Ependymoma is a slowly-growing tumor composed of neoplastic ependymal cells, and it accounts for 2-9% of all neuroepithelial tumors. Histologically, the classic pattern of ependymoma is characterized by the presence of round-to-oval nuclei with "salt and pepper" speckling of the chromatin. The presence of perivascular pseudorosettes and ependymal rosettes is a key histologic feature of the diagnosis. Apart from this classic pattern of ependymoma, giant cell ependymoma (GCE) is described in the World Health Organization (WHO) classification as a histopathological variant of ependymoma. Histologic analysis revealed features of a high-grade tumor with perivascular pseudorosettes and bizarre pleomorphic giant cells, which established the diagnosis of GCE. We performed a review of literatures about the cytologic features of GCE, including our case, thus proposing that intraoperative frozen diagnosis of GCE would be established by squash smear preparations featuring the mitosis and necrosis, as well as the high cellularity, and the presence of giant cells showing hyperchromatic nuclei with eosinophilic cytoplasm and intranuclear inclusions/pseudoinclusions.

CASE REPORT

A healthy 15-year-old woman was admitted to the department of neurosurgery of our institution with a chief complaint of a 1-month history of headache and dizziness. Magnetic resonance imaging (MRI) (Fig. 1) demonstrated a 6.8×5 cm-sized, oval to round cell clusters with a papillary structure in a fibrillary background. This was occasionally accompanied by the presence of bizarre pleomorphic giant cells with hyperchromatic nuclei and prominent intranuclear inclusions. These intranuclear inclusions were a key clue to diagnosis of ependymoma. Here, we present a case of anaplastic giant cell ependymoma (GCE) occurring in a 15-year-old woman. Squash smear slides for intraoperative frozen section diagnosis revealed oval to round cell clusters with a papillary structure in a fibrillary background.
The patient was 34 years old at diagnosis. The patient died suddenly with signs of respiratory insufficiency; the cause of death was ascribed to tumor progression. The patient underwent a craniotomy. Thus, grossly, the spine and brain were explored. Total resection was attempted. The macroscopic findings were compatible with a primary intracranial tumor. The surgeon noted the presence of a large intracranial mass involving the brain parenchyma. The mass was located in the left temporal lobe and was partially囊性, extramedullary/Well demarcated, cystic mass at left exterparietal

| No. | Sex/Age (yr) | Tumor site/Radiographic finding | Grade | Treatment | Recurrence (mo) | References |
|-----|--------------|---------------------------------|-------|-----------|----------------|------------|
| 1   | M/14         | Filum terminale/Well-circumscribed lumbosacral mass at the L4-L5 level | Low   | TR        | - (35)         | Zec et al.2 |
| 2   | M/14         | Filum terminale/Well-circumscribed enhanced lumbosacral mass at the L4-L5 level | Low   | TR        | - (16)         | Zec et al.2 |
| 3   | M/26         | Frontal, extra and intraventricular: Heterogeneously enhanced mass at left mesial frontal | Anaplastic | GTR, RT | + (8)         | Brown et al.3 |
| 4   | F/13         | Temporoparietal, extraventricular/Heterogeneously enhanced mass at left temporoparietal | Low   | GTR       | - (24)         | Pimentel et al.4 |
| 5   | M/50         | Cerebellar/Heterogeneously enhanced mass at the posterior aspect of the foramen magnum | Anaplastic | STR, C/RT | + (8)         | Jeon et al.5 |
| 6   | M/22         | Spinal cord/Multicystic and partly enhancing cervical cord tumor from the medulla to C6-T1 | Low   | GTR       | - (9)         | Fourney et al.6 |
| 7   | M/89         | Cerebellar/Partially cystic mass with an enhancing mural nodule | Low   | GTR       | - (2)         | Cooper et al.7 |
| 8   | M/28         | Intraventricular, medullary/Well demarcated, cystic mass at enhancing forntal ventricle and cervical segments of spinal cord | Low   | ND        | ND            | Szpak et al.8 |
| 9   | F/34         | Suprasellar/Enhancing mass at the medullary junction; Enhancing suprasellar mass | Low   | STR, C/RT, RT; GTR | - (3)         | Sangoi et al.9 |
| 10  | M/17         | Occipital, extraventricular/Localized in the left occipital lobe, arising from the occipital horn of the lateral ventricle | Low   | GTR, C/RT | - (18)        | Adamek et al.10 |
| 11  | F/67         | Spinal cord/Well circumscribed, homogeneously enhancing, intramedullary lesion of the thoracic spinal cord | Low   | GTR, C/RT | - (1.5)       | Shamji et al.11 |
| 12  | F/55         | Filum terminale and conus medullaris/Well circumscribed intradural tumor | Low   | TR        | - (6)         | Shintaku and Sakamoto12 |
| 13  | F/25         | Spinal cord/Multicystic and partially enhancing cervical intramedullary tumor extending from C2 to C5 | Low   | GTR       | - (12)        | Barbagallo et al.13 |
| 14  | F/15         | Temporocerebital/Solid and cystic intra-axial mass | Anaplastic | GTR/RT | - (5)         | Present case |

M, male; F, female; TR, total resection; GTR, grossly total resection; STR, subtotal resection; C/RT, chemotherapy/radiotherapy; ND, not described.

The patient underwent a craniotomy. Thus, grossly, the supratentorial tumor was completely resected. The surgeon noted that the tumor was highly vascularized. Postoperatively, the patient received a focal fractionated radiotherapy with a total dose of 5,040 cGy. A follow-up MRI was taken on postoperative month 5, which revealed no recurrence or progression of the tumor.

For intraoperative frozen diagnosis, we used the square-smear technique (Fig. 2). This revealed a hypercellular smear in a fibrillary background. Most of the small- to medium-sized cells with papillary structures had hyperchromatic nuclei and coarse chromatin. This was occasionally accompanied by the presence of bizarre pleomorphic giant cells. They had a round-to-oval shape and contained hyperchromatic nuclei, eosinophilic cytoplasm and prominent eosinophilic intranuclear inclusions. These intranuclear inclusions were a key clue to differential diagnosis of ependymoma and meningioma. Considering the cytologic features along with the clinical and radiological data, we made an intraoperative frozen diagnosis of ependymoma. With a retrospective review of the slides, we identified a perivascular pseudorosettes-like lesion. Thus, we supported a frozen diagnosis of "giant cell tanyctye ependymoma."
Fig. 1. Preoperative magnetic resonance imaging scans. A 6.8 × 5 cm-sized solid and cystic intra-axial mass is present in the right temporo-occipital area, compressing the posterior horn of the right lateral ventricle. (A) Transverse and (B) sagittal views.

Fig. 2. Hematoxylin and eosin-stained squash slides for frozen diagnosis show a hypercellular smear (A) in a fibrillary background (C, sharp arrow). Multiple pleomorphic giant cells with hyperchromatic nuclei and eosinophilic cytoplasm are seen. Eosinophilic intranuclear inclusions are prominent (B-D, arrowheads). Perivascular pseudorosettes-like lesions are also noted (B, D, arrows).
and CD99 (MIC2).

As shown in Fig. 3, a histopathologic examination showed that the tumor had perivascular pseudorosettes; this is one of the characteristic features of ependymoma. The tumor cells had histopathological findings that are consistent with squash smear ones described above. This was also accompanied by the frequent presence of bizarre pleomorphic giant cells with prominent intranuclear eosinophilic inclusions. According to the WHO criteria, it had features of an anaplastic tumor, including a marked cellularity, abundant mitoses, vascular proliferation and necrosis. Immunohistochemically, the tumor showed a diffuse expression of both GFAP and synaptophysin. That is, it had a high intensity, a dot-like expression of CD99 and that of EMA. In addition, the tumor cells had a Ki-67 labeling index of about 10% (Fig. 4). Based on all of these findings, a diagnosis of anaplastic GCE was established.

**DISCUSSION**

A rare variant of ependymoma, GCE poses a diagnostic challenge for the pathologists on the intraoperative frozen section as well as the permanent section. The presence of perivascular pseudorosettes is a key histologic clue to diagnosis of ependymoma. But pseudorosettes are not present in all the case of GCE. According to Zec et al., who first described two cases of GCE in 1996, the absence of perivascular pseudorosettes in GCE might reflect the failure of the neoplastic cells to elaborate perivascular process. Moreover, perivascular pseudorosettes cannot be easily found on the intraoperative frozen section. This often leads to the misdiagnosis of GCE as glioblastoma multiforme, anaplastic astrocytoma, subependymomal giant cell astrocytoma or tanycytic ependymoma on intraoperative frozen section. In addition, GCE should also be differentially diagnosed from anaplastic oligodendroglioma, clear cell ependymoma, pleomorphic xanthoastrocytoma and giant cell glioblastoma.
Despite these diagnostic challenges, there has been an increase in the demand for rapid intraoperative diagnosis. This is particularly case with the neurosurgical practice. A simple, reliable, and rapid method, the squash smear technique is useful to present detailed cytologic features of lesions. It is useful in making an intraoperative diagnosis of central nervous system lesions.\(^{14}\)

To our knowledge, however, there are no reports about the cytologic features of GCE.

We performed a review of literatures about GCE, focusing on the cytologic features seen on the tissue sections, whose results
including our case are summarized in Table 2. The cytologic features are classified based on the cellularity, hyperchromatic nuclei, binucleation or multinucleation, eosinophilic cytoplasm, intranuclear inclusion/pseudoinclusions, perivascular pseudorosettes, brisk mitosis, necrosis and fibrillary background. Basically, all the 14 cases showed hypercellularity, mitosis and necrosis. Of the total cases, 93% (13/14) had eosinophilic cytoplasm and perivascular pseudorosettes; 71% (10/14) did hyperchromatic nuclei; 57% (8/14) did intranuclear inclusions/pseudoinclusions; and 50% (7/14) did binucleation or multinucleation.

The cytologic features of GEC are described in Table 2. It is noteworthy, however, that these features are based on tissue sections of GCE rather than cytology specimens such as the squash smear preparations. It is, therefore, a matter of course that there is no consistency in the cytologic features between the tissue sections and the cytology specimens. In our case, there were perivascular pseudorosettes on the tissue sections, but not found on the squash smear preparations. But both diagnostic modalities showed such findings as mitosis and necrosis, giant cells and intranuclear inclusions/pseudoinclusions. Further comparative descriptions are warranted to define the cytologic features of GCE between tissue sections and cytology specimens.

In making an intraoperative frozen diagnosis based on squash smear preparations featuring the mitosis and necrosis, as well as the high cellularity, and the presence of giant cells showing hyperchromatic nuclei with eosinophilic cytoplasm and intranuclear inclusions/pseudoinclusions would be key histologic features that are helpful for establishing a diagnosis of GCE. This is particularly true to our case; the presence of giant cells with intranuclear inclusions and papillary structures was a critical clue to intraoperative frozen diagnosis. In addition to the cytologic features, the clinical and radiologic findings are helpful for improving the diagnostic accuracy.

Due to a relatively smaller number of reported cases, we failed to establish the relationship between the histological pattern of GCE and its prognosis. In patients with anaplastic GCE, however, a poor prognosis is expected with a relatively higher rate of recurrence (Table 1). In our patient, there was no disease progression or recurrence. Due to a shorter length of follow-up, however, further long-term follow-up studies are warranted to predict clinical outcomes of anaplastic GCE.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. WHO classification of tumours of the central nervous system. 4th ed. Lyon: IARC Press, 2007: 74-8.
2. Zec N, De Girolami U, Schofield DE, Scott RM, Anthony DC. Giant cell ependymoma of the filum terminale: a report of two cases. Am J Surg Pathol 1996; 20: 1091-101.
3. Brown DE, Chason DP, Schwartz LF, Coimbra CP, Rushing EJ. Supratentorial giant cell ependymoma: a case report. Mod Pathol 1998; 11: 398-403.
4. Pimentel J, Kepes JJ, Moura Nunes JF, Bentes C, Migues J, Antunes JL. Supratentorial giant cell ependymoma. Clin Neuropathol 2001; 20: 31-7.
5. Jeon YK, Jung HW, Park SH. Infratentorial giant cell ependymoma: a rare variant of ependymoma. Pathol Res Pract 2004; 200: 717-25.
6. Fournier DR, Siadati A, Bruner JM, Gokaslan ZL, Rhines LD. Giant cell ependymoma of the spinal cord: case report and review of the literature. J Neurosurg 2004; 100(1 Suppl Spine): 75-9.
7. Cooper PB, Katus M, Moores L, et al. Rare giant cell ependymoma in an octogenarian: case report and review of the literature. J Neurosurg 2006; 105: 908-11.
8. Szpak GM, Lewandowska E, Schmidt-Sidor B, et al. Giant cell ependymoma of the spinal cord and fourth ventricle coexisting with syringomyelia. Folia Neuropathol 2008; 46: 220-31.
9. Sangoi AR, Lim M, Dalai M, Vogel H, Chang S. Suprasellar giant cell ependymoma: a rare neoplasm in a unique location. Hum Pathol 2008; 39: 1396-401.
10. Adamek D, Dec M, Sobol G, Urbanowicz B, Jaworski M. Giant cell ependymoma: a case report. Clin Neurol Neurosurg 2008; 110: 176-81.
11. Shamiji MF, Benoit BG, Perry A, Jansen GH. Giant cell ependymoma of the thoracic spine: pathology case report. Neurosurgery 2009; 64: E566-7.
12. Shintaku M, Sakamoto T. Tanycytic ependymoma of the filum terminale with pleomorphic giant cells. Brain Tumor Pathol 2009; 26: 79-82.
13. Barbagallo GM, Caltabiano R, Parisi G, Albanese V, Lanzafame S. Giant cell ependymoma of the cervical spinal cord: case report and review of the literature. Eur Spine J 2009; 18 Suppl 2: 186-90.
14. Goel D, Sundaram C, Paul TR, et al. Intraoperative cytology (squash smear) in neurosurgical practice: pitfalls in diagnosis experience based on 3057 samples from a single institution. Cytopathology 2007; 18: 300-8.