

Mixed or metachronous germ-cell tumor?

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Abstract

Objective and importance We report the extremely rare occurrence of a second germ-cell tumor at a different site and with different histological types long after total resolution of a pineal germinoma.

Clinical presentation A 21-year-old man who presented with headache and diplopia was admitted to our hospital. Neuroradiological studies revealed a tumor in the pineal region. The tumor was biopsied with endoscope, and third ventriculostomy was performed. Histologically, the tumor proved to be a germinoma. The patient received 3 cycles of combination chemotherapy consisting of carboplatin and etoposide with radiotherapy. The tumor was totally resolute. Twelve months later, he was readmitted with headache and diplopia. Neuroradiological studies showed a tumor in the right temporal lobe.

Intervention The second tumor was totally removed. Histologically, the tumor proved to be a mixed germ-cell tumor, which consisted a yolk-sac tumor and a germinoma. After the second course of chemotherapy, magnetic resonance image studies revealed no evidence of the tumor.

Conclusion The second tumor was considered to be a metachronous neoplasm rather than a recurrence of the original mixed germ-cell tumor, which consisted a yolk-sac tumor and a germinoma.

Keywords Germ-cell tumor · Metachronous · Germinoma · Mixed germ-cell tumor

Introduction

Germ-cell tumors in the central nervous system usually arise in the midline of the brain. They are commonly seen in the pineal region, the suprasellar cistern, the basal ganglia, and the thalamus. Intracranial germ-cell tumors are classified histologically into teratoma, germinoma, embryonal carcinoma, endodermal sinus tumors, and choriocarcinoma and their mixed types. Pineal region tumors are uncommon, comprising 3–11% of all childhood tumors [1, 2] with a somewhat higher incidence in Asian races. Most brain tumors in the pineal region are intracranial germ-cell tumors, especially germinoma [3]. The ratio of their incidence in men to their incidence in women is 7 to 3. It is common for man to have intracranial germ-cell tumors in the pineal region. The incidence of germ-cell tumors originating simultaneously from the pineal and suprasellar regions was reported to be 12.8% [4] and 5.9% [3]. The curability of these tumors depends on the histology. Germinomas can be cured by radiotherapy and/or chemotherapy. The 5-year survival rate of patients with germinomas treated with radiotherapy is more than 90% [5–9]. Pure germinomas are considered to have a good prognosis and a low recurrence rate after total resolution. It is rare for a second germ-cell tumor to occur at a different site and with different histological types after total resolution of a pure pineal germinoma [10]. In the case of the mature teratomas, which were totally removed surgically, radiation therapy does not perform usually. Therefore, recurrence and distant metastasis of mature teratoma were reported not uncommonly. However, because pure germinomas usually received radiation therapy, the recurrence and distant metastasis are very rare. In addition, the metachronous, mixed germ-cell tumor after total resolution of germinoma, which received chemotherapy and radiation

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therapy, is very unusual and extremely rare. In the literature, the metachronous germ-cell tumors are mostly from mature teratomas, but our case is mixed germ-cell tumor from the germinoma, which consisted a yolk-sac tumor and a germinoma. The first tumor, germinoma, was diagnosed with endoscopic biopsy. Thus, underestimation of mixed component was possible. However, serum and cerebrospinal fluid marker studies are compatible with germinoma. Moreover, the response to the additional treatment suggested the pure germinoma. Because the location of the second tumor was parenchyma of the right temporal lobe, not the temporal horn of the ventricle, the possibility of the ventricular seeding was very low.

There was a report of recurrence as a yolk-sac tumor in the peritoneal cavity through the ventriculoperitoneal shunt. The patient was initially diagnosed with germinoma and received chemotherapy and radiation therapy. The tumor totally disappeared after the treatment, but 13 months later, intraperitoneal tumor was detected. The tumor was eradicated with a combination of systemic chemotherapy and local irradiation, with no residual viable tumor cells confirmed at final surgical extirpation [11]. The direct seeding through the shunt system was possible.

This may be the first case report about the intracranial, metachronous, mixed germ-cell tumor which is from the totally resolute germinoma.

Case presentation

The first admission

In September 2003, a 21-yr-old man was admitted with headache and diplopia. On admission, he was lethargic and showed a mild degree of medial gaze paresis of left eyeball.

No other abnormal neurological deficits were noted. Results of hormonal tumor marker studies including alpha-fetoprotein (α -FP) and beta-human chorionic gonadotropin (β -hCG) were in normal ranges. Magnetic resonance image (MRI) showed strongly enhancing mass lesion in the pineal region accompanied by moderate obstructive hydrocephalus (Fig. 1a,b). No abnormality was found on his spinal MRI. To obtain the tumor tissue for diagnosis and relieve the hydrocephalic symptom, an endoscopic surgery was performed. Through the right Kocher's point, the tumor was removed partially with endoscope. A gross morphology of the tumor via endoscopic view was a germinoma. The endoscopic third ventriculostomy was performed to relieve the hydrocephalic symptom. Surgical specimen proved to be a germinoma, which was composed of large polygonal cells with large, round, and vesicular nuclei and sheath-like arrangement. No malignant features were observed within the prepared specimen (Fig. 2). The patient received 3 cycles of combination chemotherapy consisting of carboplatin and etoposide. And then, he received 30.6 Gy of localized irradiation on pineal gland for 5 weeks. The tumor was totally resolute (Fig. 3a,b). And then, he was followed in the outpatient clinic. One month after the completion of adjuvant therapy, the patient suffered from headache and diplopia. Brain computed tomography with contrast enhancement was taken. There was no abnormal finding except for the minimal contrast enhancement on the pineal region, which was not considered as tumorous condition. At 3 months after the completion of adjuvant therapy, the condition of the patient was good, and the hormone was within the normal range. Therefore, we considered the patient to have a complete resolution. We tried to see him 6 months later and to take brain MRI, but the patient did not appear.

Fig. 1 Pretreatment gadolinium-enhanced axial (a) and sagittal (b) T1-weighted MR images show strongly enhancing intraventricular mass in the pineal region with moderate ventriculomegaly

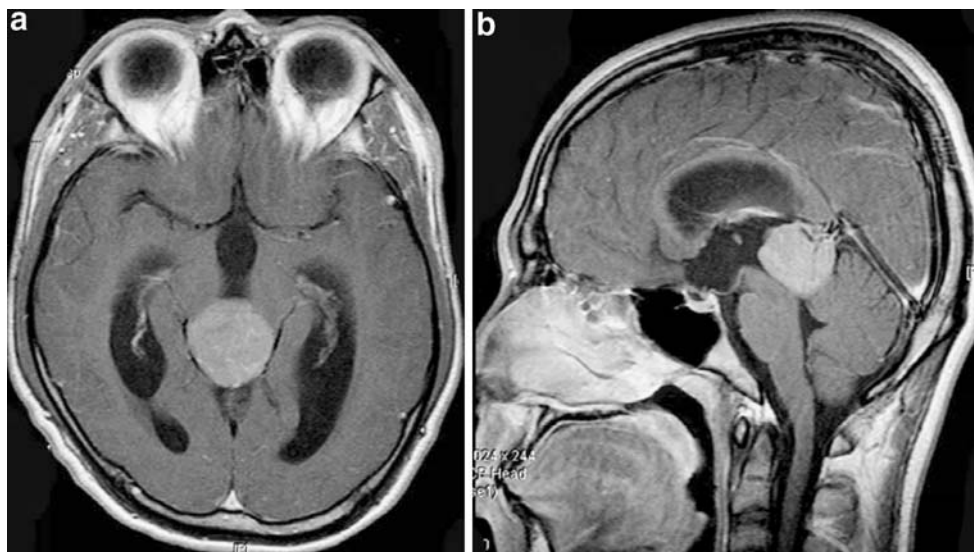
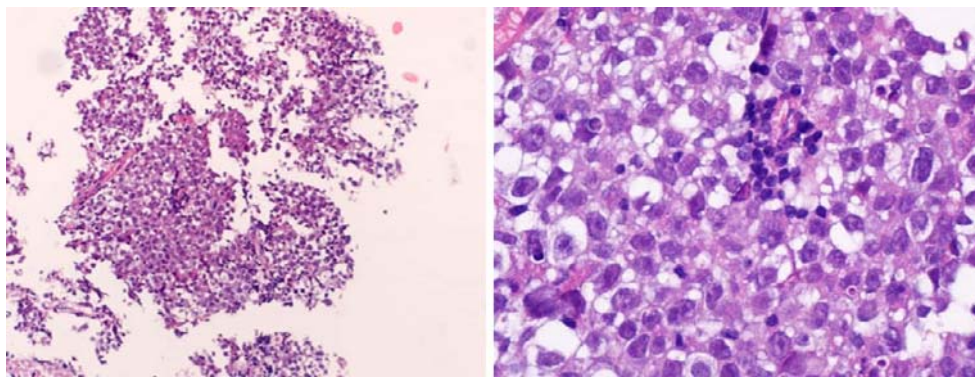


Fig. 2 The tissue of pineal region tumor was taken with endoscope. The prepared specimen showed pure germinoma. **a** Relatively uniform-sized large polygonal cells arranged something like a sheet. **b** In high-power magnification view, large polygonal cell with large, round, and vesicular nuclei and abundant cytoplasm



The second admission

He was readmitted in March 2005 for aggravation of headache and diplopia.

Gadolinium-enhanced MR images depicted a homogeneously enhanced, 2.8×2.8-cm-sized, round-shaped mass at the right temporal lobe (Fig. 4). Results of hormonal tumor marker studies, including α -FP and β -hCG, were 21,468.66 IU/ml (NL 0~7 IU/ml) and <2.0 IU/ml (NL 0~10 IU/ml), respectively. On April 4, 2005, the tumor was totally resected via transcortical, transinferior temporal gyrus approach. The tumor consisted of a solid portion, and total extirpation of the tumor was done easily. Histopathologic examination confirmed a diagnosis of a mixed germ-cell tumor containing the component of a yolk-sac tumor and a germinoma. Shüller–Duval bodies, the typical finding of the yolk-sac tumor, were noted (Fig. 5a). The immunohistochemical staining of the tumor was performed to confirm the diagnosis. Placenta alkaline phosphatase and α -fetoprotein were all positive on certain area of the tumor specimen. The main component of the tumor was the yolk-sac tumor, whose area was well stained with α -fetoprotein

(Fig. 5c). The placenta alkaline phosphatase stained relatively small area at the periphery of the yolk-sac tumor component (Fig. 5b). Postoperative days were uneventful. The follow-up MRI was performed, and there was no evidence of residual tumor. Further postoperative adjuvant therapy was planned. Eventually, he was discharged without any neurological deficits. He received the 4 cycles of high-dose adjuvant chemotherapy with peripheral blood stem-cell transplantation. During the course, the level of serum α -FP was gradually decreased. The α -FP was 353.07 IU/ml at 1 month after the second operation. After the second course of high-dose chemotherapy, the α -FP was 6.72 IU/ml. After the completion of 4 cycles of high-dose chemotherapy and peripheral blood stem-cell transplantation, the serum α -FP was within the normal range. At that time, the brain MRI was performed, and there was no evidence of recurrence. After that, the patient was followed at the outpatient department. The patient was doing well, and the α -FP was within the normal range which was taken in 3 months interval. The brain MRI was performed 1 year after the second operation, and there was no evidence of recurrence.

Fig. 3 The follow-up MRI after 3 cycles of chemotherapy and radiation showed total resolution of pineal region tumor

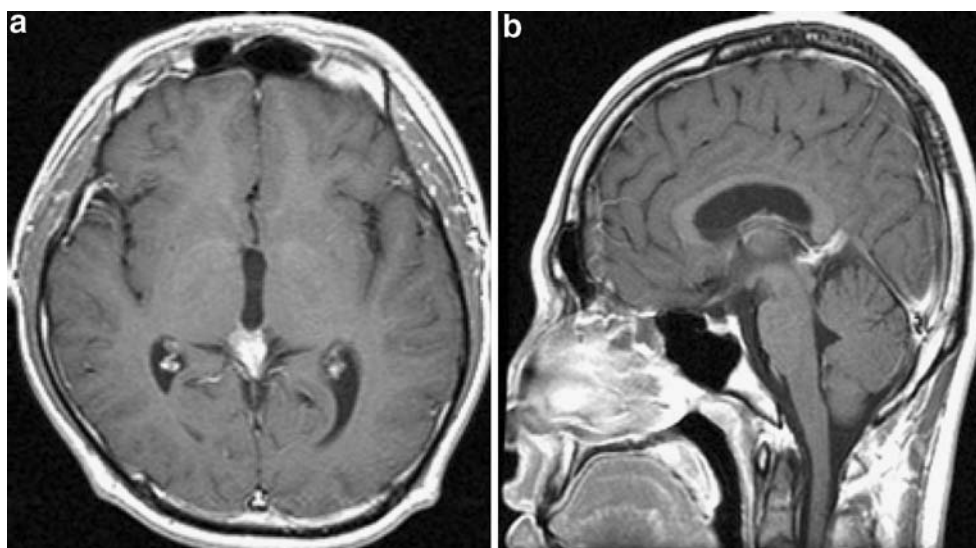
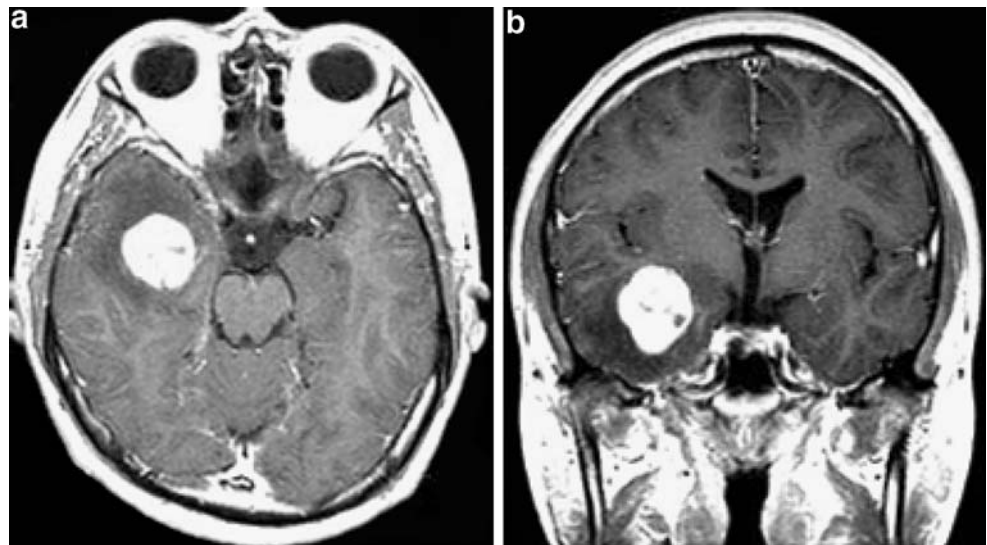


Fig. 4 Gadolinium-enhanced T1-weighted axial (a) and coronal (b) MR images showed homogeneously enhancing oval-shaped mass at the right temporal lobe

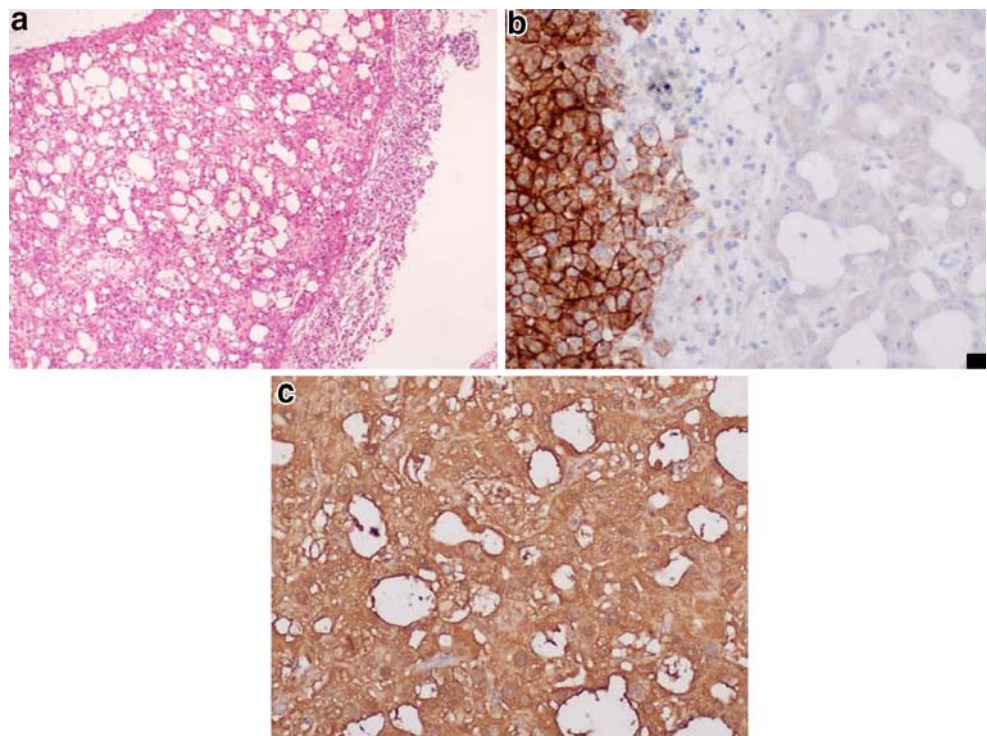


Discussion

Based on histology, intracranial germ-cell tumors are largely classified into germinomas, nongerminomatous germ-cell tumors (teratoma, embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma), and mixed germ-cell tumors [12, 13]. The most common subtype is germinoma consisting of 50% or more in Far Eastern Asian countries and 41% in Western countries. Each subtype of nongerminomatous germ-cell tumors is less common and frequently occurs as a component of mixed germ-cell tumors, which accounts for 10–30% of all germ-cell

tumors. Teratoma is next to germinoma, accounting for about 15–20% and yolk-sac tumor, and choriocarcinoma is the least common, comprising less than 5% [7, 14]. Mixed germ-cell tumors are composed of at least two different germ-cell elements, of which at least one is primitive. The most common association is germinoma and mature teratoma, which has been estimated to occur in one-fifth of all reported cases. Other mixtures of germinoma and yolk-sac tumor, immature or mature teratoma with embryonal carcinoma, and/or choriocarcinoma may also be present. However, mixture of germinoma and choriocarcinoma is extremely rare [7]. Our mixture of germinoma and

Fig. 5 The surgical specimen was composed of two components. The specimen was composed mainly of a yolk-sac tumor area (a), which contained the typical finding of yolk-sac tumor, Shüller–Duval bodies. The small area of germinoma was found at the periphery of the yolk-sac tumor component. The area of the yolk-sac tumor was stained with α -fetoprotein (c) and the germinoma area with placenta alkaline phosphatase (b)



yolk-sac tumor is relatively not common. Moreover, the tumor was metachronous.

The age distribution of intracranial teratomas showed a peak incidence during the first two decades of life and mostly in children [15, 16], whereas for germinoma, it was in the early pubertal years. Jennings et al. [14] postulated that the neuroendocrine events of puberty might be a “triggering” effect on the abrupt rise of germ-cell tumors in the puberty. The author’s case was a 21-year-old man. Thus, the neuroendocrinological triggering effect on its recurrence was not very likely.

Initial presentation of our case was germinoma. The tumor markers were all negative on both cerebrospinal fluid and serum. The tumor was completely resolute after chemotherapy and radiotherapy. Thereafter, the tumor recurred in the distant region, temporal lobe. The location of the tumor in the temporal lobe was outside of the radiation field, not either in the trajectory of endoscope or cerebrospinal fluid pathway. Therefore, the tumor recurred from neither the cerebrospinal fluid nor the surgical inoculation. Ono et al. [17] described the four patterns of recurrence with respect to mechanism and appropriate treatment. Type-I germinoma recurrence, characterized by intracranial recurrence caused by an inadequate initial irradiation field, was treated by total craniospinal irradiation. Type-II recurrence, characterized by a benign teratoma caused by late growth of the teratoma component, was treated by surgery alone. All patients with these patterns of recurrence are still alive. Type-III local recurrence is characterized by human chorionic gonadotropin- or α -fetoprotein-producing tumors of extraembryonic origin. This pattern of recurrence should be treated by chemotherapy or radiosurgery. Type-IV germinoma recurrence consists of extraneural metastasis without evidence of intracranial recurrence. According to his classification, our case was not included in any of the subtypes.

In the literature, the relationship between serum tumor marker level and histological appearance has been studied, and it suggested the following conclusions. First, macroscopically total removal of the germ-cell tumor does not mean complete cure. Second, the measurement of serum tumor markers, such as human chorionic gonadotropin and α -fetoprotein, does not always detect recurrence of the tumor. Radiotherapy may be required to prevent the recurrence of a tumor marker-producing germ-cell tumor even though histological examination does not detect immature cells in the surgically removed tissue [18]. Macroscopically total removal of a germ-cell tumor does not signify cytologically complete removal of the tumor. The surgically removed tissue does not reveal all the characteristics of a germ-cell tumor. The occurrence of the mixed type of mature teratoma, germinoma, and malignant germ-cell

tumor, such as choriocarcinoma or endodermal sinus tumor, is an evidence of this. A recurrence long after the initial treatment is also quite common. The fate of an intracranial germ-cell tumor cannot be predicted simply by the morphological appearance of a piece of tumor that has been surgically removed. Complete clinical remission is defined as normalization of the tumor markers and the absence of residual tumor. Initial follow-up examination after completion of chemotherapy must be performed in short intervals, including frequent evaluation of the tumor marker. Nevertheless, we could not perform either follow-up MRI at 6 months after completion of treatment nor tumor marker due to follow-up loss for several months.

Sugimoto et al. [10] reported six cases of distant recurrence of mature teratoma as mixed germ-cell tumor. The primary sites were the third ventricle and the adjacent structure. The sites of recurrences were the adjacent structures of the third ventricle. The histopathologic findings of the recurring tumor were four germinomas, one mature teratoma, and one embryonal carcinoma. His recurring cases were all located around the third ventricle. In his cases, the second tumors, which occurred in the same location with the primary tumor, were most plausibly considered as a recurrence from a microscopic residue of germinoma component in previously resected mature teratoma despite the long silent period. Other possibilities include the sporadic acceleration of a localized hamartomatous and/or dysplastic process of preexisting germ cells.

Some pathogeneses have been postulated on the development of metachronous germ-cell tumors. Firstly, although the recurrence of nongerminomatous germ-cell tumor usually occurs within 1 year after treatment [19], there is a good possibility of tumor recurrence or dissemination especially in the mixed tumors that are composed of various combinations of two or more types of germ-cell tumors. Secondly, although it is uncertain whether the antecedent presence of germ cells is due to germinal aberrant migration of germ cells, embryonic “cell rest”, or localized hamartomatous or dysplastic processes [20], the preexisting germ cells have been implicated. Thirdly, it may develop due to genetic alterations that lead to mutational inactivation of tumor suppressor genes or activation of oncogenes [21].

The germ-cell tumor is originated from the totipotent germ cell. The germ cell can be found anywhere in the whole human body, especially in the midline structure. Initial follow-up examination after completion of chemotherapy must be performed in short intervals, including frequent evaluation of the tumor marker. Treatment response is evaluated by follow-up MRI scans every 6 months until the third year after diagnosis and then at 1-year interval. We must observe the rules because the germ cell is totipotent.

Conclusion

The second tumor was considered to be a de novo metachronous neoplasm rather than a recurrence of the original mixed germ-cell tumor that consisted a yolk-sac tumor and a germinoma. The location of the second tumor was in temporal lobe, which was not in the axis of the ventricular system. We think that if primordial germ-cell groups exist along the midline of the brain, more than two primordial germ cell-groups could give rise to metachronous neoplasms at different sites and with different histological types. Because the germ-cell tumor was totipotent itself, even if the tumor was totally resolute, thorough and close follow-up should be needed.

References

- Fuller BG, Kapp DS, Cox R (1993) Radiation therapy of pineal region tumors: 25 new cases and a review of 208 previously reported cases. *Radiat Oncol Biol Phys Int J* 28:229–245
- Hoffman HJ, Yoshida M, Becker LE, Hendrick EB, Humphreys RP (1994) Pineal region tumours in childhood. *Pediatr Neurosurg* 21:91–104
- Hoffman HJ, Otsubo H, Hendrick EB, Humphreys RP, Drake JM, Becker LE, Greenberg M, Jenkin D (1991) Intracranial germ-cell tumors in children. *J Neurosurg* 74:545–551
- Sugiyama K, Uozumi T, Kiyu K, Mukada K, Kurisu K, Arita K, Hotta T, Ogasawara H, Sumida M (1992) Intracranial germ-cell tumor with synchronous lesions in the pineal and suprasellar lesions: report of six cases and review of the literature. *Surg Neurol* 38:114–120
- Haddock MG et al (1997) Radiation therapy for histologically confirmed primary central nervous system germinoma. *Int J Radiat Oncol Biol Phys* 38(5):915–923
- Hardenbergh PH et al (1997) Intracranial germinoma: the case for lower dose radiation therapy. *Int J Radiat Oncol Biol Phys* 39(2):419–426
- Matsutani M et al (1997) Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. *J Neurosurg* 86(3):446–455
- Shibamoto Y et al (2001) Intracranial germinoma: radiation therapy with tumor volume-based dose selection. *Radiology* 218(2):452–456
- Shirato H et al (1997) Analysis of long-term treatment of intracranial germinoma. *Int J Radiat Oncol Biol Phys* 37(3):511–555
- Sugimoto K, Nakahara I, Nishikawa M (2002) Bilateral metachronous germinoma of the basal ganglia occurring long after total removal of a mature pineal teratoma: case report. *Neurosurgery* 50(3):613–616, discussion 616–617
- Back MR, Hu B, Rutgers J, French S, Moore TC (1997) Metastasis of an intracranial germinoma through a ventriculoperitoneal shunt: recurrence as a yolk-sac tumor. *Pediatr Surg Int* 12(1):24–27
- Jellinger K (1973) Primary intracranial germ cell tumours. *Acta Neuropathol (Berl)* 25(4):291–306
- Sano K (1995) So-called intracranial germ cell tumours: are they really of germ cell origin? *Br J Neurosurg* 9(3):391–401
- Jennings MT, Gelman R, Hochberg F (1985) Intracranial germ-cell tumors: natural history and pathogenesis. *J Neurosurg* 63(2):155–167
- Hunt SJ et al (1990) Neonatal intracranial teratomas. *Surg Neurol* 34(5):336–342
- Ventureyra EC, Herder S (1983) Neonatal intracranial teratoma. Case report. *J Neurosurg* 59(5):879–883
- Ono N et al (1994) Recurrence of primary intracranial germinomas after complete response with radiotherapy: recurrence patterns and therapy. *Neurosurgery* 35(4):615–620, discussion 620–621
- Carrillo R, Ricoy JR, Del Pozo JM, Garcia-Uria J, Herrero J (1977) Dissemination with malignant changes from a pineal tumor through the corpus callosum after total removal. *Childs Brain* 3:230–237
- DeLeo MJ et al (1988) Late recurrences in long-term survivors of germ cell neoplasms. *Cancer* 62(5):985–988
- Grote E, Lorenz R, Vuia O (1980) Clinical and endocrinological findings in ectopic pinealoma and spongioblastoma of the hypothalamus. *Acta Neurochir (Wien)* 53(1–2):87–98
- Hollstein M et al (1991) p53 mutations in human cancers. *Science* 253(5015):49–53