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Extremely Late Recurrence 21 Years after Total Removal of Immature Teratoma: A Case Report and Literature Review

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Abstract

Immature teratoma (IMT) is normally treated by resection and adjuvant therapy. The present unusual case of recurrent germinoma occurred 21 years after total resection of pineal IMT. A 3-year-old boy presented with headache, disturbance of consciousness, and Parinaud's syndrome. Magnetic resonance (MR) imaging revealed a pineal mass lesion, and total resection of the tumor was achieved. The histological diagnosis was mature teratoma. He did not receive further treatment, and did well without recurrence for 20 years. However, he suffered headache 21 years after resection, and MR imaging revealed a homogeneously enhanced pineal mass with low minimum apparent diffusion coefficient value and proton MR spectroscopy showed a huge lipid peak. The levels of tumor markers were not elevated. Cerebrospinal fluid (CSF) cytology found atypical cells with large nuclei and irregularly shaped nucleoli. To elucidate the relationship between the primary and recurrent tumors, we reviewed the histological specimens and CSF cytology at the initial treatment and found a subset of incompletely differentiated components resembling fetal tissues in the histological specimen and atypical large cells in the CSF. Based on these radiological and histological findings, we presume that the recurrent disease was disseminated germinoma after the resection of disseminated IMT. He received chemotherapy and craniospinal radiation therapy, and the enhanced lesion and atypical cells in the CSF disappeared. This case demonstrates that disseminated IMT can be controlled for the long term without adjuvant therapy, but may recur as germinoma. Tumor dormancy may account for this unusual course.

Key words: immature teratoma, total resection, late recurrence

Introduction

Intracranial teratomas are uncommon neoplasms occurring mainly in the pediatric population. Teratomas, including malignant types, account for 0.4% of all brain tumors in Japan.[1)] Teratomas are classified as central nervous system (CNS) germ cell tumors (GCTs), and can be subclassified into mature teratoma, immature teratoma (IMT), and teratoma with malignant transformation. IMT contain incompletely differentiated components resembling fetal tissues and have a much higher recurrence rate than mature teratoma.[2,3)] Consequently, combined treatments of resection, radiation therapy, and chemotherapy are generally recommended for the control of such aggressive IMTs.[2,3)] On the other hand, radiation and chemotherapy can be deferred or omitted if gross total resection is achieved in patients with low-grade IMT, suggesting that the role of adjuvant therapy requires clarification.[4)]

Recurrence of CNS GCT could occur later than expected, especially in germinoma, as 26-36% of cases of germinoma had the first recurrence at 5 years or later, and some cases recurred more than 20 years after initial treatment.[5,6)] In contrast, late recurrence is rare in patients with non-germinomatous GCTs (NGGCTs).[6,7)] Only six cases of late recurrence of NGGCTs have been reported.[8–13)] All six cases had mature teratoma at initial treatment and three cases recurred as germinoma. However, no case of late recurrence of IMT is known. Whether such differences

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in behavior result from the effects of adjuvant therapy or the biological nature of IMT remains unclear.

We describe an unusual case of recurrent germinoma occurring 21 years after total resection of a disseminated IMT.

Case Report

A 3-year-old boy presented with headache, vomiting, and disturbance of consciousness. He was drowsy and had the Parinaud's syndrome. Head computed tomography (CT) demonstrated severe hydrocephalus (Fig. 1A). He was referred to another hospital and underwent emergent continuous ventricle drainage, followed by ventriculoperitoneal (VP) shunt. Magnetic resonance (MR) imaging obtained after the VP shunt demonstrated a heterogeneously enhanced mass in the pineal region (Figs. 1B and 1C), and he was referred to our department.

On admission, he was alert and had the Parinaud's syndrome. All tumor markers, including human chorionic gonadotropin (HCG), β-HCG, alpha-fetoprotein (AFP), and placental alkaline phosphatase, were within normal limits in both the serum and cerebrospinal fluid (CSF) obtained from the VP shunt reservoir. CSF cytology did not identify any atypical cells at that time. Based on these findings, our diagnosis was GCT mainly consisting of teratoma. Tumor resection was performed through the right occipital transtentorial approach. Intraoperatively, the tumor had a thick white capsule and did not adhere to the wall of the third ventricle. Postoperative MR imaging showed the tumor was totally resected (Fig. 1D). Histological examination revealed that the tumor contained differentiated muscles, glands, and skin, and the final diagnosis was mature teratoma (Fig. 2). The patient did not receive either radiation therapy or chemotherapy after resection, and regular follow-up MR images three times a year until first five years, twice a year until 10 years, and once a year or two-years thereafter for a lifetime. We found no recurrent disease. He continued to do well and manage his own affairs after surgery, without recurrence or newly developed neurological symptoms, for 20 years.

However, 21 years after the initial treatment, he suffered severe headache, and MR imaging with contrast medium revealed a newly developed homogeneously enhanced lesion in the pineal region and enhancement of the surface of the brainstem (Figs. 3A and 3B). Minimum apparent diffusion coefficient (ADC) value of the pineal lesion was 0.56×10^{-3} mm^2/sec. Proton MR spectroscopy of the pineal lesion found increased choline/creatine phosphate ratio, decreased N-acetyl aspartate/creatine phosphate ratio, and a huge lipid peak (Fig. 3C). The levels of HCG, β-HCG, HCG-C terminal peptide, and AFP were not elevated in either the serum or CSF obtained from the VP shunt reservoir. CSF cytology detected atypical cells with large nuclei, granular chromatin, and irregularly shaped nucleoli (Fig. 4D). These findings suggested the presence of disseminated recurrent tumor cells, but we could not make the definitive diagnosis based only on the findings of CSF cytology.

To elucidate the relationship between the primary and recurrent tumors, we carefully reviewed the findings from the initial treatment. Re-examination of the histological

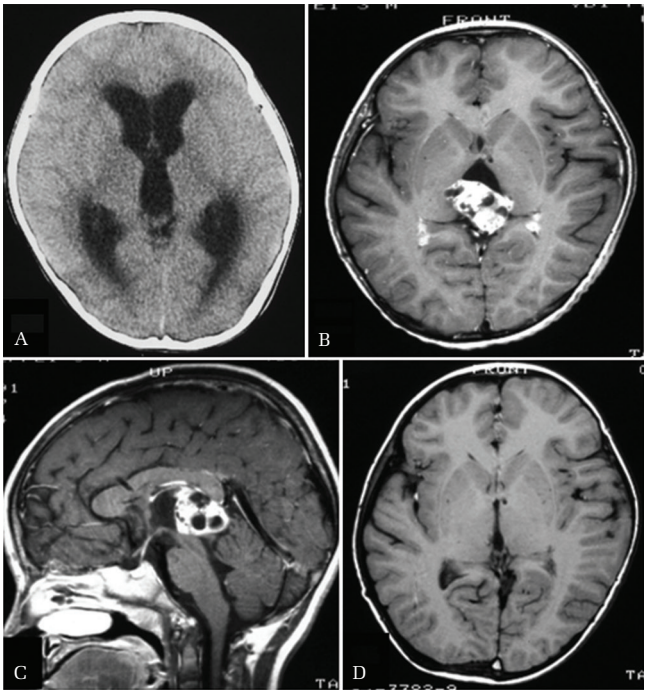

Fig. 1 Neuroimaging findings at the first presentation. A: Preoperative computed tomography scan demonstrating severe hydrocephalus. B and C: Axial (B) and sagittal (C) T_1-weighted magnetic resonance (MR) images with gadolinium on admission demonstrating a heterogeneously enhanced tumor in the pineal region. D: Postoperative T_1-weighted MR image with gadolinium demonstrating complete resection of the pineal tumor.

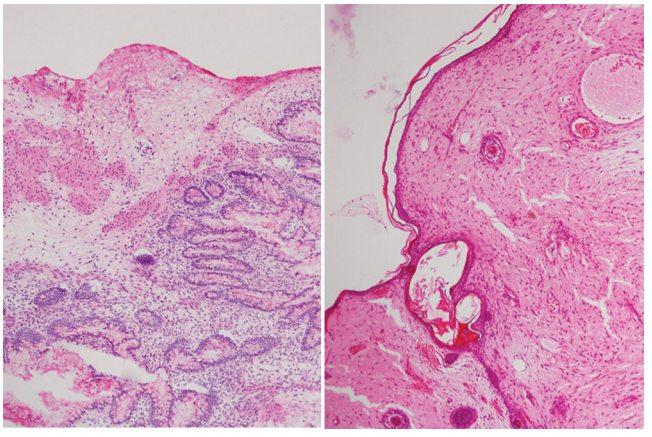

Fig. 2 Photomicrographs of the surgical specimen obtained from the primary pineal lesion demonstrating the tumor consisted of differentiated muscles and glands (*left*), and skin (*right*). Hematoxylin and eosin staining, original magnification ×100.

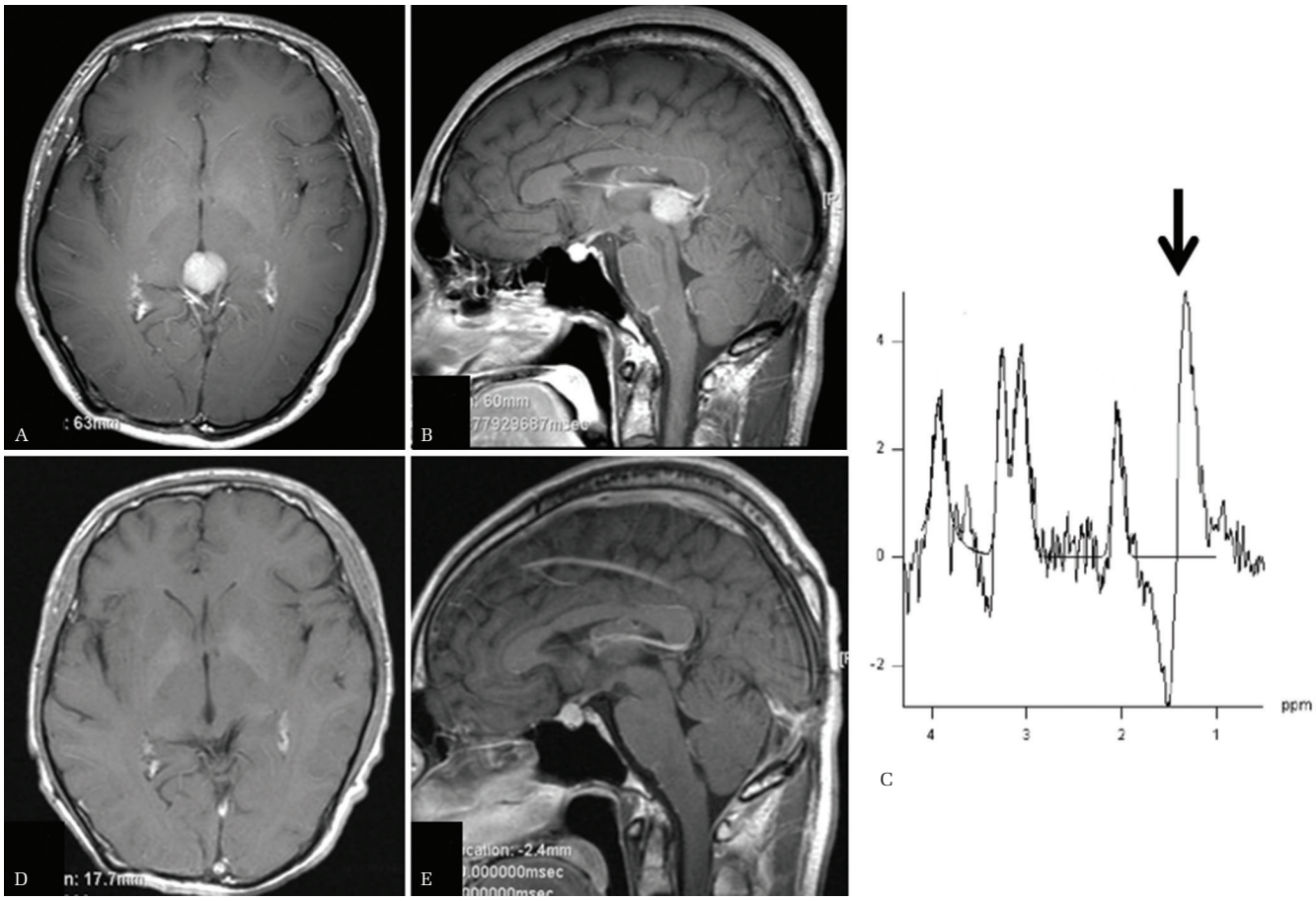

Fig. 3 A and B: Axial (A) and sagittal (B) T_1-weighted magnetic resonance (MR) images with gadolinium at recurrence demonstrating a homogeneously enhanced lesion in the pineal region and enhancement on the surface of the brainstem. C: Proton MR spectrum demonstrating a huge peak for lipid (*arrow*). D and E: Axial (C) and sagittal (D) T_1-weighted MR images with gadolinium demonstrating complete remission of the pineal and disseminated lesions after salvage chemotherapy and radiation therapy.

samples found an immature component with primitive neuroectodermal element resembling neuroepithelial rosettes (Fig. 4A), and embryogenic mesenchymal tissues (Fig. 4B). Review of the CSF cytology detected clusters of monomorphic plump cells with oval eccentric nucleus, fine granular chromatin, small single nucleolus, and abundant pale to vacuolated cytoplasm. These atypical cells had similar morphology to the cells obtained at recurrence (Figs. 4C and 4D). These findings suggested that the primary lesion was not a mature teratoma, but an IMT with CSF dissemination.

The proton MR spectroscopy findings of homogeneous enhancement with dissemination, low minimum ADC value, and the presence of huge lipid peak, the absence of tumor markers, and the findings of CSF cytology suggested that the recurrent lesion was a germinoma.[14] He received chemotherapy consisting of 3 courses of ifosfamide, cisplatin, and etoposide, followed by 24 Gy of radiation therapy to the craniospinal axis. After the first course of chemotherapy, MR imaging showed complete disappearance of the enhanced lesion (Figs. 3D and 3E) and CSF cytology detected no atypical cells. This prompt complete response to the chemotherapy supported the diagnosis of germinoma.[14] He was discharged without a newly developed neurological deficit, and had had no recurrence at 46 months after the salvage therapy.

Discussion

This unusual case of pineal IMT with CSF dissemination, which was overlooked at that time, did not progress for 20 years after only resection, but recurred at the primary site with CSF dissemination 1 year later. Although no definitive histological diagnosis of the disseminated cells in the CSF was established, we presumed that the recurrent disease consisted of germinoma based on the pre-treatment MR imaging findings, ADC value, absence of tumor markers, and sensitivity to chemotherapy.[14]

Various mechanisms have been proposed for long-term remission of disseminated IMT and late recurrence of germinoma-like lesion. Gross total resection is the most important factor to control IMT.[4,15] Adjuvant chemotherapy

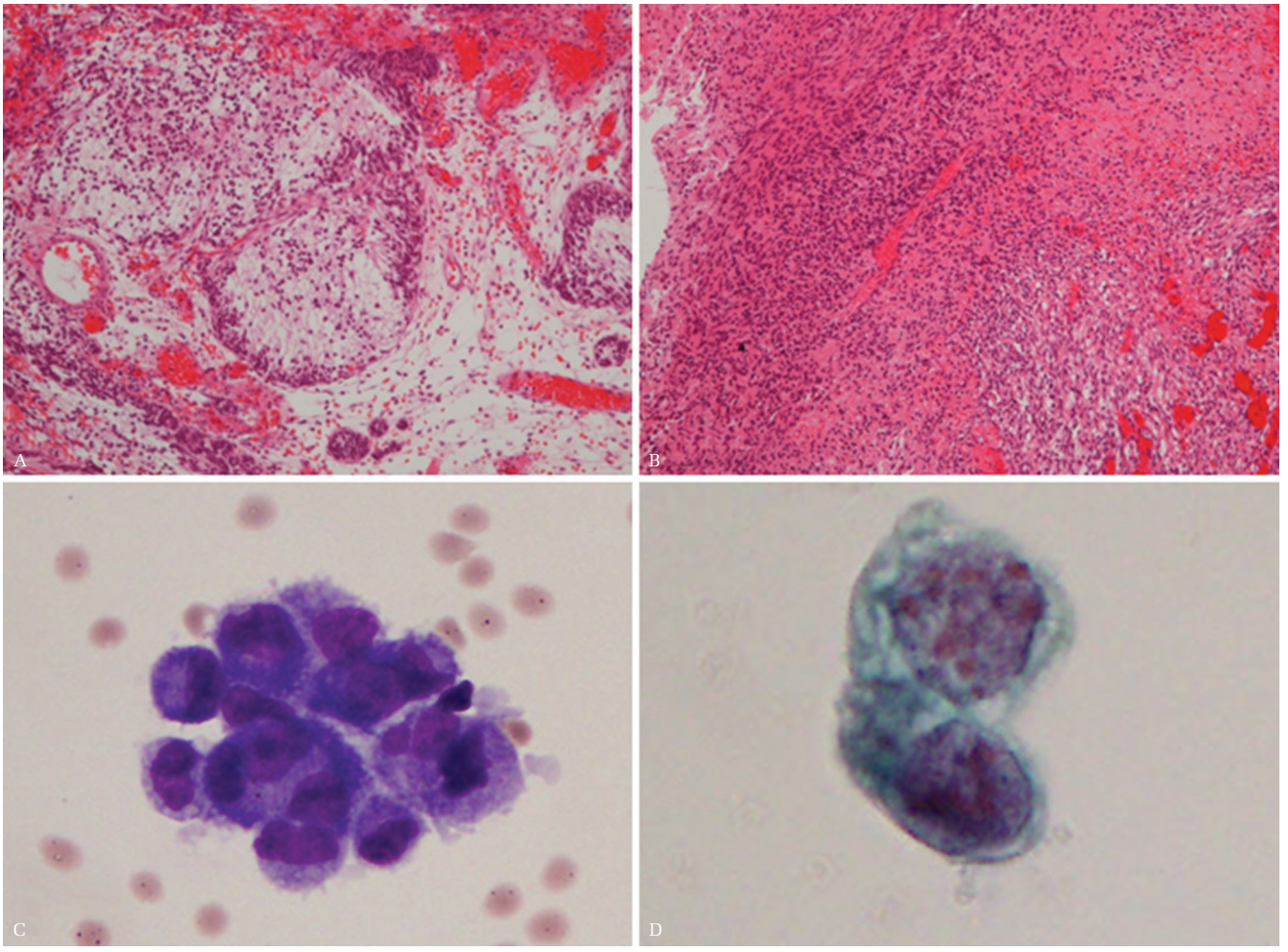

Fig. 4 A and B: Photomicrographs of the surgical specimen obtained from the primary pineal lesion demonstrating primitive neuroectodermal element resembling neuroepithelial rosettes (A), and embryogenic mesenchymal tissues (B). Hematoxylin and eosin staining, original magnification ×100. C and D: Cerebrospinal fluid (CSF) cytology at initial presentation and recurrence. Giemsa staining of the CSF sample obtained from ventriculoperitoneal (VP) shunt reservoir puncture at initial presentation demonstrating clusters of monomorphic plump cells with oval eccentric nucleus, fine granular chromatin, small single nucleolus, and abundant pale to vacuolated cytoplasm (C). Papanicolaou staining of the CSF sample obtained from VP shunt reservoir puncture at recurrence demonstrating atypical large cells with large hyperchromatic nuclei, dispersed chromatin, and vacuolated cytoplasm (D). Original magnification ×400.

and radiotherapy are generally recommended even after total resection of IMT due to the high recurrence rate.[2,3] However, the use of radiation and chemotherapy remains controversial because of the susceptibility at younger age,[1] low sensitivity to chemotherapy,[15–17] and lack of understanding of the natural course. For example, 5 of 6 children with IMT survived without recurrence for 47-158 months after only aggressive resection.[4] In the present case, long-term disease control was achieved without adjuvant therapy despite the presence of disseminated disease in the CSF.

Long-term control of the primary lesion and disseminated disease are important. Aggressive resection of primary IMT is one of the factors contributing to long-term tumor control, especially in tumors with limited content of immature neuroepithelial tissue and normal level of AFP.[4,15] Spontaneous maturation may also occur and induce dormancy in the infiltrating IMT.[18] Most reported cases with maturation of IMT were treated with chemotherapy, but 3 of 14 cases showed spontaneous maturation.[19] In the present case, these factors may have lead to the long-term control of the primary site.

Long-term control of dissemination is also unusual. Spontaneous regression is known in patients with germinoma, possibly resulting from the radiation exposure during diagnostic CT, or the immune response after surgery.[20–22] To achieve long-term tumor control, tumor cells need to remain dormant for the long term, or to disappear completely. The late recurrence in our patient indicated that the tumor cells had remained dormant for 20 years.

Therefore, prolonged dormancy may be permanent or lead to tumor cell escape and late recurrence depending on the immune response.[23]

Late recurrence of GCT has been recognized as more frequent than expected, especially in germinoma.[5,6] In contrast, most IMTs recur within 5 years after the initial treatment because of its aggressive nature.[2,3,15] No germinoma component was detected in our first specimen obtained at surgical resection, but the late recurrence in this case is more likely attributable to the presence of germinoma component rather than malignant component. The breakdown of tumor dormancy with immunological changes is considered to be one of the mechanisms for the late recurrence of germinoma. Changes in hormonal stimulation can contribute to progression in intratubular GCT of the testis.[24] In this hypothesis, abnormal gonocytes, which are susceptible to mutation, stay dormant from the intrauterine period until puberty and undergo proliferation during and after puberty under hormonal stimulation. Hormonal stimulation at puberty has also converted dormant pineal GCT to rapidly growing IMT and germinoma.[25] Our patient was apparently too old to conclude the influence of hormonal stimulation at puberty, but this mechanism must be considered as one of the causes of late recurrence.

Mature teratoma is considered to be curable with only total resection.[2,3,26] However, some patients with mature teratoma have developed recurrent GCTs even after gross total resection.[8–13,22,27–29] Histological diagnoses of the secondary lesion found pathology other than mature teratoma in most cases. One explanation for this finding is that a small component of germinoma or malignant GCT was overlooked at initial treatment as the present case. Similarly, a tiny component of IMT and germinoma was reported in two cases of mature teratoma, indicating the difficulty of diagnosis of teratoma.[2] To avoid recurrence through such a mechanism, the meticulous histological examination is essential to accurately characterize mature teratomas.

This rare case of IMT with CSF dissemination developed recurrent disease at the primary site and CSF dissemination 21 years after resection. IMT may develop even after long-term remission. Although the actual mechanism remains unknown, tumor dormancy modulated by the immune response or hormonal stimulation, or spontaneous maturation of IMT may be involved.

Conflicts of Interest Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

References

1) Committee of Brain Tumor Registry of Japan: Part I General features of brain tumors. Report of Brain Tumor Registry of Japan (1984-2000). *Neurol Med Chir* (*Tokyo*) 49 Suppl: PS1–PS25, 2009
2) Sawamura Y, Kato T, Ikeda J, Murata J, Tada M, Shirato H: Teratomas of the central nervous system: treatment considerations based on 34 cases. *J Neurosurg* 89: 728–737, 1998
3) Matsutani M, Sano K, Takakura K, Fujimaki T, Nakamura O, Funata N, Seto T: Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. *J Neurosurg* 86: 446–455, 1999
4) Phi JH, Kim SK, Park SH, Hong SH, Wang KC, Cho BK: Immature teratomas of the central nervous system: is adjuvant therapy mandatory? *J Neurosurg* 103 (6 Suppl): 524–530, 2005
5) Kamoshima Y, Sawamura Y, Ikeda J, Shirato H, Aoyama H: Late recurrence and salvage therapy of CNS germinomas. *J Neurooncol* 90: 205–211, 2008
6) Kanamori M, Kumabe T, Saito R, Yamashita Y, Sonoda Y, Ariga H, Takai Y, Tominaga T: Optimal treatment strategy for intracranial germ cell tumors: a single institution analysis. *J Neurosurg Pediatr* 4: 506–514, 2009
7) Jinguji S, Yoshimura J, Nishiyama K, Yoneoka Y, Sano M, Fukuda M, Fujii Y: Long-term outcomes in patients with pineal nongerminomatous malignant germ cell tumors treated by radical resection during initial treatment combined with adjuvant therapy. *Acta Neurochir* (*Wien*) 157: 2175–2183, 2015
8) Hirano T, Kumabe T, Murakami K, Watanabe M, Shirane R, Yoshimoto T: Metachronous neurohypophysical immature teratoma occurring 10 years after total resection of pineal mature teratoma. *Childs Nerv Syst* 17: 286–289, 2001
9) Ikeda J, Sawamura Y, Kato T, Abe H: Metachronous neurohypophyseal germinoma occurring 8 years after total resection of pineal mature teratoma. *Surg Neurol* 49: 205–208; discussion 208–209, 1998
10) Morimura T, Kubo H, Takeuchi J, Jii B: Pineal dermoid cyst developing 18 years after gross total removal of a pineal mature teratoma. *Neurol Med Chir* (*Tokyo*) 38: 297–300, 1998
11) Sugimoto K, Nakahara I, Nishikawa M: Bilateral metachronous germinoma of the basal ganglia occurring long after total removal of a mature pineal teratoma: case report. *Neurosurgery* 50: 613–616, 2002
12) Tsuchida T, Tanaka R, Kobayashi K, Ueki K, Koizumi R: [Development of 2 cell pattern pinealoma 15 years after total removal of pineal teratoma]. *No To Shinkei* 28: 893–899, 1976 (Japanese)
13) Utsuki S, Oka H, Sagiuchi T, Shimizu S, Suzuki S, Fujii K: Malignant transformation of intracranial mature teratoma to yolk sac tumor after late relapse. Case report. *J Neurosurg* 106: 1067–1069, 2007
14) Saito R, Kumabe T, Kanamori M, Sonoda Y, Watanabe M, Mugikura S, Takahashi S, Tominaga T: Early response to chemotherapy as an indicator for the management of germinoma-like tumors of the pineal and/or suprasellar regions. *J Clin Neurosci* 21: 124–130, 2014

15) Huang X, Zhang R, Zhou L: Diagnosis and treatment of intracranial immature teratoma. *Pediatr Neurosurg* 45: 354–360, 2009
16) Schild SE, Scheithauer BW, Haddock MG, Wong WW, Lyons MK, Marks LB, Norman MG, Burger PC: Histologically confirmed pineal tumors and other germ cell tumors of the brain. *Cancer* 78: 2564–2571, 1996
17) Yoshida J, Sugita K, Kobayashi T, Takakura K, Shitara N, Matsutani M, Tanaka R, Nagai H, Yamada H, Yamashita J, Oda Y, Hayakawa T, Ushio Y: Prognosis of intracranial germ cell tumours: effectiveness of chemotherapy with cisplatin and etoposide (CDDP and VP-16). *Acta Neurochir* (*Wien*) 120: 111–117, 1993
18) Shaffrey ME, Lanzino G, Lopes MB, Hessler RB, Kassell NF, VandenBerg SR: Maturation of intracranial immature teratomas. Report of two cases. *J Neurosurg* 85: 672–676, 1996
19) Lian LJ, Tang MY, Liu TH: Retroconversion of ovarian immature teratoma malignancy. *Chin Med J* (*Engl*) 93: 24–30, 1980
20) Fujimaki T, Mishima K, Asai A, Suzuki I, Kirino T: Spontaneous regression of a residual pineal tumor after resection of a cerebellar vermian germinoma. *J Neurooncol* 41: 65–70, 1999
21) Ide M, Jimbo M, Yamamoto M, Hagiwara S, Aiba M, Kubo O: Spontaneous regression of primary intracranial germinoma. A case report. *Cancer* 79: 558–563, 1997
22) Murai Y, Kobayashi S, Mizunari T, Ohaki Y, Adachi K, Teramoto A: Spontaneous regression of a germinoma in the pineal body after placement of a ventriculoperitoneal shunt. *J Neurosurg* 93: 884–886, 2000
23) Manjili MH: The inherent premise of immunotherapy for cancer dormancy. *Cancer Res* 74: 6745–6749, 2014
24) Al-Hussain T, Bakshi N, Akhtar M: Intratubular germ cell neoplasia of the testis: a brief review. *Adv Anat Pathol* 22: 202–212, 2015
25) Jinguji S, Fukuda M, Nagasaki K, Fujii Y: A pineal region germ cell tumor with rapid enlargement after a long-term follow-up: case report. *Neurosurgery* 72: E687–E693, 2013
26) Rosenblum MK, Nakazato Y, Matsutani M: Germ cell tumours, *in* Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (*eds*): *WHO Classification of Tumours of the Central Nervous System, ed 4.* Lyon, IARC, 2007, pp. 197–204
27) Carrillo R, Ricoy JR, Del Pozo JM, García-Uria J, Herrero J: Dissemination with malignant changes from a pineal tumor through the corpus callosum after total removal. *Childs Brain* 3: 230–237, 1977
28) Czirják S, Pásztor E, Slowik F, Szeifert G: Third ventricle germinoma after total removal of intrasellar teratoma. Case report. *J Neurosurg* 77: 643–647, 1992
29) Matsuda K, Maeda Y, Kodama S, Kanemaru R, Sugata I, Asakura T, Mihara T: [Problems on recurrence after removal of teratoma in pineal region—an experience of recurrence of pineal teratoma 4 years after tumor removal]. *No To Shinkei* 34: 1107–1115, 1982 (Japanese)

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