

Mixed germ cell tumor infiltrating the pineal gland without elevated tumor markers: illustrative case

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BACKGROUND Tumors in the pineal region consist of various histological types, and correct diagnosis from biopsy specimens is sometimes difficult. The authors report the case of a patient with a mixed germ cell tumor infiltrating into the pineal gland despite showing no elevation of tumor markers.

OBSERVATIONS An 18-year-old man complained of headache and nausea and showed disturbance of consciousness. Magnetic resonance imaging showed hydrocephalus associated with a cystic pineal tumor. The patient underwent tumor biopsy followed by endoscopic third ventriculostomy for hydrocephalus in a local hospital. A pineocytoma was diagnosed, and the patient was referred to the authors' hospital for treatment. Concentrations of placental alkaline phosphatase, alpha-fetoprotein (AFP), and beta-human chorionic gonadotropin in cerebrospinal fluid were not elevated. However, the authors' review of the tumor specimen revealed some immature cells infiltrating the pineal gland. These cells were positive for AFP, Sal-like protein 4, and octamer-binding transcription factor 3/4; and the diagnosis was changed to mixed germ cell tumor. Chemoradiotherapy was initiated, followed by surgical removal of the residual tumor.

LESSONS Careful examination of all tumor specimens and immunohistochemical analyses are important for accurate diagnosis of pineal tumors.

<https://thejns.org/doi/abs/10.3171/CASE20131>

KEYWORDS mixed germ cell tumor; immunohistochemistry; histological diagnosis; pineocytoma; pineal parenchymal tumor of intermediate differentiation

Tumors of the pineal region are very rare and exhibit a wide pathological spectrum, including germ cell tumors (GCTs); gliomas; and pineal parenchymal tumors, including pineocytomas, pineal parenchymal tumors of intermediate differentiation (PPTIDs), and pineoblastomas. The most common tumors in this region are GCTs, including germinomas, choriocarcinomas, and embryonal cell tumors, accounting for approximately 27%.¹ Pineal parenchymal tumors are the second-most common tumor in this region. Radiological and serological examinations can detect tumors in the pineal region, but differential diagnosis is sometimes difficult. Pathological examination is useful to differentiate tumors in this region, but biopsy specimens are sometimes unhelpful in reaching the correct diagnosis.

We report herein the case of an 18-year-old man with a pineal tumor involving cyst formation and hydrocephalus. A pineocytoma was initially diagnosed, but a mixed GCT was eventually confirmed from further immunohistochemical examinations, even though no tumor markers were elevated.

Illustrative Case

Clinical History and Examinations

The 18-year-old male had been admitted to a local hospital for evaluation of sudden severe headache, nausea, vomiting, and unconsciousness. The patient had no documented history of childhood illnesses or family history of malignancy. Magnetic resonance imaging

ABBREVIATIONS AFP = alpha-fetoprotein; β -HCG = beta-human chorionic gonadotropin; CRX = cone-rod homeobox; CSF = cerebrospinal fluid; DWI = diffusion-weighted imaging; GCT = germ cell tumor; Gd = gadolinium; ICE = ifosfamide, cisplatin, and etoposide; MRI = magnetic resonance imaging; N/C = nuclear-cytoplasmic ratio; OCT3/4 = octamer-binding transcription factor 3/4; PLAP = placental alkaline phosphatase; PPTID = pineal parenchymal tumor of intermediate differentiation; SALL4 = Sal-like protein 4; T1WI = T1-weighted imaging; T2WI = T2-weighted imaging.

INCLUDE WHEN CITING Published March 22, 2021; DOI: 10.3171/CASE20131.

SUBMITTED December 3, 2020. **ACCEPTED** December 11, 2020.

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(MRI) showed a tumor in the pineal region accompanying hydrocephalus (Fig. 1). The tumor appeared isointense on T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), and diffusion-weighted imaging (DWI); and it appeared homogeneously enhancing on gadolinium (Gd)-enhanced T1WI, accompanied by a cystic appearance. No tumors were apparent in the spinal region. Laboratory testing showed no abnormalities in hormone levels, including free triiodothyronine, free thyroxine, thyroid-stimulating hormone, growth hormone, adrenocorticotropic hormone, and prolactin-releasing hormone.

Biopsy in a Local Hospital

The patient was treated with endoscopic third ventriculostomy in combination with a tumor biopsy in a local hospital. On histopathological examination, tumor specimens comprised a cystic portion and a solid portion (Fig. 2A and B). Histopathological examination showed the cystic portion was lined by an epithelial monolayer with no atypia (Fig. 2A and C). The solid portion comprised sheets of uniform cells with round nuclei. The Ki-67 labeling index was higher than 1% in some parts (Fig. 2C–E). The patient was diagnosed with a pineocytoma, and follow-up MRI in the local hospital was recommended.

Pathological Review of the Tumor Specimen in Our Hospital

The patient visited our hospital seeking a second opinion regarding the diagnosis and treatment. Cerebrospinal fluid (CSF) showed no elevation of placental alkaline phosphatase (PLAP). Alpha-fetoprotein (AFP) concentration was < 0.6 ng/mL, and beta-human chorionic gonadotropin (β -HCG) concentration was < 0.5 mIU/mL. Serum AFP

(1.9 ng/mL) and β -HCG (< 0.5 mIU/mL) were also within normal ranges. No significant abnormalities were detected from laboratory data.

We reviewed the 2 tumor specimens from the first operation at the previous hospital: a cystic portion (Fig. 2A) and a solid portion (Fig. 2B). On the basis of the solid portion, we initially suspected a PPTID because of the relatively high Ki-67 labeling index (approximately 60% at a hot spot) and positive results from immunostaining for cone-rod homeobox (CRX, encoded by *CORD2*) (Fig. 2F). In the cystic lesion, we found a small, limited area comprising undifferentiated hyperchromatic cells with a high nuclear-cytoplasmic ratio (N/C) (Fig. 2A and C). These cells and the epithelial monolayer lining the cyst wall were positive for cytokeratin AE1/AE3 and negative for Sall-like protein 4 (SALL4), AFP, CD30, octamer-binding transcription factor 3/4 (OCT3/4), β -HCG, and oligodendrocyte transcription factor. In the solid portion, we identified a small number of tumor cells infiltrating into the pineal gland with infiltrating lymphocytes and a small number of tumor cells positive for SALL4 and OCT3/4 (Fig. 3A–C). In addition, a small part similar to the cystic portion described above was also observed in the specimen that included the solid lesion, and cells in this area were positive for AFP as well as AE1/AE3 keratin and SALL4, with a positive Ki-67 rate of about 60% at the hot spot (Fig. 3D–F). We, thus, concluded that the tumor was a mixed GCT with embryonal components and the cystic lesion was an immature part of the teratoma.

Chemotherapy, Second-Look Surgery, and Adjuvant Treatment

Based on the diagnosis of a mixed GCT, the patient underwent 3 courses of chemotherapy with ifosfamide, cisplatin, and etoposide (ICE) at 900 mg/m² on days 1–5, 20 mg/m² on days 1–5, and 60 mg/m² on days 1–5, respectively (Fig. 4A). Residual tumor after the completion of chemotherapy was totally removed via an occipital tentorial approach.

The tumor specimen obtained from the second-look surgery showed vascular proliferation, degenerated collagen fibers, and psammoma bodies. Immunohistochemistry showed negative results for AFP, SALL4, and OCT3/4 (Fig. 4B). Consequently, the tumor was confirmed as mature teratoma. Postoperatively, no neurological deficits were identified other than mild diplopia. The patient underwent 3 courses of ICE chemotherapy, followed by whole-ventricular irradiation of 35.2 Gy in 22 fractions and boost irradiation of 16.2 Gy in 9 fractions to the pineal region as adjuvant therapies. No recurrence had been observed at 12 months after the treatment (Fig. 4C).

Discussion

Observations

The precise histological diagnosis of tumors in the pineal region is critical because treatment strategies and prognosis differ according to the histological type. In the present case, the initial diagnosis from the local hospital was a pineocytoma, which is usually treated conservatively without surgical intervention. The corrected diagnosis of a mixed GCT, on the other hand, should be treated with surgery and chemoradiotherapy.^{2–5} Neuroimaging studies, a blood test, and CSF examination are useful to detect pineal tumors and helpful for monitoring response to treatment, but these examinations cannot necessarily differentiate a GCT from other tumors.^{6,7} As for MRI, GCTs tend to show a higher apparent diffusion coefficient than pineal parenchymal tumors, and a cutoff value of 125.0×10^6 mm²/sec shows 89.5% accuracy for distinguishing between the 2 tumor types.⁸ In the present case, a GCT was very difficult to confirm because of the lack

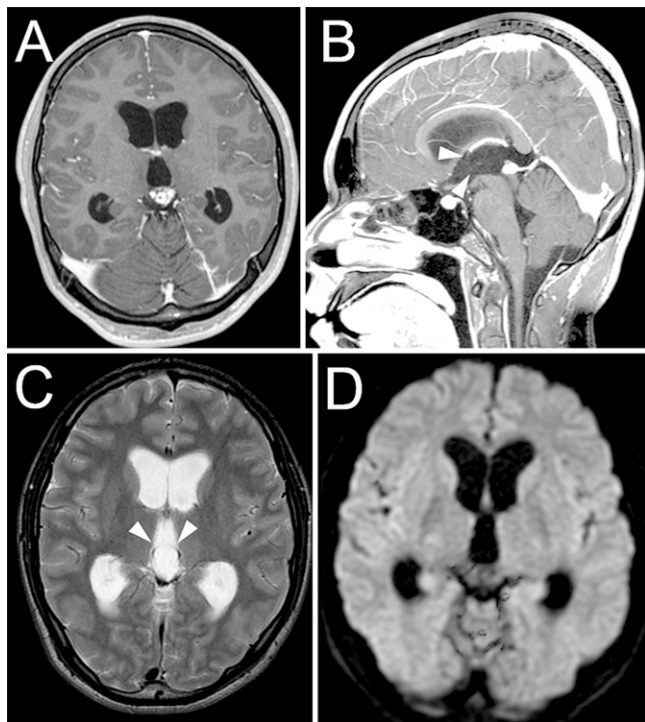


FIG. 1. Brain MRI findings at initial diagnosis. **A** and **B**: A well-demarcated tumor is observed in the pineal region and shows homogeneous enhancement on Gd-T1WI. *White arrowheads* show a cyst of the tumor. **C**: T2WI shows a cyst of the tumor (*white arrowheads*). **D**: DWI shows an isointense tumor in the pineal region.

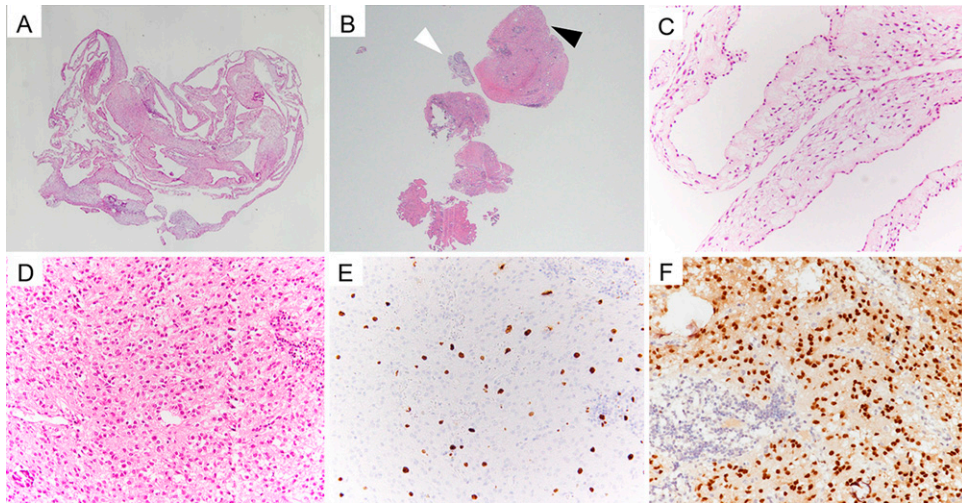


FIG. 2. Histopathological findings of biopsy specimens. **A:** Cystic portion (hematoxylin and eosin [H&E] staining, original magnification $\times 1.25$). **B:** Solid portion (H&E, original magnification $\times 1.25$). *Black arrowhead* shows the pineal gland, magnified in **D**. *White arrowhead* shows the cystic tumor, magnified in **C**. **C:** Cystic portion with a lining of monolayer epithelium without atypia (H&E, original magnification $\times 20$). **D:** Solid portion shows sheets of uniform cells with round nuclei (H&E, original magnification $\times 20$). Cells are star-shaped with projections. Atypia is mild, but cellularity is relatively high without any rosette structures. **E:** Ki-67 labeling index is $> 1\%$ in most of the solid portion but approximately 60% at the hot spot (original magnification $\times 20$). **F:** Most cells in the solid portion are positive for CRX, characteristic of a pineal gland origin, but these are not tumor cells (original magnification $\times 20$).

of characteristic findings on diagnostic imaging or elevated tumor markers.

Histopathological differentiation of GCTs from pineal parenchymal tumors is not always difficult. For example, a germinoma typically shows a 2-cell pattern with large germinoma cells and infiltrating lymphocytes, whereas a pineocytoma shows homogeneous cells characterized by amphophilic cytoplasm surrounding a round or indented nucleus. The pineocytomatous rosettes sometimes observed

in a pineocytoma facilitate differentiation of the 2 types. A PPTID and a pineoblastoma show higher cellularity than a pineocytoma. Immunohistochemically, a germinoma is positive for PLAP and/or c-kit, whereas pineal parenchymal tumors are typically positive for neurofilament protein and synaptophysin. Thus, typical features of GCTs and pineal parenchymal tumors are distinct. However, if the tumor specimen is small, differentiating the 2 pathologies is sometimes difficult. In addition, 32% of intracranial GCTs comprise 2 or more components,

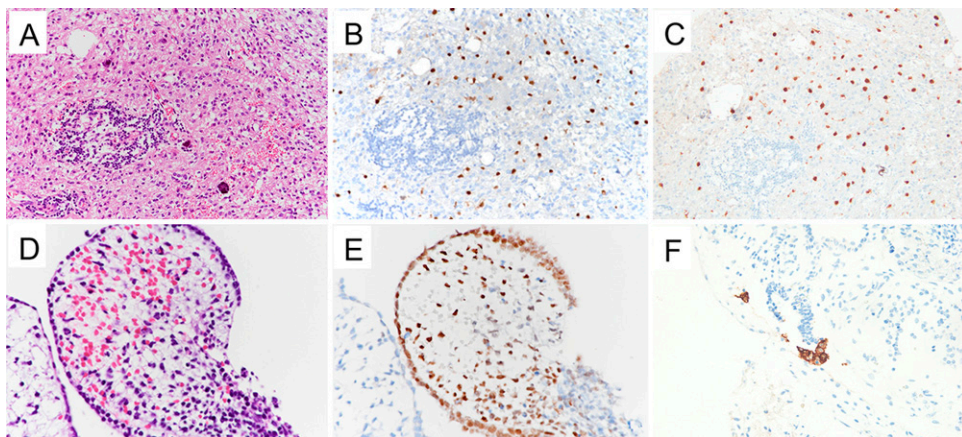


FIG. 3. A GCT infiltrating into the pineal gland. **A:** Some parts of the solid portion contain small numbers of tumor cells infiltrating the pineal gland with infiltrating lymphocytes. Some tumor cells are positive for SALL4 and OCT3/4 (H&E, original magnification $\times 20$). **B:** SALL4 staining (original magnification $\times 20$). **C:** OCT3/4 staining (original magnification $\times 20$). **D:** Cystic wall shows dense cellularity with hyperchromatic cells and a high N/C, with positive staining for SALL4 (H&E, original magnification $\times 20$). **E:** SALL4 staining (original magnification $\times 20$). **F:** Some cells are positive for AFP (original magnification $\times 20$).

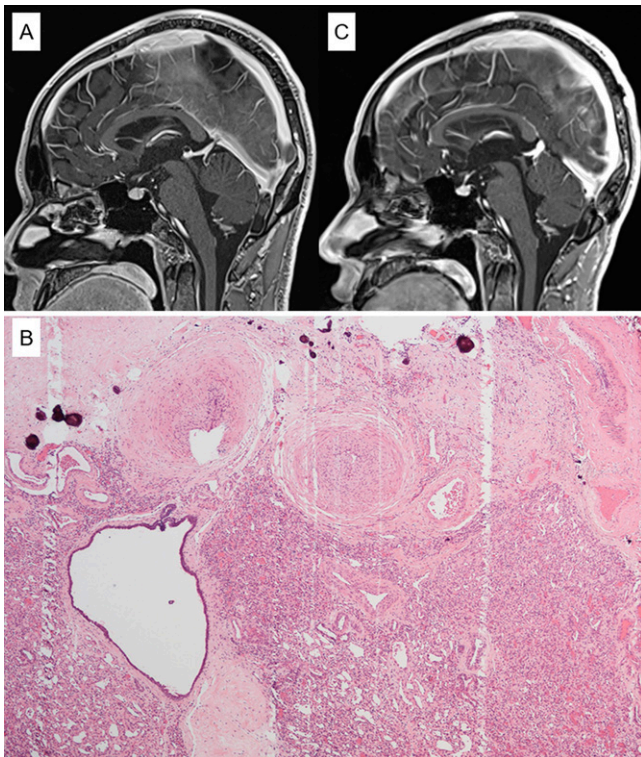


FIG. 4. MRI before and 12 months after treatment and histopathological examination of the tumor. **A:** Gd-enhanced T1WI after 3 courses of chemotherapy shows residual tumor in the pineal region. **B:** Tumor specimen from second-look surgery shows dilated tubular structures, degenerative collagen fibers, and blood vessels (H&E, original magnification $\times 4$). No embryonic cell tumors, yolk sac tumors, or immature neural tubes are present. Results for OCT3/4, SALL4, and AFP are negative. **C:** No tumor recurrence is detected on MRI at 12 months after treatment.

such as germinoma and embryonal components.⁹ Under such circumstances, accurate diagnosis will be more difficult to reach. In the present case, the lack of a 2-cell pattern and the high Ki-67 index of pineal tissue favored the diagnosis of a pineocytoma. Furthermore, only a small number of tumor cells were positive for SALL4, OCT3/4, and AFP, so a correct diagnosis was very difficult to make from histopathological findings alone.

Histopathological examination is important for precise diagnosis and subsequent treatment planning. In this case, histopathological examination revealed a mixed GCT, and the patient was classified to an intermediate-risk group because of the component positive for AFP, rather than a low-risk group, even though tumor markers were negative. Otherwise, the chemotherapy would have been even weaker than ICE, and the radiation field and dose would have been much weaker. Even if tumor markers are negative, biopsy is important because malignant components may be present in limited areas.

Although open surgery, including open needle biopsy, has been shown to represent an accurate procedure with an acceptable complication rate,¹⁰ recent advances in neuroendoscopic surgery have enabled less invasive approaches. In addition, endoscopic surgery can resolve hydrocephalus, commonly caused by pineal region tumors, within the same operative procedure used for biopsy. Actually, hydrocephalus is identified in 58–90% of patients with tumors of the

pineal region.¹¹ Endoscopic third ventriculostomy is safe and highly effective without increasing the chance of CSF dissemination of the tumor.^{12,13} At the same time, CSF sampling can be performed to measure PLAP, which may help to diagnose a germinoma. On the other hand, a disadvantage of neuroendoscopic biopsy is the small amount of tissue sampled, which can lead to misdiagnosis due to sampling error, particularly when the tumor has multiple components. The accurate diagnosis rate in endoscopic biopsy varies from 20% to 100%, although most studies have shown an accuracy $\geq 60\%$, with an average of 81.1%.^{14,15} To avoid misdiagnosis, a broader range of sampling points and sampling of a sufficient volume of tumor are necessary.

Lessons

We have reported the case of a patient with a mixed GCT infiltrating the pineal gland without any elevation of tumor markers. Tumors of the pineal region show a variety of pathologies, and accurate diagnosis is sometimes difficult when only a small specimen is obtained from biopsy. An extensive search for heterogeneous portions within the tumor specimen and confirmation by immunohistochemistry are needed for accurate diagnosis.

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Disclosures

Dr. Arakawa reported grants from Siemens, Philips, Sanofi, Nihon Medi-Physics, MitsubishiTanabe, Takeda, Stryker, Taiho Pharma, Astellas Pharma, and Pfizer, all outside the submitted work; personal fees from Nippon Kayaku, Novocure, AbbVie, UCB Japan, and Otsuka, all outside the submitted work; and grants and personal fees from Ono Pharmaceutical, CLS Behring, Brainlab, Merck, Chugai, Eisai, Meiji Seika, Daiichi Sankyo, and Zeiss, all outside the submitted work. No other disclosures were reported.

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