Impacts of Elevated Level of hCG in Serum on Clinical Course and Radiotherapy Results in the Histology-confirmed Intracranial Germinomas

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The prognosis of intracranial germinoma producing the human chorionic gonadotropin (hCG) is controversial due to limited information. We undertook a retrospective analysis to determine whether this type of tumor has similar clinical course and prognosis to hCG non-secreting germinoma. Thirty-one histologically confirmed intracranial germinoma patients who had pretreatment hCG examination in serum/CSF were treated with radiotherapy between 1980 and 1996. hCG level was measured by immunoradioassay of β subunit of hCG. Six patients had elevated serum hCG levels and were defined as having hCG secreting germinoma. All except three patients received craniospinal axis irradiation. The follow-up ranged from 19–175 months with a median of 63 months. hCG secreting germinoma accounted for 19% of intracranial germinoma cases. Elevated hCG levels ranged from 39–260 IU/l in serum. No difference was found between hCG non-secreting germinoma and hCG secreting germinoma in terms of patient or treatment characteristics. There was no recurrence among the six hCG secreting germinoma patients. The 5-year overall and disease-free survival rates were 96% for patients with hCG non-secreting germinomas and 100% for the patients with hCG secreting germinomas. The survival difference was not significant ($p = 0.59$). Our results suggest that elevated level of hCG did not result in any differences in the clinical characteristics or survival after radical radiotherapy in histologically confirmed intracranial germinoma.

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Intracranial germinoma comprises approximately 7.5% of all pediatric brain tumors in Japan or Taiwan and is more common in East Asia than in Western countries (1, 2). Notwithstanding its low incidence, clinicians have great interest in intracranial germinoma because it usually occurs at a young age and is curable with radiotherapy that could induce late sequelae in the less developed central nervous system.

Elevated levels of alpha-fetoprotein (AFP) or the human chorionic gonadotropin (hCG) in intracranial germ cell tumors (IGCT) were considered to be closely correlated with non-germinomatous germ cell tumors (NGGCT) such as embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma, with hCG and AFP elevated in the first two and hCG alone elevated in latter (3, 4).

The existence of hCG secreting germinoma is well known and it has been shown that hCG is produced by syncytiotrophoblastic giant cells (STGC) often present in germinoma, but which differ from choriocarcinoma by having two trophoblastic components (5). Because germinoma with STGC is a recently established subtype of germinoma, there are several controversies in terms of its clinical characteristics and prognosis compared to hCG non-secreting germinoma. Some have suggested that hCG secreting germinoma has a higher relapse rate and thus needs more intensive treatment than hCG non-secreting germinoma (5–8), while others have not found any difference in prognosis (9). The proper cut-off level of hCG by which germinoma is diagnosed rather than NGGCT is also debatable in the clinical setting without histologic confirmation (6, 9). There is too little information available to answer these questions and previous reports have been concerned with germ cell tumor with or without histologic evidence (5, 9).

Our goal was to clarify the influence of the elevated level of hCG in the histology-confirmed intracranial germinoma

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on the clinical course and result of radical radiotherapy by retrospective analysis of consecutive patients in a single institution.

MATERIAL AND METHODS

We reviewed the records of 39 consecutive cases of intracranial germinoma treated with curative radiotherapy after obtaining histologic confirmation between 1980 and 1996. Among these there were six cases without hCG examination, one who failed to complete radiotherapy and one with an elevated hCG level of 4500 mIU/mL were excluded and thus 31 cases were eligible. There were 22 males and nine females. Age at diagnosis ranged 8–41 years with a median of 12 years. Histological diagnosis was confirmed after surgical excision (22 patients) or biopsy (9 patients). Pathologic examination and review was done using archival glass slides which consisted of H&E stain, PAS stain, and immunohistochemical stains for β subunit of hCG and AFP. On microscopic examination, the tumor consisted of sheets of large cells with pale abundant cytoplasm, round vesicular nuclei and prominent nucleoli. Lymphoid aggregates were also frequently noted. No other germ cell tumor component was mixed, and all the cases were confirmed as pure germinoma. No syncytiotrophoblastic giant cell was noted in the cases with increased hCG as well as in the cases with normal hCG level. It might represent the limitation of pathologic specimen.

Tumors were located in the pineal region in four, the suprasellar region in 13, both pineal and suprasellar regions in 3, the basal ganglia in 8, and other regions in 3. Among these, two in the pineal region, one in the suprasellar region and three in the basal ganglia were hCG secreting germinomas. hCG non-secreting germinomas were preferentially located in the suprasellar region (12 cases) and similarly hCG secreting germinoma were more frequent in the basal ganglia (3 cases). Three cases had unusual locations namely multiple sites of pineal/suprasellar/cerebellar vermis, the right frontal lobe area and the optic nerve/pituitary stalk.

Serum and CSF hCG levels were examined in 10 cases and only the serum levels in 21 cases. hCG level was measured with immunoradiometric assay (RADIM, Italy and Nichols Institute Diagnostics, USA) by detecting β subunit of hCG. The sensitivity of the assays was 0.5–2.0 IU/l and specificity was almost 100% for hCG and the β subunit of hCG. We defined germinoma with a normal hCG level of 3 IU/l or lower as an hCG non-secreting germinoma because we used the cut-off level as border between the normal and abnormal. For the value lower than 3 IU/l, we did not keep the exact value. No patient had elevated AFP levels. Spinal myelography or magnetic resonance imaging (MRI) was performed in all cases and CSF cytology in 20 cases. At presentation, spinal seeding was found in 3 patients (10%) by CSF cytology in one, by MRI in another and by both CSF cytology and MRI in the third.

Radical radiotherapy to the craniospinal axis was delivered with a daily dose of 1.8 Gy for the primary tumor or the whole brain and with 1.5 Gy for the whole spinal axis using 6 or 10 MV x-rays. The total dose was 54 Gy to the primary tumor, 36 Gy to the whole brain and 24 Gy to the whole spinal axis. We modified the radiation dose by individual disease status or age. The craniospinal axis irradiation was not performed in two patients because of myelosuppression. Two patients with spinal seeding by MRI at presentation received focal spinal boost with doses of 10 and 19.8 Gy in addition to the spinal axis dose. One patient with spinal seeding by CSF cytology was irradiated with a whole spinal axis dose of 36 Gy. All these three patients with spinal seeding (two with hCG non-secreting germinoma and one with hCG secreting germinoma) received two to four courses of adjuvant systemic chemotherapy with cisplatin and etoposide (VP-16). No treatment alterations were made for hCG secreting germinoma patients.

Differences in characteristics of patients or of treatment were examined. Non-parametric median tests were performed for continuous variables such as age and tumor dose. Fisher's exact test was used for categorical data such as sex, ECOG, tumor location, spinal seeding, tumor resection, chemotherapy or radiation field. For the purpose of this study, we combined ECOG scale, tumor location and tumor resection into two categories because of small patient numbers.

Patients follow-up was performed using physical examination, assay for β subunit of hCG, and CT/MRI at 1 month after radiotherapy, every 6 months till 2 years, and every year thereafter. All except one were followed up for 19–175 months with median of 63 months. The date of the last follow-up was October 1999. Overall and disease free survival rates were calculated from the first day of radiotherapy using the Kaplan–Meier method, and differences in survival curves were examined using the log-rank test.

RESULTS

Clinical course and characteristics

Of the eight hCG non-secreting germinoma cases that were examined for hCG in both serum and CSF, the serum and CSF findings were concordantly normal. As is shown in Table 1 only two patients underwent both serum and CSF examinations, and the levels were discordant. Elevations in serum hCG ranged from 39 to 260 IU/l.

The patient and treatment characteristics of those with hCG non-secreting germinoma and hCG secreting germinoma are shown in Table 2. There was no difference between the two groups with regard to age, sex, ECOG, tumor location, spinal seeding, tumor resection,

Table 1

Cases with intracranial hCG secreting germinoma

Age/Sex	Location	hCG level (IU/l)		Extent of surgery	Radiation therapy		Status
		Serum	CSF		Field	Tumor dose (Gy)	
12/M	P	41	–	Partial	CSI	54.3	132 Mo NED**
18/M	B	260	–	Biopsy	CSI	50	75 Mo NED
16/M	B	39	–	Subtotal	CSI	55.8*	64 Mo NED
10/M	P	42	227	Partial	WB	55.2*	55 Mo NED
12/M	B	200	20	Subtotal	CSI	54	43 Mo NED
22/M	SS	78	–	Partial	WB	57.6	19 Mo NED

Abbreviations: P = pineal region; B = basal ganglia; SS = suprasellar region; CSI = craniospinal axis irraidation; WB = whole brain.
* Combined with cisplatin/VP-16 chemotherapy. ** No evidence of disease.

chemotherapy, radiation field or tumor dose. Male preponderance was seen in both groups, especially in the hCG secreting germinoma but the difference was not significant. The incidences of spinal seeding were two (8%) and one (17%) in each group and again there was no significant difference.

Radiotherapy results

Fig. 1 shows the overall survival curves for the two groups. The 5-year overall survival rates were 96% for patients with hCG non-secreting germinoma and 100% for those with hCG secreting germinoma, and 10-year survival was the same as 5-year survivals. The results of disease-free survival rates were the same as the results of overall survival. The survival difference between the two groups was not significant ($p = 0.59$). The only failed case was a patient with hCG non-secreting germinoma treated with whole brain radiotherapy of 50 Gy after the partial removal of a suprasellar tumor. He died 2 months after treatment with a persistent tumor. Including three patients who had spinal seeding at diagnosis, there were no spinal recurrences. In the patients younger than 16 years of age, two out of 14 patients showed reduced sitting heights below the fifth percentile after receiving whole spinal axis doses equal or more than 24 Gy. One of these patients received growth hormone supplementation.

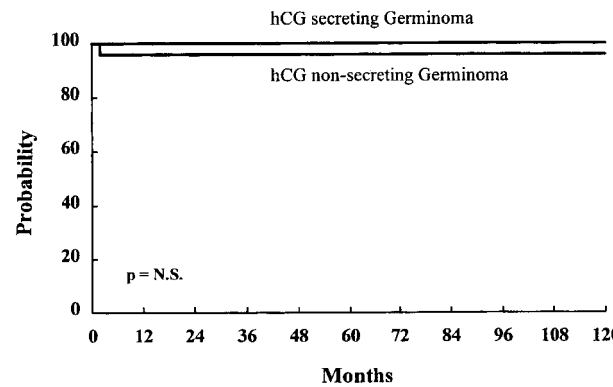

Fig. 1. Overall survival of patients with intracranial germinoma by the level of hCG in serum. The 5- or 10-year survival rates were 96% for patients with hCG non-secreting germinoma and 100% for those with hCG secreting germinoma. The disease-free survival rates were as same as the overall survival. The difference between the survival of two groups was not significant ($p = 0.59$).

Table 2

Characteristics of intracranial germinoma cases and treatment parameters

Characteristics	hCG non-secreting germinoma ($N = 25$)	hCG secreting germinoma ($N = 6$)	p-value*
Age** (years)	14 ± 6	15 ± 5	0.93
Sex (M/F)	16 : 9	6 : 0	0.15
ECOG (0–2)/(3–4)	18 : 7	5 : 1	0.67
Tumor site (P+SS+PSS)/(BG+O)	17 : 8	3 : 3	0.38
Spinal seeding	2 (8%)	1 (17%)	0.49
Surgery extent (G+S+P)/(Bx)	17 : 8	5 : 1	0.64
Chemotherapy (done)	3 (12%)	2 (33%)	0.24
Radiation field (WB)/(CSI)	1 : 24	2 : 4	0.09
Tumor dose (Gy)	52.8 ± 4.4	54.5 ± 2.5	0.93

Abbreviations: intracranial tumor site: P = pineal region; SS = suprasellar region; PSS = pineal and suprasellar regions; BG = basal ganglia; O = other. Extent of surgical resection: G = gross total; S = subtotal; P = partial; Bx = biopsy. Extent of radiotherapy field: WB = whole brain; CSI = craniospinal axis irradiation.
* Median test for age and tumor dose, Fisher's exact two-tail test for other parameters. ** Mean $\pm$ SD.

DISCUSSION

We confirmed that the secretion of hCG did not result in any differences in the clinical characteristics of the intracranial germinoma or its survival after radical radiotherapy. It was also confirmed that efficacy of radiotherapy on intracranial germinoma was quite excellent as we previously reported (10, 11).

Whereas an elevated hCG level is known to be associated with a more advanced stage or a heavier tumor burden in testicular seminoma, it is unknown in intracranial germinoma mainly due to the small patient numbers (12, 13), In this study, hCG non-secreting germinoma and hCG secreting germinoma patient groups also showed similar incidences of spinal seeding, and spinal seeding rate (3/31) is markedly lower than the 18–55% rate of malignant cytology or positive myelography reported elsewhere (14, 15). It has been reported that there are no differences of clinical characteristics between the two groups (9), except that precocious puberty may be seen in young patients with hCG secreting germinoma (5). We also found no differences between the two groups with respect to age, sex, ECOG performance score or tumor location.

Controversy remains whether hCG production in itself or the presence of STGC in germinoma is an indicator of an unfavorable prognosis. Some have reported a poorer prognosis of seminoma with STGC compared with cases showing normal hCG levels (16), while others have reported a similarly favorable prognosis (17, 18). According to the limited data in the literature, it is also controversial whether germinoma with STGC shows a higher recurrence rate. Rather higher recurrences were observed by Wolden et al. (one recurrence among three), Uematsu et al. (5/9), Utsuki et al. (3/11) and Yoshida et al. (3/6), while no recurrence among the 20 patients with high hCG levels was reported by Shibamoto et al. (5–9). The present data can give additional information in this area.

The level of hCG, not only by giant cells but also by mononuclear seminoma tumor cells, was high in about 30% of the patients in the peripheral venous blood (13, 18–20), but STGC was less frequently detected in histological specimens (18). We also did not find syncytiotrophoblastic giant cells in pathologic specimen of hCG secreting germinoma. The proportion of hCG secreting germinoma (19%; 6/31) in our data was within lower range of those (19–45%) previously reported (5, 6, 9).

In addition, the cut-off level of hCG that allows pure germinoma to be differentiated from NGGCT should be commented. This issue is important for the patients to be managed without histopathogic diagnosis. The cut-off level of 100 or 1000 IU/l was suggested for intracranial germinoma (6, 9) and 200 IU/l did for seminomas (18). In our data, serum hCG levels of four hCG secreting seminoma patients ranged from 39 to 78 IU/l and two patients showed serum hCG levels of 200 and 260 IU/l. Thus we suggest that 300 IU/l might be a reasonable cut-off level.

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