90-93
3. Albright AL, Guthkelch AN, Packer RJ, Price RA (1986) Prognostic factors in pediatric brain-stem gliomas. *J Neurosurg* 65: 751-755
4. Allegranza A, Ferraresi S, Bruzzone M, Giombini S (1991) Cerebromeningeal pleomorphic xanthoastrocytoma: report on four cases - clinical, radiologic, and pathological features (including a case with malignant evolution). *Neurosurg Rev* 14: 43-49
5. Alpers CE, Davis RL, Wilson CB (1982) Persistence and late malignant transformation of childhood cerebellar astrocytoma: case report. *J Neurosurg* 57: 548-551
6. Altermatt HJ, Scheithauer BW (1992) Cytomorphology of subependymal giant cell astrocytoma. *Acta Cytologica* 36: 171-175
7. Alvord EC, Lofton S (1988) Gliomas of the optic nerve or chiasm: outcome by patient's age, tumor site, and treatment. *J Neurosurg* 68: 85-98
8. Anonymous (1988) A study of childhood brain tumors based on surgical biopsies from ten North American institutions: sample description: Childhood Brain Tumor Consortium. *J Neuro-Oncol* 6 :9-23
9. Auer RN, Riel GP, Hinton GG, Amacher AL, Gilbert JJ (1981) Cerebellar astrocytoma with benign histology but malignant clinical course. *J Neurosurg* 54: 128-132
10. Bernell WR, Kepes JJ, Seitz EP (1972) Late malignant recurrence of childhood cerebellar astrocytoma. report of two cases. *J Neurosurg* 37: 470-474
11. Bernstein M, Hoffman HJ, Halliday WC, Hendrick EB, Humphreys RP (1984) Thalamic tumors in children: long-term follow-up and treatment guidelines. *J Neurosurg* 61: 649-656
12. Bernstein M, Laperriere N (1991) Radiation injury to the nervous system. In: *Radiation induced tumors of the nervous system*, Gutin PH, Leibel SA, Sheline GE (eds): New York: Raven Press Ltd, pp 455-472
13. Boesel CP, Paulson GW, Kosnik EJ, Earle KM (1979) Brain hamartomas and tumors associated with tuberous sclerosis. *Neurosurg* 4: 410-417
14. Bonnin JM, Rubinstein LJ, Papasozomenos SC, Marangos PJ (1984) Subependymal giant cell astrocytoma: Significance and possible cytogenetic implications of an immunohistochemical study. *Acta Neuropathol* 62: 185-193
15. Borit A, Richardson EP Jr (1982) The biological and clinical behavior of pilocytic astrocytomas of the optic pathways. *Brain* 105: 161-187
16. Budka H (1975) Partially resected and irradiated cerebellar astrocytoma of childhood: malignant evolution after 28 years. *Acta Neurochir (Wien)* 32: 139-146
17. Burger PC, Breiter SN, Fisher PG (1996) Pilocytic and fibrillary astrocytomas of the brain stem - a comparative clinical, radiological, and pathological study. *J Neuropath Exp Neurol* 55: 640
18. Burger PC, Scheithauer BW, Vogel FS (1991) *Surgical Pathology of the Nervous System and Its Coverings*, 3rd Edition, Churchill Livingstone
19. Burger PC, Scheithauer BW (1994) *Tumors of the Central Nervous System, Atlas of Tumor Pathology*, Third Series, Fascicle 10, Armed Forces Institute of Pathology, Washington D.C.
20. Casadei GP, Arrigoni GL, D'Angelo V, Bizzozero L (1990) Late malignant recurrence of childhood cerebellar astrocytoma. *Clin Neuropathol* 9: 295-298
21. Chow CW, Klug GL, Lewis EA (1988) Subependymal giant cell astrocytoma in children: an unusual discrepancy between histological and clincial features. *J Neursurg* 68: 880-883
22. Coakley KJ, Huston J III, Scheithauer BW, Forbes GS, Kelly PJ (1995) Pilocytic Astrocytomas: Well-Demarcated Magnetic Resonance Appearance Despite Infrequent Infiltration Histologically. *Mayo Clin Proc* 70: 747-751
23. Cohen MS, Kushner MJ, Dell S (1981) Frontal lobe astrocytoma following radiotherapy for medulloblastoma. *Neurology* 31: 616-619
24. Connor JM, Stephenson JPB, Hadley MDM (1986) Non-penetrance in tuberous sclerosis. *Lancet* 2: 1275 (letter)
25. Costantini S, Houten J, Miller DC, Freed D, Ozek MM, Rorke LB, Allen JC, Epstein FJ (1996) Intramedullary spinal cord tumors in children under the age of 3 years. *J Neurosurg* 85: 1036-1043
26. Cushing H (1931) Experiences with the cerebellar astrocytomas. A critical review of seventy-six cases. *Surg Gyne Obstet* 52: 129-191
27. Daumas-Duport C, Scheithauer BW, O'Fallon J, Kelly P (1988) Grading of astrocytomas. A simple and reproducible method. *Cancer* 62: 2152-2165
28. Dropcho EJ, Wisoff JH, Walker RW, Allen JC (1987) Supratentorial malignant gliomas in childhood: a review of fifty cases. *Ann Neurol* 22: 355-364
29. Dirks PB, Jay V, Becker LE, Drake JM, Humphreys RP, Hoffman HJ, Rutka JT (1994) Development of anaplastic changes in low-grade astrocytomas of childhood. *Neurosurg* 34: 68-78
30. Flickinger JC, Torres C, Deutsch M (1988) Management of low-grade gliomas of the optic nerve and chiasm. *Cancer* 61: 635-642
31. Forsyth PA, Shaw EG, Scheithauer BW, O'Fallon JR, Layton DD Katzmann JA (1993) Supratentorial pilocytic astrocytomas. *Cancer* 72: 1335-1342
32. Furuta A, Takahasi H, Fusahiro I, Onda K, Takeda N, Tanaka R (1992) Temporal lobe tumor demonstrating ganglioglioma and pleomorphic xanthoastrocytoma components. *J Neurosurg* 77: 143-147
33. Garcia DM, Latifi HR, Simpson JR, Picker S (1989) Astrocytomas of the cerebellum in the children. *J Neurosurg* 71: 661-664
34. Gaskill SJ, Marlin AE, Saldivar V (1988) Glioblastoma multiforme masquerading as a pleomorphic xanthoastrocytoma. *Childs Nerv Syst* 4: 237-240
35. Giannini C, Scheithauer BW, Burger PC, Christensen MR, Wollan PC, Sebo TJ, Forsyth PA, Hayostek CJ (1996) The MIB-1 LI in pilocytic and diffuse astrocytomas. *J Neuropathol Exp Neurol* 55: 605
36. Gilles FH, Leviton A, Hedley-White ET, Sobel E, Tavare' CJ, Sobel RS and Rorke LB (1992) Childhood brain tumors that occupy more than one compartment at presentation. *J Neurooncol* 14: 45-56
37. Gjerris F, Klinken L (1978) Long-term prognosis in children with benign cerebellar astrocytoma. *J Neurosurg* 49: 179-184
38. Gomez JG, Garcia JH, Colon LE (1985) A variant of cerebral glioma called pleomorphic xanthoastrocytoma: Case report. *Neurosurg* 16: 703-706
39. Gomez MR (1988) Varieties of expression of tuberous sclerosis. *Neurofibromatosis* 1: 330-338

40. Grant JW, Gallagher PJ (1986) Pleomorphic xanthoastrocytoma: immunohistochemical methods for differentiation from fibrous histiocytomas with similar morphology. *Am J Surg Pathol* 10: 336-341
41. Griffen TW, Beaufait D, Blasko JC (1979) Cystic cerebellar astrocytomas in children. *Cancer* 44: 276-280
42. Halmagyi GM, Bignold LP, Allsop JL (1979) Recurrent subependymal giant cell astrocytoma in the absence of tuberous sclerosis: Case report. *J Neurosurg* 50: 106-109
43. Hayostek CJ, Shaw EG, Scheithauer BW, O'Fallon JR, Weiland TL, Schomberg PJ, Kelly PJ, Hu TC (1993) Astrocytomas of the cerebellum. A comparative clinicopathological study of pilocytic and diffuse astrocytomas. *Cancer* 72: 856-869
44. Hirose T, Scheithauer BW, Lopes MBS, Gerber HA, Altermatt HJ, Hukee MJ, Vandenberg SR, Charlesworth JC (1995) Tuber and subependymal giant cell astrocytoma associated withtuberous sclerosis: an immunohistochemical, ultrastructural, and immunoelectron microscopic study. *Acta Neuropath* 90: 387-399
45. Hirsch JR, Sainte Rose C, Pierre-Kahn A, Pfister A, Hoppe-Hirsch E (1985) Benign astrocytic and oligodendrocytic tumors of the cerebral hemispheres in children. *J Neurosurg* 62: 811-815
46. Hoffman HJ, Humphreys RP, Drake JM, Rutka JT, Becker LE, Jenkin D, Greenberg M (1993) Optic pathway/hypothalamic gliomas: a dilemma in management. *Pediatr Neurosurg* 19: 186-95
47. Hoffman HJ, Soloniuk DS, Humphreys RP, Drake JM, Becker LE, De Lima BO, Piatt JH Jr (1993) Management and outcome of low-grade astrocytomas of the midline in children: a retrospective review. *Neurosurg* 33: 964-971
48. Hosokawa Y, Tsuchihashi Y, Okabe H, Toyama M, Namura K, Kuga M, Yonezawa T, Fujita S, Ashihara T (1991) Pleomorphic xanthoastrocytoma: ultrastructural, immunohistochemical, and DNA cytofluorometric study of a case. *Cancer* 68: 853-859
49. Hoyt WF, Meshel LG, Lessell S, Schatz NJ, Suckling RD (1973) Malignant optic glioma of adulthood. *Brain* 96: 121-123
50. Iwaki T, Fukui M, Kondo A, Matsushima T, Takeshita I (1987) Epithelial properties of pleomorphic xanthoastrocytomas determined in ultrastructural and immunohistochemical studies. *Acta Neuropathol (Berl)* 74: 142-150
51. Jervis GA (1954) Spongioneuroblastoma and tuberous sclerosis. *J Neuropath Exp Neurol* 13: 105-116
52. Jones JC, Drut R, Gaglia G (1983) Pleomorphic xanthoastrocytoma: a report of two cases. *Pediatr Pathol* 1: 459-467
53. Kanamori M, Shibuya M, Takayasu M, Kageyama N (1985) Long-term followup of patients with optic glioma. *Child's Nerv Syst* 1: 272-278
54. Kepes JJ, Kepes M, Slowik F (1973) Fibrous xanthomas and xanthosarcomas of the meninges and the brain. *Acta Neuropathol* 23:187-199
55. Kepes JJ, Rubinstein LJ, Eng LF (1979) Pleomorphic xanthoastrocytoma: a distinctive meningocerebral glioma of young subjects with relatively favorable prognosis-a study of 12 cases. *Cancer* 44: 1839-1852
56. Kepes JJ, Lewis RC, Vergara GG (1980) Cerebellar astrocytoma invading the musculature and soft tissues of the neck: case report. *J Neurosurg* 52: 414-418
57. Kepes JJ, Rubinstein LJ, Ansbacher L, Schreiber DJ (1989) Histopathological features of recurrent pleomorphic xanthoastrocytomas: further corroboration of the glial nature of this neoplasm. A study of three cases. *Acta Neuropathol* 78: 585-593
58. Khatib Z, Heidemann R, Kovnar E, Sanford R, Fairclough D, Langston J, Douglas E, Ochs J, Jenkins J, Ogle L, Kun L (1992) Pilocytic dorsally exophytic brainstem gliomas: a distinct clinicopathologic entity. *Ann Neurol* 32: 458-459
59. Kim TS, Halliday AL, Hedley-Whyte ET, Convery K (1991) Correlates of survival and the Daumas-Duport grading system for astrocytomas. *J Neurosurg* 74: 27-37
60. Kingsley DPE, Kendall BE, Fitz CR (1986) Tuberous sclerosis: a clinicoradiological evaluation of 110 cases with particular reference to atypical presentation. *Neuroradiology* 28: 38-46
61. Kleihues P, Burger PC, Scheithauer BW (1993) *Histological Typing of Tumors of the Central Nervous System*, 2nd Edition, World Health Organization, Springer-Verlag, Berlin
62. Kleinman GM, Schoene WC, Waisne TM H, Richardson EP Jr (1978) Malignant transformation in benign cerebellar astrocytoma: case report. *J Neurosurg* 49: 111-113
63. Kleriga E, Sher JH, Nallainathan SK, Stein SC, Sacher M (1978) Development of cerebellar malignant astrocytoma at site of a medulloblastoma treated 11 years earlier. Case report. *J Neurosurg* 49: 445-449
64. Kros JM, Vecht CJ, Stefanko SZ (1991) The pleomorphic xanthoastrocytoma and its differential diagnosis: a study of five cases. *Hum Pathol* 22: 1128-1135
65. Kuhajda FP, Mendelsohn G, Taxy JB, Long DM (1981) Pleomorphic xanthoastrocytoma: report of a case with light and electron microscopy. *Ultrastructural Pathol* 2: 25-32
66. Laws ER Jr, Taylor WF, Clifton MB, Okazaki H (1984) Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres. *J Neurosurg* 61: 665-673
67. Lipper MH, Eberhard DA, Phillips CD, Vezina L-G, Carr WS (1993) Pleomorphic xanthoastrocytoma, a distinctive astroglial tumor: Neuroradiologic and pathologic features. *Am J Neurol* 14: 1397-1404
68. Lopes MBS, Altermatt HJ, Scheithauer BW, Shepherd CW, Vandenberg SR (1996) Immunohistochemical characterization of subependymal giant cell astrocytoma. *Acta Neuropath* 91: 368-375
69. Maat-Schieman MLC, Bots GTAM, Thomeer RTWM, Vielvoye GJ (1985) Malignant astrocytoma following radiotherapy for craniopharyngioma. *Br J Radiol* 58: 480-482
70. Macaulay RJ, Jay V, Hoffman HJ, Becker LE (1993) Increased mitotic activity as a negative prognostic indicator in pleomorphic xanthoastrocytoma. *J Neurosurg* 79: 761-767
71. Malecki M, Robitaille Y, Bertrand G (1983) Atypical xanthoastrocytoma presenting as a meningioma. *Surg Neurol* 20: 235-238
72. Marus G, Levin CV, Rutherfoord GS (1986) Malignant glioma following radiotherapy for unrelated primary tumors. *Cancer* 58: 886-894
73. MacCarty WC Jr, Russell DG (1958) Tuberous sclerosis: report of a case with ependymoma. *Radiol* 71: 833-838
74. Mercuri S, Russo A, Palma L (1981) Hemispheric supratentorial astrocytomas of children: long-term results in 29 cases. *J Neurosurg* 55: 170-173
75. Miller NR, Tiff WJ, Green WR (1974) Evaluation and management of gliomas of the anterior visual pathways. *Brain* 97: 743-754

76. Minehan KJ, Shaw EG, Scheithauer BW, Davis DL, Onofrio BM (1995) Spinal cord astrocytoma: pathological and treatment considerations. *J Neurosurg* 83: 590-595
77. Morota N, Sakamoto K, Kobayashi N, Hasmimoto K (1990) Recurrent low-grade glioma in children with special reference to computerized tomography and pathological changes. *Childs Nerv Syst* 6: 155-160
78. Munoz EL, Eberhard DA, Lopes MBS, Schneidet BF, Gonzalez-Fernandez F, Vandenberg SR (1996) Proliferative activity and p53 mutation as prognostic indicators in pleomorphic xanthoastrocytoma. A clinicopathological study of six cases. *J Neuropath Exp Neurol* 55: 606
79. Nishio S, Takeshita I, Fukui M, Yamashita M, Tateishi J (1988) Anaplastic evolution of childhood optico-chiasmatic pilocytic astrocytoma: report of an autopsy case. *Clin Neuropathol* 7: 254-258
80. Noetzli M, Malamud N (1962) Postirradiation fibrosarcoma of the brain. *Cancer* 15: 617-622
81. O'Sullivan C, Jenkin D, Doherty MA, Hoffman HJ, Greenberg ML (1994) Spinal cord tumors in children: long-term results of combined surgical and radiation treatment. *J Neurosurg* 81: 507-512
82. Özek MM, Sav A, Pamir MN, Özer AF, Özek E, Erzen C (1993) Pleomorphic xanthoastrocytoma associated with von Recklinghausen neurofibromatosis. *Childs Nerv Syst* 9: 39-42
83. Packer RJ, Savino PJ, Bilaniuk LT, Zimmerman RA, Schatz NJ, Rosenstock JG, Nelson DS, Jarrett PD, Bruce DA, Schut L (1983) Chiasmatic gliomas of childhood. A reappraisal of natural history and effectiveness of cranial irradiation. *Child's Brain* 10: 393-403
84. Pahapill PA, Ramsay DA, Phil D, Del Maestro RF (1996) Pleomorphic xanthoastrocytoma: case report and analysis of the literature concerning the efficacy of resection and the significance of necrosis. *Neurosurg* 38: 822-829
85. Palma L, Guidetti B (1985) Cystic pilocytic tumors of the cerebral hemispheres: Surgical experience with 51 cases and long-term results. *J Neurosurg* 62: 811-815
86. Palma L, Russo A, Celli P (1984) Prognosis of the so-called "diffuse" cerebellar astrocytoma. *Neurosurg* 15: 315-317
87. Palma L, Vagnozzi R, Annino L, Ciapetta P, Maleci A, Cantore G (1988) Post-irradiation glioma in a child: case report and review of the literature. *Childs Nerv Syst* 4: 296-301.
88. Pasquier B, Kojder I, Labat F, Keddari E, Pasquier D, Stoebner P, Barge M, Delpech B, Couderc P (1985) Le xanthoastrocytome du suject jeune: revue de la litterature à propos de deux observations dévolution discordante. *Ann Pathol* 5: 29-43
89. Paulus W, Pfeiffer J (1988) Does the pleomorphic xanthoastrocytoma exist? Problems in the application of immunological techniques to the classificatino of brain tumors. *Acta Neuropathol* 76: 245-252
90. Pearl GS, Mirra SS, Miles ML (1980) Glioblastoma multiforme occurring 13 years after treatment of a medulloblastoma. *Neurosurg* 6: 546-551
91. Piepmeier J, Christopher S, Spencer D, Byrne T, Kim J, Knisel JP, Lacy J, Tsukerman L, Makuch R (1996) Variations in the natural history and survival of patients with supratentorial low-grade astrocytomas. *Neurosurg* 38: 872-879
92. Pollack IF, Claassen D, Al-Shboul Q, Janosky JE, Deutsch M (1995) Low-grade gliomas of the cerebral hemispheres in children: an analysis of 71 cases. *J Neurosurg* 82: 536-547
93. Powell SZ, Yachnis AT, Rorke LB, Rojiani AM, Eskin TA (1996) Divergent differentiation in pleomorphic xanthoastrocytoma: evidence for a neuronal element and possible relationship to ganglion cell tumors. *Am J Surg Pathol* 20: 80-85
94. Preissig SH, Bohmfalk GL, Reichel GW, Smith MT (1979) Anaplastic astrocytoma following radiation for a glomus jugulare tumor. *Cancer* 43: 2243-2247
95. Puech P, Lereboullet J, Bernard P (1945) Sclerose tubereuse et tumeurs cerebrales. *Rev Neurolo* 77: 225-246
96. Raffel C, Edwards MSB, Davis RL, Ablin AR (1985) Postirradiation cerebellar glioma. Case report. *J Neurosurg* 62: 300-303
97. Revesz T, Scaravilli F, Couthino L, Cockburn H, Sacares P,, Thomas DGT (1993) Reliability of histological diagnosis including grading in gliomas biopsied by image-guided stereotactic technique. *Brain* 116: 781-793.
98. Rossitch E Jr, Zeidman SM, Burger PC, Curnes JT, Harsh C, Anscher M, Oakes WJ (1990) Clinical and pathologic analysis of spinal cord astrocytomas in children. *Neurosurg* 27:193-196
99. Rush JA, Young BR, Campbell RJ, MacCarthy CS (1982) Optic glioma. *Ophthalmology* 89: 1213-19
100. Sawyer JR, Roloson GJ, Chadduck WM, Boop FA (1991) Cytogenetic findings in a pleomorphic xanthoastrocytoma. *Cancer Genet Cytogenet* 55: 225-230
101. Schmidbauer M, Budka H, Bruckner R, Vokapic P (1987) Glioblastoma developing at the site of a cerebellar medulloblastoma treated 6 years earlier: case report. *J Neurosurg* 67: 915-918
102. Schneider JH, Raffel C, McComb JG (1992) Benign cerebellar astrocytomas of childhood. *Neurosurg* 30: 58-63
103. Schwartz AM, Ghatak NR (1990) Malignant transformation of benign cerebellar astrocytoma. *Cancer* 65: 333-336
104. Scott RM, Ballantine HT Jr (1973) Cerebellar astrocytoma: malignant recurrence after prolonged postoperative survival. Case report. *J Neurosurg* 39: 777-779
105. Shapiro K, Katz M (1983) The recurrent cerebellar astrocytoma. *Childs Brain* 10: 168-176.
106. Shapiro K, Shulman K (1976) Spinal cord seeding from cerebellar astrocytomas. *Childs Brain* 2: 177-186
107. Shepherd CW, Scheithauer BW, Gomez MR, Altermatt HJ, Katzmann JA (1991) Subependymal giant cell astrocytoma: a clinical,pathological and flow cytometry study *Neurosurg* 28: 864-868
108. Spallone A, Gagliardi FM, Vagnozzi R (1979) Intracranial meningiomas related to external cranial irradiation. *Surg Neurol* 12: 153-159
109. Spoor TC, Kennerdell JS, Martinez AJ, Zorub D (1980) Malignant gliomas of the optic pathways. *Am J Ophthalmol* 89: 284-292
110. Steinberg GK, Shuer LM, Conley FK, Hanbery JW (1985) Evolution and outcome in malignant astroglial neoplasms of the cerebellum. *J Neurosurg* 62: 9-17
111. Strom EH, Skullerud K (1983) Pleomorphic xanthoastrocytoma: Report of 5 cases. *Clin Neuropathol* 2: 188-191
112. Stuart G, Appleton DB, Cooke R (1988) Pleomorphic xanthoastrocytoma: report of two cases. *Neurosurg* 22: 422-427

113. Tenny RT, Laws ER, Young BR, Rush JA (1982) The neurosurgical management of optic gliomas: results in 104 patients. *J Neurosurg* 57: 452-458

114. Thomas C, Golden B (1993) Pleomorphic xanthoastrocytoma: report of two cases and a brief review of the literature. *Clinical Neuropathol* 12:97-101

115. Tomlinson FH, Scheithauer BW, Hayostek CJ, Parisi JE, Meyer FB, Shaw EG, Weiland TL, Katzmann JA, Jack CR, Jr (1994) The significance of atypia and histological malignancy in pilocytic astrocytoma of the cerebellum: a clinicopathologic and flow cytometric study. *J Child Neurol* 9: 301-310

116. Tsuchida T, Kamata K, Kawamata M, Okada K, Tanaka R, Oyake Y (1981) Brain Tumors in tuberous sclerosis: report of 4 cases. *Childs Brain* 7: 271-283

117. Ushio Y, Arita N, Yoshimine T, Ikeda T, Mogami H (1987) Malignant recurrence of childhood cerebellar astrocytoma: case report. *Neurosurg* 21: 251-255

118. Vandertop WP, Hoffman HJ, Drake JM, Humphreys RP, Rutka JT, Amstrong DC, Becker LE (1992) Focal midbrain tumors in children. *Neurosurg* 31: 186-194

119. Waga S, Handa H (1976) Radiation induced meningioma: with review of the literature. *Surg Neurol* 2: 161-164

120. Wallner KE, Gonzales MF, Edwards MSB, Wara WM, Sheline G (1988) Treatment results of juvenile pilocytic astrocytoma. *J Neurosurg* 69: 171-176

121. Whittle IR, Gordon A, Misra BK, Shaw JF, Steers JW (1989) Pleomorphic xanthoastrocytoma: report of four cases. *J Neurosurg* 70: 463-468

122. Wilson WB, Feinsod M, Hoyt WF, Nielsen SL (1976) Malignant evolution of childhood chiasmal pilocytic astrocytoma. *Neurology* 26: 322-325

123. Wisoff HS, Llena JF (1989) Glioblastoma multiforme of the cerebellum five decades after irradiation of a cerebellar tumor. *J Neuro-oncol* 7: 339-344

124. Wisoff JH, Abbott R, Epstein F (1990) Surgical management of exophytic chiasmatic-hypothalamic tumors of childhood. *J Neurosurg* 73: 661-667

125. Wong JYC, Uhl V, Wara WM, Sheline GE (1987) Optic gliomas. A reanalysis of the University of California San Francisco experience. *Cancer* 60: 1847-1855

126. Yoshino MT, Lucio R (1992) Pleomorphic xanthoastrocytoma. *Am J Neuroradiol* 13: 1330-1332

127. Zorzi F, Facchetti F, Baronchelli C, Cani E (1992) Pleomorphic xanthoastrocytoma: an immunohistochemical study of three cases. *Histopathology* 20: 267-269

128. Zulch KJ (1979) *Histological typing of tumors of the central nervous system*. Geneva, World Health Organization