Cerebellopontine angle SHH-activated embryonal tumor without interaction from the cerebellum in Cowden syndrome: A case report

Takahiro Ishikawa[1], Kohei Fukuoka[1], Daiju Oba[1], Kayoko Ichimura[1], Yonehiro Kanemura[2], Yutaka Tanami[1], Hirofumi Ohashi[1], Atsuko Nakazawa[1], Jun Kurihara[1], and Katsuyoshi Koh[1]

[1]Saitama Kenritsu Shoni Iryo Center
[2]Kokuritsu Byoin Kiko Osaka Iryo Center

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Abstract

Among intracranial embryonal tumors, genetic/epigenetic analysis can help unveil the molecular background. Herein, we report a case of a cerebellar pontine angular embryonic tumor complicated by Cowden syndrome in an infant. The tumor radiologically lacked evidence of interaction with the cerebellum and appeared to show continuity with the pons. Pathological appearance was similar to that of a medulloblastoma with extensive nodularity. DNA methylation analysis indicated that the tumor was a "medulloblastoma, sonic hedgehog-activated" with a substantial confidence. Although the diagnosis deviated from the definition of medulloblastoma, clinical, pathological and molecular data suggested that it was an "ectopic" medulloblastoma.

Introduction

A recent research using genome-wide DNA methylation analysis by Sturm et al. highlighted that embryonal tumors of the central nervous system (CNS), formerly called CNS-primitive neuroectodermal tumors (PNET), consisted of various types of tumors including a number of novel tumor entitiessuch as *BCOR* -altered high-grade neuroepithelial tumors[1)]. Considering the clinical and molecular heterogeneities, performing genetic and epigenetic analysis has become essential to reveal the molecular background of the tumor and establish a "true" diagnosis in patients with CNS embryonal tumors, not otherwise specified (NOS).

Herein, we report a case of an isolated cerebellar pontine angular embryonal tumor associated with Cowden syndrome in an infant. This report highlights the clinical importance of molecular and genetic diagnostic approaches accompanied by conventional pathological and radiological techniques for establishing accurate diagnosis to enable effective treatment of patients with embryonal CNS tumors based on underlying genetic/epigenetic conditions.

Case

A 1-year-old female infant was referred to our hospital from a local hospital due to the detection of a tumor in the left cerebellopontine angle (CPA) on brain magnetic resonance imaging (MRI). Physical examination and blood tests revealed no notable abnormal findings, except for an enlarged head circumference (+2.1SD). The patient also presented with an intermittent squall for a short period of time, with lacrimation only from the left eye. Radiologically, the tumor did not directly interact with the cerebellum but appeared to show continuity with the left border of the pons (Figure 1). The left trigeminal nerve was compressed by the tumor (Figure 1). The patient underwent a biopsy with craniotomy, and the postoperative course was uneventful. The tumor morphologically consisted mainly of large nodular structures with well-defined

borders and low-to-moderate cell densities within the nodules. Between the nodules, a dense network of cells with a high nuclear/cytoplasm ratio and round nuclei with hyperchromatic chromatin was observed. Silver staining revealed numerous reticular fibers in the dark background surrounding the bright nodules. The MIB-1 index score was low at the nodules but high (68%) around the nodules. Immunohistochemical staining was positive for synaptophysin and NeuN and negative for GFAP. INI-1 immunoreactivity was retained in all specimens (Figure 1). Overall, the pathological appearance was very similar to medulloblastoma with extensive nodularity. Based on the recently-updated WHO's classification of central nervous system tumors, an initial diagnosis of "embryonal tumor, NOS" was made owing to the unusual tumor location and the lack of evidence of an interaction with the cerebellum, which is regarded as the origin of a medulloblastoma. Molecular analysis was performed to elucidate tumor pathogenesis. Based on expression analysis using NanoString technology, the case was included into the SHH subgroup with a high confidence value. Using DNA methylation analysis with the molecular classifier v12.5, developed by the German Cancer Center, the tumor was also classified as "Medulloblastoma, SHH-activated" with a substantially calibrated score of 0.766. A mutation panel sequencing of the tumor revealed a pathogenic variant of *PTEN* (c.493G>T:p.Gly165Ter) with a variant allele frequency of 84.62%. Subsequent sequencing of normal tissue confirmed that the variant was a germline mutation, indicating a diagnosis of Cowden syndrome (Figure 2A). Additionally, copy number analysis revealed a loss of heterozygosity at 10q, where the *PTEN*was located (Figure 2B). Altogether, the molecular analyses supported the classification of the tumor as medulloblastoma despite its atypical location and no radiological sign of the relationship with the cerebellum. She underwent four courses of chemotherapy consisting of cyclophosphamide, etoposide, cisplatin, vincristine, and intrathecal methotrexate, followed by high-dose chemotherapy with thiotepa and melphalan, according to the protocol of the Japanese Pediatric Brain Tumor Consortium[2)]. We performed a second-look surgery for partial resection of the tumor following high-dose chemotherapy due to minimal reduction in the size of the lesion, as observed on brain MRI, even after intensive treatment. The pathological specimen obtained from the second operation revealed disappearance of the high-cellularity area among the nodules, and the MIB-1 index was reduced to 5%, suggesting the cytoreductive effectiveness of chemotherapy. The patient has remained well without evidence of recurrence for 18 months since the diagnosis. The periodic squall, initially interpreted as a trigeminal neuralgia due to nerve compression by the tumor, has persisted with a mild reduction of the symptoms after administration of carbamazepine.

Discussion

In this report, we presented the case of an infant with SHH-activated embryonal tumor that developed as an isolated CPA lesion, diagnosed using both pathological and molecular diagnostics. Molecular classification using DNA methylation analysis has emerged as a novel diagnostic tool because most CNS tumors including medulloblastoma may have distinct methylation profiles. With this analysis, several previous reports have been documented about "medulloblastoma" occurring in different regions of the cerebellum or fourth ventricle. Liu et al. reported seven cases of embryonal tumors in the pineal region, classified as "Medulloblastoma, WNT-activated (MB-WNT)." All cases exhibited missense mutations in exon3 of *CTNNB1* and three cases exhibited monosomy 6, which is unusual in pineoblastomas but typically observed in WNT-activated medulloblastomas[3)]. Arnault et al. also reported the case of a 5-year-old girl with an embryonal tumor in the sellar and suprasellar regions, which was initially diagnosed as CNS-PNET but later classified as a WNT-activated medulloblastoma based on DNA methylation analysis[4)]. In terms of SHH-activated medulloblastoma, Grammel et al. presented evidence of tumor development outside the cerebellum. In their report, granule neuron precursors, known to be the cells of origin of SHH medulloblastoma, were observed in the cochlear nuclei of the brainstem and was suggested to be the cellular origin of the tumor[5)]. The tumor in the present case appeared to have developed from the ventral side of the pons, which is not concordant with the location of the cochlear nuclei in the pons.*PTEN* alteration possibly led to mismigration of granule cells, leading to tumor occurrence in an unusual location, because the gene may play a critical role in cell migration during brain development[6)].

In our case, the patient was diagnosed with Cowden syndrome based on genetic testing of the tumor, which may also support the diagnosis of medulloblastoma. Cowden syndrome is an autosomal dominant genetic

disease in which multiple hamartomatous lesions. *PTEN* mutations have been identified as causative genetic alterations in 80% of the patients; malignancies occur frequently in young adulthood, and the most common sites are the breast, thyroid, and uterus[7]. Development of malignant brain tumors is extremely rare in patients with Cowden Syndrome.

Only six cases of Cowden syndrome with intracranial embryonal tumors have been reported till date, and all of them were actually medulloblastomas[8][9]. In these reports, all patients with Cowden syndrome were diagnosed with medulloblastoma at the age of <2 years. Among the patients with detailed information regarding pathology and molecular subgroups, two were diagnosed with pathologically confirmed desmoplastic/nodular subtype or MBEN, and four were diagnosed with SHH-activated type medulloblastoma based on molecular analysis[8]. These clinical and molecular features are consistent with those in our case, except for the site of tumor development.

Conclusion

Herein, we reported the case of an isolated cerebellar pontine angular embryonal tumor complicated by Cowden syndrome. Although its location did not meet the definition of medulloblastoma, the clinical, histological, and molecular genetic findings strongly suggested its presence. Therefore, the tumor was considered to be an "ectopic" medulloblastoma. Molecular genetic analysis is essential for revealing the underlying molecular genetic background of CNS embryonal tumors, NOS, as it can facilitate optimal treatment.

Acknowledgement

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Figure legends:

Figure 1 . Tumor imaging findings

(a–d) A tumor measuring approximately 1.5 cm can be visualized in the left cerebellopontine angle (red arrow).

(a) Contrast enhancement effect was observed only in the anterior area on gadolinium-enhanced, T1-weighted images. (b) Diffusion-weighted images showed diffusion limitation. (c–f) The tumor appeared to be continuous with the left border of the pons. (d) The right trigeminal nerve (green arrowhead) is compressed by the tumor.

(g and h) The tumor morphologically consists mainly of large nodular structures with well-defined borders, and low-to-moderate cell densities within the nodules. Between the nodules, cells with a high N/C ratio and round nuclei with densely packed hyperchromatic chromatin are observed. (i) Silver staining reveals reticular fibers in the dark background surrounding the bright nodules. (j) The MIB-1 index is low at the nodules, but high at 68% around the nodules.

Figure 2. DNA sequencing

(a) DNA sequencing of normal tissue confirms the germline pathogenic variant of *PTEN* . (b) Copy number analysis of the tumor reveals copy number neutral loss of heterozygosity of chromosome 10q, where*PTEN* is located.

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