CLINICAL PICTURE

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15 years old male patient presented with symptoms of nausea, vomiting, and ataxia, with evidence of torticollis, papilledema, nystagmus, and palsies of the sixth and seventh cranial nerves at physical examination. Long-tract signs were conspicuously absent.
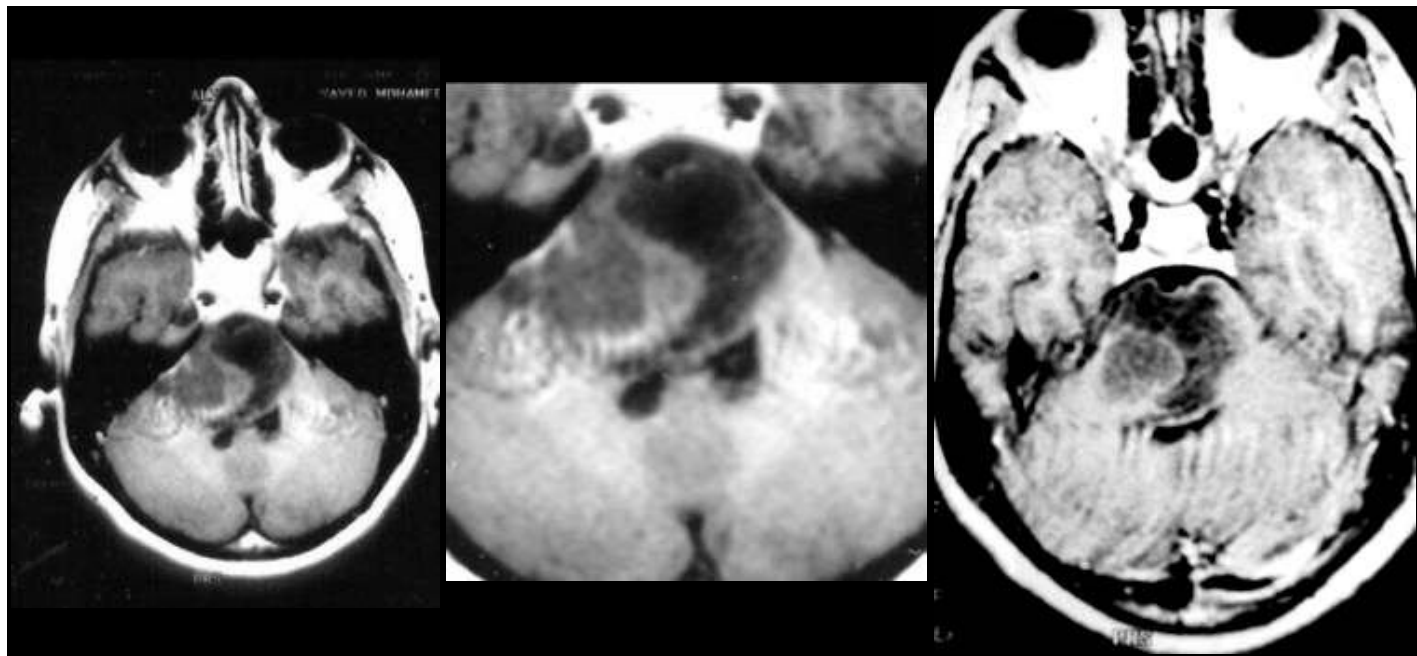
RADIOLOGICAL FINDINGS

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Figure 1. MRI T1 postcontrast images showing a large cystic lesion diffusely expanding the pons. The lesion is seen compressing and pushing the 4th ventricle posteriorly. A large mural nodule is seen projecting inside the pontine cystic lesion, the mural nodule itself is cystic. The signal intensity of the mural nodule cyst is different from the signal intensity of the pontine cyst. The walls of the mural nodule showed faint enhancement, while the wall of the pontine cyst did not show any enhancement.

Figure 2. MRI T1 postcontrast images showing a large cystic lesion diffusely expanding the pons. The lesion is seen compressing and pushing the 4th ventricle posteriorly. A large mural nodule is seen projecting inside the pontine cystic lesion, the mural nodule itself is cystic. The signal intensity of the mural nodule cyst is different from the signal intensity of the pontine cyst. The walls of the mural nodule showed faint enhancement, while the wall of the pontine cyst did not show any enhancement.
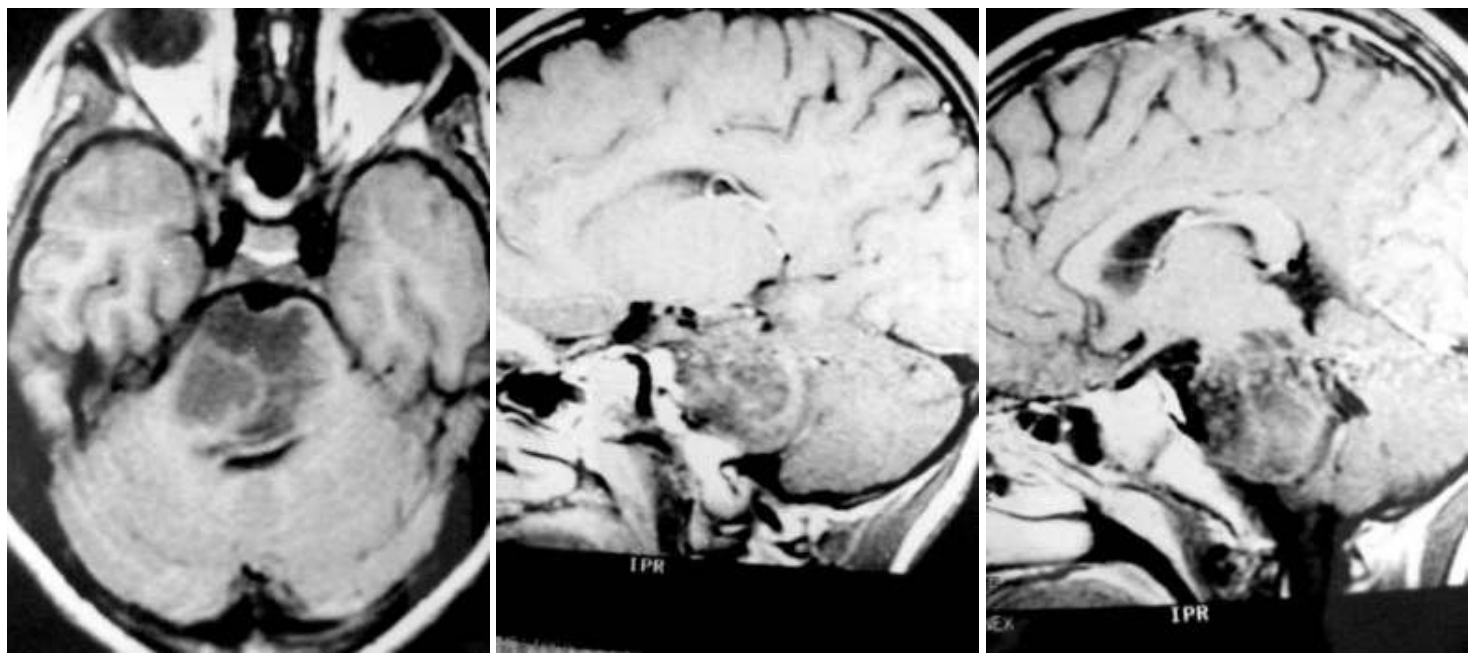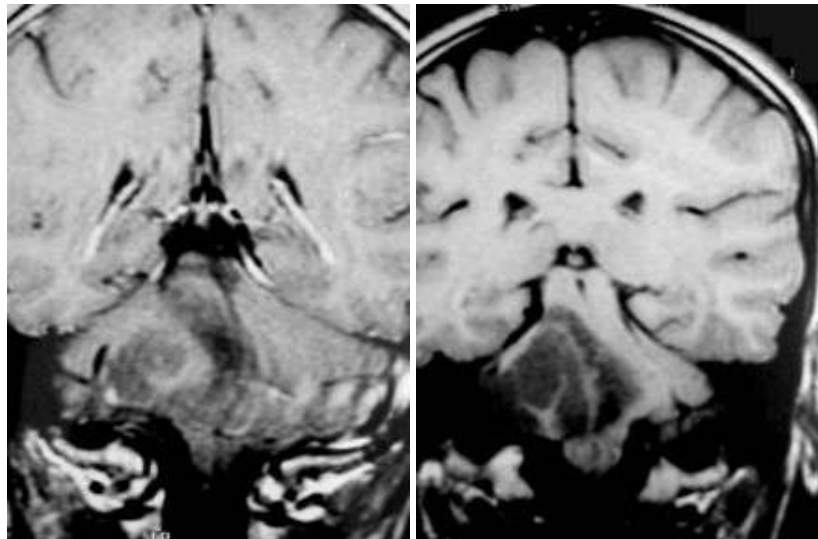

Figure 3. The intrapontine cystic lesion and the cystic mural nodule. Notice that the lesion is seen extending (exophytosis) into the right cerebellopontine ojn the right side
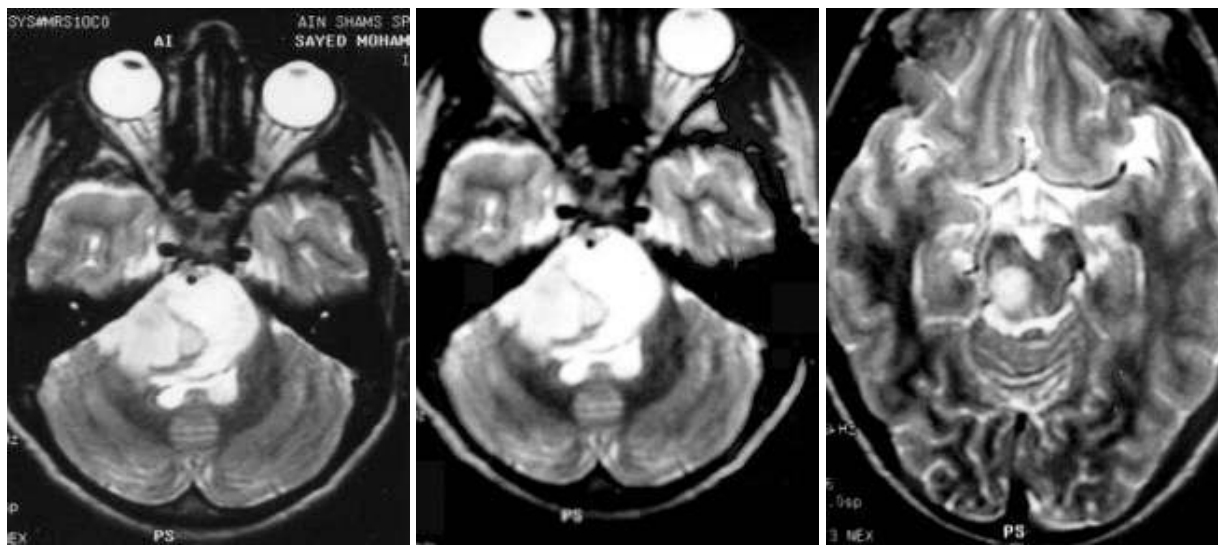
Figure 4. MRI T2 images showing the intrapontine cystic lesion and the large cystic mural nodule projecting inside the pontine cyst, notice the upward extension of the mass up to the level of midbrain (C). The basilar artery is encased by the pontine lesion. The wall of the cystic mural nodule is hypointense probably because of the existence of calcification

Stereotactic biopsy showed that the lesion is a pilocytic astrocytoma

- **Radiological pathology of pilocytic astrocytoma**

Grossly, PA is a well-circumscribed yet unencapsulated mass. The lesion grows primarily by expansion rather than the infiltration characteristic of most astrocytomas. In many cases, lesions are easily separated from the adjacent uninvolved cerebellar folia. Most PA have a significant grossly visible cystic component. In many cases, the tumor has the classically described cyst with nodule morphology- in which neoplasm is confined to a nubbin of tissue embedded in the wall of a fluid-filled cavity. In these cases, the cyst fluid is surrounded by nonneoplastic compressed or gliotic tissue. Calcification can be seen in 25% of cases. Microscopically, there is a biphasic pattern of dense areas with elongated bipolar hairlike (pilocytic) astrocytes alternating with looser regions that may have microcysts. One distinctive feature is the presence of eosinophilic curvilinear Rosenthal fibers within the dense regions. The capillaries may be abnormal and can be coiled (angiomatous) and thick-walled. Apparently the blood-brain barrier is not well formed in these tumors. The proteinaceous fluid that accumulates as both microcysts and macrocysts probably leaks from the abnormal vessels. Mitosis and necrosis are distinctly uncommon. Despite this, occasional PA show microscopic hemorrhages or brownish staining.

Table 1. The mural nodule is composed of two main parts as follows

Part	Appearance	Histopathology
Part I	Dense compact appearance	Composed of elongated bipolar hairlike (pilocytic) astrocytes with high nuclear to cytoplasmic ratio and with minimal extracellular fluid. This part is relatively vascular.
Part II	Loose appearance	Relatively acellular and composed mainly of microcysts and enlarged extracellular fluid filled spaces. This part is relatively avascular.

* The spatial distribution of each part within the mural nodule will determine the neuroimaging appearance of the mural nodule.

Figure 5. Cystic (pilocytic) brain stem glioma.

Many astrocytomas, particularly in the cerebellum, hypothalamus, and optic pathways of children, exhibit a typical histologic appearance previously termed polar spongioblastoma and now universally referred to as juvenile pilocytic astrocytoma. These tumors frequently contain both macrocysts (as in cystic cerebellar astrocytoma) or microcysts. Rosenthal fibers, strongly eosinophilic coalescences of neurofibrillary elements, are characteristic of juvenile pilocytic astrocytoma, but may be found in other forms of tumor, particularly as a glial reaction surrounding craniopharyngioma. Endothelial proliferation is common in these tumors and has none of the ominous connotations in this context that it implies in other forms of astrocytomas.
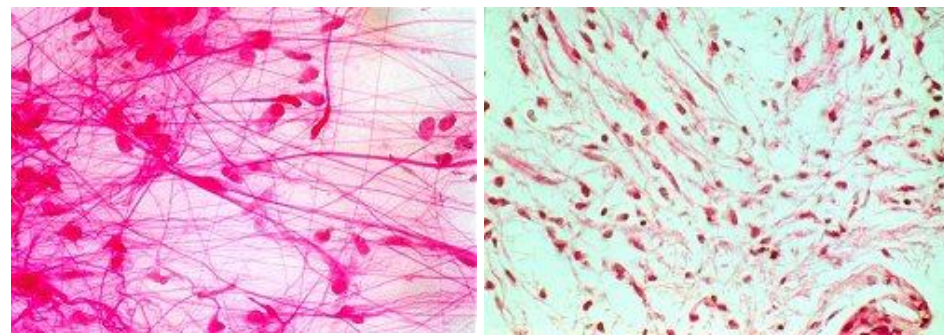

Figure 6. Pilocytic astrocytoma with hair-like cells

From the pathological point of view pilocytic (hair cells) astrocytomas are composed of two main parts, a fluid-filled large cyst and a projecting mural nodule. The neoplastic cells are confined to the mural nodule and the cyst walls are composed of non-neoplastic compressed or gliotic neural tissues. Pilocytic astrocytomas do not have true capsule, yet they can easily be separated from the surrounding tissues. Calcification can be seen in 25% of cases. These tumors frequently have microcysts and macrocysts. Microscopically, there is a biphasic pattern of dense areas with elongated bipolar hairlike (pilocytic) astrocytes alternating with looser regions that may have microcysts. One distinctive feature is the presence of eosinophilic curvilinear Rosenthal fibers and strongly eosinophilic coalescences of neurofibrillary elements within the dense regions. The capillaries may be abnormal and can be coiled (angiomatous) and thick-walled. Apparently the blood-brain barrier is not well formed in these tumors. The proteinaceous fluid that accumulates as both microcysts and macrocysts probably leaks from the abnormal vessels. Necrosis, mitotic activity, endothelial proliferation are selectively absent in pilocytic astrocytomas. Pilocytic astrocytomas are very slowly growing tumors, with long premonitory symptoms before clinical presentation, that selectively grow by expansion rather by infiltration of the surrounding neural tissues that is more characteristic of diffuse astrocytomas.

A pilocytic astrocytoma usually starts as hypercellular solid tumor with elongated bipolar hairlike (pilocytic) astrocytes with high nuclear to cytoplasmic ratio and with minimal extracellular fluid (purely solid tumors). Solid tumors are vascular and their capillaries may be abnormal and can be coiled (angiomatous) and thick-walled.

Apparently the blood-brain barrier is not well formed in these tumors and proteinaceous fluid probably leaks from the abnormal vessels and accumulates in the tumors as microcysts, first, and macrocysts later on. With progressive enlargement of the macrocysts (microcysts enlarge and coalesce forming a single large cyst), the viable tumor tissues are progressively compressed into a smaller, dense and hypercellular peripheral mural nodule. Progressive leakage of proteinaceous fluid within the core of the mural nodule will result in progressive enlargement of the mural nodule, the core of which will be cystic with a thin outer cover of viable tumor tissues (pattern I). Although the typical appearance of a pilocytic tumor is a large single cyst with a mural nodule, however the spatial distribution of the solid (hypercellular/vascular) and the cystic components within the tumors can vary, also the share taken by the solid the cystic parts in the histopathological make-up of the tumors might vary. These histopathological variations might result in tumors that have quite atypical appearance with irregular cystic and solid parts and with irregular or patchy contrast enhancement.
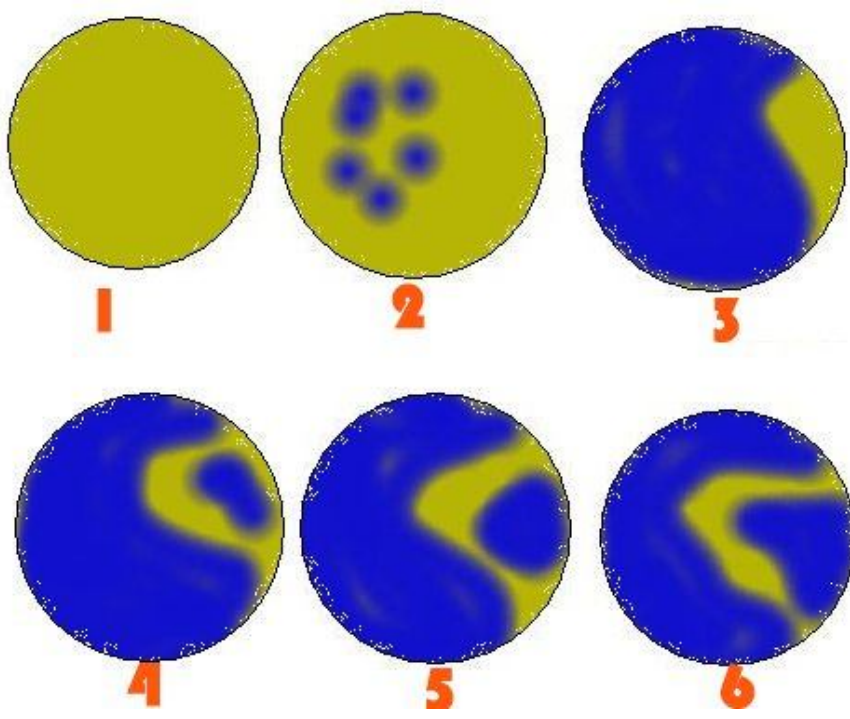

Figure 7. A pilocytic astrocytoma commonly starts as a solid mas (1), however due to defective blood brain barrier in the newly formed blood vessels proteinaceous fluid probably leaks and accumulates inside the tumor as microcysts, first (2), and macrocysts later on (3). With progressive enlargement of the macrocysts (microcysts enlarge and coalesce forming a single large cyst), the viable tumor tissues are progressively compressed into a smaller, dense and hypercellular peripheral mural nodule (pattern II) against a large cyst (3). Progressive leakage of proteinaceous fluid within the core of the mural nodule will result in progressive enlargement of the mural nodule, the core of which will be cystic with a thin outer cover of viable tumor tissues (pattern I) (4,5,6). (Blue = cystic parts and brown = solid parts of the tumor)
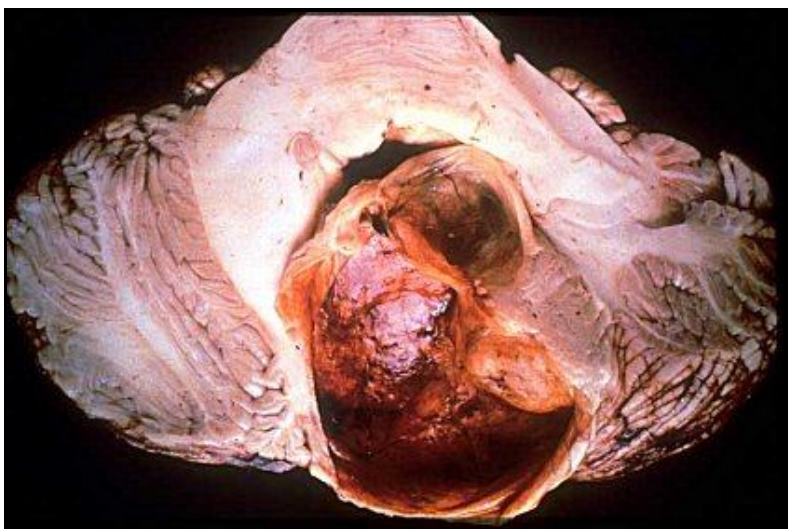
Figure 8. This figure shows a gross specimen of a pilocytic astrocytoma of the posterior fossa. Identify the cerebellar hemispheres, the pons and the fourth ventricle. The fourth ventricle is nearly obliterated due to the large cystic tumor in the midline. Note the white nodule to one side of the cyst. This is the actual tumor. Many pilocytic astrocytomas in the posterior fossa will have an associated cyst and a contrast enhancing "mural" nodule. Pilocytic astrocytomas are one of the most common pediatric brain tumors and most occur in the posterior fossa, but in children with Neurofibromatosis type I, they may occur in the optic tracts.

Juvenile pilocytic astrocytomas tend to be well circumscribed and to grow slowly with long periods of premonitory symptoms before presentation. This pattern is especially true of tumors that arise in the cerebellum. Tumors of the anterior third ventricle tend to be well-defined superiorly but diffusely infiltrating the optic mechanisms and hypothalamus inferiorly. The course of these tumors is normally benign but may be unpredictable thereby making treatment decisions extremely difficult. The presence of a juvenile pilocytic astrocytoma that extends into the subarachnoid space is common.

DIAGNOSIS:

DIAGNOSIS: BRAIN STEM JUVENILE PILOCYTIC ASTROCYTOMA

DISCUSSION

DISCUSSION

Pilocytic astrocytoma is the most common pediatric central nervous system glial neoplasm and the most common pediatric cerebellar tumor. This tumor has a noteworthy benign biologic behavior that translates into an extremely high survival rate—94% at 10 years—that is by far the best of any glial tumor. Most patients present in the first 2 decades, and clinical symptoms and signs are usually of several months duration and directly related to the specific location of the tumor. The cerebellum, optic nerve and chiasm, and hypothalamic region are the most common locations, but the tumor can also be found in the cerebral hemisphere, ventricles, and spinal cord. Surgical resection is the treatment of choice for all tumors, except for those involving the optic pathway and hypothalamic region, which may be treated with radiation therapy and chemotherapy. Cross-sectional imaging often demonstrates a classic appearance: a cystic mass with an enhancing mural nodule. Less common appearances are quite nonspecific. Surrounding vasogenic edema is rarely present, and this feature provides a valuable clue to the correct diagnosis. Accurate interpretation of imaging studies plays an essential role in directing treatment of these tumors, particularly when they arise in the optic pathway of patients with neurofibromatosis type 1. Disseminated disease and recurrence are extremely rare.

Originally identified in a series of 76 cases of cerebellar astrocytomas by Harvey Cushing in 1931, the pilocytic astrocytoma occupies a unique place among cerebral neoplasms (1). With its notable indolent biologic behavior, pilocytic astrocytoma carries one of the highest survival rates of any brain tumor and certainly the highest rate for any astrocytoma. Yet, as reviewed herein, there are numerous oddities about this neoplasm. It appears well circumscribed, yet occasionally it infiltrates the surrounding brain tissue, as seen at histologic examination. It enhances intensely, sometimes with a ringlike pattern that is more commonly seen in highly malignant astrocytomas, yet it is not a high-grade neoplasm. In rare cases, it can even produce widespread dissemination, which seems incongruous for a brain tumor with slow growth and fairly bland histologic characteristics. Even more fascinating, such metastatic spread can occur without associated increased mortality, in contrast to the poor prognosis so common in patients with metastatic high-grade tumors. In view of these many contradictions, pilocytic astrocytoma qualifies as "the tumor that is the exception to the rule."

- **Epidemiologic Characteristics**

Pilocytic astrocytoma is the most common pediatric cerebellar neoplasm and the most common pediatric glioma, constituting 85% of all cerebellar astrocytomas and 10% of all cerebral astrocytomas in this age group (2). Overall, it accounts for 0.6%–5.1% of all intracranial neoplasms and 1.7%–7% of all glial tumors (3).

Pilocytic astrocytoma occurs most commonly in children and young adults, with most cases (75%) manifesting in the first 2 decades of life (2,4). No gender predilection is reported (2). Most of the lesions occur in or near the midline, usually arising from the cerebellum, the optic nerve and chiasm, or the region of the hypothalamus-thalamus. Less common locations include the cerebral hemispheres, the cerebral ventricles, velum interpositum, and spinal cord (5–9). In adults, the tumor more frequently occurs in the cerebral hemisphere (8,10).

The association of pilocytic astrocytoma with neurofibromatosis type 1 (NF1) is well documented. Pilocytic astrocytoma is the most common tumor seen in this population, occurring in up to 15%–21% of all NF1 patients, and typically involves the optic nerve or chiasm (3,11–16). Because the vast majority of optic pathway gliomas are histologically regarded as pilocytic astrocytoma, it has been suggested that the most appropriate term for this entity

should be "pilocytic astrocytoma of the optic pathway" (16). Nearly all optic pathway gliomas in NF1 patients manifest before the age of 6 years and females are more commonly affected by a 2:1 ratio (16,17). Of all patients with an optic pathway glioma, about one-third have NF1, and, of all tumors in this region, 40%–70% occur in NF1 patients (14,16,18).

Pilocytic astrocytomas account for 1.5%–3.5% of all orbital neoplasms and two-thirds of all neoplasms of the optic nerve (3). Most optic pathway pilocytic astrocytomas (75%) arise in children less than 12 years old; in addition, the tumor is more likely to arise in the optic nerve in children, whereas it is more commonly located in the optic chiasm in adolescents and young adults (19,20). Involvement of the chiasm and hypothalamus has been reported to occur in 25%–60% of patients (11,19,20). Optic pathway gliomas much less commonly manifest in adult patients without NF1; when they do, these tumors have a dramatically different biologic behavior and are regarded histologically as anaplastic astrocytoma or glioblastoma multiforme (21).

- **Clinical Features**

Clinical presentation of patients with a pilocytic astrocytoma varies with its site of origin. Headache, vomiting, gait disturbance, blurred vision, diplopia, and neck pain are common symptoms in patients with a cerebellar pilocytic astrocytoma (22–24). Clinical signs usually include hydrocephalus, papilledema, truncal ataxia, appendicular dysmetria, head tilt, sixth nerve palsy, and nystagmus (22,24).

When a pilocytic astrocytoma arises in the brainstem, it typically extends exophytically from its dorsal margin and causes symptoms of nausea, vomiting, and ataxia, with evidence of torticollis, papilledema, nystagmus, and palsies of the sixth and seventh cranial nerves at physical examination (25–27). Long-tract signs are conspicuously absent (25,27). Pilocytic astrocytomas arising from the tectum characteristically manifest with headache, vomiting, paresis, abnormal gait, somnolence, Parinaud syndrome, and diplopia (28,29).

Pilocytic astrocytoma of the optic pathway frequently produces visual loss or visual-field deficit, with optic disk pallor and optic nerve atrophy in the involved eye secondary to axonal damage and ischemia (3,21,30). Proptosis may be seen with larger masses. Papilledema is common for lesions arising from the optic nerve but unusual for those originating from the optic chiasm (21). Some patients may show spasmus nutans, a nystagmus characterized by high frequency and low amplitude and associated with head nodding movements (31). Precocious puberty is commonly seen (39% of cases) in NF1 patients with an optic pathway glioma and has not been reported in its absence (16). Less specific manifestations include amblyopia (30). Smaller lesions may not be associated with any symptoms at all (2).

Pilocytic astrocytoma of the hypothalamus may produce symptoms related to obesity, diabetes insipidus, and other symptoms of hypothalamic-pituitary dysfunction (2). On occasion, these masses may produce the so-called diencephalic syndrome, which is characterized by emaciation despite a normal to slightly decreased caloric intake, alert appearance, hyperkinesis, irritability, and normal to accelerated growth (20,32,33). Although this syndrome may occur with any hypothalamic mass, the vast majority of reported cases are secondary to a pilocytic astrocytoma, with widespread dissemination noted in some cases (32). When the tumor involves the thalamus, hydrocephalus or hemiparesis secondary to compression of the corticospinal tract within the nearby internal capsule is typical (2,34).

Headache, seizure activity, hemiparesis, ataxia, nausea, and vomiting are common clinical manifestations for pilocytic astrocytomas arising in the cerebral hemispheres (7). The occurrence of seizure activity generally indicates cortical gray matter involvement (2). Papilledema is noted in about one-third of these patients (7).

- **Pathologic Characteristics**

Pilocytic astrocytoma has been known by many names over the years. Because of its resemblance histologically to the spongioblastic cells of the fetus, German pathologists called it "spongioblastoma polare," a term that has now been abandoned (35,36). Russell and Rubenstein (37) distinguished the tumor into adult and juvenile forms. In addition, many generic pseudonyms and euphemisms based on the geographic location of the tumor have persistently appeared in the prior pathology lexicon to describe these lesions. Hence, a variety of names—optic nerve glioma, hypothalamic glioma, cerebellar astrocytoma, microcystic astrocytoma, cystic astrocytoma, and others—have inadvertently blurred the true identity of the pilocytic astrocytoma and led to confusion (26).

Although this tumor may be found in many central nervous system locations and may account for a significant proportion of the tumors in those locations, pilocytic astrocytoma is now regarded by the latest World Health Organization (WHO) classification as a distinct clinicopathologic entity, and use of these less specific terms should be avoided if the pathologic findings warrant the diagnosis (26).

The macroscopic appearance of pilocytic astrocytoma varies with its location within the central nervous system. Tumors of the cerebellum and cerebral hemisphere are typically well-circumscribed, cystlike masses with a discrete mural nodule, whereas those arising in the hypothalamus and optic chiasm tend to be large, soft, cystlike masses. When the tumor arises within the optic nerve, it infiltrates and engulfs the nerve to produce fusiform enlargement of that structure, with peripheral extension into the surrounding leptomeninges. Brainstem pilocytic astrocytomas are usually peripheral and are attached to the brainstem surface without extensive infiltration (38).

At histologic examination, pilocytic astrocytoma classically manifests in a noteworthy biphasic pattern composed of a combination of loose glial tissue punctuated by numerous vacuoles, microcysts, occasional macrocysts, and compacted piloid tissue (38). The piloid tissue component is composed of dense sheets of elongated bipolar cells that demonstrate fine fibrillary (hairlike) processes, a highly distinctive feature, and typically an abundance of Rosenthal fibers (38). In contrast, the multipolar cells of the loose glial tissue, frequently called protoplasmic astrocytes, are much less fibrillated and commonly are intermixed with degenerative products of astrocyte formation, known as eosinophilic granular bodies or "protein droplets" (2). These "classic" but nonspecific granular bodies are believed to indicate slow growth and low histologic grade and are associated with a favorable prognosis (38). Calcification is an uncommon feature, usually occurring in those tumors arising from the optic nerve or hypothalamic-thalamic region, but it can be extensive (2,38). The tumor is suspected to arise from reactive astrocytes (2).

There is considerable variability in the contribution of each pattern to the overall histologic appearance of pilocytic astrocytomas. Some tumors have a predominance of the glial component, whereas others show more of the piloid tissue. A minority of pilocytic astrocytomas demonstrates both components equally (38). More recently, a subset of pilocytic astrocytomas known as the pilomyxoid variant has been identified with monomorphous histologic features and lack of Rosenthal fibers. The few reported cases have occurred in the chiasmatic-hypothalamic region in children less than 2 years of age; these tumors were associated with a higher rate of recurrence and cerebrospinal fluid dissemination (2,39). These tumors have some ultrastructural features that have fueled speculation that this subtype may be of tanycytic origin, leading some authorities to describe it as a "tanycytoma." However, more evidence is needed to prove this cellular lineage and justify use of this term (40).

Slow growth is the rule for most pilocytic astrocytomas (41). However, some tumors, particularly those of the optic nerve and chiasm, may show a propensity for periods of accelerated growth (19). Growth of the tumor, especially those occurring in the cerebellum, may overrun normal ganglion cells (neurons), producing the "trapped neuron" appearance (2,38). The growth pattern of optic pathway glioma (including pilocytic astrocytoma) correlates with the presence or absence of NF1 in the patient. When the tumor arises in patients with NF1, it tends to grow within the nerve, whereas a circumferential pattern is observed when it occurs in patients without NF1 (42).

Although many pilocytic astrocytomas appear well circumscribed macroscopically, they may infiltrate into the surrounding brain parenchyma for several millimeters (2). Infiltration occurs more commonly for those tumors that arise from the optic nerve and chiasm, where there is frequently no clear demarcation between the tumor and normal tissue (2). Infiltration of the adjacent leptomeninges is a signature feature of a cerebellar pilocytic astrocytoma, causing fixation of the cerebellar folia and filling of the sulci (2). This infiltration, along with perivascular space extension, may also be seen with tumors in other locations (2).

Pilocytic astrocytomas are highly vascular (2). Some long-standing tumors, such as those of the cerebellum and cerebral hemisphere, frequently have markedly hyalinized and glomeruloid vessels (2). This new vessel formation is particularly evident within the cyst wall, and it is believed that the fluid within the cyst directly supports vascular proliferation (2) The presence of these glomeruloid vessels accompanied by extensive nuclear pleomorphism may mimic some of the features of high-grade astrocytomas (2,38). The increased vascularity of pilocytic astrocytoma may explain why it may even be a target for metastatic disease, as in one case of a breast carcinoma that spread to a pilocytic astrocytoma (43).

The overwhelming majority of pilocytic astrocytomas are regarded as grade I tumors in the WHO classification (2,38). Most tumors demonstrate sufficient characteristic histologic features that a definitive diagnosis can be

rendered with confidence. However, the variety of histologic patterns among pilocytic astrocytomas and the lack of specific immunohistochemical, cytogenetic, and molecular markers may occasionally make the diagnosis difficult (2). Occasional hyperchromasia and pleomorphism, especially when they are noted in a diffuse tumor, may cause pilocytic astrocytoma to be confused with a higher-grade astrocytoma (2). In rare cases, some tumors, especially those arising in patients who underwent radiation therapy, may have frankly malignant features (increased mitotic activity, hypercellularity, endothelial proliferation, and necrosis with pseudopalisading) and also demonstrate aggressive biologic behavior (38).

Very rarely, a pilocytic astrocytoma may undergo malignant transformation with an aggressive histologic appearance; such a tumor is called an anaplastic (malignant) pilocytic astrocytoma. Although fatal cases have been reported, this event does not necessarily carry a less favorable outcome (2,8,44–46). Many cases of malignant transformation have occurred after administration of radiation therapy, leading to speculation that irradiation is at least a contributing factor in the development of this change, which may manifest up to 52 years after initial treatment (45).

Cytogenetic studies of pilocytic astrocytomas have revealed loss of genetic material involving the long arm of chromosome 17 (17q) near the same locus for the NF1 tumor suppressor gene (47). Furthermore, lack of expression of an NF1 gene product, neurofibromin, has been documented in NF1-associated pilocytic astrocytomas (48). These findings have fueled speculation that the NF1 tumor suppressor gene is linked with the expression of pilocytic astrocytoma. Additional chromosomal mutations have been identified on chromosomes 7, 8, 11, 19, and 21 (2,49).

Pilocytic astrocytomas differ from the more common diffuse astrocytomas from the pathological, nosological, genetic and prognostic point of view. From the pathological point of view diffuse astrocytomas are neoplasms of widely varying potential that are unencapsulated, poorly marginated and diffusely infiltrate into the surrounding brain. These diffuse astrocytomas appear to form a continuum of both biological and histological aggression. They vary from lesions with almost normal cytology (grade II astrocytomas) through intermediate stages (grade III, anaplastic astrocytomas) and up to the most aggressive of all human brain tumours (grade IV astrocytomas or glioblastoma multiforme). (99)

From the nosological point of view, and according to the WHO classification of brain tumours, pilocytic astrocytomas are ranked as grade I benign gliomas while diffuse astrocytomas are ranked as grade II, grade III (anaplastic astrocytomas) and grade IV (glioblastoma multiforme). The following pathological differences are present between diffuse and pilocytic astrocytomas. (99)

- Diffuse astrocytomas, unlike pilocytic astrocytomas, have a peculiar tendency to change its grade over time and the condition is age dependant. A change in the grade of diffuse astrocytoma is more likely to occur in the older age group. In older age group (over the age of 40 years) diffuse low grade astrocytomas (grade II astrocytoma according to WHO) have a bad prognosis because they have a great tendency for anaplastic transformation (to grade III or grade IV astrocytoma according to WHO), while at a younger age group anaplastic transformation of diffuse low grade astrocytomas (grade II astrocytoma according to WHO) is extremely uncommon, also the probability for diffuse low grade astrocytomas to have a highly malignant component (i.e, grade III or IV mixed with grade II) is higher in the older age group. On the other hand pilocytic astrocytomas (grade I astrocytoma according to WHO) never change its grade over time.(99)

- Diffuse astrocytomas (grade II, III or grade IV astrocytomas) grow by infiltration of the nearby neural tissues (commonly in the form of remote neoplastic cells radiating from the mother tumour) and so they are poorly marginated and, practically, complete surgical resection is not possible and some neoplastic cells are almost invariably left behind after surgical resection. On the other hand pilocytic astrocytomas grow by expansion and so they are well circumscribed and subsequently complete surgical resection is possible. (99)

- Diffuse astrocytomas, unlike pilocytic astrocytomas, are highly cellular neoplasms with cells that range from normal appearing astrocytes (grade II) to cells with marked pleomorphism and hyperchromatic nuclei (grade III, and IV). On the other hand pilocytic astrocytomas are histopathologically composed of scanty elongated cells, Rosenthal fibers and microcysts and this combination constitutes the classic of pilocytic astrocytomas. Cells are only confined to the mural nodule in pilocytic astrocytomas and subsequently the mural nodule is the only neoplastic part of the tumour.(99)

- Pilocytic astrocytomas are truly benign gliomas while diffuse astrocytomas are, at best, of low grade

malignancy. (99)

Radiologically pilocytic astrocytomas differ from diffuse astrocytomas in the following points

1. **Pilocytic astrocytomas are typically "cystic tumours with a mural nodule" and with prominent mass effect, while diffuse astrocytomas with a lower grade (grade II) are typically solid tumours with minimal or no mass effect that appear homogeneously hypodense on CT scan, hyperintense on the MRI T2 images and hypointense on the T1 MRI images. The neuroimaging appearance of diffuse astrocytomas is due to increased cell count. The mural nodule of pilocytic astrocytomas might or might enhance while diffuse low grade astrocytomas usually do not enhance on postcontrast scan. Diffuse low grade astrocytomas (grade II) diffusely expand the affected part of the brain with poor margin, while pilocytic astrocytomas are well circumscribed rounded or oval tumours.(99)**

2. **Although central necrosis in highly malignant glioblastoma multiforme might, morphologically, creates the appearance of a cyst with a projecting mural nodule, however this can easily be differentiated from pilocytic astrocytomas by the fact that the walls of the cyst in pilocytic astrocytomas, being composed of non-neoplastic compressed neural tissues, never enhance while the walls of the cyst in glioblastomas with central necrosis invariably enhance because it is composed of viable tumour tissues. Wall enhancement is characteristic of glioblastomas with central necrosis and when it is observed radiologically should shift the tumour grade from the most benign pilocytic astrocytoma to the most malignant glioblastoma multiforme,The presence of significant edema and short history before clinical presentation favor the diagnosis of glioblastoma multiforme. In general glioblastoma multiforme occurs at an older age compared with pilocytic astrocytoma. (99)**

From the genetic point of view pilocytic astrocytoma is different from diffuse astrocytomas in the following points (99)

- **The analyses of the genetic lesions of pilocytic astrocytoma have targeted the TP53 gene on chromosome 17. Investigations have not confirmed a critical role for alterations of this gene in the development of these tumors, however. In one series, the cytogenetic analysis of 14 pilocytic tumor cultures did not identify a specific pattern of chromosomal aberration. Patients with tumors characterized by normal stem line karyotypes had the most favorable outcomes. The presence of clonal structural abnormalities and the presence of markers were associated with a high risk of early recurrence. (99)**

- **On the other hand genetic lesions associated with the development and malignant transformation of diffuse astrocytomas have been well described in the cytogenetic literature. To date, three distinct clinical, histologic, and genetic patterns of glioblastoma multiforme have been characterized. In younger patients, most diffuse astrocytomas are believed to begin as low-grade astrocytoma, with progression to glioblastoma multiforme through a stepwise acquisition of genetic lesions. These secondary glioblastoma multiforme often contain areas of well-differentiated residual tumor. The most frequent chromosomal abnormality identified in diffuse astrocytomas is the abnormal gain of chromosome 7 with an associated loss of one of the sex chromosomes. Additionally, allelic loss or mutation of 17p, resulting in critical alterations of the TP53 gene, has been targeted as an essential step in the early development of glioma. Mutant TP53, identified in at least one third of all astrocytomas, may contribute to the formation of these tumors by inhibiting programmed cell death. glioblastoma multiforme in older patients are usually primary-that is, they occur as glioblastoma multiforme from their inception, without progression from a lower- grade tumor. In this group, the development of glioblastoma multiforme involves a parallel sequence of genetic alterations, including amplifications and deletions, that up-regulate growth factor receptors and drive cell proliferation. (99)**

- **Imaging Characteristics**

At computed tomography (CT), most cerebellar and cerebral pilocytic astrocytomas have a well-demarcated appearance with a round or oval shape smaller than 4 cm in size, cystlike features, smooth margins, and occasional calcifications (8,50,51). Most tumors (82% in one series) are located near the ventricular system, and almost all (94%) enhance, typically intensely, on postcontrast images obtained after intravenous administration of contrast material (51).

At MR imaging, pilocytic astrocytoma is typically isointense to hypointense relative to normal brain with T1-

weighted pulse sequences and hyperintense compared with normal brain with T2-weighted pulse sequences (50). As expected for a tumor of low biologic activity, the degree of surrounding vasogenic edema is diminished in comparison with that seen in high-grade (WHO grade III and IV) glial neoplasms (8,9). When it does occur, the area of edema is smaller in size than the diameter of the tumor (51). Postcontrast imaging features are similar to those reported with CT. Because of its superiority to CT in assessing the posterior fossa and the usefulness of multiplanar imaging, MR imaging is regarded as the imaging study of choice for evaluation of pilocytic astrocytomas (24). The well-demarcated appearance of virtually all (96%) pilocytic astrocytomas is misleading, as most (64%) show infiltration into the surrounding brain parenchyma at histologic examination (51).

Four predominant imaging patterns of pilocytic astrocytoma have been described: (a) mass with a nonenhancing cyst and an intensely enhancing mural nodule (21% of cases), (b) mass with an enhancing cyst wall and an intensely enhancing mural nodule (46%), (c) necrotic mass with a central nonenhancing zone (16%), and (d) predominantly solid mass with minimal to no cystlike component (17%) (24). Hence, two-thirds of all cases demonstrate the classic imaging manifestation of a cystlike mass with an enhancing mural nodule. Although most cyst walls do not enhance, some may enhance intensely, even as much as the mural nodule (52). Although most cyst walls do not enhance, some may enhance intensely, even as much as the mural nodule; however, cyst wall enhancement is not necessarily indicative of tumor involvement (52). Beliefs vary among neurosurgeons regarding whether to resect the cyst itself in cases of pilocytic astrocytoma. Some advocate complete resection, others biopsy, and still others no resection (52). Removal of the cyst wall has not been linked with improved survival (53).

There is contradictory evidence in the literature regarding the most common location of pilocytic astrocytoma in the cerebellum. In one series of 132 patients, 16% of the tumors arose in the vermis, 53% in the cerebellar hemisphere, and 26% in both; 34% also involved the brainstem (54). However, in another review of 168 cases, 71% of the tumors were located in the vermis, whereas 29% occurred in the hemisphere (24). Those tumors arising in the cerebral hemisphere are more likely to occur in the temporal lobe (7,53). Location, enhancement, and the presence or absence of calcification seen at the time of initial presentation are not reliably predictive of the future clinical behavior of a pilocytic astrocytoma (55).

In contrast to the more biologically aggressive fibrillary astrocytoma (which is most common in the pons), pilocytic astrocytoma may be found throughout the brainstem and frequently extends in an exophytic fashion from its dorsal surface (56,57). Pilocytic astrocytoma typically demonstrates sharp delineation with cystlike regions and fourth ventricle obliteration (25,27,57). The distinction between these two entities is more than an academic curiosity, since the fibrillary brainstem astrocytoma carries a dismal prognosis compared with the excellent outlook associated with the pilocytic variety (57). Because available tissue for histologic analysis from this exquisitely sensitive region of the central nervous system is generally limited, knowledge of the differences in imaging manifestations of the two diseases may help establish the correct diagnosis (26).

When pilocytic astrocytoma arises within the optic nerve, it manifests on both CT and MR images with enlargement of the optic nerve as an intraconal mass with characteristic kinking or buckling of the nerve secondary to the neoplasm itself and vascular congestion (21). Isointensity on T1-weighted MR images and heterogeneous hyperintensity on T2-weighted MR images are typical, with variable enhancement following intravenous contrast material administration (21).

Differences in the imaging appearance of optic pathway gliomas in patients with NF1 versus that of tumors in patients without NF1 have been noted in one study (58). NF1-associated tumors affected the optic nerve and chiasm with nearly equal prevalence, preserved the optic nerve shape, rarely extended beyond the optic pathway, and usually were not cystic. In contrast, the majority of tumors not associated with NF1 involved the optic chiasm rather than the optic nerve, extended extraoptically, and frequently contained cystic areas. The imaging findings did not statistically correlate with the biologic behavior of the tumors (58).

Atypical imaging manifestations may be seen occasionally. Multiple cystlike masses and association with an area of gray matter heterotopia have been reported (59,60). Hemorrhage, either within the tumor or within the subarachnoid space, is a rare phenomenon (61–63). Pilocytic astrocytoma may masquerade as a cerebellopontine angle mass that mimics the imaging appearance of a vestibular schwannoma with widening of the internal auditory canal (64,65). When the tumor is located in or near the optic chiasm, a bilobed shape may be seen occasionally (50). The small number of pilomyxoid astrocytomas reported have occurred in the chiasmatic-hypothalamic region, with a tendency to have more intense homogeneous enhancement and homogeneous hyperintensity on T2-weighted images compared with that seen in pilocytic astrocytomas (39).

Reports of MR spectroscopy performed on the soft-tissue portions of pilocytic astrocytomas have documented elevation in the choline (Cho) to N-acetylaspartate (NAA) ratio, ranging from 1.80 to 3.40 (compared with 0.53–0.75 for normal cerebellum) (61,66). Elevated Cho/creatine (Cr) and lactate/Cr ratios have also been noted, whereas the NAA/Cr ratio has not been significantly elevated (61,66). There is some controversy regarding whether the Cho resonance in these tumors is truly elevated compared with that in normal tissue (67). The lipid resonance is minimally elevated, in contrast to significant elevation noted in glioblastoma multiforme and metastatic disease (61). Elevated lactate doublet resonance and diminished Cr and NAA peaks were observed in all eight patients of one study that used point-resolved spectroscopy (PRESS) (61). It is clear that this lactate elevation is not related to necrosis, which is a rare histologic feature in pilocytic astrocytomas. Instead, the lactate elevation most likely reflects alterations in mitochondrial metabolism or represents variability in glucose utilization rates among low-grade astrocytomas (61).

Follow-up surveillance imaging of cerebellar pilocytic astrocytoma is recommended at every 3 months for 2 years, followed by every 6 months for an additional 2 years, and then annually after 4 years from the time of treatment (68). A similar follow-up pattern is used to assess changes in patients with pilocytic astrocytoma of the optic pathway (16). Routine contrast-enhanced MR imaging to exclude spinal dissemination is not indicated in patients with a single primary mass and without corroborative symptoms (69). Screening imaging for this tumor in NF1 patients without symptoms is not currently recommended, because the disease rarely progresses and early detection does not currently affect the long-term outcome (17).

- **Therapy**

Just as its clinical manifestations vary according to its different locations, treatment of pilocytic astrocytoma can also vary, depending on where it arises. Surgical resection of cerebellar and cerebral pilocytic astrocytomas is considered the treatment of choice and is generally regarded as curative when a gross total resection is attained (4,6,22,24,54,68,70–72). For lesions in less favorable locations (eg, basal ganglia), stereotactic resection may be used (34). Radiation therapy is strictly avoided, given its risk of causing significant morbidity in children younger than 5 years of age and the absence of clinical proof that it prevents recurrence (71,72).

Resection of the mural nodule, when present, is the key surgical objective, since the surrounding cyst occurs as a simple reactive change in most cases (4). However, neoplastic changes in the cyst wall, even in the absence of findings at gross inspection or at imaging studies, have been documented; these observations have led to considerable debate among neurosurgeons regarding the optimal surgical management of this structure (24). No statistical difference in survival has been noted in patients who have undergone resection of the cyst wall compared with those in which the cyst is left alone (53). Direct neurosurgical evaluation of the extent of resection is surprisingly unreliable, and postoperative contrast-enhanced cross-sectional imaging, preferably MR imaging, is essential for definitive assessment (4,68,73,74).

Patients with optic pathway gliomas and stable symptoms are managed conservatively with clinical and imaging follow-up (15,16,20). In contrast, patients who have progressive symptoms or evidence of hydrocephalus may be treated with surgical resection or radiation therapy, with the former recommended for those whose tumor is located in the optic nerve and the latter for those with an optic chiasm tumor (75,76). Large cystic masses of the chiasm may be amenable to surgical resection, thus allowing radiation therapy to be delayed (15). To avoid the deleterious effects of radiation therapy on the developing brain, chemotherapy is recommended for children younger than 5 years of age (15). Intraarterial delivery of chemotherapy to treat recurrent disease has also been reported (77).

- **Prognosis, Recurrence, and Dissemination**

Overall, the prognosis for patients with a pilocytic astrocytoma is excellent, with a 10-year survival rate of up to 94% and a 20-year survival rate of 79%, which is in marked contrast to the more guarded prognosis seen with the diffuse (WHO grade II) astrocytoma (4,54,78,79). Other factors besides the native biologic behavior of the tumor influence this favorable outcome. The increase in 10-year survival rate (about 90% after 1970, compared with about 70% before 1970) has been attributed to improvements in neurosurgical techniques and equipment (80).

The location of the pilocytic astrocytoma directly affects the prognosis for the patient. For patients with non–optic pathway pilocytic astrocytomas, the most important factors for improved survival appear to be good neurologic status at the time of diagnosis and gross total surgical resection (6,54). Pilocytic astrocytomas arising in the optic

pathway or hypothalamus have the least favorable prognosis (75). For patients whose tumor was confined to the optic pathway, the 17-year survival rate was 85%, compared with only 44% who survived 19 years when the tumor extended into the hypothalamus (81). It is believed that many, if not all, of the tumors in this latter group may represent the pilomyxoid subtype (82).

Pilocytic astrocytoma appears to have a more benign biologic behavior when it occurs in patients with NF1 (20). Only a small number of patients with NF1 and an isolated intraorbital glioma showed progression of the tumor 10 years after the time of diagnosis (16). For patients with an optic pathway tumor and NF1, the interval between primary diagnosis and first recurrence tends to be longer, compared with that for patients who do not have NF1 (11,19,76).

In contrast to the generally poor outcome (a 5-year survival of usually only 30%) for patients with an infiltrating brainstem glioma (WHO grade II), those with a dorsally exophytic brainstem pilocytic astrocytoma enjoy a much brighter outlook, with stable neurologic status and long-term survival likely (25,27). Subtotal resection and cerebrospinal fluid diversion are the recommended treatment for these tumors. Recurrence may be treated with a second surgical intervention (25,27).

Although recurrence rates are low if gross total resection has been attained, they are substantially increased when only partial resection is achieved (24). Most recurrences are noted within 4 years of the initial surgery, although recurrent disease has been documented as late as 36 years after initial removal (71,83). Survival rates among patients with partial resection, compared with those for patients with gross total resection, are not statistically different (22,24,68).

Distant dissemination from pilocytic astrocytoma is rare, with a reported prevalence of 2%–12% (72). The occurrence of distant dissemination appears increased in three settings: (a) for those tumors located in the hypothalamus (presumably because of their proximity to the ventricular system or because of the tendency of the pilomyxoid subtype to occur in this region); (b) for tumors that have been partially resected; and (c) for tumors occurring in patients less than 4 years of age at initial diagnosis (35,36,72). Dissemination in reported cases tends to manifest within 3 years of initial diagnosis (72). Dissemination from a pilocytic astrocytoma, unlike virtually all other glial neoplasms, does not necessarily correlate with a poorer prognosis, and many patients are asymptomatic with long-term survival (36,72,84–86). Reoperation for recurrent disease is preferred, whereas radiation therapy or chemotherapy is recommended for the treatment of multicentric or surgically inaccessible dissemination (24,72).

There are numerous reports of spontaneous regression of pilocytic astrocytomas arising in the optic pathway, diencephalon, and tectal region (75,87–92). Most of these cases have occurred in children with NF1, but spontaneous regression of the tumor may also occur in patients without that phakomatosis and in adults (18,75,91,93). Numerous theories have been proposed for this finding and include postsurgical apoptosis (programmed cell death), host immune reaction, thrombosis or infarction of tumor vessels, alteration of growth kinetics, removal of the offending carcinogen, genetic programming, and hormonal factors (89,94–98).

SUMMARY

The pilocytic astrocytoma has exceptionally slow growth and a usually indolent biologic behavior that directly effects an extraordinarily promising prognosis for patients with the disease. Characterized by its classic "cystic mass with enhancing mural nodule" imaging appearance, the tumor is easily recognizable in most circumstances. MR imaging is essential in facilitating appropriate therapeutic management.

Because pilocytic astrocytomas grow by expansion rather by infiltration of the nearby neural structure (infiltration results in tumour cells being found histologically radiating diffusely from the mother tumour to the surrounding

normal neural structures), they remain circumscribed and can be separated from normal neural tissues , thus allowing complete surgical removal without leaving behind any residual tumour cells and it is because of this that postoperative radiotherapy or chemotherapy are not indicated and probably even contraindicated The prognosis in pilocytic astrocytoma is good with a five year survival rate reaching up to 95% to 100% in many studies after complete surgical removal. Recurrence was attributed in most studies to incomplete surgical removal in technically difficult anatomical sites as it was the case in our patient with hypothalamic neoplasm.(99)

Because of the very good prognosis of this neoplasm it is important to be familiar with its clinical and neuroimaging pictures. The presence of a cystic component in these lesions is suggestive. The lesions may appear on both CT and MR as a classic cyst with a nodular mass. Purely solid masses are not common. Complex shapes (e.g., multiloculated) can occur and may create a misleading appearance. With contrast infusion, both on CT and on MR, the mural nodule might or might not enhance, however the cyst wall does not enhance. Histopathological confirmation is invariably needed for the ultimate diagnosis of this neoplasm. Although the word astrocytoma is typed in the name of this neoplasm, however it should not be equated with the more common diffuse astrocytoma. "Overgrading" occurs when the generic name "astrocytoma" is applied to pilocytic astrocytomas, so it is very important to distinguish between diffuse astrocytoma and pilocytic astrocytoma as there is a real chance that pilocytic astrocytomas are cured by surgery alone once the neoplasms are completely removed. (99)

Finally it must be mentioned that brain stem pilocytic astrocytoma is indeed a rare occurrence and it is of interest to report a case with pontine pilocytic astrocytoma. (99)

- **Addendum**

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