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CASE REPORT

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Gliosarcoma developing from an irradiated ependymoma

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Abstract A 17-year-old girl was operated for a cystic mass located deep within the left parieto-occipital white matter. Histologically the tumor was an ependymoma with a vascular stroma. In spite of irradiation the tumor recurred locally twice, 1 and 2 years respectively after the original operation. The ependymoma portion of the tumor remained unchanged, but the stroma showed increased vascular hyperplasia at the time of the second operation and transformation into a fibrosarcoma in the third operative specimen. Proliferating cell markers (MIB-1) were positive only in the ependymoma cell nuclei in the first two specimens, but were also extensively present in the nuclei of the fibrosarcoma cells in the third specimen. In the latter, the fibrosarcoma portion greatly overwhelmed the residual ependymoma islands, but remained sharply delineated from them. This is the first observed case of a gliosarcoma originating from an ependymoma. The histological pattern of this mixed tumor clearly indicates that the source of the sarcomatous portions was the neoplastically transformed fibrovascular stroma of the original tumor, rather than "desmoplastic" alterations of the neoplastic ependymal cells themselves.

Key words Ependymoma · Vascular stroma · Gliosarcoma

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Introduction

Gliosarcomas are malignant neoplasms of the central nervous system that contain a gliomatous as well as a sarcomatous component [4]. The latter is usually a fibrosarcoma, but there may be prominent neoplastic smooth muscle elements [10], occasionally endothelial cells [21], rarely bone and cartilage [11], and the sarcoma may also closely resemble a malignant fibrous histiocytoma [17]. Gliosarcomas were first reported by Stroebe [22] in 1895, followed by a report by Bailey and Ley [2], pertinent observations by Rubinstein [20] and the extensive studies by Feigin and associates [7, 9]. For a detailed review of historical data on the subject, see the article by Cerda-Nicolas and Kepes [5]. In the great majority of reported cases the glioma portions of these mixed tumors are malignant astrocytomas (glioblastomas), but in some cases the glioma component may be an oligodendroglioma [8, 18] and one case is on record where the sarcoma developed in conjunction with a subependymoma [15, 16]. The present case appears to be the first observed instance of gliosarcoma developing from an ependymoma. The change from "regular" to focally hypercellular and hyperplastic vascular stroma, to full-blown fibrosarcoma could be followed in three subsequent operative specimens. The ependymoma remained sharply demarcated and distinct from the sarcoma and did not undergo any "desmoplastic" alterations of its own.

Case report

A 17-year-old girl presented to the Department of Neurosurgery of the University of South Alabama Medical Center with symptoms and signs of increased intracranial pressure and focal signs pointing to a lesion in the left parieto-occipital area. CT and MRI showed the presence of a partly solid, partly cystic mass within the deep parieto-occipital white matter on the left side. The original radiological impression was a cystic astrocytoma. The patient underwent a gross total resection of the tumor followed by 5,400 cGy in the form of external irradiation. However, the tumor recurred 16 months later, necessitating a second resection and additional irra-

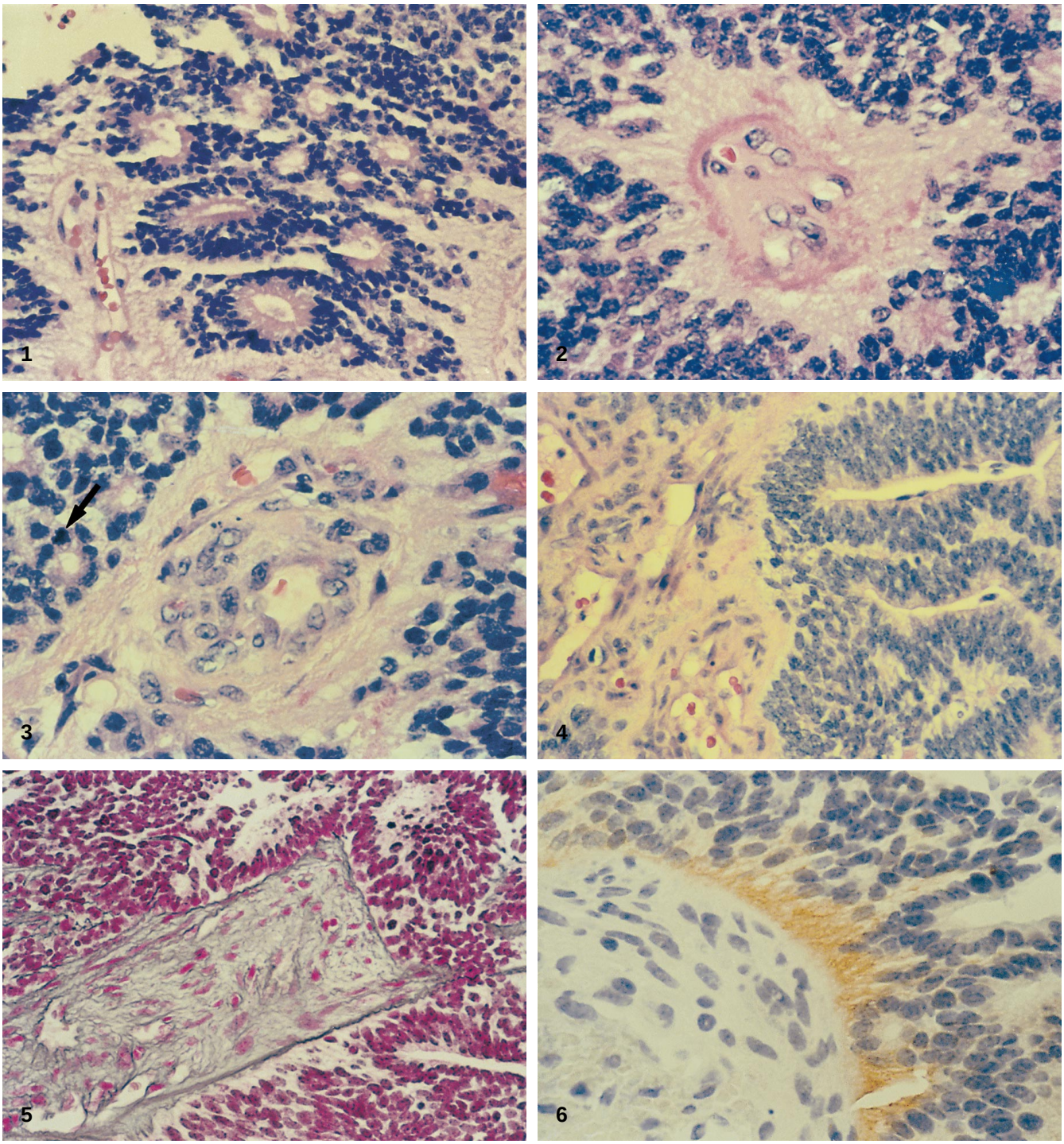


Fig. 1 A cluster of ependymomatous canaliculi in a sample from the first operative specimen. Parts of perivascular rosettes are seen in left and right lower corners. H&E, × 200

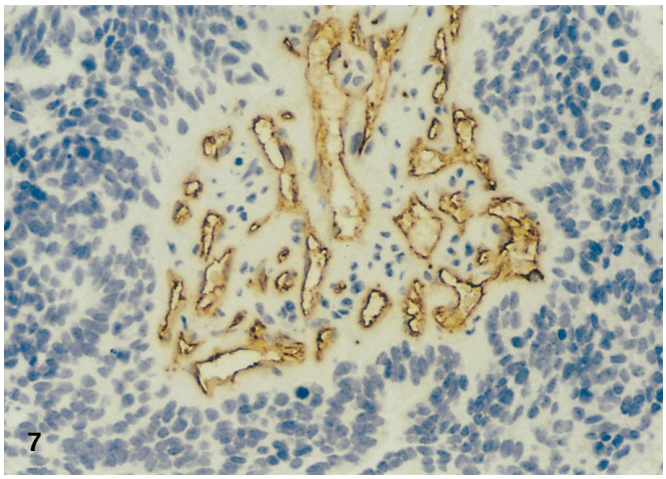
Fig. 2 Perivascular rosette centered on a small group of capillaries. First operative specimen, H&E, × 400

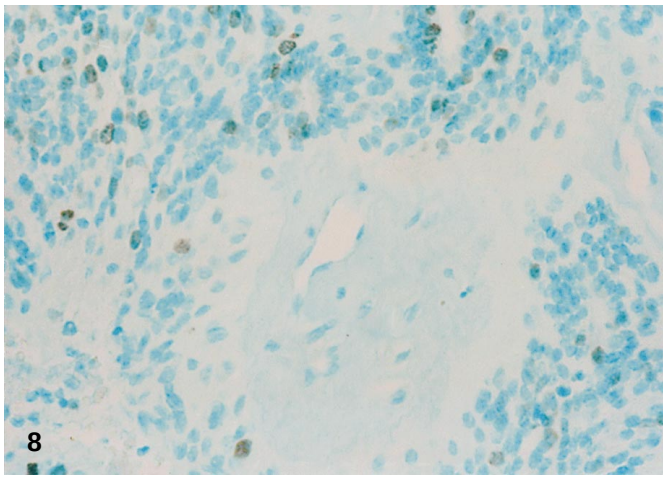
Fig. 3 Slight hyperplasia of adventitial cells surrounding a small vessel in the stroma of the ependymoma. The tumor cells form small canaliculi. *Arrow* points at mitotic figure. First operative specimen, H&E, × 400

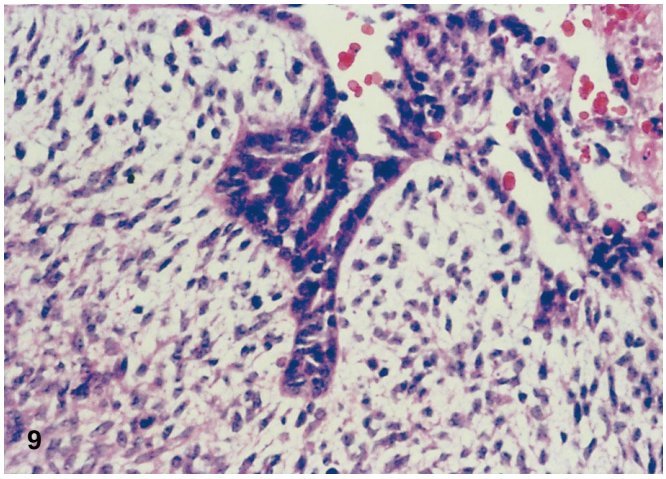
Fig. 4 Typical ependymoma on the right; stroma on the left shows more blood vessels and increased numbers of adventitial fibroblasts compared to first excision. Second operative specimen (first recurrence), H&E, × 220

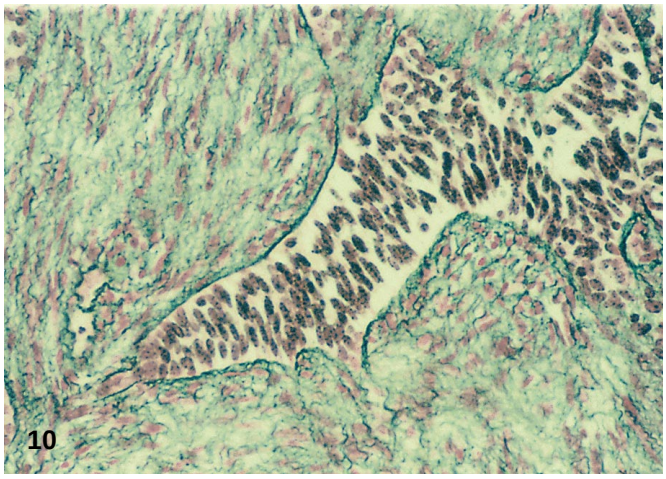
Fig. 5 The area representing stroma in the center is rich in reticulin fibers; the ependymomatous area surrounding it has no reticulin fibers except as capillary basement membranes. Second operative specimen, Wilder's reticulin stain, × 200

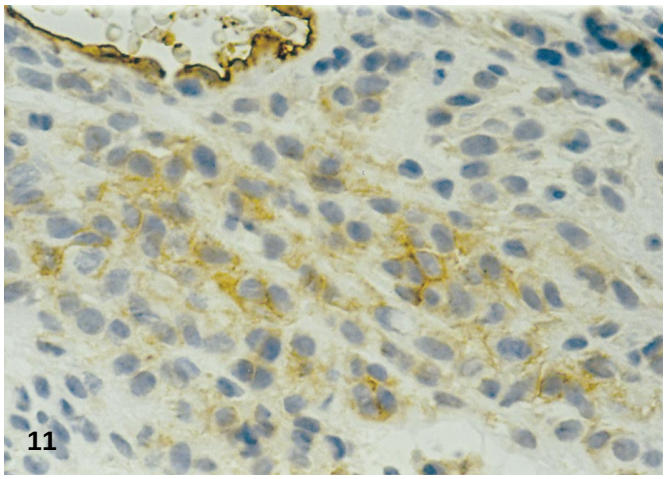
Fig. 6 At the interface between tumor and stroma, cytoplasmic processes of tumor cells extending perpendicularly towards stroma in center are highlighted by positive immunostaining for glial fibrillary acidic protein (GFAP). Second operative specimen, immunoperoxidase stain for GFAP, × 380











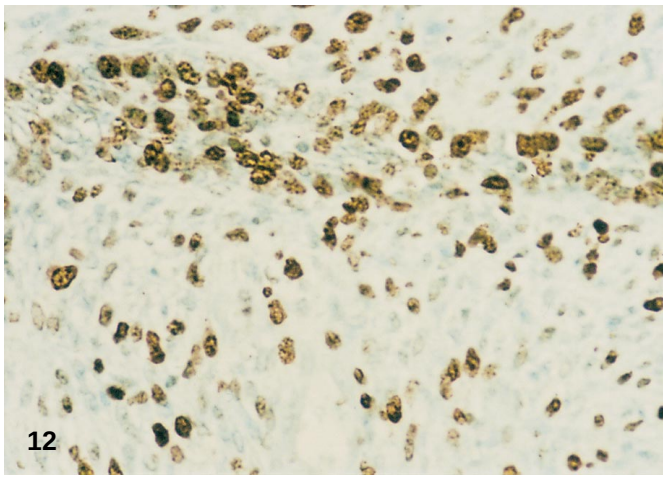


Fig. 7 Increased numbers of stromal vessels in center of figure. Their endothelial lining stains positively for CD-34 endothelial cell marker. Second operative specimen, immunoperoxidase stain for CD-34, × 180

Fig. 8 Nuclei of numerous neoplastic ependymal cells stain positively for MIB-1 proliferating cell marker. None of the nuclei of cells that form part of the stroma stain positively. Second operative specimen, MIB-1 stain, × 200

Fig. 9 In this figure the stroma has become transformed into highly cellular fibrosarcoma with small dark anaplastic nuclei. This second tumor is compressing and indenting the ependymomatous tissue, but remains sharply demarcated from it. Third tumor excision, H&E, × 200

Fig. 10 Reticulin stain shows a rich reticulin network in the fibrosarcomatous area but no reticulin produced by the ependymoma cells. Third tumor excision, Wilder's reticulin stain, × 200

Fig. 11 In contrast to the stroma of previously excised tumor, the fibrosarcoma that developed from the stroma has relatively few blood vessels, but in some areas sarcoma cells of solid clusters stain positively for the CD-34 endothelial marker. Third tumor excision, × 280

Fig. 12 MIB-1 stain for proliferation markers in nuclei is positive both in the compressed islands of ependymoma and in cells of the surrounding fibrosarcoma. Third tumor excision, immunostain for MIB-1, × 300

diation, this time as stereotactic radiosurgery delivered by an external beam linear accelerator "LINAC" (1,500 cGy). After 13 more months a second recurrence developed, necessitating still another operation followed by two courses of GMCFS (cyclophosphamide plus granulocyte-monocyte colony stimulating factor) protocol of chemotherapy. Seven months after this third operation the patient died with symptoms of "otitic type" hydrocephalus secondary to thrombosis of the superior sagittal sinus, apparently brought about by tumor invading the sinus. No autopsy was performed.

Materials, methods and microscopic findings

The three operations provided three separate surgical specimens, all of which showed neoplastic tissue involving cerebral white matter. Although not encapsulated, the first tumor specimen was rather sharply delineated from the surrounding brain tissue, while a less distinct delineation was seen in subsequent specimens.

The first operative specimen showed a classical ependymoma, mostly well differentiated, but displaying atypical nuclei and mitoses in several areas. The tumor contained both ependymal canaliculi (Fig. 1) and perivascular rosettes with delicate cytoplasmic processes of tumor cells extending in a perpendicular fashion towards the walls of blood vessels (Fig. 2). As to the latter, in most areas they had a bland and hypocellular appearance, but in a few areas slight proliferation of adventitial fibroblasts could be observed (Fig. 3). In the second operative specimen (the first recurrence), the character of the ependymomatous areas had not changed, but the stroma showed more marked vascular and adventitial fibroblastic proliferation (Fig. 4). As in the first specimen, reticulin stain showed a fairly dense network of reticulin fibrils in the stroma, but none in the ependymoma portions (Fig. 5).

Immunoperoxidase stain for glial fibrillary acidic protein (GFAP) nicely outlined the cellular processes of the ependymoma cells abutting on the stroma, which was entirely negative for GFAP (Fig. 6). At this time a fairly significant component of proliferating stromal areas was still represented by multiple branching capillaries whose endothelial lining could be well highlighted by CD-34 (Q-Bend-10) immunoperoxidase stain for endothelial cells (Fig. 7). As in the first surgical specimen, the ependymoma portions of the tumor were fairly cellular, included some atypical nuclei and showed occasional mitotic figures. On this second operative specimen we performed immunostaining for MIB-1 (paraffin section eqivalent of Ki-67 proliferating cell nucleus marker used on frozen sections). Approximately 7% of ependymoma cell nuclei stained positive with this method, but none of the stromal elements, whether endothelial or adventitial, did so (Fig. 8).

The operative specimen from the second recurrence (third excision) showed striking departures from the pattern observed in the first two specimens. The ependymoma portions of the lesion were still present, but the stromal elements were now predominant. They have virtually overrun the ependymomatous areas and compressed the remaining islands of ependymoma, sometimes causing external indentations on them somewhat reminiscent of stromal impression on mammary ducts in cases of "intracanalicular" fibroadenomas. Nevertheless, these ependymomatous areas still remained sharply separated from the stromal elements (Fig. 9). Reticulin fibrils were still restricted to the stromal component; none were seen in the residual ependymomatous areas (Fig. 10). The "stroma" was now sufficiently exuberant and cellular with a great deal of nuclear variation and anaplasia as well as mitotic acitivity, to be considered sarcomatous. The principal element in this sarcoma appeared to be anaplastic fibroblasts. None of the stromal cells expressed GFAP and immunostains for smooth muscle cells (HHF-35 and smooth muscle specific actin) were also negative. Endothelial-lined vascular channels as outlined by CD-34 immunostain were now sparse, but a number of individual cells in the sarcomatous cell mass, apart from still recognizable vascular channels, showed cytoplasmic staining for CD-34, this being compatible with endothelial derivation of such cells (Fig. 11). The fibrosarcoma-like elements that were negative for CD-34 stain could well have originated form adventitial fibroblasts. Finally, MIB-1 immunostain for proliferating cell nuclei, formerly positive only in the ependymoma cells, showed positively staining nuclei in both the residual ependymoma (about 50%) and in the fibrosarcoma (about 30%) (Fig. 12).

Discussion

This case illustrates that sarcomas may develop from the hyperplastic vascular stroma of an ependymoma. This has not been reported before. Our case has certain similarities with the reports of Louis et al. [15, 16] on a subependymoma whose vascular stroma also underwent malignant (sarcomatous) changes. Since the original tumor in their case was an essentially benign neoplasm, it was not too surprising that the sarcoma portion (in their case consistent with a malignant fibrous histiocytoma) eventually overtook the subependymoma, and the latter was no longer identifiable in the final recurrence of the tumor. In our case the last excisional specimen did show that the sarcoma became predominant over the ependymoma, but did not replace it entirely.

Our case helps to clarify further the difference between a gliosarcoma that has two distinct (gliomatous and sarcomatous) components and a malignant glioma which focally has undergone "desmoplastic" metaplasia, i.e. the neoplastic glial cells assume spindly outlines and lay down pericellular reticulin and even collagen fibers as seen in desmoplastic astrocytomas of infancy [6, 23] and various forms of gliofibromas, some of which may be malignant [14]. Based on such malignant gliofibromas or desmoplastic glioblastomas, some authors went as far as to suggest that gliosarcomas of a truly double (gliomatous and sarcomatous) cell population may not exist [3, 12]. In some cases of desmoplastic glioblastomas, particularly in the spindle-cell variant, such distinction may indeed be difficult to make. In our case the marked delineation of the ependymoma component from the first hyperplastic but eventually clearly sarcomatous stroma was maintained and the ependymoma did not share in any of its territories the desmoplastic (reticulin-forming) capacities and activities of the fibrosarcomatous stroma. It has been proposed that the fact that in gliosarcomas both the gliomatous and sarcomatous component has in its population cells that express p53 protein indicates that both the gliomatous and sarcomatous cells share a common progenitor [1]. Since, however, p53 protein may be found in any malignant neoplasm regardless of its histogenesis, unless additional and more specific similarities can be detected between the glial and sarcomatous elements of a gliosarcoma, a common progenitor cannot be assumed. In their elaborate and elegant study Paulus et al. [19], analyzing interphase cytogenetics of gliosarcomas, found that sarcoma and glioma elements in some cases did, and in others did not, share numerical chromosomal aberrations. This suggests varying histogenetic pathways in the development of the sarcoma-like portion of these tumors. In our case the persistent sharp delineation of mesenchymal and ependymomatous elements with the total lack of any "desmoplastic" tendencies of the latter in the original tu-

mor or in its recurrences allow us to conclude, using more traditional histological and immunohistological approaches, that our case represents a true gliosarcoma of the "Feigin type," the first time such has been observed originating from an ependymoma. Expression of the endothelial marker CD-34 in the cytoplasm of tumor cells that were part of solid portions of the fibrosarcoma appears to establish a direct link to vascular endothelium of the tumor stroma, as has also been reported by Slowik et al. [21] using antibody against UEA I lectin.

Our patient received external radiation treatment after both the first and second operation. It is well known that irradiation of the central nervous system may cause the eventual development of various types of malignant cerebral and meningeal tumors, predominantly sarcomas, a subject recently reviewed by Kaschten et al. [13]. Whether radiation was a causative factor in this patient developing a fibrosarcoma from previously non-malignant stroma of her ependymoma can neither be established nor ruled out with certainty. The 29 months that passed between the first time patient received postoperative irradiation and the appearance of a sarcoma in the second postoperative specimen provide sufficient time to allow one to postulate a certain role for irradiation in the stromal changes towards malignancy. In some published cases (e.g. the one by Louis et al. [15] of a subependymoma) sarcoma was not present in the original operative specimen but only in the recurrence, after the patient received irradiation. There are other examples of this nature in the literature. At the same time, gliosarcomas have been encountered in patients who have not undergone prior irradiation. In those instances a change from hyperplasia of the stroma to real sarcoma has to be postulated without the contributing role of irradiation. How significant a role irradiation had in the development of a sarcoma in our present case must remain speculative.

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