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CASE REPORT

Anaplastic ependymoma simulating glioblastoma in the cerebrum of an adult

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Abstract A case of anaplastic ependymoma of the cerebral hemisphere in which the histopathological features closely simulated those of glioblastoma is reported. The patient was a 72-year-old woman with a large, well-demarcated tumor in the left temporal lobe. The tumor was totally extirpated, but recurred 18 months later, and the patient died after 4 months. The extirpated tumor was well circumscribed from the surrounding brain tissue and consisted of a sheet-like, dense proliferation of atypical, short spindle or polygonal cells. Extensive geographic necrosis with nuclear pseudopalisading was seen. Although perivascular pseudorosettes were observed in many areas, true ependymal rosettes were absent. Immunohistochemistry for glial fibrillary acidic protein and epithelial membrane antigen and ultrastructural study confirmed the ependymal nature of tumor cells. The histopathological spectrum of anaplastic ependymoma is very wide and reflects the basically dual characteristics of ependymal cells: epithelial and glial phenotypes. The present case indicates that some anaplastic ependymomas strongly express the glial phenotype and also show remarkable anaplastic cytological features, thus closely simulating glioblastoma. The diagnostic criteria for anaplastic ependymoma, and the nosological position of highly anaplastic ependymoma and its possible clinical implications, are briefly discussed.

Keywords Anaplastic ependymoma · Differential diagnosis · Glioblastoma · Immunohistochemistry · Ultrastructure

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Introduction

Anaplastic ependymoma is a malignant form of ependymoma, and although there was previously some confusion with ependymoblastoma, it has been recognized as a distinct clinicopathological entity in the current World Health Organization (WHO) classification of brain tumors [1]. However, because anaplastic ependymoma is a relatively rare neoplasm and its histopathological spectrum is very wide, the criteria for the pathological distinction of this tumor from ordinary ependymoma on the one hand and from glioblastoma on the other have not yet been established. The histopathological basis for grading the malignancy in ependymal neoplasms is not as well established as that in astrocytic neoplasms.

Considering the relative rarity of this neoplasm and many unsettled issues surrounding the diagnostic criteria, pathogenesis, and treatment, further accumulation of detailed clinico-pathological documentation of individual cases remains necessary. We report here a primary (de novo) anaplastic ependymoma in the cerebral hemisphere of an adult, showing histopathological features closely resembling those of glioblastoma. The clinico-pathological issues described above are briefly discussed.

Clinical history

The patient was a 72-year-old woman who complained of language disturbance. Starting 2 months prior to consulting our hospital, she began to experience difficulty in understanding the names of objects as well as difficulty in finding adequate words while talking. Because these symptoms gradually progressed, she was admitted to our hospital. Mild right hemiparesis and aphasia of mixed type were noted on admission, and magnetic resonance (MR) imaging of the head demonstrated a large mass lesion in the left temporal lobe. The lesion measured about 7 cm in maximal dimension and had spread from the temporal cortex to the white matter (Fig. 1). The mass was a relatively well-demarcated, solid and spherical lesion, and contained a few large cystic areas in the medial region. The solid portion and the rims of the cystic areas were intensely enhanced by the administration of contrast medium. Left parieto-temporal craniotomy was performed under a clinical diagnosis of glioblastoma or anaplastic ependymoma, and a relatively well-demarcated reddish gray tumor containing cystic areas was extirpated totally. The contiguity of the tumor to the lateral ventricular wall was confirmed during surgery. Postoperatively, right hemiparesis disappeared, and aphasia improved remarkably. The patient was treated postoperatively by regional radiation (60 Gy) and chemotherapy (75 mg/m^2 of temozolomide for 7 weeks), but local tumor recurrence spreading to the right cerebral white matter through the corpus callosum was found 18 months later. The recurrent tumor rapidly increased in size, and left hemiplegia and swallowing difficulty appeared and progressed. The patient died 4 months later at the age of 74. Permission for autopsy was not obtained.

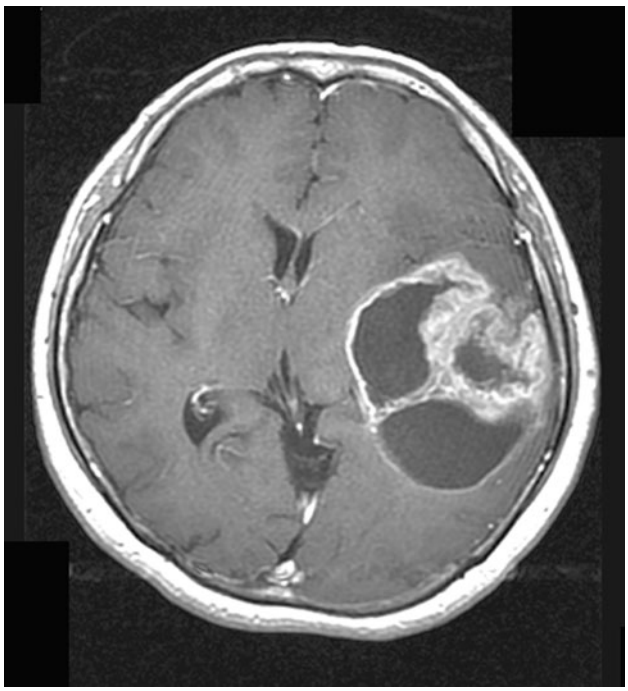

Fig. 1 T1-weighted MR image with contrast enhancement. A large, well-demarcated tumor with cystic changes is seen in the left temporal lobe. The solid portion and the wall of the cysts are intensely enhanced

Pathological findings

The extirpated tumor was sharply demarcated from the surrounding cerebral tissue, and the tendency for invasive growth was scant (Fig. 2). There were no entrapped neurons within the tumor tissue. The tumor was highly cellular and consisted of a sheet-like, dense proliferation of medium-sized, short spindle or polygonal cells. Confluent, large, serpentine areas of coagulation necrosis were seen throughout the tumor, and nuclear pseudopalisading was prominent around the necrotic areas (Fig. 3). In many areas, tumor cells were irregularly stratified around small blood vessels and formed distinct perivascular pseudorosettes (Fig. 4). Tumor cells forming the pseudorosettes extended long and fine cytoplasmic processes toward the central blood vessels, and an "anuclear zone" was formed around the vessels. These pseudorosettes were occasionally dissociated from each other and formed a growth pattern resembling a papillary architecture. True ependymal rosettes or ependymal canals were not detected.

Individual tumor cells had round or elliptical nuclei with a moderate amount of chromatin. Nuclear atypism and pleomorphism were marked (Fig. 5), and a few bizarre giant cells were observed. Mitotic figures were very common (about 30 per 10 high-power fields). The cytoplasm was palely or densely eosinophilic and relatively abundant. It was spindle-shaped or polygonal, and exhibited a

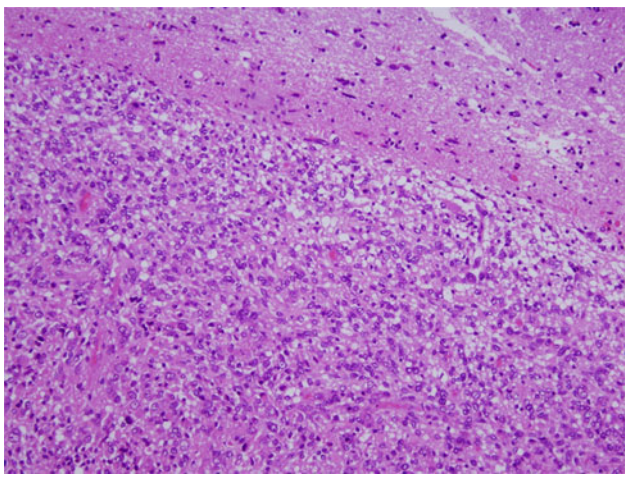

Fig. 2 The boundary between the tumor and the surrounding brain tissue is clearly demarcated (H&E stain ×25)

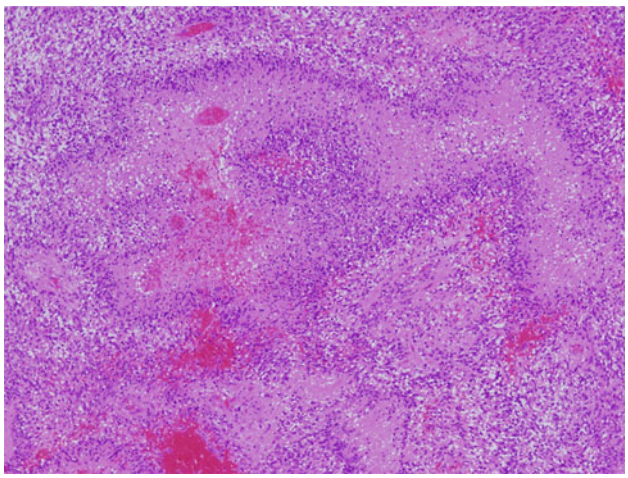

Fig. 3 Confluent, serpentine zones of coagulation necrosis with nuclear pseudopalisading are seen throughout the tumor (H&E stain ×10)

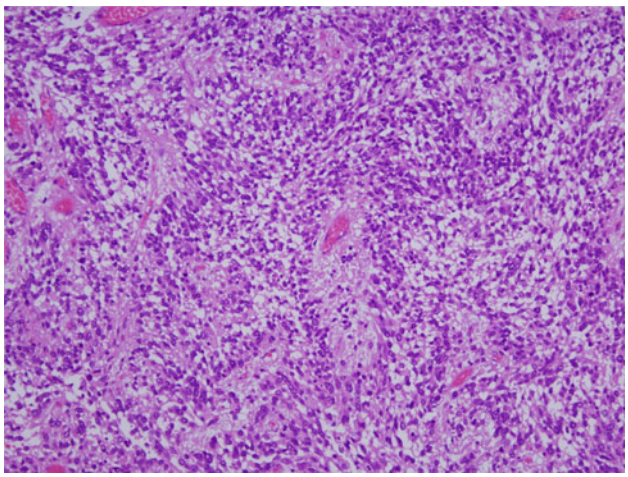

Fig. 4 Distinct perivascular pseudorosettes with the formation of an "anuclear zone" are found in some regions of the tumor. Tumor cells have hyperchromatic, elliptical nuclei (H&E stain ×25)

fibrillary or ground-glass appearance. Some tumor cells had small, short spindle-shaped hyperchromatic nuclei, and the perinuclear cytoplasm was hardly discernible. Although proliferation of small to medium-sized blood vessels was prominent throughout the tumor, there was no apparent formation of "glomeruloid structures."

Immunohistochemical studies were performed using Envision Plus detection system (Dako, Glostrup, Denmark) and employing primary antibodies against the following substances: glial fibrillary acidic protein (GFAP) (polyclonal, Dako, 1:100), epithelial membrane antigen (EMA) (clone E29, Dako, 1:100), p53 protein (clone DO-7, Dako, 1:100), epidermal growth factor receptor (EGFR) (clone 2-18C9, Dako, prediluted) and Ki67 protein (clone MIB-1, Dako, 1:100). Most tumor cells were immunoreactive for

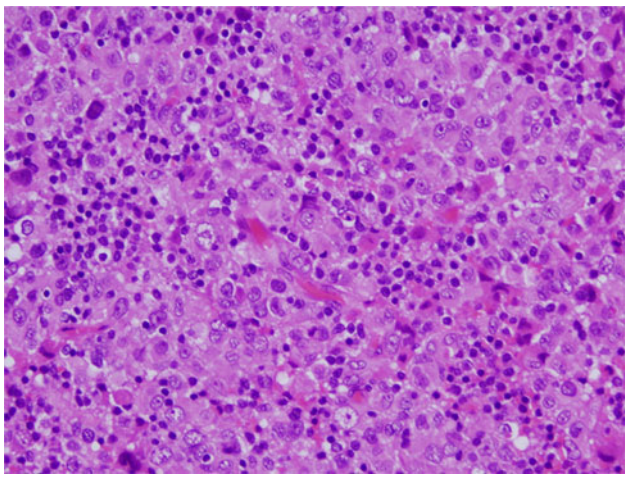

Fig. 5 In some areas, pleomorphic, polygonal tumor cells show a sheet-like proliferation. There is an abundance of lymphocytes between tumor cells in this field (H&E stain ×50)

GFAP (Fig. 6a), and the cytoplasmic processes forming pseudorosettes were clearly immunostained. A small number of tumor cells contained tiny ring- or dot-like structures immunoreactive for EMA within the cytoplasm (Fig. 6b). Nuclear immunoreactivity for p53 protein was observed in about 5% of tumor cells, and only a very small number of tumor cells showed a faint cytoplasmic immunoreactivity for EGFR. Ki67-labeling index was 25.9%.

On ultrastructural examination, tumor cells had irregularly indented, elliptical nuclei with sparse heterochromatin and prominent nucleoli, and relatively abundant cytoplasm filled with well-developed intracytoplasmic organelles. Some tumor cells contained conglomerates or dense bundles of intermediate filaments in the perinuclear region or within the long cytoplasmic processes, respectively (Fig. 7). The intercellular junctional apparatus was poorly developed, and there were no long "zipper-like" junctions. In a few cells, small intracytoplasmic microlumina surrounded by the membrane equipped with poorly developed microvilli were observed (Fig. 8). Distinct basal lamina with formation of hemidesmosomes was found on the surface of tumor cells adjacent to the capillaries.

Discussion

An ependymal cell is a cell that has basically dual morphological and functional characteristics as an epithelial cell covering the surface of the ventricular system and as a glial cell that shows alterations closely resembling those of astrocytes under various pathological conditions [2]. These dual characteristics are also expressed to varying degrees in ependymal neoplasms [3]. Anaplastic ependymoma is a malignant form of ependymoma chiefly arising in the

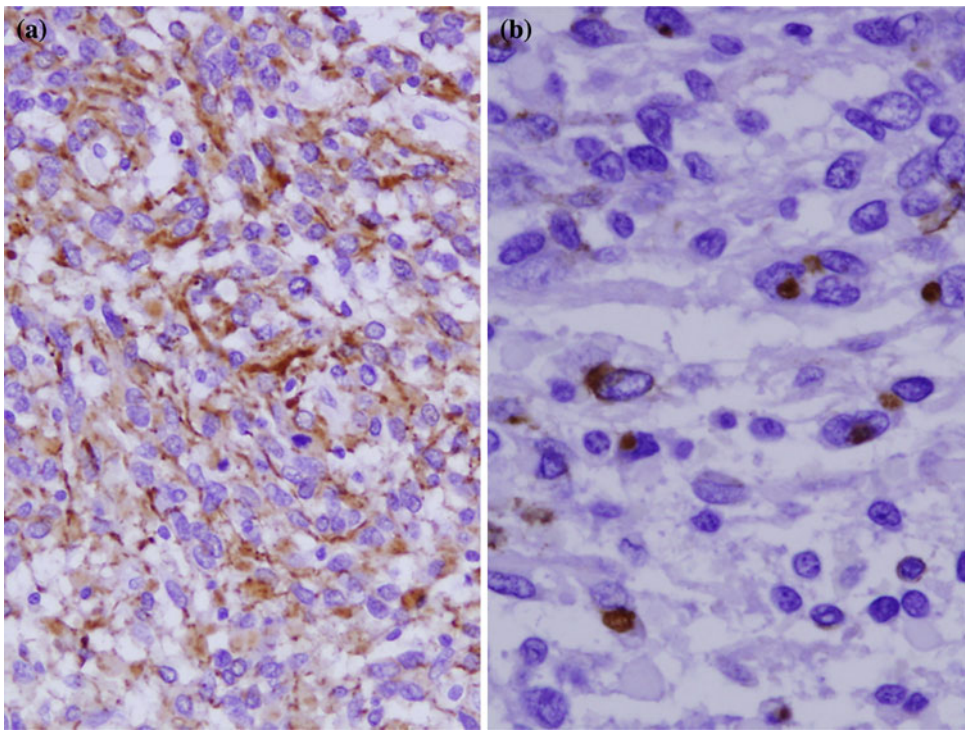

Fig. 6 **a** Tumor cells show fibrillary immunoreactivity of the cytoplasm for GFAP. **b** Dot- or ring-like immunoreactivity for EMA is found in a small number of tumor cells (immunostaining, **a** ×50, **b** ×100)

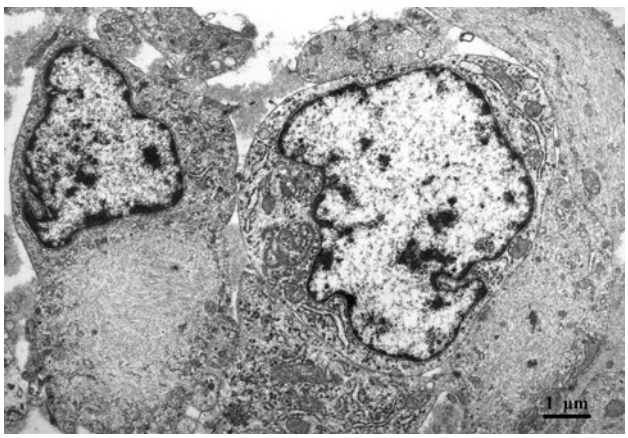

Fig. 7 Tumor cells have irregular nuclei and abundant cytoplasm filled with well-developed organelles and aggregates of densely packed intermediate filaments. Intercellular junctional devices are poorly developed (×11,800)

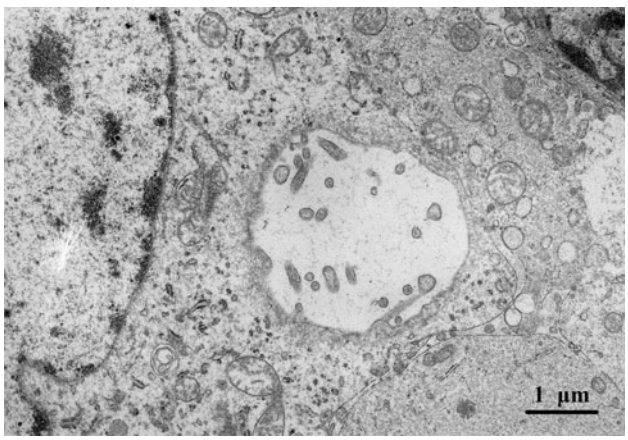

Fig. 8 In the cytoplasm of a few tumor cells, a microlumen containing a small number of microvilli is found (×19,200)

supratentorial region, and the hemispheric intraparenchymal ependymomas especially show a greater frequency of histopathological anaplasia than those in the posterior fossa [4–7]. Pathologically, the dual characteristics of ependymal cells are retained in anaplastic ependymoma. A case of anaplastic ependymoma that strongly expressed the epithelial phenotype was reported by Moritani et al. [8]. In that case, the tumor was composed of large, polygonal, atypical cells forming a papillary architecture and closely resembled metastatic papillary adenocarcinoma. In our case, the glial phenotype of tumor cells was strongly expressed, and the histopathological appearance closely resembled that of glioblastoma. Several cases of anaplastic ependymoma showing a close histopathological resemblance to glioblastoma or medulloblastoma have been described [4, 9, 10], and all of these cases, including those of Moritani et al. [8] and our own, demonstrate that the histopathological spectrum of anaplastic ependymoma is very wide.

The diagnostic criteria of anaplastic ependymoma have not been well established, and the prognostically predictive value of each histopathological finding for ependymal neoplasm remains unclear. Some investigators claimed that there is no significant relationship between the

histopathological features and patient outcomes [11, 12], but other investigators reported a correlation of certain histopathological features, such as high cell density, nuclear atypism, an increased mitotic activity, necrosis and microvascular proliferation, with the rate of recurrence or length of survival of the patients [5, 6, 10, 13–15]. Ho et al. [16] proposed diagnostic criteria for anaplastic ependymoma employing a scoring system, but the validity and efficacy of this scoring system remains to be determined. Many authors regarded increased mitotic activity or high Ki67 labeling index as the most significant correlate with the prognosis of ependymal neoplasms [10, 13–15, 17, 18]. In the current WHO classification, anaplastic ependymoma is defined as ependymal neoplasms "characterized by high mitotic activity, often accompanied by microvascular proliferation and pseudopalisading necrosis," and it is classified as a grade III tumor [1].

A review of the literature suggests that there are two pathogenetic pathways of anaplastic ependymoma, similar to those observed in astrocytic neoplasms, which give rise to primary (de novo) and secondary (progressive) anaplastic ependymoma [1, 6, 19]. The majority appears to belong to the former category, whereas cases of secondary anaplastic ependymoma that evolved from ordinary (benign) ependymoma are recorded infrequently [9, 10]. However, the genetic events that occur in the oncogenetic processes of anaplastic ependymoma are largely unknown [1, 19, 20]. In the present case, the nuclear expression of p53 protein was observed in only about 5% of tumor cells, and the cytoplasmic expression of EGFR was found only faintly in a very small number of tumor cells. Although an increase in p53 nuclear expression by immunohistochemistry has been reported in some cases of anaplastic ependymoma [6, 17], p53 mutations are generally considered uncommon in ependymal neoplasms [1], in contrast to their common occurrence in diffuse astrocytoma [21]. The role of EGFR amplification in tumor progression has not been known in ependymoma [20], but Korshunov et al. [6] reported higher expression of EGFR in anaplastic ependymoma than ordinary ependymoma.

The histopathological appearance of the present tumor initially suggested a diagnosis of glioblastoma because the tumor consisted of a sheet-like, dense proliferation of medium-sized atypical cells showing geographic necrosis with prominent nuclear pseudopalisading throughout the tumor. However, the clear demarcation of the neoplasm from the surrounding brain tissue and the formation of distinct perivascular pseudorosettes in many areas suggested a diagnosis of anaplastic ependymoma. Differentiation of tumor cells along the ependymal lineage was confirmed by immunohistochemical and ultrastructural studies. The absence of cytoplasmic overexpression of EGFR also helped distinguish the present tumor from glioblastoma [21]. The nosological position of neoplasms that show only focal or slight ependymal differentiation on the overall glioblastoma-like background has not yet been determined. Some investigators call ependymal neoplasms showing pseudopalisading necrosis and microvascular proliferation "highly anaplastic ependymoma" [22]. One textbook indicates that these tumors should be practically included within the category of glioblastoma [23]. Although the term "highly anaplastic ependymoma" has been applied to a variety of anaplastic ependymal neoplasms, including those showing predominantly epithelial differentiation and mimicking adenocarcinoma [8], we consider that the "highly anaplastic ependymoma," especially showing marked glial phenotypes, can be dealt with in a similar manner to glioblastoma in the daily pathological practice.

The present case indicates that when we encounter a tumor with prominent pseudopalisading necrosis, a diagnosis of anaplastic ependymoma should be considered in addition to that of glioblastoma, in particular when the boundary between the tumor and surrounding brain tissue is distinct. Anaplastic ependymoma is ascribed to grade III in the current WHO classification [1], suggesting a more favorable clinical outcome than grade IV tumors such as glioblastoma. However, in our case the recurrent tumor invaded the contralateral cerebral white matter, spreading through the corpus callosum, which is a spread pattern typical of glioblastoma [21, 23]. Anaplastic ependymoma that histologically resembles glioblastoma may also behave clinically like glioblastoma. Patients harboring these neoplasms may be better treated using modalities similar to those for patients with glioblastoma.

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