SYMPTOMATIC SUBEPENDYMOMAS OF THE VENTRICLES. REVIEW OF TWENTY CONSECUTIVE CASES

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AZ AGYKAMRÁK TÜNETEKET OKOZÓ SUBEPENDYMOMÁI. HÚSZ, EGYMÁS UTÁNI ESET ÁTTEKINTÉSE
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Background and purpose – Intraventricular subependymomas are rare benign tumors, which are often misdiagnosed as ependymomas. To review the clinicopathological features of subependymomas.
Patient selection and methods – Retrospective clinical analysis of intraventricular subependymomas and systematic review of histological slides operated on at our center between 1985 and 2005.
Results – Twenty subependymomas presented at the median age of 50 years (range 19-77). Two (10%) were found in the third, three (15%) in the forth, and 15 in the lateral ventricles. There was male preponderance (12 vs. 8). Ataxia (n=13) and papilledema (n=7) were the most common clinical presentations. Fifteen patients underwent gross total resection, and five had subtotal resection. None of the cases showed mitotic figures, vascular endothelial proliferation or necrosis. Cell proliferation marker MIB-1 activity (percentage of positive staining tumor cells) ranged from 0 to 1.4% (mean 0.3). Two cases were treated with preoperative radiation therapy (50 Gy) before the CT era, three other patients received postoperative radiation therapy for tumors originally diagnosed histologically as low grade ependymomas. Three patients (15%) died of surgical complication between one and three months postoperatively, and three patients died of unrelated causes in eight, 26 and 110 months. Fifteen patients were alive without evidence of tumor recurrence at a median follow-up time of 10 years.
Conclusion – Subependymomas are low-grade lesions and patients do well without adjuvant radiotherapy. Small samples from more cellular areas may be confused with low grade ependymomas, and unnecessary radiotherapy may follow. Recurrences, rapid growth rates should warrant histological review, as hypocellular areas of ependymomas may also be a source of confusion.

Keywords: *subependymoma, surgery, radiotherapy, prognostic factors*

Háttér és célkitűzés – Az intraventricularis subependymomák ritka, jóindulatú daganatok, amelyeket gyakran tévesen ependymomáknak diagnosztizálnak. Áttekintettük a subependymomák klinikopatológiai jellemzőit.
Betegek kiválasztása és módszerek – Az intraventricularis subependymomák retrospektív klinikai elemzése és a szövettani metszetek szisztematikus áttekintése a központunkban 1985 és 2005 között operált betegek anyagaiból.
Eredmények – Összesen 20 subependymomás beteget kezeltünk, medián életkoruk 50 év volt (19–77 év). Két daganat (10%) a III., három (15%) a IV. és 15 az oldalkamrákban volt található. Több beteg volt férfi (12 vs. 8). A leggyakoribb klinikai tünet az ataxia (n=13) és a papillaoedema (n=7) volt. Nagy totális reszekció történt 15 esetben, öt esetben szubtotális reszekció. Egyik esetben sem észleltünk mitotikus mintázatot, vascularis endothelialis proliferációt vagy nekrózist. A sejtproliferációs marker MIB-1 aktivitása (a pozitívan festődő tumorsejtek százalékos aránya) 0–1,4% között változott (átlag 0,3). Két beteg részesült preoperatív sugárkezelésben (50 Gy) a CT-korszak előtt, három másik beteg posztoperatív sugárkezelést kapott a szövettanilag eredetileg differenciált ependymomának diagnosztizált tumorra. Három beteg (15%) műtéti szövődmény miatt meghalt a műtét után 1–3 hónappal, három beteget független ok miatt veszítettünk el a 8., 26. és 110. hónapban. Összesen 15 beteg volt életben a tízéves követés végére a tumorrecidíva jele nélkül.
Következtetés – A subependymomák differenciált laesiók, a betegek jó állapotban maradnak adjuváns sugárkezelés nélkül is. Sejtdús területből vett kis mintákból tévesen differenciált ependymomát diagnosztizálhatnak, amit szükségtelen sugárkezelés követhet. A recidívák, a gyors ütemű növekedés szövettani felülvizsgálatot tesz szükségessé, mivel az ependymomák sejtszegény területei is zavart okozhatnak.

Kulcsszavak: *subependymoma, műtét, sugárkezelés, prognosztikai faktorok*

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Subependymoma was first described as a separate entity by *Sheinker* in 1945[1]. It is a slow growing benign neoplasm with male predominance, typically attached to the wall of lateral or fourth ventricles. Various estimates put the incidence of subependymomas between 0.2% and 0.7% of all brain tumors[2] and approximately 100 cases were reported until 2005[3, 4]. According to the literature, more than half of them are incidentally found at autopsy in the middle-aged or elderly and symptomatic cases requiring surgical intervention account for 37% of all cases[5].

Subependymomas are of benign character with favorable prognosis although the histology sometimes may reveal atypical, large and polymorphous nuclei[6]. The benign nature of this entity is confirmed by low MIB-1 labeling indices[7] and diploid patterns[8].

According to some investigators mitoses and patchy necroses may occur. However, these are rather considered as the mixture of ependymomas and subependymomas[9], blurring of higher grade lesions to the scope of this very distinct low grade entity. In the present paper we review the clinicopathological features of subependymomas at our institute, focusing on the possible effect of adjuvant radiation therapy (RT) in the misdiagnosed cases.

Materials and methods

PATIENT CHARACTERISTICS

Twenty consecutive patients (12 males and eight females) were identified and approved by review board of our institution as subependymoma based on systematic review of histological slides of intraventricular tumors operated on at our center between 1985 and 2005. The median age at operation was 50 years (range 19–77). The majority of the tumors were located in the frontal horns, three in the forth and two in the third ventricles. While typically large tumors were found in the lateral ventricles, mostly small tumors were located to the fourth ventricle, and subependymomas in the third ventricle were rare.

DIAGNOSIS AND TREATMENT

CT was performed in 11, MRI in nine, and carotid angiography in four patients. Extent of surgery was assessed by postoperative CT scans and operational notes, classified as subtotal (< 90% of tumor bulk resected), or gross total resection.

The available original histological slides were reviewed and paraffin blocks were recut for MIB-1 staining (Dako, 1:250). Histological review reclassified two subependymomas to ependymomas, and three ependymomas to subependymomas.

RT was given prior to surgery and definitive histological diagnosis in two cases, and three patients received RT within six weeks after surgery (these were the cases that were initially classified as ependymomas, and reclassified after our histopathological review as subependymomas). The median dose of radiation was 54 Gy (range 50-60) administered over 5-6 weeks using conventional fractionation (2 Gy/day). Irradiation was given via two lateral opposed telecobalt or 6-9 MV photon beam with a margin of 2-3 cm.

FOLLOW-UP AND DATA ANALYSIS

Patients were checked annually, more frequently if clinically indicated. Survival was calculated from the date of surgery to the time of death, or to the time of preparation of the manuscript. The median follow-up time of the 15 long surviving patients from tissue diagnosis to the last known status was 10 years (range 6-24). The clinical, radiological, histological, and treatment parameters and follow-up information were analyzed, supplemented by medical record review and contacting the patients, if needed.

Results

STATISTICAL DATA

Gross total surgical removal was achieved in 15 and subtotal in five patients. Some degree of contrast enhancement on the post-operative CT scan was observed in eight cases.

There were three (15%) postoperative deaths. Two patients died of concomitant diseases (leukaemia and liver cancer) in 26 and eight months, and one patient died of cardiac failure at 110 months, all others were disease free at the time of preparation of manuscript **(Figure 1.)**.

CLINICAL DATA

The subjective complaints and clinical symptoms in all patients were very similar to that of ependymomas. Duration of complaints took generally less than 12 months, but one patient had epileptic seizures for 15 years. Headaches, nausea and vomiting only occurred during the last 3-4 months. Signs of increased intracranial pressure as head-

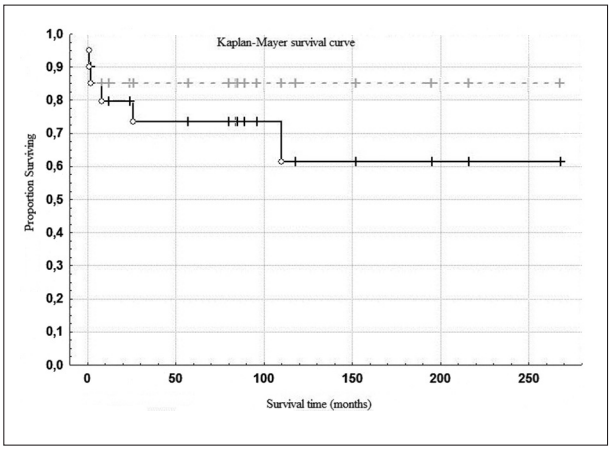

Figure 1. *Kaplan-Meier survival curve of our series*

Table 1. *Clinical features of subependymomas*

No.	Sex	Age (years)	Duration of symptoms (months)	CT	Location	Extent of surgery	RT/Gy	Survival (months)	Complication
1.	M	53	42	HO	l.frontal	total	50	1*	surgical complication
2.	M	36	36	HO-e	bifrontal	subtotal	50	2*	surgical complication
3.	M	41	1	HD-e	r.frontal	total	50	268	
4.	F	19	1	HO-e	r.frontal	total	50	216	
5.	M	35	8	HD-e	r.frontal	subtotal	54	152	reoperated
6.	M	35	5	HD	l.frontal	total		195	
7.	M	41	1	HO	l.frontal	total		110*	unrelated cardiac disease
8.	F	39	15	HO	l.frontal	total		118	
9.	M	51	2	HD-e	r.frontal	total		96	
10.	F	62	12	HO	IV.ventricle	subtotal		8*	liver cancer
11.	M	57	2	HO	l.frontal	total		80	
12.	F	65	6	HO	l.frontal	total		89	
13	M	55	24	HO	bifrontal	subtotal		57	
14	F	77	2	HD-e	l. frontal	total		85	
15	F	62	2	HD-e	l.frontal	total		26*	leukemia
16	F	34	72	HO	III.ventricle	total		84	
17	M	60	12	HO-e	IV.ventricle	subtotal		2	reoperated
18	M	69	12	HO	IV.ventricle	total		24	
19	M	50	4	HO	III.ventric.	total		1*	surgical complication
20	F	50	1	HO	r.frontal	total		12	

HO - hypodense, HD - hyperdense, e - contrast enchancement, CT - computer tomography, RT/Gy: radiotherapy in Gray, * - expired

aches, mental impairment and drowsiness were frequent. The clinical features are summarized in **Table 1**.

All tumors were verified by contrast enhanced CT and/or MRI investigations. In 13 cases lesion was hypodense/hypointense and in seven cases hyperdense/hyperintense, and contrast enhancement occurred in eight cases. Cystic degeneration was seen in three, and calcification was observed in one case **(Figure 2.)**. Carotid and vertebral angiography were performed in four patients and showed slightly vascular mass. However, it was insufficient for proper differential diagnosis.

Most tumors were found in the frontal horns, three of them partly extended into the third ventricle and one up to the trigonal region with small satellites on the ventricle wall. Concomitant hydrocephalus was characteristic in all but one cases due to obstruction of the CSF pathway.

Surgical removal of the supratentorial tumors was performed mostly through transcortical-transsulcal, and only once through parasagittal transcallosal approach. The third ventricle tumor removal was performed through supracerebellar approach. The tumors localized in the fourth ventricle was operated using suboccipital approach. Tumors appeared as gray-white, smooth surfaced, hard, rubbery hypovascular masses, although two tumors were moderately vascular.

Five patients received conventional radiotherapy. Two of them were investigated at our institute before the CT era. Both tumors were diagnosed by pneumoencephalography and angiography as bifrontal tumors involving the corpus callosum and were considered inoperable. RT had been applied to both patients, but proved to be ineffective. They were reinvestigated two and three years later due to disease progression and proper diagnosis was made

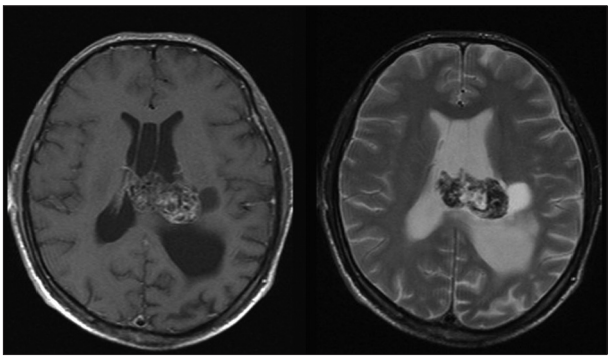

Figure 2. *Subependymoma on T1-wighted MR image (left-sided photo): isointense tumor with mild contrast enhancement showing cystic degeneration. On T2-weighted MR image (right-sided photo): heterogenity due to blood products, calcification and cystic changes with hyperintense tumor mass*

by CT and these intraventricular, relatively circumscribed masses were operated on. Both tumors were large (6×6 and 4×5 cm), occupying the frontal horn. One of them extended into the trigonal region, infiltrating the white mater, and was accompanied by small satellite lesions on the ipsilateral lateral ventricle wall. Both of these patients died of surgical complications at one and two months following surgery.

HISTOLOGICAL DATA

Microscopic examination showed predominantly low cellularity with alternating clustering of cells with acellullar, fibrillar matrix with microcysts. Tumor nuclei were small, round to ovoid, with indistinct cytoplasmic borders. Rosenthal fibers and eosinophil granular inclusions were noted in 4/20 cases **(Figure 3.)**.

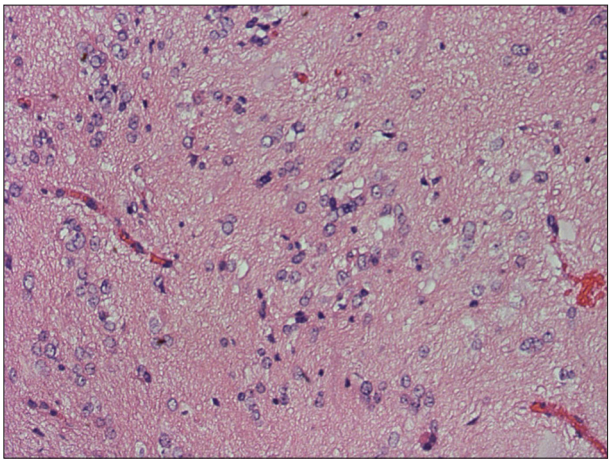

Figure 3. *Rosenthal fibers noted in one of our cases. H&E staining, magnification 1:200*

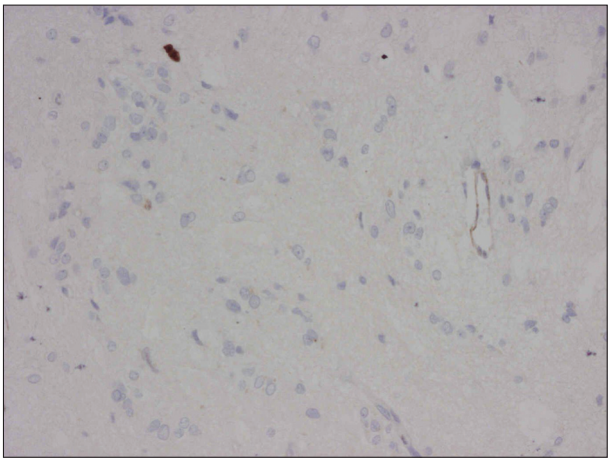

Figure 4. *In the entire section only one core was positive. Ki-67/MIB-1 activity below 1%, strongly suggesting low proliferating activity and benign nature of the lesion. MIB-1 stain, magnification 1:250*

Focal areas of higher cellularity showing mild nuclear pleimorphism were noted in 3/20 cases. Neither mitotic activity nor necrosis were observed in any of the cases, and MIB-1 activity was generally below 1% **(Figure 4.)**, reaching 3% only in the cellular areas of the above mentioned three cases. Dilated, thin-walled, cavernous vascular channels, reminiscent of vascular malformations were embedded within the tumor tissue in two of the cases.

Discussion

The intraventricular localization of subependymomas renders radiographic diagnosis relatively easy[10]. CT typically demonstrates a solid, hypodense lesion and the rare contrast enhancement is focal or irregular at best. However, marked, inhomogenous enhancement have been found in some posterior fossa tumors[11]. MRI characteristics are similar, nearly always hypo- or isointense lesions on Tl-weighted, and occasionally hyperintense on T2-weighted images. Contrast enhancement is rare. Cystic forms, some degree of calcification occur sporadically in individual cases **(Figure 2.)**. The tumors are usually lobulated and sharply demarcated from the surroundings[2, 6, 12]. Tumor specific preoperative diagnosis is complicated by similar presentation of various intraventricular tumors, e.g. neurocytomas and especially low grade ependymomas[2, 13]. It has been emphasized by some authors[14, 15] that the lack of contrast enhancement could distinguish them from other lateral ventricle tumors. However, low grade ependymomas and neurocytomas do not necessarily enhance, while in our series eight subependymomas showed foci of enhancement.

Similarly, there are no characteristic clinical symptoms: the signs of increased intracranial pressure are dominating in most cases including papilledema, mental disturbances and eventually 6th nerve palsy. Focal neurological signs are rare as well as preoperative epileptic fits in the history of these tumors[12]. Subarachnoid hemorrhage may also be the first clinical sign in exceptional cases[16–18].

Subependymomas are more often found between the fourth and sixth decades of life[7] but it has been observed at any age group. Interestingly, half of the symptomatic subependymomas was younger than 40 years of age in our material. There is slight male preponderance, the male to female ratio being nine to seven, which is similar to our material (12 to eight). Perioperative mortality is infrequent. It mostly occurred among earlier cases, before CT and microsurgical methods were introduced[1, 19]. However, it has also been reported in recent studies as well[2, 20], mostly due to meningitis or sepsis. Recurrence of the tumor is extremely rare. Although in one of our patients a recurrence was initially considered, based on the review of the operative notes and original films, the case is best viewed as a large residuum requiring second operation.

The benign nature of this entity was confirmed by the low MIB-1 labeling indices[5, 7] and by diploid patterns[8]. Satellite lesions on the ventricular wall, so called candle guttering, should not be confused with true metastatic foci. According to some investigators, mitoses, patchy necroses may occur. However, based on our experience, these are better

viewed as mixed ependymomas-subependymomas rather than allowing the blurring of higher grade lesions to the scope of this very distinct low grade entity.

The radiosensitivity of the tumor was mentioned in some papers[6, 8]. *Im* et al.[4] reported two patients receiving radiosurgery, but in both cases tumors recurred in short time. In our series of the five irradiated patients two were incorrectly diagnosed clinically without histology, while three further cases were considered low grade ependymomas originally. Radiation therapy was without benefit in the latter group.

Conclusion

Subependymomas are low-grade lesions and patients do well without adjuvant therapy.

Subependymomas are easily diagnosed with either CT or MRI scans.

Radical surgical excision is the treatment of choice when possible, as adjuvant therapy has little or no effect on lesion control.

Recurrences or rapid growth rates should warrant histological review, as hypocellular areas of ependymomas may be the source of diagnostic confusion.

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