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Intraventricular gliomas

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Gliomas remain the most common symptomatic primary brain tumor in adults. Those arising within or relating to the ventricular surface represent a relatively small but important proportion of all gliomas. Intraventricular gliomas comprise a unique spectrum of histologic subtypes, the most common of which include ependymomas, subependymomas (SEs), and subependymal giant cell astrocytomas (SEGAs). Other less common variants, including chordoid glioma [1–3], glioblastoma multiforme [4,5], and mixed glial-neuronal tumors [6] among others, have been reported. Each type of intraventricular glioma has its own unique epidemiologic, clinical, radiologic, and pathologic characteristics. Furthermore, each type commands its own constellation of management considerations, and each is associated with different prognostic indicators and outcomes.

Considerable advances have been made in the contemporary understanding and management of these tumors, particularly over the last several decades. The advent and widespread implementation of advanced microsurgical technique coupled with advancements and refinements in adjuvant therapies and their indications for use have helped to improve the care of patients harboring these lesions. Studies into the basic biology of these tumors using modern molecular biologic techniques are increasingly more common [7–10]. Despite this, however, the need for continued progress cannot be overemphasized, particularly in the management of ependymomas.

The following sections address the individual types of intraventricular gliomas, focusing on the unique characteristics and management considerations pertinent to each.

Ependymomas

Intracranial ependymomas refer to tumors of neuroepithelial tissue arising from ependymal cells lining the cerebral ventricles or from rests of ependymal cells situated in the cortical white matter. They occur most commonly in children and young adults. Contemporary perspectives on ependymomas have evolved considerably since the original reported description of tumors of ependymal cell origin by Virchow [11] in 1863.

General comments and epidemiology

Ependymomas comprise between 3% and 10% of intracranial tumors in most series [12–17]. The estimated incidence of ependymomas is approximately 0.2 to 0.8 per 100,000 persons per year [14,18]. The median age at diagnosis is between 3 and 8 years [19,20], with 70% to 80% occurring in

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children less than 8 years of age and 40% occurring in those less than 4 years of age [19,21–23]. There has been a recent trend reported by the Childhood Brain Tumor Consortium study in the relative proportion of older children (>11 years of age) with ependymomas (especially supratentorial) [21]. Although some series have shown a slight male predominance [15,19], there does not appear to be a gender difference across most series [20,22,24]. Ependymomas predominantly arise from a ventricular surface (being of ependymal origin), although they may rarely develop without any direct association to a ventricular surface [25]. Approximately two thirds are infratentorial in location (most commonly arising from the floor of the fourth ventricle in children) with the remaining one third originating within the supratentorial compartment [19,20].

Clinical presentation

Not unexpectedly, the most common presenting signs and symptoms stem from raised intracranial pressure from mass effect or obstruction of cerebrospinal fluid (CSF) flow and hydrocephalus. Supratentorial ependymomas most commonly present with signs and symptoms of raised intracranial pressure but may also cause seizures from cortical irritation or rarely present with apoplexy and intracerebral hemorrhage [26]. Patients with infratentorial tumors often present with a longer clinical history, although this varies. Common symptoms include headache, emesis, lethargy, irritability, and poor balance, whereas clinical signs observed include increasing head circumference (across percentiles), bulging fontanelle, papilledema, meningismus, ataxia, nystagmus, and cranial nerve palsies [19,22]. The expeditious diagnosis is more difficult in younger children, particularly in those with nonspecific symptoms, such as lethargy and irritability with occasional emesis. To avoid significant delay in diagnosis (and, ultimately, delay in necessary treatment), the clinician must maintain a high degree of suspicion, especially in this age group.

Imaging

Clinical suspicion of a possible ependymoma is confirmed with CT or MRI. On CT scanning without contrast, ependymomas often appear hyperdense, with some heterogeneity in approximately 85% of cases, secondary to the presence of solid and cystic components as well as calcification (although infratentorial lesions less commonly have a cystic component [17,27]) [28,29]. Specifically, calcification on CT scanning is encountered in 50% to 80% of cases [27,28,30]. Ependymomas demonstrate significant contrast enhancement that may assume a heterogeneous or homogeneous pattern [27,28,30]. Additionally, peritumoral edema is present surrounding the typically well-delineated tumor margins [27,29].

MRI of ependymomas most clearly defines the pathologic findings in each case. Tumors typically demonstrate hypo- to isointense signal on T1-weighted images relative to parenchyma, with hyperintense signal on T2-weighted sequences [31], although signal characteristics may be relatively nonspecific [32]. Calcification is less well appreciated on MRI but seems to be present in approximately 50% of cases [31]. As with CT, tumors appear fairly well demarcated on MRI, with considerable contrast enhancement after gadolinium injection (Fig. 1). Again, supratentorial lesions are more often of variable consistency (solid and cystic) than infratentorial lesions [31]. Evidence of intratumoral hemorrhage may be seen in nearly 60% of supratentorial lesions and approximately 30% of infratentorial lesions [32]. All infratentorial lesions are, at least in part, intraventricular in location on MRI, whereas 50% of supratentorial lesions appear to be intraventricular, with the remainder appearing to be entirely intraparenchymal [27,31]. With respect to the infratentorial lesions, at least half of the tumors extend from the fourth ventricle out the foramina of Luschka or Magendie into the cerebellopontine (CP) angle or cisterna magna, respectively [27,31].

Likely because of their intimate association with CSF pathways, ependymomas have a propensity for CSF spread, with between 5% and 22% of children at diagnosis appearing to have documented leptomeningeal spread [19,20,23]. Consequently, it has become well accepted to obtain preoperative MRI of the entire spine in combination with sampling of CSF for cytology for staging, particularly for fourth ventricular lesions (see Fig. 1). There has been an apparent increase over the last several decades in the proportion of cases with documented metastases at diagnosis, likely secondary to advancements in imaging and emphasis on thorough staging.

Pathology

The World Health Organization categorizes ependymal tumors into the following four distinct categories [33]:

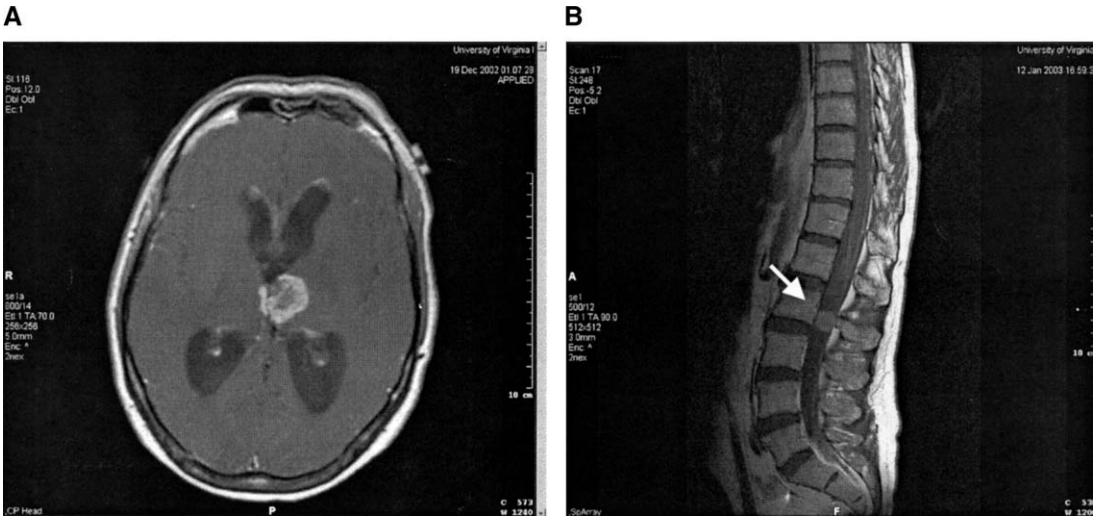

Fig. 1. Grade III ependymoma. (*A*) Head MRI reveals ventricular dilatation and an intensely enhancing mass in the third ventricle on T1-weighted images after intravenous gadolinium administration. (*B*) The patient had evidence of spinal drop metastases at the time of diagnosis (*arrow*).

- Ependymoma (subtypes cellular, papillary, clear cell, and tanycytic)
- Anaplastic ependymoma
- Myxopapillary ependymoma
- Subependymoma

SEs are discussed in a separate section, and myxopapillary ependymomas, found almost exclusively in the conus medullaris–filum terminale–cauda equina region of the spine, are not discussed further.

Ependymomas are characterized by unique histologic, immunohistochemical, and ultrastructural features. They typically seem to be well circumscribed and moderately cellular with monomorphic nuclear morphology [33]. On light microscopy, important histologic features include perivascular pseudorosettes and ependymal rosettes with rare or absent mitotic figures. The perivascular pseudorosettes occur in most ependymomas, with tumor cells being radially arranged around a blood vessel. True ependymal rosettes are diagnostic, although rare, and consist of columnar cells arranged concentrically around a central lumen. Fibrillary elements are commonly observed, in addition to regressive changes, including evidence of myxoid degeneration, intratumoral hemorrhage, calcifications, intratumoral hemorrhage and foci of cartilage, and bone formation on occasion [33].

Cellular ependymomas have increased cellularity with an increased mitotic rate. Pseudorosettes and ependymal rosettes may be absent [33]. Papillary ependymomas are rare, being characterized by well-formed papillae in which blood vessels are enveloped by smooth layers of tumor cells [33]. With cells exhibiting clear perinuclear halos similar to oligodendroglial tumor cells, clear cell ependymomas seem to occur disproportionately in supratentorial ependymomas arising in young patients [33]. The presence of rosettes, immunoreactivity for glial fibrillary acidic protein (GFAP), and electron microscopy studies are useful in differentiating this subtype from other tumors, such as oligodendroglioma, clear cell carcinoma, hemangioblastoma, and central neurocytoma [33]. Tanycytic ependymomas consist of arrangement of tumor cells into fascicles of varying width and cell density [33]. Ependymal rosettes are often absent, and pseudorosettes are poorly formed. There is a predisposition for involvement of the spinal cord in this ependymal subtype [33].

Electron microscopic examination of ependymomas demonstrates the presence of frequent glandlike lumina with microvilli and cilia, basal bodies, intracytoplasmic intermediate filaments, and long distinct junctional complexes [33]. Microrosettes may also be seen.

Anaplastic ependymomas typically exhibit frequent mitoses, marked cellular polymorphism, a high nuclear-to-cytoplasmic ratio, necrosis, and microvascular proliferation [33]. The distinction

between low-grade and anaplastic ependymomas is difficult, however, with different tumors displaying a spectrum of pathologic changes. Additionally, a focus or foci of anaplastic tissue may be seen in an otherwise low-grade lesion, the significance of which has not been established.

Uniform and accurate diagnosis of an ependymoma is obviously important to management, especially after surgery. It must be realized, however, that there is considerable discrepancy in diagnosis between skilled pathologists. For instance, a recent prospective randomized trial conducted by the Children's Cancer Group demonstrated a discordant pathologic diagnosis between an individual's treating institution and the Central Review Board in 69% of cases [20]. This lack of uniformity has hampered past studies, and data must be scrutinized in the present body of literature. Future efforts to improve the precision and accuracy of diagnosis should help to rectify this issue.

Treatment and outcome

The mainstay of treatment in the management of patients harboring ependymomas remains surgical resection, with the goal of total removal whenever possible. The use of postoperative therapy is a current area of active investigation and is dependent on multiple factors, including the extent of resection, preoperative staging, histologic type of tumor, age of the patient, and patient/family's wishes among other factors.

Surgery

The surgical approach is tailored to the individual patient and depends on all clinical, radiologic, and pathologic data. It is also influenced by intraoperative data, such as the tumor's consistency and relation to critical neural structures (ie, adherence to cranial nerves or the floor of the fourth ventricle). As previously emphasized, preoperative staging is important in guiding subsequent therapy. With widespread metastases, the surgeon's enthusiasm for removing the last minute part of the tumor densely adherent to the floor of the fourth ventricle should be dampened, given the already apparent need for potentially aggressive postoperative therapy.

When patients present with acute symptomatic hydrocephalus, immediate intervention is imperative. The first line of treatment is intravenous high-dose dexamethasone (10-mg initial dose, followed by 6 mg every 6 hours). Often, improvement is rapidly seen and may obviate the need for urgent CSF diversion procedures. If high-dose steroids are not effective, an external ventricular drainage catheter is placed as a temporizing measure until the tumor can be removed after the necessary preoperative evaluation has been performed. Permanent ventriculoperitoneal shunting is avoided if at all possible.

The authors' surgical considerations are briefly detailed. Intraoperative frameless stereotactic image guidance is frequently used, particularly with deep supratentorial tumors. Real-time intraoperative ultrasonography can be used to localize the tumor in the depths below the cortical surface. Only infrequently would the use of intraoperative mapping and electrocorticography be contemplated (eg, with tumors resulting in epilepsy). In all instances, perioperative steroids and antibiotics are administered. For supratentorial ependymomas, anticonvulsants are administered before surgery and continued for only 3 months if there has never been a seizure.

There are different surgical considerations for supratentorial and infratentorial ependymomas. For supratentorial ependymomas, the patient is placed in a three-point fixation apparatus and positioned to optimize venous outflow (head above the level of the heart with avoidance of neck kinking). The skin is infiltrated with local anesthetic (0.2% ropivacaine with 1:100,000 epinephrine) before incision. Mannitol (0.25–0.5 g/kg) and mild hyperventilation (end-tidal P_{CO_2} of 25–35 mm Hg) may be implemented in cases associated with raised intracranial pressure. An approach is chosen that allows optimal exposure while minimizing potential complications. The two major approaches, depending on the location of the tumor, include an interhemispheric transcallosal approach (anterior or posterior) and a transcortical transventricular approach. In general, the interhemispheric transcallosal approach is useful with midline lesions, particularly those of the third ventricle, whereas the transcortical transventricular approach is useful for more lateral lesions situated within the lateral ventricles. Frameless stereotactic image guidance is useful in precisely planning the proposed craniotomy. Frameless stereotaxy and intraoperative ultrasound are useful in localizing the tumor or planning the corticotomy where appropriate. The microscope is used for the tumor resection. Under high magnification, the tumor is coagulated circumferentially and subsequently debulked internally. The capsule can then be methodically

dissected and pulled away from its attachments. Meticulous hemostasis is critical, and avoidance of intraventricular blood collection is imperative for the prevention of postoperative chemical meningitis or hydrocephalus. A temporary ventricular drain may be placed during surgery at the discretion of the surgeon. If placed, the drain can usually be removed in the early postoperative period.

For infratentorial ependymomas with significant hydrocephalus refractory to steroids, an external ventricular drain alone or third ventriculostomy with a prophylactic external ventricular drain can be placed before surgery. If a drain has not been placed before surgery, a potential site is prepared and draped into the surgical field at the time of the tumor resection but is opened only if needed. The patient is placed in a prone position with the neck flexed and the head fixated in a three-point apparatus. A midline incision is used most often, which may be linear or "hockey-stick" in nature. A paramedian incision is used in the less common instance in which a tumor is located predominantly in the CP angle. We have more recently preferred posterior fossa craniotomy rather than craniectomy, especially in pediatric patients. The bony opening should permit access to the entire tumor (including exposure to the transverse-sigmoid sinus junction when exploration of tumor extrusion into the CP angle is necessary). Depending on the inferior extension of the tumor, a C1 laminectomy may have to be performed to expose the tumor completely. The dura is usually opened in a Y-shaped fashion. At times, the cerebellum may be under considerable pressure. Rapid opening of the cisterna magna is usually sufficient to alleviate this, and only in exceptional circumstances would a ventriculostomy need to be placed if not present before surgery. The tumor is often seen extruding through the obex. The posterior-inferior cerebellar arteries are identified bilaterally. Under the operating microscope, the tonsils are separated and the vermis is often split in the midline. One of the most important points of emphasis is to discern and continue to be keenly aware of the exact location of the floor of the fourth ventricle. Once identified, a moist Telfa (Kendall Company, Mansfield, MA) patty may be placed over the floor to protect it and serve as a landmark. The tumor is carefully dissected from the floor of the fourth ventricle; however, excessively aggressive attempts to remove a densely adherent tumor are tempered by the goal of preserving neurologic function. The lateral extent of the tumor may also be a significant challenge because of the potential intimate association with blood vessels and lower cranial nerves. Careful sharp dissection under high magnification is useful, but attempts to remove minute pieces of tumor at the expense of neurologic function are to be avoided. The basic technique of internal debulking, followed by dissection and "pulling in" the sides of the tumor, is useful here as well. After resection, the dura is usually closed in a watertight fashion with a dural graft.

After surgery, it is the authors' policy for patients to undergo MRI to determine the extent of resection within the first 72 hours. Postoperative imaging is believed to be more uniformly accurate than the objective intraoperative impression of the extent of resection.

The results of surgical resection reported in the literature have varied considerably. Earlier series have reported rates of gross total resection of 22% to 30% [22,34,35], whereas contemporary series have reported rates of complete resection of 43% to 71% [36,37]. When interpreting the data concerning extent of resection, it is important to consider the criteria for determining the extent of resection (surgeon's intraoperative impression versus postoperative CT or MRI). Some series have only included the extent of resection based on the surgeon's intraoperative impression [36]. In terms of operative mortality, modern series have reported mortality rates of 0% to 2% for supratentorial tumor resection [38,39] and 0% to 13% for infratentorial tumor resection [22,34,35, 39–41]. The rates of morbidity for operative intervention are less frequently carefully recorded and reported. Visual field deficits associated with disruption of the optic tract have been published to occur in 20% to 30% of patients after resection of supratentorial ependymomas [42,43]. Morbidity associated with infratentorial ependymoma resection largely stems from injury of the lower cranial nerves or their nuclei and the brain stem and may be around 10% to 14% [27]. Future appraisals of true operative morbidity must include neuropsychologic assessment, which is typically lacking in most surgical series.

Radiation therapy

Postoperative therapy after surgical resection of ependymomas has been an area of much interest but continues to be a matter of controversy. A significant amount of data has been accrued demonstrating that postoperative

radiation has a significant impact on survival [22,34,35,39–41,44–46], with increases in 5-year survival from less than 20% up to 40% to 50% in selected patients [44,45]. Radiation has become the primary postoperative adjuvant therapy in patients harboring ependymomas. Despite this, the timing, method, and extent of radiation therapy linger as areas of contention and prospective randomized study of postoperative radiation is yet to be conducted.

Pioneering work on the role of radiation therapy in patients with ependymomas established that radiation doses less than 4500 cGy to the primary tumor site did not seem to be efficacious [47–49]. Subsequent work has generally established a dose of 5000 to 5500 cGy over 5 to 6 weeks for the treatment of subtotally resected nonanaplastic ependymomas [50–52]. For patients with aggressive ependymomas, some authorities have recommended escalated doses (5500–6000 cGy) over 6 to 7 weeks. Recent interest has also been given to the use of stereotactic radiosurgery for recurrent ependymoma and has been suggested for use in the initial postoperative treatment of ependymomas [53]. The early results of stereotactic radiosurgery seem to be somewhat promising, and future study is warranted.

The target for radiation therapy administration has also received considerable attention. In general, supratentorial low-grade ependymomas can be treated with focused radiation targeting the surgical site, because the incidence of leptomeningeal spread is quite low [50,51,54]. When compared with whole-brain irradiation, local field radiation therapy (with or without a boost) demonstrated a significant 10-year progression-free survival rate [42]. The literature concerning postoperative radiation therapy for infratentorial ependymomas is more heterogeneous, and the practice across institutions is quite variable, especially in those cases with benign histology and no evidence of leptomeningeal metastases [42,52,54–60]. The authors' practice is to administer local radiation therapy in cases of subtotally resected benign ependymoma without prophylactic craniospinal irradiation. Craniospinal radiation therapy is reserved for those patients with evidence of leptomeningeal dissemination by MRI or CSF cytology and for selected patients with malignant ependymomas. It is important to note that 80% of cases with leptomeningeal spread occur in patients with high-grade ependymomas [50,51,61].

One of the emerging paradigms with postoperative radiation therapy is to avoid its administration to children less than 3 years of age because of its potential deleterious long-term neurologic and neuropsychologic sequelae. We have also chosen not to administer postoperative radiation therapy in selected patients with low-grade ependymomas in whom complete resection was achieved and confirmed by postoperative MRI, particularly with young patients and supratentorial tumors. These patients are followed closely with serial imaging for any sign of recurrence. Other reports of this practice have demonstrated long-term survival in patients who underwent total resection without postoperative radiation therapy [43,62].

Chemotherapy

Another facet of postoperative care that remains controversial is the administration of adjuvant chemotherapy. The overall efficacy of chemotherapy has been disappointing, although most reports on the treatment of patients with ependymomas are based on anecdote and small numbers [19,20,39,63–76]. The most extensively studied and potentially active agent in patients with ependymomas has been cisplatin [76–79]. These data, taken collectively, demonstrate an overall response rate of 33% with cisplatin, of which 18% were complete responses. Other less well-studied agents that have demonstrated at least some efficacy include carmustine, lomustine, etoposide, cyclophosphamide, dibromodulcitol, and carboplatin [64,80–83]. Other agents, including 1-(2-chloroethyl)-3(2,6 dioxo-1-piperidyl)-1-nitrosource (PCNU), thiotepa, ifosfamide, and idarubicin, have been investigated, with a paucity of demonstrated efficacy [84–92]. Anecdotal unpublished data also suggest occasional partial response or stable disease with temozolomide and procarbazine.

Overall, the response rate to single chemotherapy agents in patients with ependymomas seems to be 11%, with less than 5% complete responses [76]. Combination drug regimens have also been investigated, with limited efficacy, including mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) and eight agents in 1-day regimens [20,67,69–75,78,93,94]. The use of high-dose chemotherapy with bone marrow/stem cell rescue has been disappointing thus far in patients with ependymomas [95,96]. Nevertheless, an area of emerging promise and recent interest has been in the use of adjuvant chemotherapy in place of radiation therapy in young children to circumvent the deleterious effects of radiation

exposure to the immature and rapidly developing nervous system [37,65,70,71,75,97]. In particular, the Pediatric Oncology Group presented interesting data demonstrating success with the administration of chemotherapy, especially in patients aged 24 to 36 months, in terms of safely delaying adjuvant radiation therapy and improving survival [75].

In summary, based on the available data, chemotherapy has not proven to be particularly efficacious in the treatment of ependymomas. Chemotherapy should probably be used largely in clinical trials and protocols. Future appropriately powered prospective investigations are warranted to delineate the role of chemotherapy in patients harboring ependymomas. Of special interest remains the delineation of the role of chemotherapy in young patients, in whom radiation therapy is highly undesirable.

Prognostic factors and outcome

The ability to predict prognosis for patients with ependymomas is important from both patients' and clinicians' perspectives. The establishment of predictive factors has been an arduous task, in part, because of significant difficulty in comparing outcomes between different studies and even within studies at times. Ependymoma is a relatively rare tumor, and significant experience with treatment has accrued slowly over time. Hence, an individual institution's experience is relatively limited and has developed over different eras, thereby introducing heterogeneity within and between series. Furthermore, as previously alluded to, there has been considerable difficulty in arriving at consensus pathologic diagnoses between different observers, thereby introducing additional variability. The nature of most series has also been retrospective case series with its own inherent biases, also limiting the quality of available data.

Extent of resection. The preponderance of available data demonstrates that the completeness of resection (especially gross total resection) is correlated with improved prognosis [20,22,24,36, 37,39,46,75,98–100]. From these data, 5-year survival has ranged from 60% to 93% after gross total resection compared with 21% to 46% after subtotal resection. As mentioned, the means by which assessment of the extent of resection is made is clearly important, and the present gold standard is establishment by postoperative MRI. In fact, there have been data demonstrating that radiologic imaging rather than the surgeon's intraoperative impression is statistically predictive [101]. Furthermore, even a small amount of residual tumor (< 1.5 cm^2) may predict improved survival [20].

Age. In children, age seems to be an important prognostic factor in most studies, with children older than 3 or 4 years of age seeming to have longer survival, with 5-year survival rates ranging from 55% to 83% compared with 12% to 48% for their younger counterparts [19,22,24,39, 59,100]. Even in subgroups of patients less than 3 years old, those older than 2 years of age seem to fare better, with 5-year survival rates of 63% versus 26% between groups [75]. It should be noted that not all reports have confirmed age as a prognostic factor [20,61,98,102].

Histologic grade. Histologic grade as a prognostic factor has been controversial across different series. This may be due, at least in part, to difficulty in establishing consensus diagnoses between pathologists. A diagnosis of higher grade/anaplastic ependymoma portending a poorer prognosis makes intuitive sense but has not been universally borne out. Considerable data exist to suggest that anaplastic ependymomas or those with higher grade features are associated with a poorer prognosis [22,24,36,38,43,61,99,102–107]. There exists a significant body of literature in which histologic grade was not established as an independent prognostic factor, however [19,20,37, 39,75,108]. Of note, two of these studies were prospective in nature, including a prospective cohort study from the Pediatric Oncology Group [75] and a randomized trial from the Children's Cancer Group [20]. These studies are still limited in sample size, however, and disagreement in the pathologic diagnosis occurred in a disappointing 69% of cases in an independent review process in the Children's Cancer Group study [20], which makes it difficult to draw firm conclusions.

Tumor location. Numerous studies suggest that an infratentorial location is associated with better prognosis compared with supratentorial lesions, with 5-year survival rates for infratentorial tumors ranging from 35% to 59% compared with 22% to 46% for supratentorial tumors [19,24,98,109,110]. Furthermore, certain features of infratentorial tumors may help to predict prognosis. A significant lateral extension into the CP angle seems to be a poor prognostic factor, which may be

ascribed to additional difficulty in complete removal because of intimate association with lower cranial nerves and critical vascular structures [34].

Miscellaneous factors. Although the aforementioned prognostic factors have been best characterized, several other factors have surfaced as putative prognostic indicators. Gender, race, and duration of symptoms have been suggested as possible prognostic factors [19,99,100], although they are questionable in their predictive ability. Additional evidence is needed before any of these latter factors could be considered a firm prognostic indicator.

Despite considerable progress in the management of patients with ependymomas, overall prognosis remains relatively poor. Most patients eventually develop recurrence, and the most common site for recurrence seems to be the primary tumor site [24,61,71,109]. Local recurrence remains the primary cause of progressive neurologic deficits [24]. Tumor recurrence manifesting as metastases without local recurrence is quite rare, occurring in 7% to 8% of cases [20,104]. The most important factors in preventing recurrence are thus the same factors as those for establishing local tumor control. Unfortunately, treatment of tumor recurrence is quite limited. Repeat surgery is contemplated for local recurrence. Radiation therapy has usually been administered; hence, further radiation therapy is not usually an option. Chemotherapy may be administered, but its efficacy has been disappointingly poor.

The overall 5-year survival rate for children with ependymomas is approximately 39% to 93% [19,20,22,34,36,37,99,101,104,111]. The 10-year survival rates range from around 45% to 75% [34,36,37,100,101]. The absolute survival rates do not reveal the burden of neurologic morbidity with which these patients may live. In children, survivors have relatively low IQs and impaired academic and psychosocial functioning that limit their ability to interact with their environment. Much of this morbidity may be iatrogenic, and future efforts directed toward minimizing insult by treatment on the developing nervous system are clearly necessary.

Subependymomas

General comments and epidemiology

SEs are relatively uncommon well-differentiated tumors associated with the ventricular system; they are generally characterized by slow growth and an indolent clinical course. SEs are thought to originate from the subependymal glial matrix, consisting of a mixture of astrocytic, ependymal, and transitional cell clusters surrounded by neuroglial fibers [112]. Scheinker [113] is generally given credit for the description of SE as a distinct entity in 1945, although tumors had been described previously that contained both astrocytic and ependymal features. The exact etiology of these tumors remains in doubt. SEs have been reported to occur in families and twins, leading to speculation of a specific genetic mechanism, although, to date, a mechanism has not been clearly identified [114–116]. Some suggest that SEs might represent hamartomas, in part, because of the fact that they have been associated with heterotopic neuroglial tissue in the leptomeninges [117]. A reactive origin has also been postulated as a result of reports of concurrent presentation of SE with hydrocephalus, ependymitis, and meningitis, but this mechanism remains in doubt [118]. On occasion, SE arises concurrently with other primary neoplasms, such as glioblastoma, meningioma, or choroid plexus papilloma, but this seems to be coincidental [119,120].

The incidence of SE at autopsy is 0.4%, and the incidence of SE in intracranial surgical tumor specimens ranges from 0.2% to 0.7% [121]. The most common site of presentation is the fourth ventricle, but SEs may also occur in the lateral ventricle and the aqueduct of Sylvius. SEs may occur at extraventricular locations, which include the septum pellucidum and the cervicothoracic spinal cord. In one series of 69 surgical patients, 70% were male and the average age was 39 years [122]. In this report, two thirds of patients had tumors in an infratentorial location, one third had supratentorial tumors, and 2% had tumors in the cervicothoracic spinal cord [122]. SEs are relatively rare in the septum pellucidum, consisting of 5% of all reported cases [112].

Clinical presentation

Whether incidental or symptomatic, SEs occur far more frequently in the adult population. There do not seem to be reports of SE detected in infants. Most SEs are asymptomatic during the life of the patient and discovered at the time of autopsy, despite the fact that some of these lesions are quite sizable. Of those patients who present in the clinic, there seems to be a bimodal age distribution that

depends on the mode of presentation. Symptomatic patients usually present with obstructive hydrocephalus and tend to be younger (average age of 40 years) as opposed to those asymptomatic patients who present at an average age of 60 years [123]. It is estimated that 40% of SEs become symptomatic [124]. Most asymptomatic patients have lesions that are discovered on imaging studies performed for clinical indications that are unrelated to the neoplasm (Fig. 2). Nevertheless, there is a report of a sudden death related to a previously asymptomatic SE [125]. Symptomatic SEs usually present either with increased pressure because of CSF obstruction or hemorrhage [126]. Predictably, tumors that arise from the septum pellucidum, the region of the foramen of Monro, or the aqueduct of Sylvius are the most likely to cause symptoms because of obstruction of CSF flow. Symptomatic tumors tend to be larger, and obstructive hydrocephalus is present in up to 88% of cases [122].

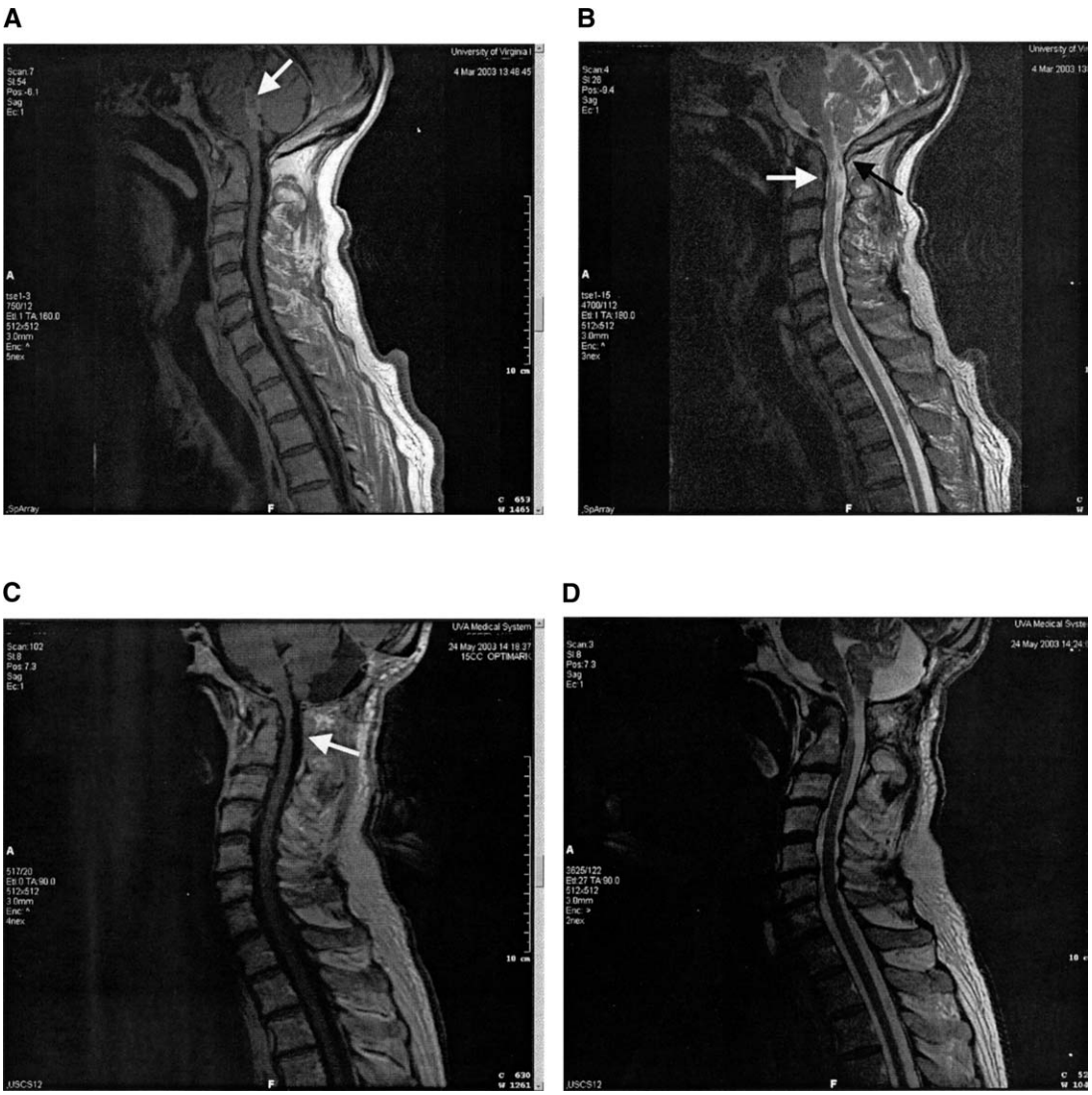

Fig. 2. Subependymoma. This patient originally presented with progressive ataxia. (*A*) Initially, the symptoms were attributed to the mildly enhancing fourth ventricular mass (*white arrow*). (*B*) On closer inspection, the patient had significant spinal cord signal abnormality and myelomalacia (*white arrow*) related to basilar invagination and an occipitalized atlas (*black arrow*). (*C*) The patient underwent posterior fossa and C-1 decompression, total resection of the subependymoma, and fusion.

Prominent symptoms and signs on presentation are headache, visual disturbance, papilledema, gait ataxia, memory disturbances, cranial nerve paresis, nystagmus, spasticity, vertigo, and vomiting. Tumors arising in the area of the septum pellucidum may produce personality disorder, memory impairment, loss of consciousness, or seizure disorder [127]. Spinal cord SEs usually result in cord compression and produce symptoms referable to the spinal level of involvement.

Radiology

SEs most often arise from the region of the lower medulla and project into the fourth ventricle. Fourth ventricular tumors grow from the floor or roof and may extend laterally via the foramina of Luschka to occupy the subarachnoid space. In fact, a tumor originating in the lateral recess of the fourth ventricle may grow out the foramen of Luschka, erode the petrous bone, and simulate other CP angle tumors [128]. Another common location is in the frontal horn of the lateral ventricle, where they may attach to the septum pellucidum or the lateral ventricular wall. A few SEs are found along the midbody of the lateral ventricle [123]. CT reveals a well-delineated mass, which is hypodense, isodense, or even slightly hyperdense to brain parenchyma. Contrast enhancement is often not seen on CT, but, when present, enhancement tends to be homogeneous but not intense (Fig. 3). Edema tends to be uncommon. On CT, intense diffuse enhancement with edema should arouse suspicion of a mixed ependymoma-SE, which has a significantly more aggressive natural history [129]. Cyst formation, focal calcification, and hemorrhage can be seen on CT. Dense calcifications are more common for tumors that arise in the fourth ventricular location.

MRI reveals homogeneous hypointense to isointense masses on T1-weighted imaging. SEs may be mildly hyperintense on T2-weighted and gradient echo imaging. Signal heterogeneity can be present as a result of cyst formation. Contrast enhancement is typically absent, but gadolinium enhancement may occur (Fig. 4). When contrast enhancement is present, it is more likely to occur in fourth ventricle sites [130,131]. The differential diagnosis of fourth ventricular SE with similar imaging characteristics includes metastasis or ependymoma. Central neurocytoma is one of the major differential considerations for frontal horn SE.

Cerebral angiography may disclose arterial displacement around the mass and stretched subependymal veins indicating ventricular dilatation, but neovascularity is absent. Cerebral angiography probably does not have significant utility as a diagnostic test because of lack of significant tumor vascularity.

Pathology

SEs are characterized by their intraventricular location, circumscribed nature, lobulated appearance, infrequent multiplicity, sharp demarcation, slow growth, and usually noninvasive nature. Growth is typically by expansion rather than by infiltration. These lesions originate immediately beneath the ependymal surface and tend to displace the ependymal surface as they enlarge over time. On gross inspection, SEs are firm, well-demarcated, grayish-white to tan, avascular, intraventricular masses that are firmly attached to their site or origin at the septum pellucidum, foramen of Monro, lateral ventricle, or inferior fourth ventricle. In the fourth ventricle, the tumor may be primarily attached to the floor, roof, or lateral recesses via a vascular pedicle. Secondarily, SEs may adhere to adjacent ependymal surfaces other than the site or origin, particularly as the tumors grow larger. The gross appearance may be modified by calcification, hemorrhage, or cyst formation.

Once considered a variant of ependymoma, SEs are now placed in a separate subcategory of ependymal tumors. SEs are designated as World Health Organization grade I. The cell of origin for SE may be a bipotential subependymal cell with capabilities to differentiate into ependymal or astrocytic cells [116,128]. Microscopic examination discloses a sparsely cellular neoplasm with a prominent fibrillary background. The concept of ependymal differentiation in SE is supported by its nuclear characteristics, ultrastructural features, and occasional coexistence of a mixed ependymoma component. Supporting an astrocytic lineage is the abundance of long processes that are rich in glial filaments. This characteristic microscopic appearance led to the term *subependymal glomerate astrocytoma* [132]. Microcystic changes are common, but hypercellularity, true ependymal rosette formation, neovascularity, and necrosis are generally absent. Nuclear atypia and limited mitotic activity do not seem to be of prognostic significance. Lateral ventricular SEs have occasional mitoses and hyalinized vessels, are more infrequently calcified, and are more "astrocytic" in appearance. SEs of the fourth ventricle are usually more suggestive of ependymomas. Tumors

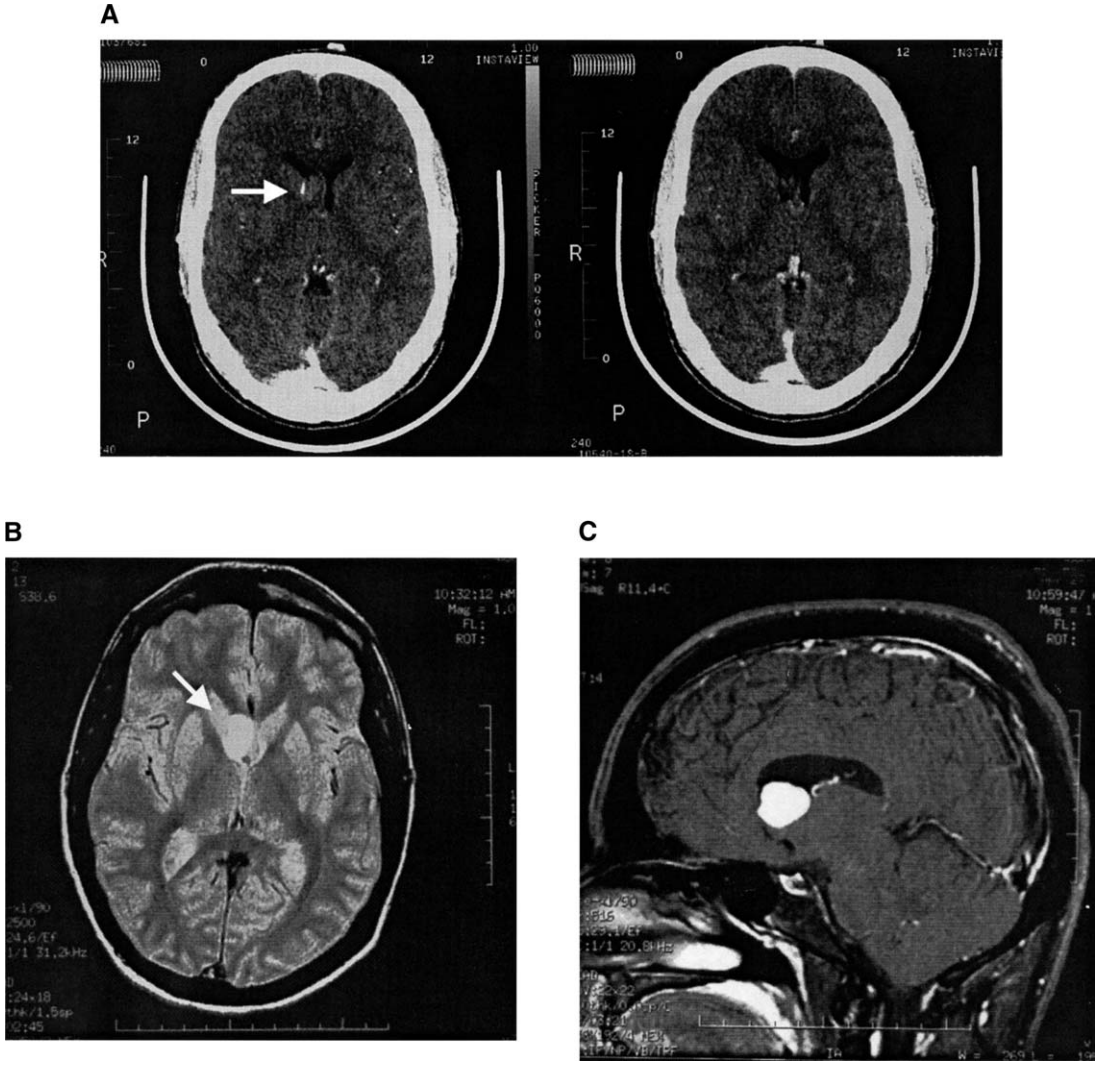

Fig. 3. Subependymoma. (*A*) A nonenhancing lesion in the right frontal horn of the lateral ventricle. (*B*) The mass has significant hyperintensity on gradient echo MRI. (*C*) An unusual appearance of intense homogeneous enhancement after administration of intravenous gadolinium.

at these locations usually lack microcystic change, calcification is more common, and the nuclear chromatin pattern is more reminiscent of ependymal cells.

Immunohistochemical analysis reveals frequent GFAP positivity and common vimentin and S-100 positivity, but the Ki-67 labeling index (MIB-1) is normally quite low [133]. Electron microscopy shows closely packed cell processes filled with intermediate glial filaments. Ultrastructural ependymal features, such as microvilli and cilia, are most frequent among tumors arising in the fourth ventricle. Some histologic variants of SE have been reported, including rhabdomyosarcomatous differentiation, sarcomatous proliferation of the vasculature, and the presence of melanin pigment [134–136]. When mixed with ependymoma, these areas reveal true or pseudorosettes, increased vascularity, increased mitosis, necrosis, and increased cellularity [129].

Treatment and prognosis

Surgery

Advances in microsurgery have improved surgical outcomes. One study compared the

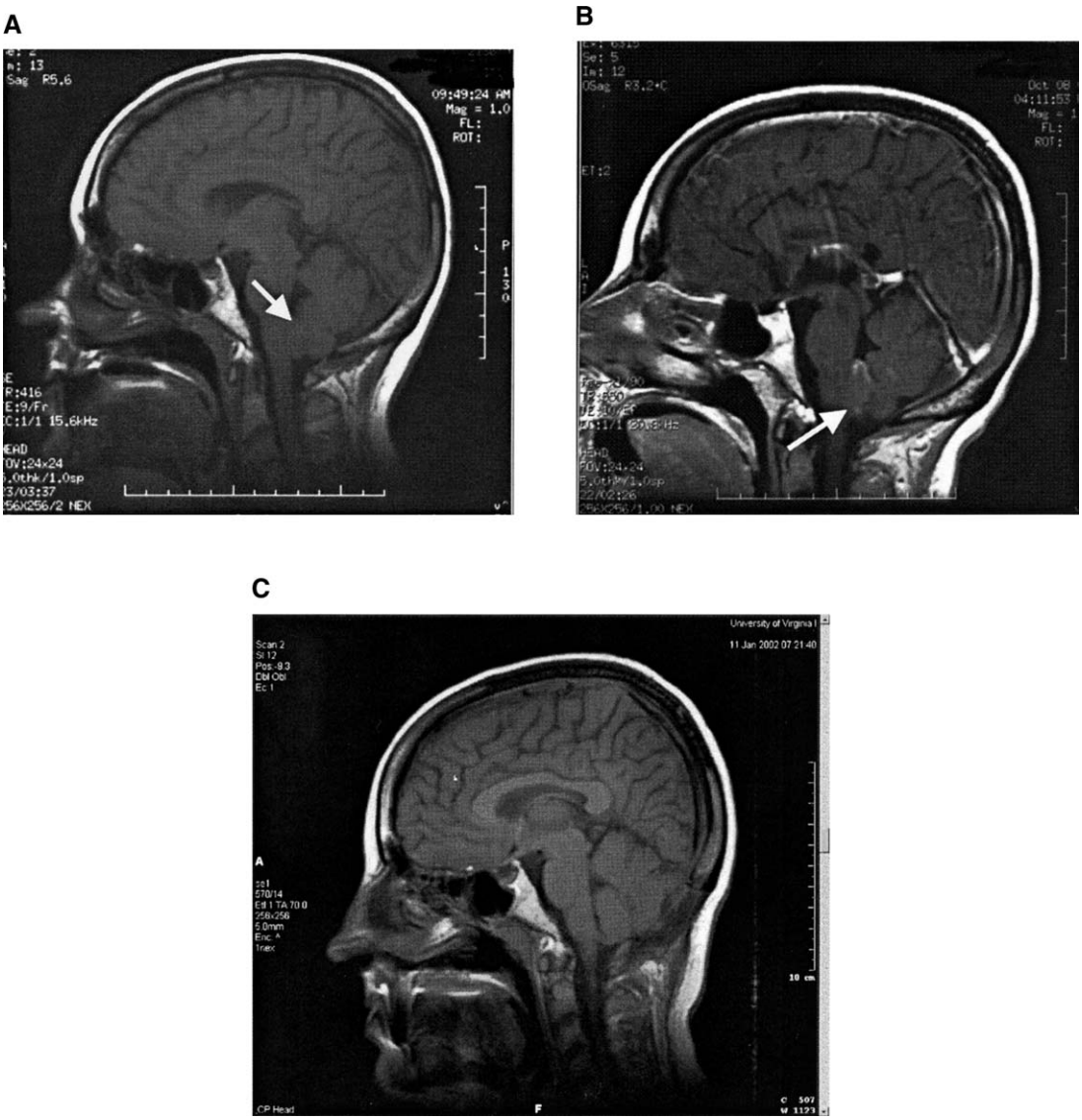

Fig. 4. Subependymoma. (*A*) Isointense mass on T1-weighted images in patient with headaches and nystagmus. (*B*) Minimal enhancement after intravenous gadolinium administration. (*C*) Total resection was achieved despite broad attachment to the floor of the ventricle.

outcome of patients who underwent resection between 1950 and 1974 with the outcome of those who underwent surgery between 1975 and 1989 [137]. Mortality decreased from 25% to 0%. The plan for surgical treatment is usually radical excision. This goal is often achievable, because SE growth patterns tend to be expansive rather than infiltrative.

Tumor location and extent of resection are the most important prognostic factors. SEs of the lateral ventricle may be resected with relative ease. Septum pellucidum and frontal horn lesions may be approached either through a transcallosal or transcortical transventricular route as previously described. Total excision of fourth ventricular tumors may be more difficult because of attachment to the floor of the fourth ventricle. Reports have described sharp demarcation allowing complete removal in about half of the cases and higher perioperative morbidity in fourth ventric-

ular locations [121]. Fourth ventricular SEs are usually approached through a standard midline posterior fossa approach with splitting of the vermis, similar to the approach described for ependymomas. For symptomatic lesions, surgical debulking may re-establish CSF flow. Particularly in older patients, debulking may be equivalent to a cure in some instances, because it could take many years for a symptomatic mass to have a substantial recurrence. In a retrospective review, no tumor recurrence was noted in a series of 12 patients who underwent total or subtotal resection [133].

Treatment of asymptomatic lesions that are incidentally discovered is decidedly less clear. If the lesions remain asymptomatic and do not exhibit growth on serial imaging, expectant management is usually undertaken. If ventricular enlargement is proven, tumor growth is detected radiographically, or there is considerable doubt with regard to the diagnosis, surgical treatment should be considered, however.

Radiation and chemotherapy

The literature is too sparse to draw conclusions for a significant benefit from radiation therapy. Thus, radiation therapy is generally not recommended for incompletely resected asymptomatic tumors. Nevertheless, it is important to differentiate SEs from ependymomas because of a much better prognosis and differing treatment strategies. Perhaps as many as one fourth of symptomatic tumors may have an admixture of both SE and ependymoma components and seem to have a less favorable prognosis resembling that of pure ependymoma [129]. In cases of mixed ependymoma-SE or where there is significant nuclear pleomorphism, radiation has been proposed [138]. CSF dissemination of SE has not been reported. We are not aware of any study that advocates chemotherapy for the treatment of SE.

Subependymal giant cell astrocytomas

General comments and epidemiology

SEGAs are a relatively rare form of astrocytoma that is characteristically associated with tuberous sclerosis complex, an autosomal dominant phakomatosis. SEGAs may occur independent of tuberous sclerosis, although spontaneous cases may occasionally represent a forme fruste of the neurocutaneous syndrome. After tubers, SEGAs are the second most common tumor affecting patients with tuberous sclerosis [139]. Reports reveal that 3% to 14% of patients with tuberous sclerosis have SEGAs [139,140]. In a large series of 345 tuberous sclerosis patients, 6.1% had SEGAs [141]. Rarely is there an association between malignant glial tumors and tuberous sclerosis [142].

Clinical presentation

The peak age of incidence is between 5 years of age and the midteens [139,140]. The earliest reported occurrence is of that in a premature infant [143]. Approximately 20% of SEGAs present in adulthood, however [144]. There does not seem to be a racial or gender predilection. In most cases, the tumors are found associated with the ventricular wall near the foramen of Monro, resulting in a presentation that is characteristic for obstructive hydrocephalus. Symptoms in infants include enlarging head circumference, irritability, lethargy, and vomiting. Older children may present with headache, nausea, vomiting, or exacerbation of seizure disorder. The diagnosis is usually made by the location of the tumor and by the association of other stigmata of tuberous sclerosis, including adenoma sebaceum, mental retardation, and myoclonic seizures (Vogt's triad for clinical diagnosis), and the presence of subependymal or cortical tubers and heterotopic gray matter. The differential diagnosis for tumors of the lateral ventricle also includes ependymoma, SE, neuroblastoma, astrocytoma, oligodendroglioma, meningioma, central neurocytoma, and choroid plexus papilloma.

Radiology

On CT, SEGAs are well-circumscribed isodense or hyperdense masses that demonstrate intense homogeneous contrast enhancement. The tumors tend to protrude into the ventricle and arise from the sulcus terminalis [145]. The tumors may contain some calcification. SEGAs associated with tuberous sclerosis are typically heavily calcified and have strong but inhomogeneous enhancement after contrast administration. Tubers, although they may calcify, do not enhance after intravenous injection of contrast dye [146].

On MRI, SEGAs are isointense or hypointense on T1-weighted imaging and hyperintense or heterogeneous on T2-weighted imaging and may enhance significantly with contrast administration (Fig. 5). Calcifications may be seen as signal voids.

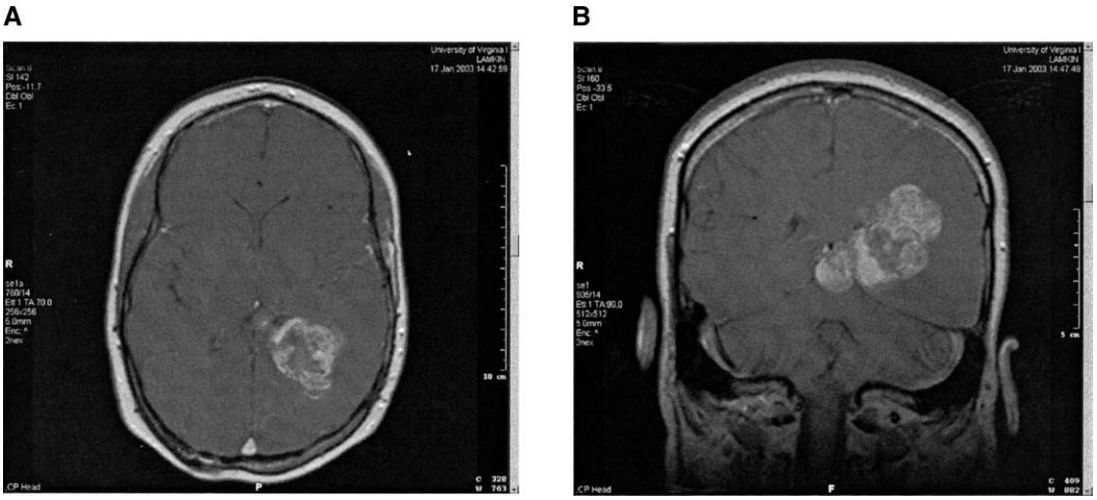

Fig. 5. Subependymal giant cell astrocytoma. Axial (*A*) and coronal (*B*) MRI after intravenous gadolinium administration demonstrating an intensely enhancing mass expanding the atrium of the left lateral ventricle. This patient did not have stigmata of tuberous sclerosis.

Most SEGAs inhomogeneously enhance after gadolinium administration. In contradistinction, tubers generally do not exhibit hyperintensity on T2-weighted imaging and do not usually show contrast enhancement [147]. The current diagnostic imaging modality of choice is MRI with T2-weighted images, with and without gadolinium, including coronal sections through the region of the foramen of Monro.

SEGAs have variable vascularity on angiography; a prominent blush may be present on the late arterial phase. Venous phase films show stretched and elongated subependymal veins when ventriculomegaly is present.

Pathology

SEGAs are usually well-demarcated lobulated masses that often appear calcified. Even macroscopically, cysts are not uncommon. SEGAs may be quite vascular and have a reddish or hemorrhagic appearance. An origin of SEGA from subependymal tubers has been postulated and supported by the observations that there are transitional lesions between tubers and SEGA and that serial imaging studies have demonstrated transformation of subependymal nodules into symptomatic tumors [148–150]. Current molecular studies suggest that SEGAs are the neoplastic counterpart in the spectrum of central hamartomatous tuberous sclerosis complex lesions [151].

Microscopically, SEGAs consist of bizarre spindle cells, large swollen astrocytes packed with glial filaments (giant cells), prominent thick processes, and occasional ganglion cells. Angiocentric arrangement of glial cells around vascular structures to form pseudorosettes is common. The vasculature is typically devoid of endothelial proliferation. There can be an association with microscopic hemorrhage. Rare focal areas of atypia, mitosis, or necrosis do not indicate aggressive behavior [141,152]. Calcification is infrequently noted. Mast cells may be present, and these are detected only in SEGAs, hemangioblastomas, and meningiomas in the CNS. Histologically, the differential diagnosis for SEGA includes gemistocytic astrocytoma and giant cell glioblastoma.

GFAP staining is variable. One report found that approximately half of SEGAs stain for GFAP but that 6 of 7 tumors were S-100 positive and postulated that SEGAs may arise from cells in the germinal matrix that have not yet fully differentiated along astrocytic or neuronal pathways [153]. Interestingly, another author reports that tumors associated with tuberous sclerosis were less likely to stain positively for GFAP [154], but this is not a widely held opinion [151]. In an analysis of 20 tuberous sclerosis–associated tumors, investigators found immunoreactivity for both glial- and neuron-associated epitopes and neuropeptides within tumor cells with the same morphology, suggesting that SEGAs have the ability to undergo divergent glioneuronal and

neuroendocrine differentiation, perhaps to a greater extent than other mixed glial-neuronal neoplasms [151]. The Ki-67 labeling index (MIB-1) is usually low [155].

Treatment and prognosis

Surgery

The surgical management of SEGAs is based on the patient's symptoms and the serial changes on neuroimaging. An asymptomatic patient with minimal changes in tumor size may be followed expectantly with serial imaging. Patients who have symptomatic obstructive hydrocephalus require surgical intervention. In this instance, the treatment of choice is surgical resection, with gross total resection as the surgical goal. In the past, unilateral or bilateral shunting without tumor resection has been advocated. With advances in neuroanesthesia and microsurgery, however, these lesions may be approached safely through transcallosal or transcortical transventricular approaches with acceptable morbidity as described previously. Gross total tumor resection and ventriculoventriculostomy (fenestration of the septum pellucidum) may obviate the need for shunting. It is recommended that neonates undergoing surgical treatment have preoperative cardiac clearance because there is a reported incidence of cardiac rhabdomyomas of tuberous sclerosis complex, resulting in potential fatal arrhythmias [156].

The frequency of tumor recurrence is low, with a 10-year survival rate of nearly 80% after surgical treatment [141]. Long-term survival is possible, even after subtotal resection, because of the limited growth potential of remaining tumor. Because of the fact that rapid tumor regrowth is reported [157], however, yearly follow-up MRI should be obtained to monitor for tumor regrowth and hydrocephalus.

Radiation and chemotherapy

There is no significant experience of the treatment of SEGA with radiation therapy or chemotherapy, although radiation can be considered in the rare setting of malignant degeneration. The treatment of choice in the primary and recurrent settings remains surgery.

Miscellaneous intraventricular glial tumors

Although the most common and important forms of intraventricular gliomas have been discussed, case reports of other types have appeared in the literature. Nearly 30 cases of chordoid gliomas of the third ventricle have recently been reported [1–3]. Chordoid gliomas refer to a slow-growing and rare neoplasm of the third ventricle with an uncertain histogenesis and chordoid appearance, occurring predominantly in middle-aged women [1–3]. The clinical signs and symptoms seem to be nonspecific and relate to mass effect in the tumor's vicinity (including visual loss, hydrocephalus, endocrine disturbances, memory changes, and psychiatric disorders). On imaging studies, the lesions are typically well circumscribed with an ovoid shape. They appear hyperdense on CT imaging and isointense on T1-weighted MRI with intense enhancement [1–3]. The pathology is quite consistent [158] and involves clusters of oval-to-polygonal epithelioid tumor cells with plentiful eosinophilic cytoplasm with a mucinous, vacuolated, and periodic acid–Schiff-positive matrix similar to chordomas. A paucity of mitotic figures and anaplastic features is noted. Additionally, a lymphoplasmacytic infiltrate with Russell bodies without formation of follicles and germinal centers is usually seen. The tumors generally possess low growth potential, and there are no physaliphorous cells, whorl formations, psammoma bodies, or nuclear pseudoinclusions and no ependymal canals or rosettes. Given the rarity of this tumor, optimal treatment after histologic diagnosis is unclear. Surgery followed by radiation therapy has been reported [3]. Future reports of this unusual tumor should help to define its nature and appropriate treatment further. Other common tumors may also present in an uncommon intraventricular location, including glioblastoma multiforme, oligodendrogliomas, and gangliogliomas [4–6,159].

Summary

Gliomas are the most common primary brain tumor in adults, and those within or relating to the ventricular surface represent a less common but important subcategory. The most common intraventricular gliomas include ependymomas, SEs, and SEGAs. Other less common varieties have been reported, including chordoid gliomas, glioblastoma multiforme, and mixed glial-neuronal tumors. Each type of intraventricular glioma is associated with its own unique constellation of epidemiologic, clinical, radiologic, and pathologic defining characteristics. Each tumor type has its

own management considerations and nuances with unique prognostic indicators and outcomes.

The outcome for certain intraventricular gliomas (especially ependymomas) remains relatively poor. Future advancements in surgical technique are likely to have only a modest impact on improvement of outcome. Translational research aiming to advance the knowledge of tumor biology into new targeted cellular and molecular therapies holds tremendous promise to improve the overall outcome. Additionally, more thorough delineation of prognostic factors as well as modifications and refinements to radiation and chemotherapy may help to improve the still significantly poor outcomes for patients harboring these lesions. Future cooperative intra- and interinstitutional efforts between scientists and clinicians will hopefully culminate in an improved outlook and eventual cure for patients with gliomas.

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