Patient Report

Medulloblastoma with epithelioid features in the cerebellar vermis

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Abstract

A 6-year-old girl was admitted with a mass lesion in the cerebellar vermis. She underwent subtotal tumor resection, and on immunohistopathology the tumor consisted of two different parts: typical medulloblastoma (MB) characteristics and atypical teratoid/rhabdoid tumor (AT/RT) features, despite positive integrase interactor 1 expression. The patient was diagnosed with MB with epithelioid features. Chemoradiation therapy was started because of tumor recurrence at the primary site and dissemination to the spinal cord, as determined on magnetic resonance imaging 2 weeks after surgery. The patient died due to tumor progression 13 months after initial diagnosis, although transient partial remission was achieved.

Key words atypical teratoid/rhabdoid tumor, cerebellar vermis, integrase interactor 1, medulloblastoma, rhabdoid cell.

Case report

A 6-year-old girl was admitted to hospital with persistent morning headache and vomiting lasting for 6 months. She also suffered from ataxia beginning 2 weeks before admission. Physical and neurological examinations were unremarkable except for truncal ataxia. Serum laboratory tests were also unremarkable, whereas tumor cells were observed on cerebrospinal fluid cytology. Computed tomography and magnetic resonance imaging (MRI) showed a mass lesion in the cerebellar vermis associated with obstructive hydrocephalus and calcification (Fig. 1). Subtotal tumor resection (90%) and ventricular drainage were performed. Histopathology indicated that the tumor consisted of two different parts. A large part of the tumor consisted of small round cells with hyperchromatic nuclei, scanty cytoplasm, apoptosis, necrosis, and calcification (Fig. 1). On immunohistochemistry the tumor cells were immunopositive for synaptophysin, vimentin, and INI1 (Fig. 2; Table 1); typical characteristics of MB. The other part of the tumor consisted of homogeneous epithelioid cells with large eccentric vesicular nuclei that were strongly eosinophilic with a pale cytoplasm, apoptosis, necrosis, and no calcification (Fig. 1). In this part of the tumor, almost all cells were immunopositive for vimentin and INI1, and some cells were also immunopositive for α-smooth-muscle actin (αSMA) and epithelial membrane antigen (EMA; Fig 2; Table 1). Mindbomb E3 ubiquitin protein ligase 1 (MIB-1) index was 60% in the former part and <5% in the latter part. The immunohistochemical features of the latter part were compatible with AT/RT except for positive INI1 expression. Thus, the patient was diagnosed with MB with epithelioid features.

Paralysis of the lower extremities occurred 1 month after surgical resection. MRI showed hyperintense lesions at the

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Fig. 1 Neuroimaging findings. (a–c) Computed tomography (CT) and magnetic resonance imaging (MRI) at initial diagnosis. (a) Enhanced CT showed a mass lesion occupying the fourth ventricle. Spotty calcifications and heterogeneous enhancement were observed in the tumor. (b) Enhanced T1-weighted imaging showing heterogeneous enhancement in the tumor and obstructive hydrocephalus. (c) The tumor showed a mixture of low, iso-, and high intensity. (d–f) MRI after relapse. (d) Fluid-attenuated inversion-recovery imaging showing a small nodular lesion with mildly increased signal intensity at the primary site (arrow). (e,f) Spinal T2-weighted imaging showing multiple intramedullary tumors between Th5 and L4 (arrows).

Fig. 2 Pathological findings. Medulloblastoma (MB)-like lesions: HE staining showed small round cells with nucleoli and scanty cytoplasm. Tumor cells were immunopositive for vimentin, but were negative for epithelial membrane antigen (EMA) and α-smooth-muscle actin (αSMA). The nuclei of the tumor cells and vascular endothelial cells were immunopositive for integrase interactor 1 INI1. Atypical teratoid/rhabdoid tumor (AT/RT) lesions: HE staining showed epithelioid cells with large and eccentric vesicular nuclei, which were strongly eosinophilic and had pale cytoplasm. Tumor cells were immunopositive for vimentin and EMA, but were negative for αSMA. The nuclei of the tumor cells and vascular endothelial cells were immunopositive for INI1.

Table 1 Immunopathology

<table>
<thead>
<tr>
<th></th>
<th>Synaptophysin</th>
<th>EMA</th>
<th>Vimentin</th>
<th>MIB-1 index</th>
<th>αSMA</th>
<th>AE1/AE3</th>
<th>INI1</th>
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<tbody>
<tr>
<td>MB-like lesions</td>
<td>+</td>
<td>–</td>
<td>Focal</td>
<td>60%</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>AT/RT-like lesions</td>
<td>–</td>
<td>Focal</td>
<td>+</td>
<td>&lt;5%</td>
<td>+</td>
<td>Focal</td>
<td>+</td>
</tr>
</tbody>
</table>

+, >50%; –, negative; αSMA, α-smooth-muscle actin; AT/RT, atypical teratoid/rhabdoid tumor; EMA, epithelial membrane antigen; focal, limited and <50%; INI1, integrase interactor 1; MB, medulloblastoma; MIB-1, mindbomb E3 ubiquitin protein ligase 1.
primary site and spinal cord between Th5 and L4 on T2-weighted and fluid-attenuated inversion recovery imaging (Fig. 1). Chemotherapy with cisplatin, vincristine, cyclophosphamide, etoposide, and methotrexate was started in combination with radiation therapy (local 18 Gy and cerebrospinal irradiation 36 Gy). Dissemination of tumor, however, was recognized at 8 months after initial diagnosis. Transient partial remission was achieved after chemotherapy with three courses of ifosfamide, cisplatin, and etoposide. At 12 months after the initial diagnosis, the patient had meningeal dissemination and obstructive hydrocephalus. Although emergency ventricular drainage and treatment with bevacizumab and intrathecal topotecan were performed, they were ineffective. The patient died 13 months after initial diagnosis. Postmortem examination was not performed because informed consent was not obtained from the parents.

Discussion

We treated a patient who presented with a rare case of a cerebellar tumor with coexistence of two different pathological features. Part of the tumor had typical immunohistochemical properties of MB, whereas the other part had epithelioid features except for positive INI1 staining. Thus, diagnosis and treatment were challenging. Although the patient was treated with intensive chemotherapy targeting AT/RT, it was ineffective. There have been few reports on tumors containing histopathological evidence of MB with epithelioid features. Donner reported a 10-year-old boy with typical MB who developed extraneural metastases with rhabdoid cells after relapse. In that patient, rhabdoid features were not observed on the first pathological examination. In the present patient, however, MB with epithelioid features was already present at initial diagnosis.

Atypical teratoid/rhabdoid tumor can occur anywhere in the central nervous system: 52% in the supratentorial regions, 40% in the infratentorial regions, 5% in the pineal gland, and 2% in the spinal cord. Tumor location is similar between AT/RT and MB. MRI findings are also similar between these tumors, showing low to iso-intensity on T1-weighted imaging and heterogeneous enhancement.Histological features are also similar between AT/RT and MB and, as such, are not always useful for distinguishing between these two tumors. Immunohistochemical staining, however, is a useful technique for this purpose. Rhabdoid cells of AT/RT typically express EMA, vimentin, and αSMA, although the positive expression of this triad is not found in MB. The present tumor was extremely rare because it had two regions with entirely different characteristics. One large part of the tumor was immunopositive for vimentin and synaptophysin expression, and the other part was immunopositive for vimentin, EMA, and αSMA.

It is interesting that INI1 expression was seen in the AT/RT-like part of the tumor. INI1, also known as hSNF5 or SMARCB1, is located at chromosome 22q11.2 and is a member of the ATP-dependent SWI/Sucrose Non-Fermentable (SWI/SNF) chromatin-remodeling complex. Deletion or mutation of INI1 is a specific genetic aberration in the pathogenesis of rhabdoid tumors. Loss of INI1 protein expression caused by deletion or mutation of INI1 is associated with rhabdoid tumors. Therefore, the lack of INI1 expression on immunohistochemical staining is an important clue to the diagnosis of AT/RT. There is a possibility, however, that INI1 can be expressed in AT/RT, as in the present case. INI1-immunopositive rhabdoid cells have recently been identified in tumors that fulfilled histopathological and other biomarker criteria of AT/RT. In addition, a small population of AT/RT has been reported to carry a nonsense mutation or inactivation of BRAHMA related gene 1 (BRG1) (SMARCA4), instead of INI1 mutations. BRG1 is a tumor suppressor gene that belongs to the ATP-dependent SWI/SNF chromatin-remodeling complex as well as INI1. Although the present patient did not have a BRG1 mutation, Ho et al. reported five cases of INI1-immunopositive AT/RT that were all immunopositive for BRG1. Further studies are necessary to clarify the relationship between AT/RT and genetic aberrations including INI1 and BRG1.

In conclusion, we have described a patient with a mixture of AT/RT and MB in one tumor. Immunohistochemistry clearly demonstrated the differences in the two components and contributed to the diagnosis and determination of the treatment regimen, although the tumor was resistant to multidisciplinary therapy. Further studies are necessary to clarify the relationship between AT/RT and MB.

Acknowledgments

This study was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology (26293252 and 26461551) and Grants-in-Aid from the Research Committee of Rare Intractable Epilepsy Syndrome Registry, the Ministry of Health, Labour and Welfare of Japan.

Disclosure

The authors declare no conflicts of interest.

Author contributions

E.T. and J.H. gave pathological conceptual advice. T.H. and A.O. critically reviewed the manuscript and supervised the whole process. All authors read and approved the final manuscript.

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