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The clinicopathological features of liponeurocytoma

Li Xu1 · Jiang Du1 · Junmei Wang1 · Jingyi Fang1 · Zhaoxia Liu1 · Yanjiao He1 · Guilin Li1

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Abstract To discuss the clinicopathological features of liponeurocytoma, we retrospectively reviewed three liponeurocytoma cases and compared their immunophenotypes and genotypes with those of similar tumors. Furthermore, we reviewed the literature and compared the similarities and differences between cerebellar and intraventricular liponeurocytomas. Two cerebellar and one intraventricular liponeurocytomas were included in the present study. The liponeurocytomas comprised small tumor cells and lipomatous cells. The tumor cells expressed SYN, MAP-2, and NeuN. One case showed atypical histological features. By reviewing the literature, we found that cerebellar liponeurocytoma tended to be more common in females, whereas the converse was true for intraventricular liponeurocytoma. Compared with cerebellar liponeurocytoma, intraventricular liponeurocytoma was more commonly noted in younger adult patients. A high MIB-1 index (>10%) and incomplete tumor resection might represent adverse prognostic factors in patients with liponeurocytoma. We suggest that ‘central liponeurocytoma’ should be used to include all putative liponeurocytoma sites. The present study identified several morphological, immunohistochemical, and genetic features that may aid in the differential diagnosis of liponeurocytoma. In addition, surgery should be the preferred treatment, and complete tumor resection should be the goal. Additional cases with long-term follow-up are needed to develop optimal management protocols for liponeurocytoma.

Keywords Liponeurocytoma · Neurocytoma · Glioma · Embryonal tumor · Immunohistochemistry

Introduction

Cerebellar liponeurocytoma is a rare neuroectodermal tumor, first described in 1978 by Bechtel et al. [1]. It was initially recognized as a subtype of medulloblastoma, described by various names, such as “lipomatous medulloblastoma,” “lipidized medulloblastoma,” “neuropeocytoma,” “medullocytoma,” “lipomatous glioneurocytoma,” and “lipidized mature neuroectodermal tumor.” However, molecular-genetic studies have indicated that liponeurocytoma is distinct from medulloblastoma [2]. Because of its favorable prognosis, in 2002, the WHO Working Group moved liponeurocytoma from the primitive neuroectodermal tumor category and placed it as a separate entity among glioneuronal tumors, categorized as WHO grade I [3]. However, because local recurrence was documented [4–8], it was regarded as a WHO grade II tumor in the 2007 classification scheme [9].

Liponeurocytomas are mainly located in the cerebellum, followed by the ventricular system. In the present study, “cerebellar liponeurocytoma” refers to tumors located in the cerebellum, and “intraventricular liponeurocytoma” refers to tumors located in the lateral, third, or fourth ventricle. To date, only 59 liponeurocytoma cases have been reported. Because of this scarcity, the pathogenesis of liponeurocytoma is not fully understood. We here describe the clinicopathological features of three liponeurocytoma cases and compare their immunophenotypes and genotypes.
with those of similar tumors, including central neurocytoma, extraventricular neurocytoma, oligodendroglioma, diffuse astrocytoma, ependymoma, CNS embryonal tumor, and classic medulloblastoma. In addition, we review the literature and discuss the similarities and differences between cerebellar and intraventricular liponeurocytomas.

Patients and methods

Patients

Patient data were reviewed retrospectively, and three liponeurocytoma cases were identified. These included two patients treated at Beijing Tiantan hospital between January 2008 and December 2015. One of these cases was reported previously [10]; however, we here report on the prolonged follow-up data for that case. The third patient underwent surgery at a local hospital and was selected following a pathology consultation at our hospital. The diagnoses of liponeurocytomas were confirmed by two pathologists. All patients or the patients’ families provided informed consent. All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation of Capital Medical University, Beijing, China, which are compliant with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The clinical presentations, neuroimaging features, and treatment details of each case are summarized in Table 1. Two cases of extraventricular neurocytoma and five cases each of central neurocytoma, oligodendroglioma, diffuse astrocytoma, ependymoma, CNS embryonal tumor, and classic medulloblastoma were included as controls for the comparison of immunohistochemical and genetic features.

Methods

Routine hematoxylin–eosin and Envision-based immunohistochemical staining were performed on paraffin-embedded tissues to assess each case histologically. For antigen retrieval, slides were boiled in EDTA buffer (PH 8.0) under high pressure. The primary antibodies used included pre-diluted monoclonal antibodies against synaptophysin (SYN; #EP158), microtubule-associated protein-2 (MAP-2; #AP18), neuronal nuclear antigen (NeuN; #A60), neurofilament (NF; #2F11), glial fibrillary acidic protein (GFAP; #EP13), oligodendrocyte transcription factor-2 (Oligo-2; #EP112), S-100 (#15E2E + 4C4.9), vimentin (#V9), epithelial membrane antigen (EMA; #GP1.4), pan-cytokeratin (CK; #AE1/AE3), p53 (#EP9), Ki-67 (#MIB1), and isocitrate dehydrogenase 1 R132H mutant (IDH1-R132H; 1:50, Dianova). Pre-diluted NeoMarkers monoclonal antibodies were used (Beijing Zhongshan Golden Bridge Biotechnology Company, China). The SuperPicture™ 3rd Gen Immunohistochemistry Detection Kit (Invitrogen, Grand Island, NY, USA) was used to evaluate the staining. For immunohistochemistry, counterstaining with hematoxylin was performed.

Fluorescence in situ hybridization was performed in the two patients who underwent surgery at our hospital. Areas composed of oligodendroglioma-like cells were chosen for hybridization. Five oligodendroglioma cases were also evaluated. All reagents were purchased from Beijing Gp Medical Technologies Ltd., China. Four-micron, formalin-fixed, paraffin-embedded sections were incubated for 30 min at 70 °C. The slides were deparaffinized twice for 10 min in dimethylbenzene, followed by 10 min in 100% ethanol, and then immersed in deionized water at 99 °C for 60 min. The sections were subsequently treated with pepsin (4 mg/L in 0.9% NaCl) for 20 min in a 37 °C water bath and then dehydrated in increasing concentrations of ethanol. Dual-color, locus-specific, identifier probes targeting loci 1p36/1q25 and 19q13/19p13 were used to assess 1p and 19q deletions, respectively. Probe mixture (10 µL) was applied to the hybridized region, and the slides were hybridized using a ThermoBrite S500-24 slide hybridization/denaturing system (Leica, Beijing, China) under the following conditions: co-denaturing at 85 °C for 5 min, and hybridization at 42 °C for 20 h. The slides were washed sequentially with 0.3% NP-40 solution at 67 °C for 2 min, 0.1% NP-40 solution at 37 °C for 30 s, and 70% ethanol at 37 °C for 3 min. Next, the slides were placed in the dark to dry and were subsequently counterstained using DAPI and placed in the dark for 15 min. Deletion of 1p or 19q was defined as a signal ratio of <0.8 for the region of interest to the control probe, with >25% of cells showing the deletion.

Results

Histopathology

In all patients, the tumors were composed of small tumor cells and lipomatous cells. In Cases 1 and 2, the tumor cells were homogenous cells with small, round, or oval nuclei with finely stippled chromatin, inconspicuous nucleoli, and pale eosinophilic-to-clear cytoplasm. These cells were not mitotic (Fig. 1a). In Case 3, the tumor cells were round-to-polygonal cells with hyperchromatic nuclei, which were closely packed in some areas. Endothelial cell proliferation, hyaline degeneration of the vascular walls, and focal necrosis were evident (Fig. 1b, c). The mitotic figures were 0–1/50 high-power fields. Variable amounts of lipomatous
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Tumor location</th>
<th>History and symptoms</th>
<th>MRI/CT findings</th>
<th>Preoperative diagnosis</th>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>F</td>
<td>Left cerebellar hemisphere and vermis</td>
<td>Swaying gait (6 months). Physical examination: unremarkable. Neurological examination: broad-based gait and pluridirectional oscillations at the Romberg position</td>
<td>CT: a well-demarcated solid lesion without perilesional edema. Contrast-enhanced imaging was not performed</td>
<td>ND</td>
<td>Gross total resection</td>
<td>ND</td>
<td>Postoperative-period was uneventful and the patient was subsequently lost to follow-up</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>F</td>
<td>Right cerebellar hemisphere and the inferior vermis, extending through the foramen magnum to the C2 level</td>
<td>Occipital headaches (18 months) Physical examination: unremarkable Neurological examination: hoarse voice, occasional deglutition, diminished pinprick sensations in the right arm and leg, acroesthesia of the left side and a broad-based gait</td>
<td>MRI: a well-demarcated solid lesion with moderate heterogeneous enhancement. No perilesional edema</td>
<td>Ependymocytoma</td>
<td>Gross total resection</td>
<td>No</td>
<td>No recurrence at 4 years and 6 months</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>M</td>
<td>Right lateral ventricle</td>
<td>Headache (1 month). Physical and neurological examinations: unremarkable</td>
<td>MRI: a well-demarcated solid lesion with multiple small cysts and moderate heterogeneous enhancement No perilesional edema</td>
<td>Central neurocytoma</td>
<td>Gross total resection</td>
<td>No</td>
<td>No recurrence at 1 year and 5 months</td>
</tr>
</tbody>
</table>

*Table 1* Clinical data of our three liponeurocytoma cases

*M* male, *F* female, *ND* no data available, *CT* computed tomography, *MRI* magnetic resonance imaging
cells were grouped and sparsely distributed among the tumor cells. These lipomatous cells contained a single fat vacuole or several small vacuoles that pressed the nuclei to the cell periphery.

Immunohistochemical features

The immunohistochemical results are summarized in Table 2.

In liponeurocytomas, the tumor cells were positive for cytoplasmic SYN (Fig. 1d) and MAP-2 (Fig. 1e)
and nuclear NeuN, and negative for cytoplasmic IDH1-R132H, EMA, and CK, and nuclear Oligo-2. In the lipomatous cells, the lipid vacuole membranes were positive for SYN, MAP-2, vimentin, and S-100. In all patients, GFAP was expressed in the fibrillary matrix, as well as in some tumor and lipomatous cells (Fig. 1f). NF immunostaining was apparent in the fibrillary matrix alone. In Case 2, several tumor cell nuclei were immunopositive for p53. The MIB-1 labeling indices were 1, <1, and 5% in Cases 1, 2, and 3, respectively.

### Discussion

We searched the Medline database and found 47 and 12 previous cases of cerebellar and intraventricular liponeurocytomas, respectively, in the English literature. The cerebellar liponeurocytomas included 37 cases described by Oudrhiri et al. [11] and 10 cases reported in other studies [12–20]. The patient’s mother in the report by Wolf et al. [19] and the patient’s sister in the report by Pikis et al. [20] were included in our review. Intraventricular liponeurocytomas included 11 cases reported by Karabagli et al. [21] and one case reported by Owler et al. [22]. The cases in the present study were also included in the review.

The cerebellar liponeurocytomas were mainly located in the cerebellar hemisphere and vermis, and some extended into the cerebellopontine angle [5, 23–26], fourth ventricle [12, 27, 28], and spinal canal [5, 15, 17, 29]. The intraventricular liponeurocytomas were mainly located in the lateral ventricle, followed by the third and fourth ventricles. In the present study, two tumors were located in the cerebellum, one of which extended to the C2 level, and one tumor was located in the right lateral ventricle. Based on these findings, we suggest that ‘central liponeurocytoma’ should be used to replace the term ‘cerebellar liponeurocytoma’ to ensure that all putative liponeurocytoma sites are included.

For cerebellar liponeurocytoma, the male-to-female ratio was 9:16, showing a female predisposition. All tumors occurred in adults, with a mean age of 49.2 years (range 30–74 years), and >60% of tumors appeared in the fourth and fifth decades of life. The tumors were usually solitary, and only two multifocal cases were reported [17, 18]. One presented multiple nodules in the cerebellum, and the other had a cerebellar tumor and two intradural extramedullary

### 1p/19q fluorescence in situ hybridization

Neither liponeurocytoma type showed 1p/19q deletions, whereas co-deletions of 1p/19q were found in all oligodendrogliomas.

### Table 2 Immunophenotypes of liponeurocytoma and similar tumors

<table>
<thead>
<tr>
<th></th>
<th>SYN</th>
<th>MAP-2</th>
<th>NeuN</th>
<th>NF</th>
<th>GFAP</th>
<th>Oligo-2</th>
<th>S-100</th>
<th>Vimentin</th>
<th>EMA</th>
<th>CK</th>
<th>p53</th>
<th>IDH1-R132H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liponeurocytoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−/−</td>
<td>−/+−</td>
</tr>
<tr>
<td>Central neurocytoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−/−</td>
<td>−/−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−/−</td>
<td>−/+−</td>
</tr>
<tr>
<td>Extraventricular neurocytoma</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−/−</td>
<td>−/+−</td>
</tr>
<tr>
<td>Oligodendrogioma</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−/−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−/+</td>
<td>−/+−</td>
</tr>
<tr>
<td>Diffuse astrocytoma</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−/−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−/+</td>
<td>−/+−</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−/−</td>
<td>+</td>
<td>−/−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−/+</td>
<td>−/+−</td>
</tr>
<tr>
<td>Primitive neuroepithelial tumor</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+</td>
<td>−/+</td>
<td>+</td>
<td>−</td>
<td>−/+</td>
<td>−/+−</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−/+</td>
<td>−/+−</td>
</tr>
</tbody>
</table>

Synaptophysin, MAP-2 microtubule-associated protein-2, NeuN neuronal nuclear antigen, NF neurofilament, GFAP glial fibrillary acidic protein, Oligo-2 oligodendrocyte transcription factor-2, EMA epithelial membrane antigen, CK cytokeratin, IDH1-R132H isocitrate dehydrogenase 1 R132H mutant

+/−, positive in ≥50% cases; −/+, negative in ≥50% cases

*Immunohistochemical staining was not performed

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nodes at the C6 and L5–S1 levels. Most cases were sporadic. Wolf et al. [19] and Pikis et al. [20] reported two cases with possible familial predisposition.

For intraventricular liponeurocytoma, the male-to-female ratio was 10:3, with a clear male predilection. The tumors usually occurred in adults, with a mean age of 33.3 years (range 4–59 years), and >60% occurred in the third decade of life. Therefore, intraventricular liponeurocytoma showed a younger age tendency compared with cerebellar liponeurocytoma.

Cerebellar and intraventricular liponeurocytomas share some similar histological features. Both have a biphasic histologic appearance comprising small cells that exhibit some immunohistochemical features of neurons and lipomatous cells, the latter of which resemble mature adipocytes. The tumor cells are usually uniformly round-to-oval-shaped, although spindle-shaped [7] or multinuclear and bizarre-shaped pleomorphic cells [27] have been reported. Mitosis is rare or absent. Other histological features, such as a sharp circumscription from the adjacent brain tissues [12, 30], cell-free fibrillary neuropils [12, 31], vessel hyalinization [19, 27, 30, 31], hemorrhagic foci [30–34], and calcification [19, 32], are occasionally seen. Cystic degeneration was present in two of the reported cases of intraventricular liponeurocytomas [30, 32]. On the other hand, neural rosettes [19, 20], Homer–Wright rosettes [27, 34], pseudorosettes [34], perivascular lymphocytosis [19], and leptomeningeal infiltration [7] were present in some reports of cerebellar liponeurocytomas. However, ganglionic differentiation within the tumors is rarely observed. Furthermore, the MIB-1 index in the majority of reported liponeurocytomas was low (<5%), including in Cases 1 and 2 in the present study (≤1%).

Although most liponeurocytomas show benign histological features, several cases of cerebellar [20, 28, 34] and intraventricular liponeurocytomas [6, 8, 22] with atypical features have been documented. These atypical features included hyperchromatic nuclei, nuclear and cytoplasmic atypia, increased mitoses, focal necrosis, microvascular proliferation, and/or a high MIB-1 index. Case 3 reported herein was such a case with atypical features. However, in the new 2016 WHO classification of brain tumors, there is no consensus regarding atypical liponeurocytomas [35].

Immunohistochemically, in the present study, the tumor cells expressed the neuronal markers SYN, MAP-2, and NeuN. Lipomatous cells also expressed SYN and MAP-2, indicating their neuronal origin. Some tumor and lipomatous cells expressed GFAP, indicating astrocytic differentiation. Furthermore, focal myogenic differentiation has been demonstrated in cerebellar liponeurocytomas exhibiting positive desmin staining [7, 13, 36], and ependymal differentiation was observed in a case of recurrence involving the fourth ventricle that exhibited positive CK and EMA staining [8].

Although liponeurocytomas share similar immunophenotypes with central neurocytoma and extraventricular neurocytoma, the latter diseases rarely show regions of lipomatous change. Conversely, liponeurocytomas show different immunophenotypes and genotypes to oligodendroglioma, diffuse astrocytoma, and ependymoma. Compared with liponeurocytomas, CNS embryonal tumors and classic medulloblastomas display more prominent malignant characteristics, such as higher cellularity, greater nuclear and cellular polymorphism, more extensive necrosis, and higher mitotic activity and MIB-1 index.

Although considered benign tumors, local recurrences have been reported for both cerebellar [4, 5, 7, 17, 34, 37, 38] and intraventricular liponeurocytomas [6, 8, 31]. In most of these recurrent tumors, the MIB-1 index was elevated [6, 8, 17, 31, 34, 37]. Furthermore, the disease-free survival time was significantly shorter after the second recurrence compared with after the first recurrence [4, 5, 7]. Among these recurrent cases, the recurrence time was >5 years in five cerebellar cases and one intraventricular case [4, 5, 31, 37, 38]; those recurrent cases had a low MIB-1 index (<5%) and were denoted as complete tumor resection. The recurrence time was ≤5 years in four cerebellar cases and one intraventricular case [7, 8, 17, 34, 38]. Most of those cases had a high MIB-1 index (>10%) and/or were denoted as incomplete tumor resection. Therefore, a high MIB-1 index (>10%) and incomplete tumor resection might represent adverse prognostic factors, and complete tumor resection should be the surgical aim.

Presently, there is no consensus on the utility of postoperative radiotherapy for liponeurocytomas, and its role in preventing recurrence is unknown. Cacciola et al. [39] suggested that, if recurrence develops after a long period and with only a slightly more aggressive histology, then radiotherapy should be avoided to prevent exposing the patient to the risks and discomfort associated with this treatment. However, in patients who underwent gross total resection alone, a high recurrence rate of approximately 50% was observed, prompting Châtillon et al. [40] to propose that radiotherapy should be considered in patients with incomplete resection and in those with complete resection who have an elevated proliferation index (>6%). In the present study, because of a moderate MIB-1 index, the patient in Case 3 did not undergo radiotherapy, despite the atypical histology of the tumor. However, long-term follow-up is needed to determine if patients with atypical tumors have a worse prognosis.

There are some limitations in the present study. First, the number of patients is small. Second, the duration of follow-up was short. Finally, at the time of the study, the patients...
had stable disease, and further surveillance is hence required to determine the tumor progression. In conclusion, we advocate that ‘central liponeurocytoma’ should be used to include all putative liponeurocytoma sites. The present study identified a number of morphological, immunohistochemical, and genetic features that may aid in the differential diagnosis of liponeurocytoma from similar tumors. A high MIB-1 index (>10%) and incomplete tumor resection may represent adverse prognostic factors in patients with liponeurocytoma, and complete tumor resection should be the surgical goal. However, additional liponeurocytoma cases with long-term follow-up are needed to better estimate the patient prognosis and to develop optimal management protocols.

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Compliance with ethical standards Conflict of interest The authors declare that they have no conflict of interest.

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