Abstract. Anaplastic ependymomas are rare malignant tumors of the central nervous system. Few studies are available regarding their neuroradiological characteristics. The present study aimed to retrospectively review a series of patients with extraventricular anaplastic ependymoma and to analyze the magnetic resonance imaging (MRI) characteristics to distinguish anaplastic ependymoma from other intracranial tumors. The clinical and pathological images of 11 patients who presented with histologically proven anaplastic ependymoma at Nanfang Hospital (Southern Medical University, Guangzhou, Guangdong, China) between September 2004 and March 2015 were retrospectively reviewed. MRI scans were obtained in all 11 cases. Computed tomography scans were obtained in only 3 cases. In total, 8 tumors were located at the supratentorial parenchyma, and 3 tumors were derived from the cerebellar hemisphere. Images displayed quasi-circular (4/11), irregularly-lobulated (7/11) variable-intensity masses. The masses presented with cysts or necrosis (8/11), hemorrhage (7/11), marked (9/11) or mild (2/11) enhancement, and moderate (4/11), mild (3/11) or absent (4/11) peritumoral edema. The tumors were also frequently closely associated with the lateral ventricle (6/11). Tumors appeared isointense to hypointense on T1-weighted imaging (T1WI) and heterogeneously hyperintense or hypointense on T2WI, demonstrating wreath-like and ring-like characteristics, with intratumoral nodules (3/11) or marked flake-like inhomogeneous (6/11) enhancement on post-contrast MRI. Only 2 solid lesions showed mild enhancement (2/11). Although the MRI features of the extraventricular anaplastic ependymomas varied and were non-specific, these characteristic MRI findings, combined with the locations of the lesions, the age of onset and the short disease course, could be useful in differentiating anaplastic ependymomas from other intracranial neoplasms in the future.

Introduction

Anaplastic ependymoma is a high-grade malignant neoplasm of the central nervous system (CNS), World Health Organization (WHO) grade III (1), which is also known as malignant ependymoma. This tumor was listed as a new type between 1993 and 2007, and was classified as WHO grade III in 2007 (2). Ependymoma arises from differentiated ependymal cells lining the ventricles (1,3), and the proportion of ependymomas among intracranial glial tumors is 3-9% (4-7). The majority of these tumors occur in the ventricle, and while intraparenchymal tumors are rare, intraparenchymal anaplastic ependymomas are even less commonly observed (8).

Anaplastic ependymomas are malignant in terms of their biological behavior, and patients with anaplastic ependymomas are at high risk of metastasis and relapse, which are responsible for the poor prognosis (2,5-7,9). A combination of surgery, radiation therapy and chemotherapy can improve the patient outcome (10). There is a considerable difference in the treatment and prognosis among the different subtypes of ependymoma (5), particularly for anaplastic ependymoma, which requires comprehensive treatment; therefore, a correct diagnosis is extremely important.

These tumors have various imaging features, some of which are specific. Few studies have specifically described the magnetic resonance imaging (MRI) characteristics of these tumors (7,11), and the majority of these studies have been case reports. The purpose of the present study was to retrospectively analyze the characteristics of the tumors in MR images and pathological findings to improve the accuracy rate of diagnosis. To the best of our knowledge, the study is the largest collection thus far of supratentorial extraventricular anaplastic ependymomas with MRI.

Case report

Patients. The clinical and pathological images of 11 patients who presented with histologically proven anaplastic ependymoma at Nanfang Hospital (Southern Medical University, Guangzhou, Guangdong, China) between September 2004 and March 2015 were retrospectively reviewed. The histological features of an anaplastic ependymoma include perivascular pseudorosettes and true rosettes. MRI scans were obtained in all 11 cases. Computed tomography scans were obtained...
in only 3 cases. Tumor recurrence and patient mortality were recorded, among other data.

Clinical characteristics. The majority of intraparenchymal anaplastic ependymomas (6/11) appeared in adult patients between the second and fifth decades of life, while 3 tumors (3/11) occurred during the first decade. The total male-to-female ratio was 4.5:1 (9:2).

The average symptom duration was 4 months, with a range of 1-7 months. The majority of the patients complained of non-specific symptoms, including headaches (n=9), dizziness (n=4) and vomiting (n=6). Other presenting symptoms included limb numbness and weakness with impaired movement (n=4), memory deterioration (n=1), language disorders (n=2), unconsciousness (n=1) and an unsteady gait (n=2). All 11 patients underwent surgical removal of the tumor (total resection), and post-operative radiation therapy (n=6) or chemotherapy (n=4) was performed in certain cases. It was found that the tumors were distributed to the brain parenchyma and the boundaries were not clear in surgery. Following the resection, the post-operative follow-up period ranged from 1 - 48 months (median, 1.5 months; mean, 8 months). Two patients relapsed after follow-up times of 5 months and 4 years (Fig. 1), respectively, and 1 patient succumbed after a follow-up time of only 1 month. Notably, 1 patient was initially diagnosed with focal cortical dysplasia (FCD), and the lesion grew rapidly over 1 month, resulting in the loss of consciousness (Fig. 2).

Imaging findings. Overall, 8 out of 11 lesions were supratentorial (Figs. 1-4), while 3 tumors were infratentorial (Fig. 5). Of the former group, 2 tumors were located in the temporoparietal occipital lobe close to the posterior horn of the lateral ventricle (Fig. 2), 2 were located in the frontal lobe close to the anterior horn of the lateral ventricle and 3 were located in the thalamus (Figs. 3 and 4). The infratentorial tumors were located in the bilateral cerebellar hemispheres or the right cerebellar hemisphere (Fig. 5).

The tumors ranged in size from 3.0-7.3 cm in the longest diameter, with a mean longest diameter of 5.1 cm. The lesions were irregularly lobulated (n=7) (Figs. 1 and 2) or well-demarcated and quasi-circular (n=4) (Figs. 3-5). In total, 4 of the tumors presented as mainly solid masses (Figs. 3-5), 5 tumors presented as solid masses with multiple small cysts (Fig. 2) and 2 lesions were solid-cystic (Fig. 1).

On T1-weighted imaging (T1WI), all 11 of the tumors were iso-hypointense relative to the gray matter, and 7 tumors exhibited additional small (n=3) (Fig. 3A) or medium-sized (n=4) (Fig. 4A) foci of hyperintensity. By contrast, all these lesions presented as heterogeneous (with areas of hypointense and hyperintense signal intensity) or slightly hypointense relative to the gray matter on T2WI. Contrast-enhanced MRI presented areas of marked (n=9) or mild (n=2) enhancement; among the former were wreath-like or ring-like appearances with intratumoral nodule enhancement (n=3) (Figs. 1 and 2) or flake-like heterogeneous enhancement (n=6) (Figs. 3 and 4). Certain patchy areas of hypointensity on T2WI showed no contrast enhancement (Figs. 1, 3 and 4). Cystic or necrotic areas were frequently observed in 8 of the lesions, and multiple cysts of different sizes coexisted, with regions of them merged together; indeed, in 2 lesions, the cystic region occupied more than half of the tumor (Fig. 1). Small point-like enhancements were found in the frontal and occipital lobes of infratentorial lesions. The tumors presented with moderate (n=4) (Figs. 1 and 2), mild (n=3) (Fig. 6) or absent (n=4) (Figs. 3 and 4) peritumoral edema.
On computed tomography (CT) scans, the tumors of 3 of the patients presented as low density or equidensity lesions. In the diffusion-weighted sequences, moderate restriction was observed in 3 patients. MR spectroscopy for 1 patient demonstrated reduced N-acetylaspartate and elevated choline levels. In the susceptibility-weighted angiography (SWAN) sequence of 1 patient, the tumor presented with multiple patchy hypointense areas in the center.

Pathology findings. All of the tumors were surgically resected and displayed a gray-red or gray-white fish flesh-like appearance, mixed with cysts, necrosis, hemorrhage and vascular proliferation. Surgery confirmed that the tumors were derived...
Microscopic examination revealed that the resected tumor cells in all patients were plentiful and distributed diffusely. Perivascular pseudorosettes were frequently observed (Fig. 6A). The space around the vessels without cells was wide. The tumor cells were small, round or fusiform, lacking cytoplasm, and the cell nuclei appeared large and polymorphic (Fig. 6B). Nuclear fission was active. In all 11 cases, immunohistochemical staining demonstrated that the tumors were positive for glial fibrillary acidic protein (GFAP) and p53 protein, negative or positive for vimentin and S-100 protein, and negative or weakly positive for epithelial membrane antigen (EMA).

**Discussion**

Ependymoma is a neoplasm consisting of cellular elements derived from the differentiated ependymal cells lining the ventricles of the brain or the central canal of the spinal cord (3). Intracranial ependymomas mostly occur in the fourth ventricle, while other ependymomas occur in the lateral ventricle, brain parenchyma, spinal cord or cauda equina. The lesions vary in biological behavior (2,12). Of all intracranial ependymomas, ~60% are infratentorial and 40% are supratentorial (13). According to a previous study, supratentorial ependymomas have a higher occurrence rate among high-grade tumors compared with infratentorial tumors, and they principally occur in the brain parenchyma, while infratentorial extra-ventricular lesions are more often located in the cerebellar hemispheres (14). In the present series, 8 supratentorial lesions were derived from the parenchyma, while 1 infratentorial case was rooted in the bilateral cerebellar hemispheres and 2 infratentorial tumors were derived from the right cerebellar hemisphere. Ependymomas are rare neoplasms of the CNS, accounting for 3-9% of intracranial glial neoplasms (4-7), while anaplastic ependymomas are even less commonly observed (8), accounting for ~25% of ependymomas (15). This lesion is the most malignant of all ependymomas (1,5,7) and can also develop from low-grade ependymoma.

Histologically, ependymomas are moderately cellular tumors characterized by perivascular pseudorosettes (2,5). The cellular atypia and karyokinesis, cell proliferation and necrosis of anaplastic tumors are more evident than those of low-grade
ependymomas. A positive Ki-67 labeling index is more common in anaplastic ependymoma than in low-grade ependymoma (15). Shuangshoti et al (3) reported that an increased Ki-67 labeling index was strongly correlated with increased mitotic activity and histological malignancy. Ritter et al (16) found an increased Ki-67 labeling index was linked to a poor prognosis. Immunohistochemical staining has demonstrated that the tumors are positive for GFAP, vimentin and S-100 protein, and negative for EMA (5,15). Shuangshoti et al (3) demonstrated positive rates for GFAP (87%), S-100 protein (77%) and EMA (17%). The present study findings confirmed these observations. All of the anaplastic ependymomas in the present series expressed p53 protein, which is consistent with the results of the study by Shuangshoti et al (3). This study found 91% of anaplastic ependymomas expressed p53 protein. Zamecnik et al (17) found that p53 immunopositivity was one of the strongest indicators of aggressive tumor behavior and a poor prognosis.

Clinically, ependymomas usually occur in individuals within the range of 3-6 years old, with approximately one-third diagnosed prior to 3 years old (18). The second peak age of onset is in the third decade of life (19). Supratentorial ependymomas frequently occur in adults (12,20). In the present series, the majority of the patients presented with tumors during the second to fifth decades, likely indicating that anaplastic ependymoma has an older age of onset than low-grade ependymoma. There is no apparent gender predilection (3), but the present series had a male predominance, with a male-to-female ratio of 4.5:1 (9:2), perhaps due to the small sample size.

In the present study, the clinical manifestations were non-specific and dependent on the lesion location (5). It has reported that the symptoms of anaplastic ependymomas can develop earlier than those of low-grade ependymomas (2). Intracranial hypertension is the most common specific symptom, particularly in children, and the present findings were in accordance with this observation (5,11). The tumors also frequently present with other neurological deficits, such as dyskinesia and seizures (11).

Various sites of extraventricular ependymoma have been reported, with these tumors appearing mainly at the angled margins of the ventricles (3). It is believed that the extraventricular location of a tumor depends on whether it originates from extraventricular ependymal cells (21). Shuangshoti et al (3) and Molina et al (22) reported that supratentorial extraventricular ependymomas frequently occurred in the left hemisphere, particularly the frontal region. Of the 8 supratentorial tumors in the present series, 4 tumors were located in the left hemisphere, while 4 lesions were derived from the right hemisphere; these results did not indicate a left predominance, perhaps due to the small sample size. It has been reported that this tumor type has higher occurrence rates in the frontal and occipital lobes (12). In the present study, the tumors were located in the frontal lobe (2/11), the temporoparietal occipital lobe (2/11), the temporal lobe (1/11), the cerebellar hemispheres (3/11) and the thalamus (3/11), similar to the distributions of tumor location observed in a previous study (12). In the present study, 6 supratentorial tumors had a close association with the lateral ventricle, indicating that the tumor cells may have originated from the ependymal cells lining the ventricles of the brain or perhaps indicating the direct evolution of ectopic original ependymal cells around the lateral ventricle.

Anaplastic ependymomas are malignant and easily metastasize or relapse, and the prognosis is poor (2,5-7); these ependymomas, particularly infratentorial tumors, often metastasize into the CNS, displaying multifocal nodules in the subependymal region. In the present series, 3 patients relapsed after resection; 1 patient suffered a relapse 5 months after tumor resection, displaying multiple nodular enhancements in the left occipital lobe and centrum semiovale, in line with the previous literature (2,5-7). Occasionally, the tissue around the tumors displays nodules or patchy enhancement, perhaps revealing CSF dissemination; in the infratentorial case in the present study, point-like enhancements were found in the frontal and occipital lobes, likely indicating that the tumor invaded the surrounding parenchyma. Therefore, when abnormal enhancement is present in the surrounding parenchyma, it may be indicative of anaplastic ependymoma. It is worth noting that 1 tumor in the present study demonstrated rapid deterioration; it was diagnosed as FCD with a patchy high signal on T2WI imaging in the initial diagnosis. The tumor had developed markedly 5 months later. The short duration and quick deterioration of anaplastic ependymoma can aid in distinguishing anaplastic ependymomas from low-grade ependymomas, perhaps suggesting that anaplastic ependymoma, with its rapid growth, poor clinical course and biological behavior, should be defined as malignant.

Imaging features facilitate the pre-treatment diagnosis when an anaplastic ependymoma is clinically suspected. However, only a few studies have specifically described the MRI characteristics of supratentorial extraventricular anaplastic ependymomas (7,11), and the majority of these studies were case reports and non-specific. According to the previous literature, ependymomas appear as well-circumscribed lesions with varying degrees of contrast enhancement (5), while supratentorial ependymomas are commonly cystic (11,23). Supratentorial ependymomas also cause calcification and intra-tumoral hemorrhages, with certain studies reporting that supratentorial ependymomas can occasionally cause periphereral calcification with a cystic center (23). Peritumoral edema and brain infiltration have been observed occasionally (5). The present study confirms these findings.

MRI provides important information on these lesions, including their location, shape, boundaries and internal architecture. Anaplastic ependymomas often grow rapidly with a great volume; the diameters of 90% of reported ependymomas have been >4 cm (13,23). The majority of the tumors in the present study were large (mean longest diameter, 5.1 cm), in keeping with the previous literature. In the present series, the majority of the tumors were irregularly-lobulated, which was likely due to the fact that the tumors grew actively or the cell proliferation was not uniform. The tumors were hypointense to isointense relative to the gray matter on non-enhanced T1WI, and they were hyperintense or slightly hypointense on T2WI, similar to the appearances of other intracranial tumors (24). The architecture of the tumors in the present study was commonly heterogeneous, correlating with the MRI results and the microscopic findings; heterogeneous intensity can indicate various components of the lesion, such as cysts, necrosis, intratumoral hemorrhage, calcification, fibrosis or...
vascular proliferation (25). Cysts and necrosis are characteristic appearances of anaplastic ependymomas (21), particularly supratentorial tumors. Furie and Provenzale reported that these tumors were typically large cystic masses (11). In the present series, 8 of the lesions exhibited cystic components; multiple cysts coexisted of different sizes, with regions of them merged together, and the cystic regions occupied more than half of the tumors in 2 patients. Of the 2 solid-cystic lesions, the ratios of the diameter of the cystic regions to the tumor were 0.54 and 0.66. Thus, supratentorial lesions frequently presented as solid tumors with large or small cystic components in the present series. Notably, patients between 28 and 63 years old tended to present with solid tumors or solid tumors with small cysts, while patients between 3 and 24 years old were inclined to present with solid-cystic lesions with large cysts. The cystic components demonstrated a low signal on T1WI imaging, but a high signal on T2WI imaging, like a water signal. Necrosis may be an important indicator of malignant tumors, as malignant tumors grow rapidly and cause vascular invasion, which leads to ischemic necrosis of tumor cells.

Hemorrhage occurs occasionally in these cases, and the literature has suggested an occurrence rate of 0-13% (26). Hemorrhage can be caused by the fragility of the vessels perfusing these tumors, and by the invasion and erosion of the vessel walls. In the present series, 7 tumors caused hemorrhage, which presented as a high signal on T1WI and as a low signal on T2WI. The SWAN sequence presented with hyperintensity in the center of the tumor, which is representative of hemorrhage. The rate of hemorrhage was higher than that reported in the literature, most likely as anaplastic ependymomas can more easily cause hemorrhage than benign ependymomas. Calcification, ranging from small punctate foci to large masses, is common (2.5). Hypointensity on T1WI plus T2WI imaging can indicate calcification, but also hemorrhage. CT is superior to MRI in the detection of calcification, but only 3 patients underwent CT scans in the present series, and they did not present with calcification; if more patients had undergone CT scans, the proportion may have been different. This was a shortcoming of the present study. Certain lesions in the present series appeared hypointense at the peripheral rim of the tumor, perhaps due to a fiber envelope.

MR spectroscopy in 1 patient showed reduced N-acetylaspartate and elevated choline levels, similar to the findings of a previous report (2). The appearance of these tumors is similar to that of high-grade glioma (5), suggesting that the tumors are malignant. The diffusion-WI showed moderate restriction in the present study, which is consistent with the literature (2). The tumors mostly presented with moderate or mild peritumoral edema. As the large mass oppresses the surrounding parenchyma, it can result in ischemia or the obstruction of venous return, and 7 of the tumors displayed moderate or mild peritumoral edema in the present study.

The majority of the anaplastic ependymomas in the present series showed contrast enhancement on gadolinium-enhanced T1WI, with a variety of heterogeneous appearances, including ring-like, wreath-like with a thick wall, and intratumoral nodular enhancement. The varying enhancement patterns of anaplastic ependymoma have been described previously (7). Heterogeneous enhancement likely occurs due to the arrangement of the tumor cells, which occurs due to vascular proliferation. Cystic, calcified and hemorrhagic components also contribute to their heterogeneous nature. The ring-like and wreath-like enhancement could indicate plentiful blood vessels on the peripheral rim of the neoplasms.

According to previous studies and the present results, certain imaging features can contribute to differentiating WHO grade III ependymomas from WHO grade II ependymomas, although there is considerable overlap in the imaging features of these two tumors (2-4,8,11): i) Regarding location, WHO grade II ependymomas often derive from the brain surface close to the cerebral falx or cistern, while WHO grade III ependymomas usually occur in the deep parenchyma and close to the ventricle. ii) Regarding gross morphology, WHO grade II ependymomas are usually regularly quasi-circular with clear boundaries, and the ratio of the cystic region to the tumor is less than that of anaplastic ependymomas, while anaplastic ependymomas frequently appear irregularly-lobulated, with obscure boundaries and a solid-cystic nature, or as large cysts with solid nodules. iii) Regarding the enhancement pattern, WHO grade III ependymomas show more marked heterogeneous enhancement than low-grade tumors. iv) Regarding tumoral hemorrhage and peritumoral edema, tumoral hemorrhage is rarely observed in WHO grade II ependymomas; however, it is more frequently observed in WHO grade III ependymomas. There is always no or mild edema around WHO grade II ependymomas, while anaplastic ependymomas often present with mild or moderate peritumoral edema.

The differential diagnosis for ependymomas includes pilocytic astrocytoma, oligodendroglialoma, hemangioblastoma and glioblastoma multiform. Pilocytic astrocytoma often occurs in childhood, appearing as a large cystic component, with small enhancing mural nodules, without peritumoral edema (27). Oligodendroglialoma infrequently presents as cystic, and it usually displays mild enhancement. Hemangioblastoma appears as a solid-cystic mass, accompanied by multiple voids. The intensity of glioblastoma multiform is more heterogeneous, and the peritumoral edema is more marked; these tumors often grow contralaterally across the midline and involve the bilateral frontal lobes.

Anaplastic ependymomas are rare tumors in adults. The standard treatment consists of maximal safe resection and radiation therapy (10,28). The role of surgery is clearly extremely important. Radiotherapy is applied to manage disseminating, residual or recurrent anaplastic ependymomas (10). By contrast, chemotherapy and genetic alterations can be used and could develop into promising therapeutic strategies. Stem-like cells in ependymomas are vulnerable to certain components of the Notch pathway. It has been suggested that inhibitors of these enzymes may become a treatment in the future (10).

In summary, extraventricular anaplastic ependymomas are rare, malignant and rapidly growing tumors that usually occur in the supratentorial deep brain white matter. A correct diagnosis is important for guiding clinical therapy and estimating the prognosis. The present series of 11 patients revealed that these tumors have specific MRI features, such as an irregularly-lobulated and solid or solid-cystic mass, with different-sized cysts and necrosis; they frequently cause hemorrhage and occasionally calcification, with moderate or mild peritumoral edema and markedly heterogeneous enhancement on post-contrast MRI. If a middle-aged or elderly patient presents with a short
duration of clinical symptoms associated with a lesion that has a close association with the lateral ventricle, and if the imaging features are similar to those aforementioned, the presence of an anaplastic ependymoma should be considered.

References