Supratentorial Clear Cell Ependymoma Mimicking Oligodendroglioma: Case Report and Review of the Literature

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Clear cell ependymomas (CCEs) are rare variants of ependymomas. Tumors show anaplastic histological features and behave in an aggressive manner. CCEs have a predilection for extraneural metastases and early recurrence, and they demonstrate characteristic radiographic features. These tumors should be radiologically and pathologically differentiated from oligodendrogliomas. On microscopic examination, CCEs are composed of sheets of cells and resemble oligodendroglioma. However, upon closer examination, the nature of CCEs can be detected earlier, resulting in prompt treatment of the tumor. Although we report only one case, we emphasize the importance of early diagnosis and treatment. Future description of more cases of these rare cancers is necessary to aid in their diagnosis and treatment.

Key Words: Clear cell · Ependymoma · Oligodendroglioma · Histology · Prognosis.

INTRODUCTION

Ependymomas are primary central nervous system (CNS) neoplasms that are rare in adults but more common in the pediatric population. Ependymomas are estimated to constitute fewer than 4% of adult nervous system tumors, including both brain and spinal cord tumors.

These tumors are thought to arise from the ependymal cells lining the cerebral ventricles, spinal cord central canal, and cortical rests. Normal ependymal cells vary considerably in their morphology, ranging from partly ciliated, cuboidal epithelial cells to elongated, sometimes markedly fibrillated glial cells known as tanyocytes. Ependymomas originate from or differentiate toward ependymal cells and are divided into several histological subtypes including cellular, papillary, myxopapillary, and tanyctic ependymomas, depending on their morphology.

Traditional ependymomas have pseudorosettes resulting from perivascular convergence of tumor cell processes and true ependymal rosettes consisting of gland-like or tubular arrangements of epithelial-like cells. Recent laboratory analyses suggest significant molecular heterogeneity within each of the histologic subtypes, as well as significant differences between spinal cord tumors and brain tumors of the same histologic type. Genetic heterogeneity has also been noted when comparing pediatric and adult tumors from the same location and with the same histology. Ependymomas are difficult to diagnose because of this heterogenicity and because their appearances mimic those of other intracranial tumors. There are several primary CNS tumors that are similar in appearance to ependymomas. Predicting the prognosis of such a tumor is also difficult because ependymomas vary considerably both in their morphologic appearance and biological behavior.

Clear cell ependymoma (CCE) is an uncommon and diagnostically challenging variant which was first described by Kernohan in 1937 and was recognized by the World Health Organization (WHO) as a distinct entity in 1993. CCE is characterized by sheets of uniform cells with rounded nuclei and perinuclear, clear halos. It may closely mimic several other tumors, including oligodendroglioma, central neurocytoma, hemangioblastoma, and metastatic renal cell carcinoma. However, CCEs can be distinguished from other tumors by their classic ependymal rosettes and perivascular pseudorosettes. CCEs have a tendency to be aggressive despite therapy. It is important to distinguish this entity from others because the treatment and prognosis of each variant differ significantly. Immunohistochemical staining is known to be helpful for diagnosis. Here, we describe a patient with CCE and review the literature concerning radiological and pathological characteristics of and therapeutic implications for CCE.
CASE REPORT

A 59-year-old woman presented to our hospital with a generalized tonic-clonic seizure. There were no neurological deficits upon postictal examination. She had no previous history of seizure or other medical illness. Computed tomography (CT) revealed a calcified mass in the frontal lobes across the genu of the corpus callosum (Fig. 1). On brain magnetic resonance imaging (MRI), there was a 5 cm infiltrating mass in the right frontal lobe extending to the corpus callosum and the left frontal lobe. This mass showed heterogeneous signal intensities on T1- and T2-weighted images, with cysts and calcification. Fluid-attenuated inversion-recovery images showed irregular peritumoral edema in both frontal lobes and in the corpus callosum. The tumor was irregularly enhanced on the contrast image, suggesting that it was most likely an oligodendroglioma (Fig. 2).

Subtotal removal was carried out using the interhemispheric approach. Intraoperatively, the tumor was soft and friable in texture and yellowish brown in color. Agglomerated glittered calcification was found in some areas and scattered around the tumor margin. There were cysts filled with yellow, clear fluid. The calcified area strongly adhered to the roofs of the lateral ventricles, which were removed.

Microscopic examination revealed that the tumor was composed of sheets of clear cells with rounded nuclei, perinuclear halos and focal perivascular pseudorosettes. Cellularity was markedly increased with numerous mitoses. However, true ependymal canals and rosettes were absent (Fig. 3). Immunohistochemical staining confirmed the compatibility with CCEs. Antibodies against glial fibrillary acidic protein were positive and highlighted perivascular cytoplasmic processes. Immunoreactivity for epithelial membrane antigen was negative. Ki-67 staining confirmed an elevated proliferation rate of 2% in the tumor, but there was no anaplasia, and cytokeratin staining was negative (Fig. 4). The S-100 protein staining was not rewarded and vimentin was positive.

The patient received postoperative adjuvant fractionated radiation therapy of 60 Gray (Gy) but no chemotherapy. Although she did not exhibit neurological deficits after the surgery, she experienced intermittent partial seizures. A six-month follow-up CT showed tumor regrowth at the surgical site. One year after surgery, the tumor showed further increased in size, and there was a marked increase in the extent of white matter edema in the bilateral cerebral hemispheres (Fig. 5). The patient did not undergo another operation and symptoms were controlled by an anticonvulsant medication.

DISCUSSION

CCE was first described as a distinct pathologic entity by Kawano et al. and was classified as a variant of ependymoma by the WHO in 1993. In 2000, the WHO ratified a new classification of neoplasms affecting the CNS. The classification of brain tumors is based on the premise that each tumor results from the abnormal growth of a specific cell type. The major forms of ependymomas according to the WHO are sorted into grade I, myxopapillary, subependymoma; grade II, ependymoma; and grade III, anaplastic ependymoma. Grade II further includes cellular, clear cell, papillary and tanycytic ependymomas.

Fouladi et al. reviewed the clinicopathologic and radiologic features, treatments, and outcomes of ten children with CCE. According to their report, CCEs have a predilection for the supratentorial compartment and ranged in size from 1.5 cm to 8.0 cm. All tumors were enhanced, and eight of nine tumors had associated cysts with enhancing walls. Five tumors had associated hemorrhage, seven tumors had regions of necrosis, five tumors had vasogenic edema, and nine tumors had mass effect. Punctate cal-

Fig. 1. Brain computed tomography image at pre-operation. A: Non enhancement image : 5 cm infiltrating mass in the right frontal lobe extending to the corpus callosum and the left frontal lobe. B: Enhancement image : diffuse enhancement of the tumor mass in both frontal lobes and genu and in the anterior body of the corpus callosum.

Fig. 2. Brain magnetic resonance imaging. A: T1-weighted image (T1WI) coronal. Multiple signal voids, internal cystic or necrotic portions within the right frontal lobe mass. B: T1WI axial. C: T2-weighted image (T2WI) axial. Increased signal intensity of peritumoral edema in both frontal lobes and in the posterior body of the corpus callosum. D: T1WI enhancement. Well enhanced tumor mass.
Unlike oligodendrogliomas, CCEs are characterized by their sharp circumscript and hypervascularity, as reflected in contrast enhancement on CT and MRI, their noninfiltrative pattern of growth that displaces parenchyma, and the occasional formation of vague perivascular pseudorosettes\(^7\). Unlike central neurocytomas and glioneurocytomas, CCEs lack secretory granules, vesicles, and synapses according to electron microscopy and neuroendocrine markers in immunocytochemistry\(^14\). This morphologically distinctive cancer subtype features sheets and lobules of crowded, uniform cells with round nuclei, central nucleoli, and conspicuous cytoplasmic clearing. Since the latter feature is more common to other central nervous system tumors such as oligodendroglioma and neurocytoma, misdiagnoses are frequent. The ultrastructural features of CCEs have been fairly uniformly reported as classical ependymoma cells with well developed intercellular junctions, microvilli and cilia\(^6,14\). CCEs are more aggressive in behavior compared to anaplasia\(^5\). Anaplastic tumors have numerous discrete zones of markedly increased cellularity, microvascular hyperplasia, and numerous mitoses. Fouladi et al.\(^3\) described two cases of early CCE recurrence which contained numerous cells with enlarged, irregular shaped nuclei and prominent nucleoli. These two cases of CCEs with anaplastic features showed metastasis to extracranial lesions, lymph nodes and the jugular vein. In that study, the progression and overall survival rates at five years were 34±20% and 75±19%, respectively.

Eight patients reported by Min and Scheithauer\(^14\) received surgical resection, and five of them underwent radiotherapy. Chemotherapy was attempted on two of the five patients who received radiotherapy at doses of 40 Gy to 65 Gy. The patients who received chemotherapy relapsed into CCEs. Four of the patients had no evidence of recurrence. Oya et al.\(^16\) found that the extent of surgical resection was a significant factor in the prediction of survival since those patients with gross total resection tended to have better outcomes than did those with subtotal resections. In Ki-67 labeling studies, CCEs exhibited proliferative activity. The three cases of recurrence oc-
curred within one to nine years regardless of Ki-67 scale.

In our case study, subtotal resection was only possible because the location of the mass made total resection difficult. The patient received radiotherapy of 65 Gy after the operation. However, she experienced tumor relapse at the surgical site after six months. The Ki-67 scale was 2%. The reason for recurrence may be the limited resection because of the difficult approach to the tumor site and its misdiagnosis as an oligodendroglioma. Thus, differential diagnosis between CCE and other tumors is considered very important. Since we described only one case, additional studies with a large group of patients will be necessary to provide a comprehensive set of diagnostically useful cases.

CONCLUSION

Current reports of patients with CCE describe anaplastic histological features and aggressive tumor behavior. Diagnosis of CCEs is difficult, as is its distinction from other tumors. We found that ultrastructural examination was helpful to detect the nature of the CCE, and immunohistochemical staining was a useful method to distinguish CCE from other cancer types.

A large study is needed to determine the therapeutic responsiveness and prognosis of this rare cancer. We expect that, as more studies and case reports of CCEs become available, a common approach to the effective treatment of CCEs will emerge. However, a prospective trial study may be difficult due to the limited number of cases of this rare tumor.

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