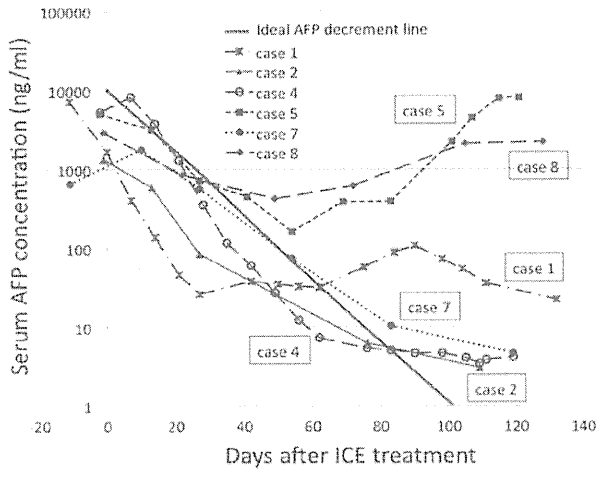

Fig. 1 Sequential changes in serum alpha-fetoprotein (*AFP*) concentration during the therapeutic period. Cases 1, 2, 4, and 7 showed logarithmic decreases to the normal range in response to therapy, whereas Cases 5 and 8 did not

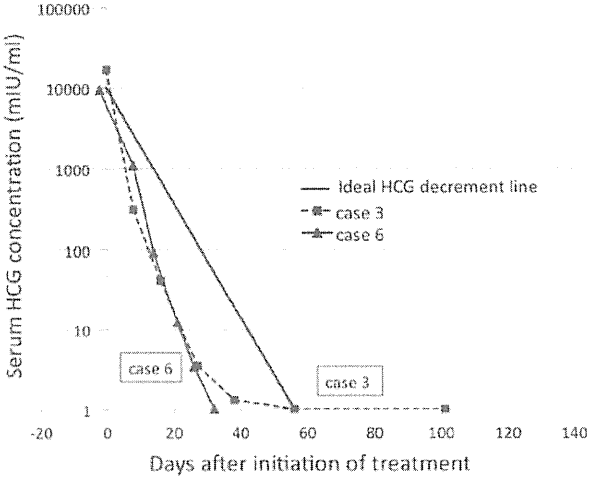

Fig. 2 Sequential changes in serum human chorionic gonadotropin (*HCG*) concentration during the therapeutic period. Cases 3 and 6 showed logarithmic decreases to the normal range in response to treatment

Six patients (Cases 2 and 4–8) were treated by neoadjuvant ICE chemotherapy, followed by radiation therapy and/or salvage surgery. MR imaging after the initial ICE chemotherapy showed no detectable lesions in three patients (Cases 2, 4, and 6), and an enhanced residual lesion in one patient (Case 7), which totally regressed with subsequent radiation therapy and maintenance chemotherapy, so did not require surgery. The serum levels of tumor markers in these four patients (Cases 2, 4, 6, and 7) decreased logarithmically to the normal range (Figs. 1, 2). In contrast, the other two patients (Cases 5 and 8) showed partial response to initial chemotherapy and recurrence in the early therapeutic period, without logarithmic decrease of the serum levels of tumor markers (Figs. 1, 2). Both patients (Cases 5 and 8) died during the therapeutic period. Case 1 had newly detected disseminated lesion so chemotherapy and radiotherapy were continued, although he died of disease progression. The other five patients had no local recurrence or dissemination. Overall survival rate and progression free survival rate are shown in Fig. 3.

Two patients underwent surgical resection before chemotherapy. A 14-year-old boy with pineal tumor (Case 3) underwent emergency surgery because of acute hydrocephalus with intratumoral hemorrhage. The tumor was gross totally removed and the histological diagnosis was choriocarcinoma. He subsequently received radiation therapy and chemotherapy. MR imaging showed no residual lesion and serum HCG level was logarithmically decreased to the normal range (Fig. 4). A 2-year-old boy with cerebellar vermis tumor (Case 1) underwent urgent surgery because of mass effect on the brain stem. The tumor was gross totally removed and the histological diagnosis was yolk sac tumor. MR imaging showed no residual lesion (Fig. 5). One week after surgery, systemic ICE chemotherapy was started and associated with a logarithmic decrease of serum AFP level and the concentration maintained around 30 ng/ml, which is slightly higher than normal range. However, 5 months after the onset of initial treatment, the serum AFP concentration suddenly elevated and a small disseminated lesion in the right

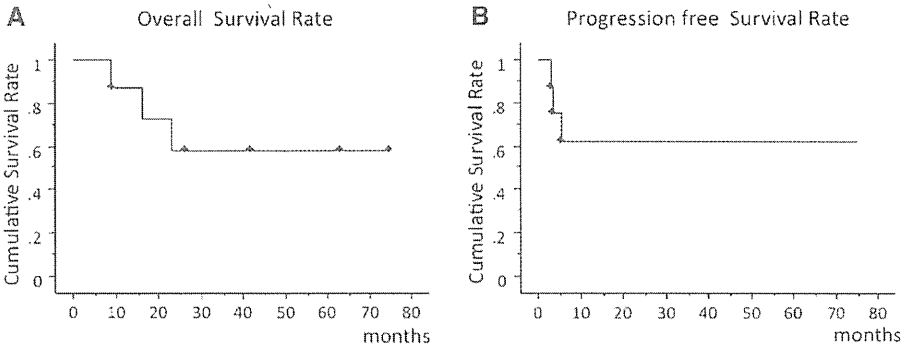

Fig. 3 Overall survival rate (**a**) and progression free survival rate (**b**) of the eight patients

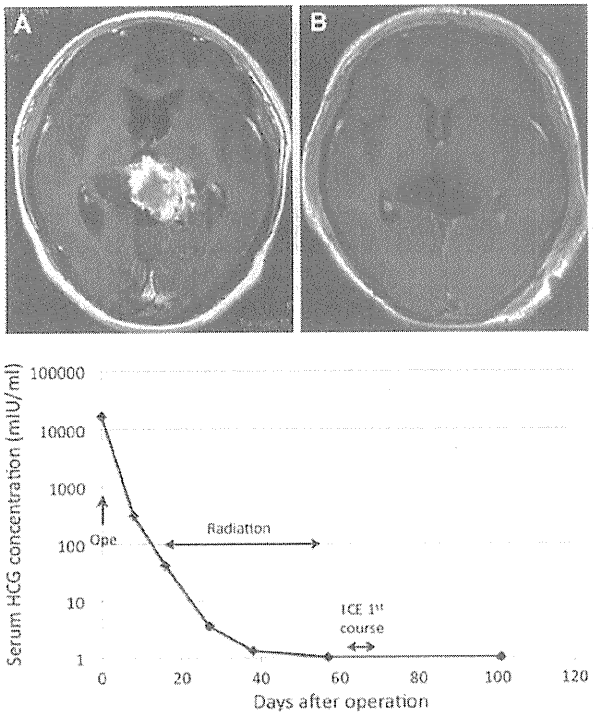

Fig. 4 Case 3 radiographical findings (**a**, **b**) and serum human chorionic gonadotropin (*HCG*) levels (*line graph*). Preoperative magnetic resonance imaging showed enhanced mass lesion with acute hydrocephalus due to intratumoral hemorrhage in the pineal region (**a**). Emergency surgery was carried out and the enhanced lesion was totally removed (**b**). Radiation and combination chemotherapy consisting of ifosfamide, cisplatin, and etoposide were carried out. Serum HCG level was logarithmically decreased after surgery and the low level was maintained (*line graph*), and no local recurrence or disseminated lesion was detected. ICE, ifosfamide + cisplatin + etoposide

ambient cistern was detected (Fig. 5). Despite multiple further therapies, he died of tumor progression 23 months after starting initial therapy. Tumor volume also decreased logarithmically associated with serum tumor marker decrement in most patients. However, the tumor in Cases 2, 4, and 6 did not decrease so much and enhanced lesion remained at the original site even when the serum tumor marker concentration was normalized (Fig. 6). Salvage surgery revealed the enhanced lesion was histologically mature teratoma without malignant features both for Case 2 and 4, and necrotic tissue containing small amount of viable cells of choriocarcinoma for Case 6, respectively.

We also sequentially measured of the concentrations of tumor markers in CSF obtained by spinal tap, at the timing of surgical resection, and via an Ommaya reservoir, in some patients. Although the number of analyzed cases was limited, they changed in synchronization with the serum concentrations (Fig. 7).

Discussion

Platinum-based neoadjuvant chemotherapy is effective for the treatment of intracranial NGGCT [6, 7, 9, 19], as both tumor volume and serum concentration of tumor markers sequentially decrease. MR imaging sometimes detects enhanced residual lesion at the primary location, even if the serum levels of tumor marker decrease to the normal range. One possible explanation is the histological heterogeneity of intracranial germ cell tumors. The teratomatous component, which is resistant to radiation therapy and chemotherapy, may persist after other therapy-sensitive components have shrunk. Three of our patients (Cases 2, 4, and 6) showed normalized tumor marker after neoadjuvant chemotherapy, but MR imaging showed enhanced mass at the original site. Radical surgery revealed teratoma without malignant features or necrotic tissue containing small amount of viable choriocarcinoma. Tumor volume is hard to calculate accurately if cystic components are included or the location is on the basal ganglia with ambiguous borders. Therefore, sequential measurement of serum tumor marker levels seems more useful than tumor volume calculation to assess the treatment effectiveness.

The importance of serum tumor marker levels is well known to make a diagnosis and consider about the treatment outcome in patients with NGGCTs. Previous large reports [16, 20–23] indicated that a complete clinical remission was defined as normalization of the tumor markers within the age-related normal range. On the other hand, no reports were available which indicated the efficacy of sequential measurement of serum tumor marker level, so it is still unclear when to consider more aggressive treatment for the patients whose tumor marker did not go down to the normal range. The ideal response of serum concentration of tumor markers is logarithmic decrease to the normal range. In fact, four of the patients (Cases 2, 4, 6, and 7) in our series showed logarithmic decrease of serum tumor marker levels, and survived without residual tumor. On the other hand, two patients (Cases 5 and 8) who did not show logarithmic decrease of serum tumor marker levels were considered resistant to the initial treatment, and disseminated lesions were identified in the early therapeutic stage. Moreover, two patients (Cases 5 and 8) with increased serum tumor marker levels during treatment soon died. Case 5 had increased tumor volume at the original site with increased serum tumor marker level. Case 8 presented with multiple disseminated lesions before starting initial chemotherapy, and further dissemination at the spinal cord was detected during chemotherapy. Therefore, induction with only chemotherapy might not be effective and too slow-acting compared to the rapid tumor growth in such cases.

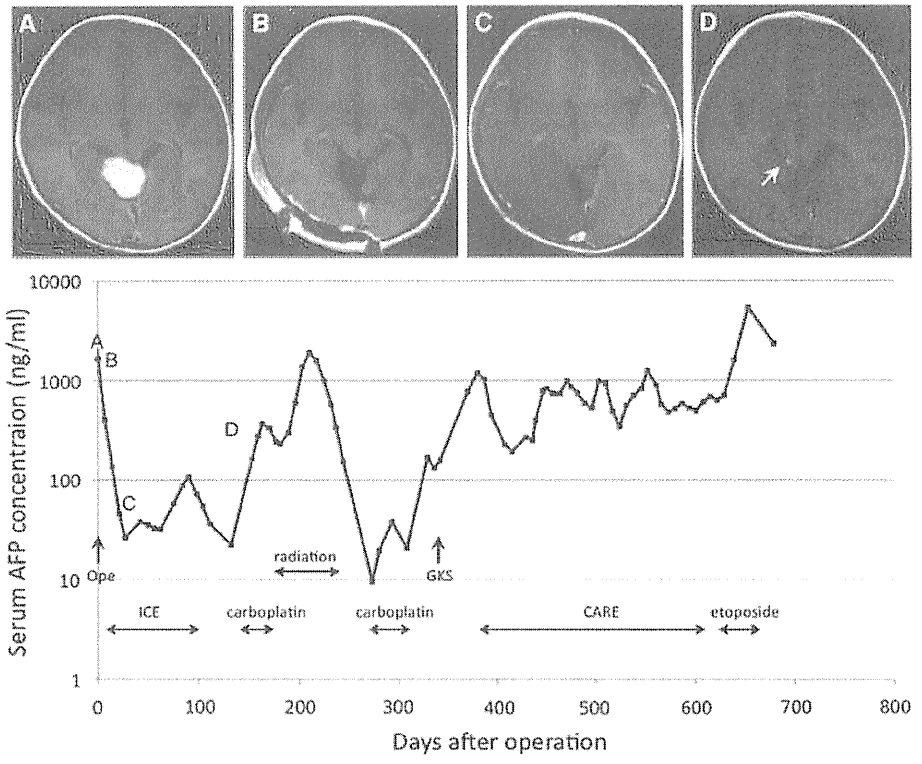

Fig. 5 Case 1 radiographical findings (**a**–**d**) and serum alpha-fetoprotein (*AFP*) levels (*line graph*). Preoperative magnetic resonance (*MR*) imaging showed enhanced mass lesion in the vermis with brain stem compression (**a**). Urgent surgery was carried out and the enhanced lesion was totally removed (**b**). Combination chemotherapy consisting of ifosfamide, cisplatin, and etoposide was carried out and no local recurrence or dissemination was detected during the chemotherapy (**c**). Five months after the onset of initial treatment, serum AFP level suddenly increased and MR imaging demonstrated a small enhanced lesion in the right ambient cistern (**d**, *arrow*). Serum AFP level was logarithmically decreased after surgery and the low level was maintained during initial chemotherapy. It was increased when MR imaging showed new disseminated lesions (*line graph*). Radiation and chemotherapy were continued but he died of tumor progression 23 months after starting of initial therapy. ICE, ifosfamide + cisplatin + etoposide; CARE, carboplatin + etoposide; GKS, gamma knife surgery

Of course, the rate of decrease of serum AFP and HCG levels cannot be compared directly, as the serum half lives are different, at 4–5 days and 18–36 h for AFP and HCG, respectively [24–26]. AFP level should halve every 5–7 days, and HCG level should halve each 2–3.5 days after treatment [27, 28]. In literatures, several reports revealed that the prolonged marker decline during the initial chemotherapy was associated with poor prognosis in testicular nonseminomatous germ cell tumors. In contrast, patients with better prognosis were shown with satisfactory marker decline which was compatible with biological half lives of them in serum [27–31]. As a general rule, a 10-fold decrease or normalization of the serum HCG concentration over 2 weeks, or serum AFP over 25–30 days is indicative of an appropriate decline following surgery or chemotherapy [29–31].

The serum concentration of AFP is low in adults, but is much higher in neonates. It rapidly decreases to the same level as adults by age 3 or 4 years, but does not decline to the normal range of adults before the end of the second year of life [32].The youngest patient in our series was a 2-year-old boy (Case 1) who underwent gross total removal of enhanced tumor and no residual lesion was detected. Logarithmic decrease of serum AFP concentration was observed at first and the concentration maintained around 30 ng/ml. The nadir of serum AFP concentration was 22.2 ng/ml, and MR imaging showed no enhanced lesion. The treatment was initially effective for his tumor with adjustment for his age, but the serum AFP concentration suddenly increased to 163.4 ng/ml, 165 days after the onset of initial treatment (Fig. 5). At that time, MR imaging revealed a small enhanced lesion in the right ambient cistern. This was considered as the time point of treatment relapse. This case suggested the serum AFP concentration of infant patients with highly malignant NGGCTs might be hard to assess the treatment effectiveness.

The association between serum tumor marker concentration and prognosis is well known in testicular

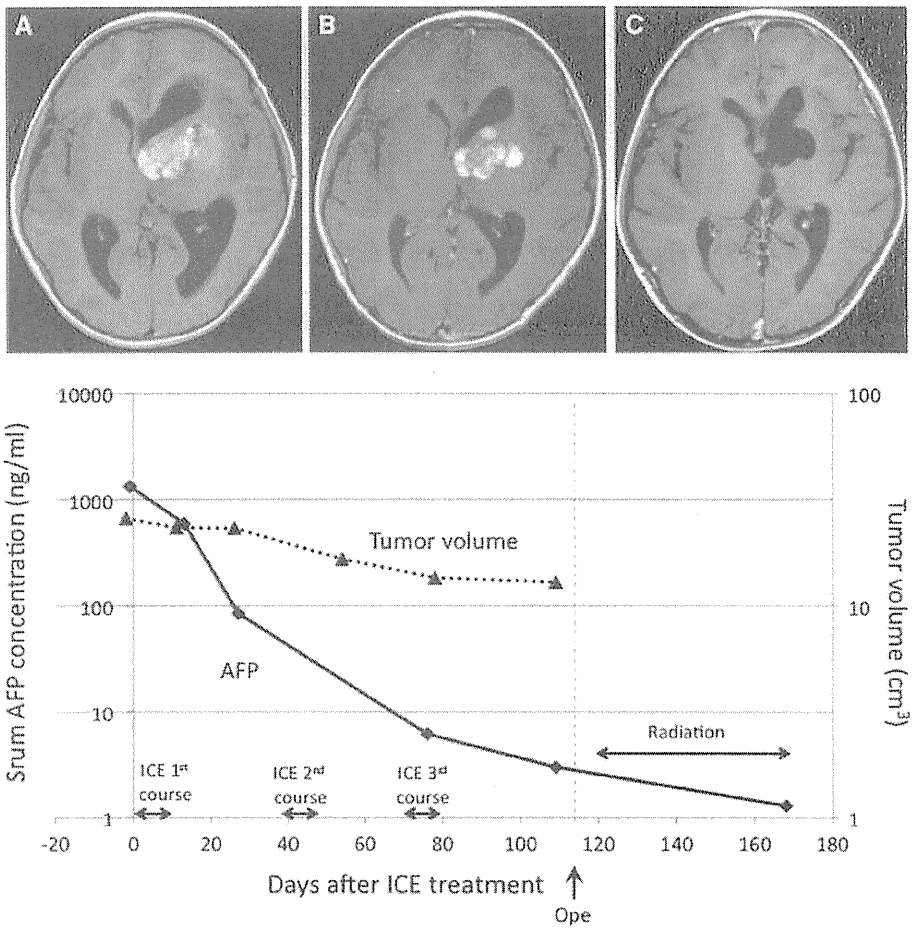

Fig. 6 Case 2 Radiographical findings (a–c) and serum alpha-fetoprotein (*AFP*) levels (*line graph*). Pretreatment magnetic resonance imaging showed an enhanced mass lesion in the left basal ganglia (a) and neoadjuvant chemotherapy was started immediately. After combination chemotherapy consisting of ifosfamide, cisplatin, and etoposide, AFP level logarithmically decreased to the normal range (*solid line* graph), but the tumor volume was not sufficiently decreased (b and *dots line* graph). Radical surgery was carried out and the residual enhanced lesion was totally removed (c). Histological diagnosis was mature teratoma

nonseminomatous germ cell tumors. Unsatisfactory decrease of tumor marker level is correlated with poor prognosis after cisplatin-based chemotherapy [28, 30]. On the other hand, tumor marker decrease cannot accurately discriminate patients with favorable versus unfavorable outcomes [27, 33–35]. Therefore, whether tumor marker decline can be used to identify patients with nonseminomatous germ cell tumor who need early salvage therapy is still controversial [36].

Evaluation of the CSF tumor marker level is certainly important for making the initial diagnosis or even picking up the recurrences. However, collection of CSF is invasive and it is not easy to follow sequentially, especially for young children. Figure 7 showed that the CSF tumor marker levels changed in synchronization with those in serum. For the sequential measurement to observe the tumor marker decrease rate, blood examination might be reliable and less invasive.

We do understand our protocol is not ideal and our series of patients was relatively small and in intracranial NGGCTs, it is not surprising that the failure of serum tumor marker normalization may indicate poor prognosis. But the present study revealed that the sequential measurement of serum tumor marker level seemed good indicator for early salvage therapy by identifying the patients with treatment relapse or slow responder for initial treatment. Patients whose serum tumor marker clearance was slower than expected was considered intractable for initial treatment. On contrary, patients whose serum concentration of tumor marker decreased logarithmically at first but raised or slowed down eventually, were considered relapsed with or without dissemination. These findings indicated poor outcome and, more aggressive treatment should be started without delay. Taken together, we suggest that serum concentration of the tumor markers should be followed sequentially and when their decrease rates get delayed compared to the ideal logarithmic decrease, the salvage therapy should be considered even if the MR findings cannot disclose the tumor progression. The optimum treatment for patients who relapsed during neoadjuvant chemotherapy is still unresolved. However, high-dose chemotherapy with bone marrow rescue or early induction of radiation therapy including the whole craniospinal axis can be a considerable salvage therapy. Further investigation, such as prospective

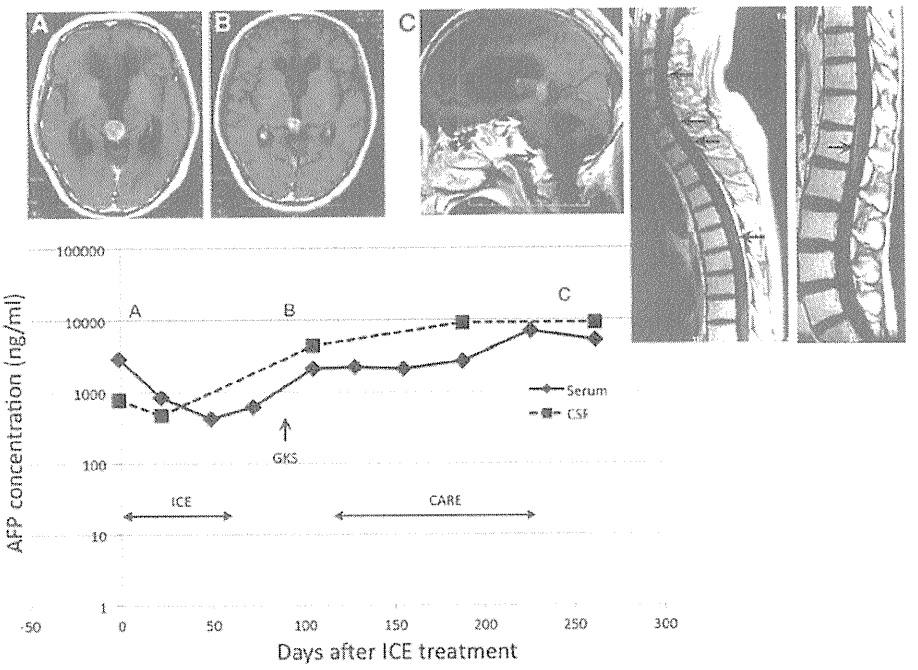

Fig. 7 Case 8 radiographical findings (**a**–**c**) and sequential changes in serum and cerebrospinal fluid (*CSF*) alpha-fetoprotein (*AFP*) levels (*line graph*). Pretreatment magnetic resonance (*MR*) imaging showed an enhanced mass lesion in the pineal region (**a**) and neoadjuvant chemotherapy consisting of ifosfamide, cisplatin, and etoposide was started immediately. Despite multiple further therapies, the enhanced lesion remained (**b**). Both serum and CSF AFP levels were high on admission and these tumor marker levels, changed synchronously, continued high even after the chemotherapy. Despite intensive treatments, MR imaging showed multiple disseminated lesions around the brain stem and spinal cord (**c**, *arrows*). Patient died of tumor progression 9 months after starting of the therapy

clinical study, is necessary in a routine clinical setting to identify better treatment options.

Conclusion

The present study suggests that the sequential measurement of serum tumor marker levels may be an effective approach to identify slow responders and recurrent cases during initial treatment for patients with poor prognostic NGGCTs. Logarithmic decrease and normalization of serum AFP or HCG levels during neoadjuvant chemotherapy may be important favorable prognostic factors, however, therapy should be intensified in patients who did not show the logarithmic decrease and normalization of serum tumor marker levels during neoadjuvant chemotherapy. This simple method may suggest the timing when to consider early salvage therapy. Further study, such as larger national or international cooperative group trial, is highly recommended to confirm the efficacy of sequential serum tumor marker measurement and to identify more aggressive therapy, including high-dose chemotherapy with bone marrow rescue.

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CLINICAL STUDY – PATIENT STUDY

Early detection of venous thromboembolism in patients with neuroepithelial tumor: efficacy of screening with serum D-dimer measurements and Doppler ultrasonography

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Abstract The efficacy of combined serum D-dimer level measurement and Doppler ultrasonography of the lower extremity was investigated for screening of venous thromboembolism (VTE) in patients with neuroepithelial tumor. Eighty-one patients with neuroepithelial tumor were prospectively studied. All patients underwent measurement of serum D-dimer levels and Doppler ultrasonography of the lower extremity. The serum D-dimer level was measured every week, and Doppler ultrasonography was performed two and two weeks after surgery, then every two weeks until discharge, or every two weeks for patients who did not undergo surgery. If the serum D-dimer level increased over 10.0 μg/ml, Doppler ultrasonography or computed tomography was performed to detect VTE. VTE occurred in 12 (14.8%) patients (seven males and five females; age 34–75, mean 59.0 years). Only one patient was symptomatic, whereas 11 patients identified by the screening were without symptoms. Five patients were treated with anticoagulant therapy, one with prophylactic inferior vena cava filter placement with anticoagulant therapy, and the other six were closely followed up without medication. No patient died of pulmonary embolism. Serial Doppler ultrasonography showed thrombus regression or organization and no thrombus extension. The maximum serum D-dimer value was significantly higher in patients with VTE than in those without VTE (mean 14.5 vs. 3.46 μg/ml, $P < 0.001$). The D-dimer cutoff value of 5.4 μg/ml could be used to identify VTE with 83% sensitivity and 84% specificity. The combination of sequential serum D-dimer measurement and Doppler ultrasonography of the lower extremity is an efficient and non-invasive procedure for identifying asymptomatic VTE in patients with neuroepithelial tumor.

Keywords Venous thromboembolism · Glioma · D-dimer · Doppler ultrasonography · Pulmonary embolism

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Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a high-risk complication of cancer with significant clinical consequences known since the 19th century [1–3]. VTE is a leading cause of death in cancer patients [4] and is associated with significantly worse survival [5, 6]. Brain tumor is associated with high incidences of VTE [7–9], and patients with glioma have the highest incidence of VTE of 7.5% and PE of 2.3% [8]. However, previous studies of the incidence of VTE or its association with glioma were retrospective and asymptomatic VTE was not carefully considered.

The clinical features and symptoms of DVT are mainly non-sensitive and non-specific, so diagnosis usually depends on imaging methods. Doppler ultrasonography is regarded as the standard method because of less invasiveness and higher sensitivity [10]. Doppler ultrasonography is performed optimally for diagnosis of symptomatic, proximal vein thrombosis [11–19]. The serum D-dimer

level is also related to DVT [17, 20] and is valuable, because measurements can be repeated easily and are quite sensitive to thrombotic events [5, 21–25]. The D-dimer value immediately increases at the onset of thrombotic events, so is one of the most reliable blood markers of VTE.

In this prospective study we tried to clarify the true incidence rate of VTE including asymptomatic occurrence, and the onset timing in patients with neuroepithelial tumor, and investigated the efficacy of combined D-dimer measurement and Doppler ultrasonography of the lower extremity for early detection of DVT to prevent fatal PE.

Clinical material and methods

Study population

Eighty-one consecutive patients with neuroepithelial tumor were prospectively enrolled in this study between July 2007 and December 2008. All patients were admitted for treatment, including surgical resection, biopsy, chemotherapy, or radiation therapy, at Tohoku University Hospital. Patients who underwent initial surgery in another hospital and were admitted for concomitant treatment were also included. Histological diagnosis was based on the World Health Organization (WHO) classification [26]. Patients with metastatic brain tumor, non-neuroepithelial tumor such as meningioma or germ cell tumor, and spinal cord tumor, and patients under the age of 18 years were excluded. Informed consent was obtained from each patient or guardian on admission and before computed tomography (CT) with contrast medium, or anticoagulant therapy.

Data collection and analysis

The following variables were prospectively recorded in a computerized data base for analysis: age, sex, lower extremity paresis, performance status at VTE occurrence, histological diagnosis (WHO grade), chemotherapy, and maximum serum D-dimer level. Neuroimaging findings, including CT, magnetic resonance (MR) imaging, and Doppler ultrasonography, were also recorded.

Protocol

The serum D-dimer measurements and Doppler ultrasonography were performed according to the following protocol. On admission, the serum D-dimer level was quantitatively measured in all patients. For patients who underwent surgery, including tumor resection and biopsy, it was measured within one week after surgical intervention and followed every week. Doppler ultrasonography of the lower extremity was carried out two and five weeks after surgery, then every two weeks until discharge. For patients who did not undergo surgery, serum D-dimer level was measured every week and Doppler ultrasonography was carried out every two weeks. It is known that serum D-dimer level is sometimes elevated after surgery, even if there is no VTE, but the increase is rarely so high. Increased serum D-dimer level exceeding 10.0 μg/ml elicited further examination for VTE by Doppler ultrasonography or CT with contrast medium of the chest, abdomen, and lower extremities (Fig. 1).

Doppler ultrasonography

Doppler ultrasonography was performed with SSA-770A (Toshiba Medical System, Otawara, Japan) or ProSound alpha10 (Aloka, Tokyo, Japan) equipment. The examination was performed in supine posture with a pillow placed beneath the knees. The diagnosis criterion for DVT was the inability to compress the veins in a cross-section (the primary basis for diagnosis). The presence of thrombus, the overall characteristics of the thrombus, absence of spontaneous venous flow, absence of respiratory phasicity, and absent or incomplete color filling signal, were adjuncts in assessment of the presence of thrombus. Dilation of the lower extremity veins or congestive venous flow was not regarded as DVT.

Clinical management

Elastic compression stockings were worn by all patients after admission for prophylaxis. Intermittent pneumatic compression was also used for all patients treated by surgery. Patients were mobilized after surgery as soon as

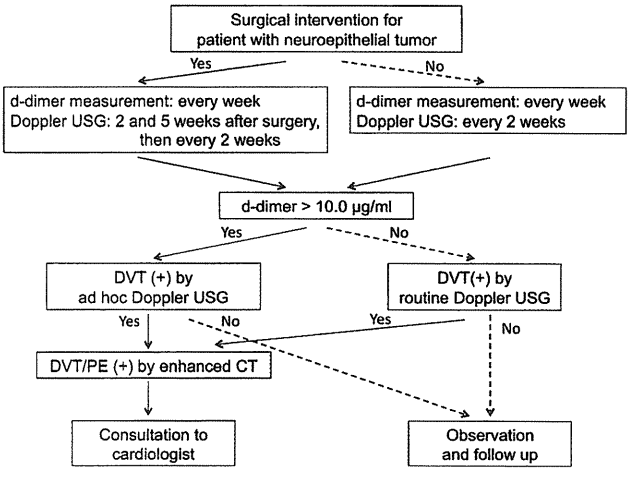

Fig. 1 Flow diagram showing the diagnosis of venous thromboembolism in patients with neuroepithelial tumor. *CT*, computed tomography; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *USG*, ultrasonography

possible, usually from the day after surgery and, if necessary, physical therapy was started. Continuous heparin infusion or low molecular weight heparin was not administered. Patients were referred to the cardiology department if VTE was detected. If the thrombus extended proximal of the popliteal vein, unfractionated heparin was administered with or without filter placement on the inferior vena cava, followed by warfarin administration.

Statistical analysis

Differences in characteristics between patients with and without VTE were examined by Fisher's exact test or Student's *t* test. Probability values ≤ 0.05 were considered statistically significant.

Results

The characteristics of the 81 patients with neuroepithelial tumor are shown in Tables 1 and 2. Sixty-one (75.3%) patients underwent resection and 11 (13.6%) patients received stereotactic biopsy. Nine patients had previously undergone surgical treatment and histological diagnosis had been obtained. After surgery, 28 (34.6%) patients received concomitant radiation therapy and chemotherapy, 21 (25.9%) received chemotherapy only, and seven (8.6%) received radiation therapy only. Sixteen (19.8%) patients received neither radiation therapy nor chemotherapy after surgery. Nine patients did not undergo surgery during this period, three (3.7%) patients received chemotherapy and radiation therapy, three (3.7%) patients received chemotherapy only, and three (3.7%) patients received neither radiation therapy nor chemotherapy.

Table 2 Histological diagnosis of 81 patients

Histology	Number of patients
WHO grade IV	
Glioblastoma	38
Gliosarcoma	1
WHO grade III	
Anaplastic astrocytoma	8
Anaplastic oligodendroglioma	8
Anaplastic oligoastrocytoma	2
Gliomatosis cerebri	3
WHO grade II	
Diffuse astrocytoma	7
Oligodendroglioma	4
Oligoastrocytoma	1
Ependymoma	1
Pleomorphic xanthoastrocytoma	1
Glioneuronal tumor	1
WHO grade I	
Pilocytic astrocytoma	3
Ganglioglioma	3

Incidence of VTE

During the follow-up period, VTE occurred in 12 (14.8%) patients (seven males and five females; age 34–75, mean 59.0 years) (Table 3). One patient who presented with loss

Table 1 Characteristics of 81 patients with neuroepithelial tumor with or without VTE

	Total	VTE	Non VTE	*P* value
Number of cases	81	12	69	
Age in years, min–max (mean)	24–78 (50.8)	34–75 (59.0)	24–78 (49.4)	0.038*
Male:female (% of females)	40:41 (50.6%)	7:5 (41.7%)	33:36 (52.2%)	0.5
Maximum value of D-dimer in μg/ml, mean ± SD	5.3 ± 6.3	14.5 ± 9.7	3.46 ± 3.6	<0.001*
Histology				
Grades I + II	6 + 15 (25.9%)	0 + 0 (0%)	6 + 15 (30.0%)	0.026*
Grades III + IV	21 + 39 (74.1%)	4 + 8 (100%)	17 + 31 (70.0%)	
Hemiparesis in the lower extremity				
MMT ≤2/5	16/81 (19.8%)	5/12 (41.7%)	11/69 (15.9%)	0.039*
MMT >3/5	65/81 (80.2%)	7/12 (58.3%)	58/69 (84.1%)	
Performance status (3–4)	31/81 (38.3%)	6/12 (50%)	25/69 (36.2%)	0.36
Corticosteroid therapy	27/81 (33.3%)	6/12 (50%)	21/69 (30.4%)	0.18
Surgery	72/81 (88.9%)	10/12 (83.3%)	62/69 (89.9%)	0.507
Radiation therapy	38/81 (46.9%)	7/12 (58.3%)	31/69 (44.9%)	0.390
Chemotherapy	55/81 (67.9%)	12/12 (100%)	43/69 (62.3%)	0.012*

MMT manual muscle test, *SD* standard deviation, *VTE* venous thromboembolism

* Statistically significant

of consciousness during rehabilitation was the only symptomatic case (Case 3) whereas 11 patients identified by screening for VTE were without symptoms. Ultrasonography and CT of the chest, abdomen, and lower extremities identified isolated DVT in nine (11.1%) patients and combined DVT and PE in three (3.7%) patients. Three of the nine patients with isolated DVT had DVT extending to the popliteal vein (Cases 1, 4, and 9), and were treated with anticoagulant therapy. The two patients with asymptomatic PE (Cases 2 and 6) were treated with anticoagulant therapy and one symptomatic patient with PE (Case 3) was treated with inferior vena cava filter placement and anticoagulant therapy. During this period, no death caused by PE occurred (Figs. 2, 3).

To determine the risk factors for VTE, we analyzed the correlations between clinical data and development of VTE. The patients were classified into two groups—patients with and without VTE. Clinical data including age, sex, WHO grade, paresis of the lower extremity, performance status, administration of corticosteroids, surgery, radiation therapy, and chemotherapy were analyzed. Statistical analysis revealed that high age ($P = 0.038$), WHO grade III or IV (grades I and II vs. III and IV, $P = 0.026$), and presence of paresis in the lower extremity (manual muscle test 0–2 vs. 3–5, $P = 0.039$) were significant risk factors for VTE (Table 1). Chemotherapy was also a significant risk factor ($P = 0.012$), in fact, 11 of 12 patients with VTE were treated with temozolomide and one patient with VTE was treated with ACNU (1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride). In contrast, sex, performance status, and corticosteroid administration had no statistical correlation with the development of VTE (Table 1).

Serum D-dimer level

Most patients had a low serum D-dimer level on admission (mean 1.06 μg/ml) and maintained this low level. The maximum D-dimer value during the observation period was significantly higher in patients with VTE than in those without VTE (14.5 ± 9.7 vs. 3.46 ± 3.6 μg/ml, $P < 0.001$). The elapsed time since surgery ranged between 1 and 103 days (Table 3). At first, additional examination with Doppler ultrasonography and/or CT with contrast medium were carried out for patients whose D-dimer level was over 10.0 μg/ml, which was observed for 12 of 81 patients (Fig. 4). We identified the cut-off value of serum D-dimer for detection of VTE as 5.4 μg/ml (75th percentile), which gave 83% sensitivity (10 of 12 patients) and 84% specificity (58 of 69 patients) for detection of VTE. In VTE patients, D-dimer level was normalized with appropriate treatment. Other causes of serum D-dimer elevation, for example atrial fibrillation, sinus thrombosis, systemic malignant diseases, or hematological diseases were not observed for any patients.

Doppler ultrasonography findings and treatment

Doppler ultrasonography detected VTE in 12 of the 81 patients. VTE was detected with ad-hoc Doppler ultrasonography because of D-dimer elevation over 10.0 μg/ml in six patients, and in the other six patients it was detected with regular scheduled (not ad-hoc) Doppler ultrasonography between D-dimer measurement intervals. Luminal thrombus was revealed in eight (66.7%) patients, organized thrombus in two (16.7%) patients, and floating thrombus in two (16.7%) patients. They were referred to the cardiology department and treated by cardiologists. Six patients received anticoagulant therapy for PE or DVT extending proximal to the popliteal vein. Serial Doppler ultrasonography showed total organization or regression of the thrombus in five of these six patients. In one patient, follow-up Doppler ultrasonography was not conducted, but no recurrent PE or death occurred. The other six patients were observed without anticoagulant therapy because the thrombus was found to be distal DVT. During the observation period, follow-up Doppler ultrasonography showed thrombus regression and organization in three and two patients, respectively. No thrombus extension was observed, although in one patient follow-up Doppler ultrasonography was not performed. No death or symptomatic VTE was observed during the observation period (Table 3). For the 12 patients, newly detected neurological deficit or other systemic symptoms after VTE diagnosis were not observed at discharge.

Duration of follow-up period

Doppler ultrasonography and serum D-dimer measurements were monitored until discharge for all patients. The median length of hospital stay was 123 days (range, 8–634 days). Patients were then followed up in the outpatient department with serum D-dimer measurements. During the follow-up period, 42 (51.9%) patients died of tumor progression. However, no VTE occurred. The median length of follow up from the initial surgery was 600 days (range, 23–1,361 days).

Discussion

Previous studies of VTE incidence were based on retrospective data analysis [8, 9, 27, 28]. The diagnosis of VTE depended on presentation with symptoms, for example leg swelling or PE. In general, PE may cause sudden death, so that early detection before symptomatic manifestation is desirable. We previously reported a retrospective analysis of the incidence of symptomatic VTE in patients with malignant glioma as 1.9% [29]. In comparison, the incidence in this study is much higher, VTE occurred in 14.8% of patients with neuroepithelial tumor and PE occurred in

Table 3 Characteristics of the 12 patients with VTE

	Age (years), sex	Histology	Maximum D-dimer (μg/ml)	Days after surgery	Paresis		DVT		PE	Treatment		Follow-up Doppler ultrasonography
					Upper extremity	Lower extremity	Doppler ultrasonography of the lower extremity	Proximal extension		Anti-coagulants	IVC filter	
1	34, M	AG	16.3	[a]	Rt.4/5	Rt.4/5	Luminal thrombus in Rt. popliteal vein and femoral vein	Yes	None	Yes	None	Not examined
2	35, M	AOA	22.9	17	Lt.3/5	Lt.3/5	Luminal thrombus in Lt. popliteal vein and femoral vein	Yes	Yes asymptomatic	Yes	None	No thrombus
3	53, M	GB	27.5	46	Rt.1/5	Rt.2/5	Luminal thrombus in Rt. soleus vein and popliteal vein	Yes	Yes symptomatic[b]	Yes	Yes	No thrombus
4	56, F	GB	21.6	5	Rt.2/5 Lt.4/5	Rt.1/5 Lt.2/5	Floating embolus in bilateral popliteal veins	Yes	None	Yes	None	No thrombus
5	57, F	AA	6.9	103	Lt.1/5	Lt.1/5	Luminal thrombus in Lt. peroneus vein	None	None	None	None	No thrombus
6	59, M	AO	23.5	1	None	None	Luminal thrombus in Lt. soleus vein and popliteal vein	Yes	Yes asymptomatic	Yes	None	No thrombus
7	60, M	GB	2.1	1	Lt.4/5	Lt.4/5	Organized thrombus in Lt. soleus vein	None	None	None	None	Organized thrombus
8	65, F	GB	6.3	7	None	None	Luminal thrombus in Lt. anterior tibial vein	None	None	None	None	No thrombus
9	69, M	GB	3.2	23	None	None	Floating thrombus in Lt. soleus vein and popliteal vein	Yes	None	Yes	None	Organized thrombus
10	70, M	GB	27.5	6	Rt.3/5	Rt.2/5	Luminal thrombus in Rt. soleus vein and peroneus vein	None	None	None	None	Organized thrombus
11	75, F	GB	8.0	8	Rt.2/5	Rt.2/5	Luminal thrombus in Rt. soleus vein	None	None	None	None	No thrombus
12	75, F	GB	8.3	44	None	None	Organized thrombus in Lt. soleus vein Dilation of Lt soleus vein	None	None	None	None	Not examined

AA anaplastic astrocytoma, *AG* anaplastic ganglioglioma, *AO* anaplastic oligodendroglioma, *AOA* anaplastic oligoastrocytoma, *DVT* deep vein thrombosis, *F* female, *GB* glioblastoma, *IVC* inferior vena cava, *Lt* left, *M* male, *PE* pulmonary embolism, *Rt* right, *VTE* venous thromboembolism

[a] Operated five years previously

[b] Presented with loss of consciousness during rehabilitation

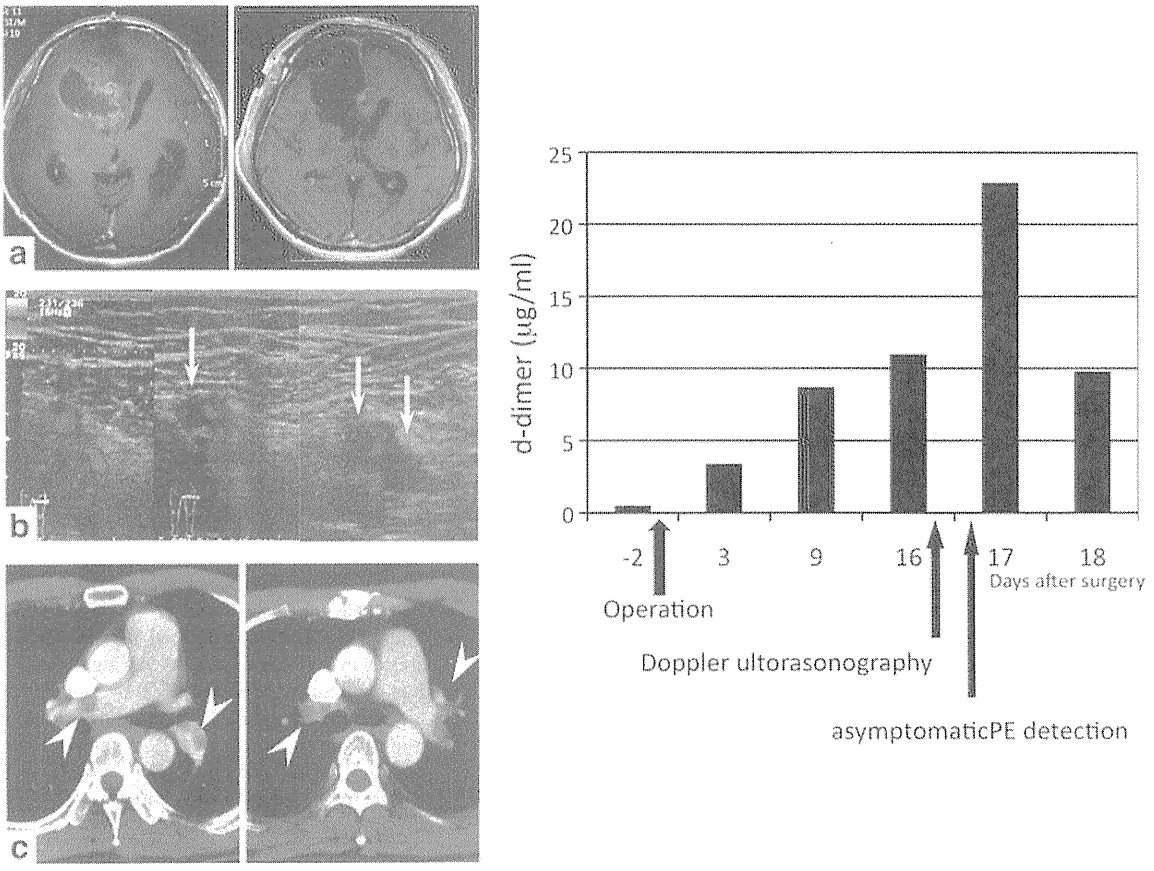

Fig. 2 Case 2. A 35-year-old male underwent gross total removal of right frontal anaplastic oligoastrocytoma (**a**, *left panel*: preoperative MR image, *right panel*: postoperative MR image). Postoperatively, he suffered slight left hemiparesis but was independent in daily life. Suddenly, D-dimer value elevated to 11.0 μg/ml 16 days after surgical resection. Doppler ultrasonograms showing luminal thrombus in the left popliteal and femoral veins (**b**, *arrows* show the blood flow defect in the femoral vein). Next day, D-dimer value was further elevated to 22.9 μg/ml. CT scans with contrast medium showing thrombus in the bilateral pulmonary arteries with no clinical symptoms (**c**, *arrowheads*). He was referred to the cardiology department and treated with heparin/warfarin. The *bar graph* shows the sequential D-dimer values of this patient

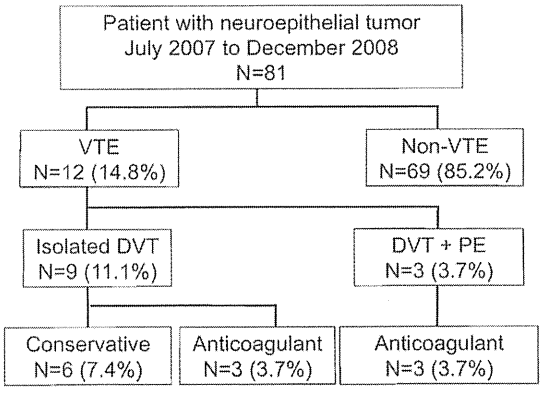

Fig. 3 Flow diagram showing the screening and treatment of 81 patients. Diagnosis of venous thromboembolism (VTE) was based on Doppler ultrasonography findings. *DVT*, deep vein thrombosis; *PE*, pulmonary embolism

3.7% of patients. One possible explanation of this discrepancy is the detection of asymptomatic VTE. In this study, only one patient (1.2%) presented with symptomatic VTE (PE), a rate compatible with our previous report. One previous prospective study found the rate of VTE was 13% in patients after elective neurosurgery [7]. Brandes et al. also reported a prospective study which revealed a 20.8% risk of DVT in glioma patients 12 months after surgery [30]. Simanek et al. focused on symptomatic VTE occurrence in patients with high-grade glioma [31]. They treated high-grade glioma patients with low-molecular-weight heparin and a compression stocking for 10 days after surgery and reported 24% of patients showed symptomatic VTE (including nine PE). Compared with these, the duration of follow up was relatively short in our study, however, it covered the high-risk period of VTE [8]. The proportion of symptomatic VTE patients in this study was much lower than in the literature, despite not using anticoagulant therapy. This might also indicate the efficacy of our screening procedure for early detection of VTE before symptomatic manifestation.

The purpose of VTE treatment is to prevent PE, which sometimes causes cardiopulmonary arrest. Therefore, DVT

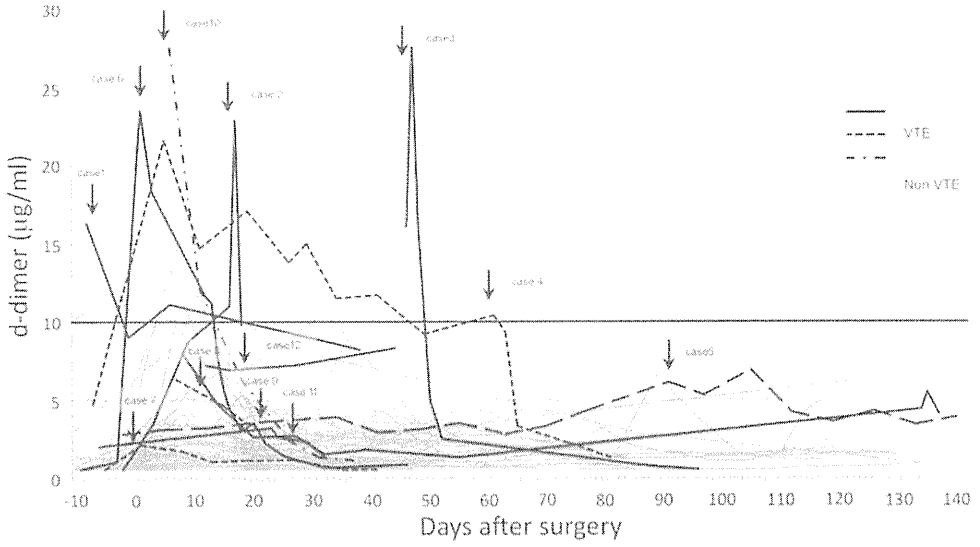

Fig. 4 Sequential D-dimer values of all patients. *Black lines* (*solid line*, *dashed line*, and *dash-dot line*) and *gray lines* indicate patients with venous thromboembolism (VTE) and without VTE, respectively. Case numbers as in Table 3. *Arrows* indicate VTE onset. The maximum D-dimer value was higher than 10.0 μg/ml for 12 patients. Although D-dimer level did not reach 10.0 μg/ml for most non-VTE patients, for patients with VTE D-dimer values were much higher. Note that D-dimer elevation occurred at random times after surgery. Case 1 underwent surgery previously and only chemotherapy was carried out during this period. For this patient, day 0 indicates the start day of chemotherapy. Case 10 lacked preoperative D-dimer data, because he underwent surgery in another hospital and was transported to our institution for further treatment. Preoperative serum D-dimer value was not available for Cases 8 and 12 also. Case 3 was the first case of this series. He suddenly presented with hypotension and a significant decrease in oxygen saturation during rehabilitation. He was diagnosed as symptomatic PE and DVT by Doppler ultrasonography of the lower extremity and CT with contrast medium of the chest. Serum D-dimer level was above 10.0 μg/ml. These findings show that sequential serum D-dimer level analysis is useful for detecting VTE. This figure indicated that patients with VTE certainly showed sudden elevation of serum D-dimer value and there is no optimum timing for Doppler ultrasonography

must be detected before it becomes symptomatic and the appropriate treatment initiated. In this study, VTE was detected in 12 patients. Six of the 12 patients harbored venous thrombus extending to the popliteal vein, and all received anticoagulant therapy. Three of the six patients harbored PE, which is a high incidence, but the other three patients did not have symptomatic or asymptomatic PE, despite the presence of massive DVT. These three patients are extremely important examples of detection of patients at high risk of PE before symptom onset.

As shown in Table 1, the risk factors for VTE in this study were identified as the presence of paresis in the lower extremity, histological diagnosis (WHO grade), age, and use of chemotherapy, which are compatible with previous reports [3, 8, 29]. D-Dimer measurement is well recognized as a marker of recurrent VTE in patients without cancer [32–35]. Moreover, measurement of serum D-dimer level also effectively detects VTE in patients with ovarian, uterine, and breast cancer and brain tumor [32, 36, 37]. A prospective study revealed that D-dimer level could be used to predict the occurrence of VTE in patients with various cancers [32]. However, Doppler ultrasonography or CT to detect asymptomatic VTE was not performed, and objective imaging methods were used to confirm that the patient had developed symptoms of VTE. They concluded that patients with elevated D-dimer level were at high risk of VTE. In comparison, our study showed that sequential D-dimer measurement was useful for screening for VTE, even in patients without elevated D-dimer level. In this study a D-dimer cutoff value of 5.4 μg/ml enabled identification of VTE with 83% sensitivity and 84% specificity. In addition, the test is easy to perform and enables close serial screening [24].

Doppler ultrasonography of the lower extremity is an efficient, less invasive method for screening for DVT in both symptomatic and asymptomatic patients [38–40]. In fact, Doppler ultrasonography findings varied widely in our patients, and included organized thrombus, luminal thrombus, floating thrombus, and congestive flow without thrombus or dilation of the deep vein. Although Doppler ultrasonography enables effective detection of DVT in patients with subarachnoid hemorrhage [10, 38], screening of all patients every week may be difficult, so this method may be secondary to general screening by D-dimer measurement. Various studies have tried to detect VTE in the early period to prevent lethal PE, but usually used non-invasive screening tests with low sensitivity, for example radioactive fibrinogen scanning or highly invasive methods such as venography and ventilation/perfusion scintigraphy [7, 41, 42]. Compared with these methods, our procedure is

not only less invasive but also provides higher sensitivity and specificity.

The method of D-dimer measurement is relatively easy to repeat and the serum D-dimer level increases immediately on VTE occurrence. However, the increased D-dimer level is indicative of a systemic thrombotic event without locational information. Isolated DVT and PE are hard to distinguish by measurement of serum D-dimer level. In contrast, Doppler ultrasonography can detect DVT directly, but is time-consuming and requires much manpower. Therefore, routine Doppler ultrasonography is not realistic for every patient. Moreover, it is hard to predict when VTE tends to occur. The first two months after surgery are the high-risk period for VTE in patients harboring glioma [8]. In this study, we decided to perform Doppler ultrasonography of the lower extremities two and five weeks after surgery, on the basis of the findings of their study, but D-dimer elevation occurred at random times after surgery (Fig. 4). This result indicates there is no optimum timing for Doppler ultrasonography, so it is not sufficient to follow up patients with Doppler ultrasonography only. In this study, no patient was followed up with Doppler ultrasonography only. Taken together, serial D-dimer measurement is regarded as the first-line screening method for VTE, followed by Doppler ultrasonography to detect DVT.

The efficacy of prophylactic heparin-based anticoagulant therapy is well recognized. Moreover, the complication of bleeding is also known to be one of the most miserable complications after neurological surgery [43, 44]. Collen et al. reviewed the literature, and performed a meta-analysis which showed the efficacy of anticoagulant therapy and the subsequent risk of bleeding. Although the study population was heterogeneous, bleeding complications, for example massive intracranial hemorrhages or minor bleeding, tend to occur in patients treated with anticoagulant. They also showed that prophylaxis with intermittent pneumatic compression was equally efficacious [43]. This means that heparin use might be limited for high-risk patients. In our study, heparin-based anticoagulant therapy was not performed for prophylaxis. However, when PE or DVT with proximal extension to the popliteal vein was detected, anticoagulant therapy was started immediately for VTE treatment. Our screening procedure gave the appropriate timing for starting anticoagulant therapy, which led to good results with no bleeding complication or low incidence of symptomatic VTE.

In our study, Doppler ultrasonography showed various venous findings. Which finding indicates the highest risk of PE remains controversial, but thrombus extending proximal to the popliteal vein is one of the risk factors of PE [40, 45]. Six patients harbored thrombus localized in the soleus, tibial, or peroneus vein. Because of the relatively low risk of PE, and potentially catastrophic bleeding complication, they were not treated with heparin-based anticoagulant therapy. The natural history of isolated distal DVT is unknown and treatment of this entity is still controversial, but our patients were treated with mechanical prophylaxis and physical therapy, which can be one treatment option. In addition, close follow up with D-dimer measurement and Doppler ultrasonography was continued even five weeks or more after surgery, which resulted in total regression or organization in five of six patients and no PE onset (Table 1).

The combination of D-dimer measurement and Doppler ultrasonography is currently the most favorable procedure for early VTE detection, but no standardized measurement method or consensus for the normal range of D-dimer values has been established, so the cutoff value of 5.4 μg/ml in this study cannot be compared directly with previous findings. Sequential measurement of serum D-dimer level is definitely valuable for VTE screening, however [17].

Conclusions

This prospective study in Japan revealed that the occurrence of VTE among patients with neuroepithelial tumor is actually higher than previously reported. Serial D-dimer sequential measurement and Doppler ultrasonography are effective methods for detection of VTE, because of low invasiveness and sensitivity/specificity. We would like to emphasize that early VTE detection using this combination enables appropriate treatment to avoid PE onset.

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Simultaneous Occurrence of Subarachnoid Hemorrhage and Epistaxis Due to Ruptured Petrous Internal Carotid Artery Aneurysm: Association With Transsphenoidal Surgery and Radiation Therapy

—Case Report—

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Abstract

A 62-year-old woman presented with simultaneous subarachnoid hemorrhage (SAH) and massive epistaxis. The patient had been treated for pituitary prolactinoma by two transsphenoidal surgeries, gamma knife radiosurgery, and conventional radiation therapy since age 43 years. Cerebral angiography showed left petrous internal carotid artery (ICA) aneurysm with slight stenosis on the adjacent left petrous ICA. She underwent superficial temporal artery-middle cerebral artery (STA-MCA) double anastomosis with endovascular internal trapping without complication the day after onset. Postoperative course was uneventful; the patient did not develop symptomatic vasospasm, recurrent epistaxis, or cerebrospinal fluid rhinorrhea. Postoperative angiography demonstrated complete disappearance of the aneurysm with patent STA-MCA anastomosis. The patient was discharged 2 months after surgery without neurological deficit. The present case is extremely rare with simultaneous onset of SAH and epistaxis caused by ruptured petrous ICA aneurysm. The transsphenoidal surgeries and radiation therapies might have been critical in the formation of the petrous ICA aneurysm.

Key words: cerebral aneurysm, epistaxis, radiation therapy, subarachnoid hemorrhage, transsphenoidal surgery

Introduction

Aneurysms arising at the petrous internal carotid artery (ICA) are rare, and their pathogenesis remains unclear. Petrous ICA aneurysms include pseudo-aneurysms caused by surgical manipulation, radiation therapy, trauma, mycotic, as well as true aneurysms.[1,2,4,6,10,12] These aneurysms are usually asymptomatic, but may manifest as hemorrhage or mass effect on the adjacent structures, and can develop variety of clinical signs and symptoms, such as epistaxis, otorrhagia, cranial nerve deficit, vertigo, and dizziness,[9] whereas association with subarachnoid hemorrhage (SAH) has not been reported. Here, we report an extremely rare case of ruptured petrous ICA aneurysm presenting with simultaneous occurrence of SAH and massive epistaxis.

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Case Report

A 62-year-old woman was referred to our institution for the treatment of pituitary prolactinoma in 1990 at the age of 43 years. The tumor was refractory to medical therapy and required surgical management. On initial admission, the huge pituitary tumor was found to extend into sphenoid sinus from the sella turcica with marked erosion of the adjacent bony structure at the skull base. Posterior extension had eroded the dorsum sellae with slight compression of the brain stem, and lateral extension had invaded the left cavernous sinus. The tumor was partially resected via the transsphenoidal approach without removal of the lateral or posterior extensions. The carotid arteries were not injured throughout the surgery. The left intracavernous tumor had gradually grown after initial surgery, which was treated by gamma knife radiosurgery in 1992 (Fig. 1A). The left ICA and surrounding structure received a dose ranging from 25 to 35 Gy (Fig. 1B). However, the

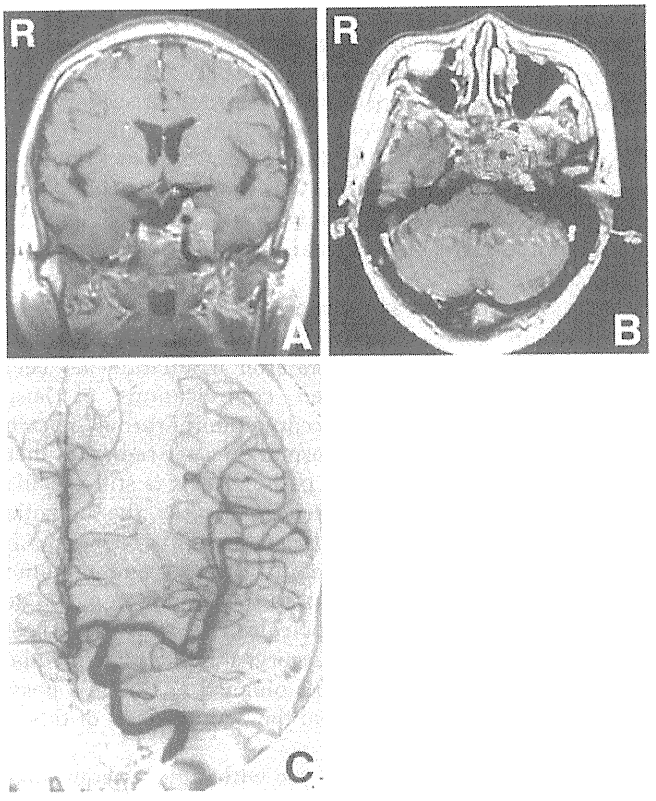

Fig. 1 A: Coronal T_1-weighted magnetic resonance image with gadolinium before gamma knife surgery in 1992 showing the tumor surrounding the left internal carotid artery (ICA). B: Gamma knife planning showing that the left ICA and the surrounding structure received a dose ranged from 25 to 35 Gy. C: Preoperative left internal carotid angiogram in 1996 showing no abnormality.

rest of the tumor outside the radiation field continued to grow. Second transsphenoidal surgery was eventually required to remove the posterior tumor extension which had eroded the clivus with marked compression of the brain stem in 1996. Preoperative angiography revealed no abnormality (Fig. 1C). The carotid arteries were not injured throughout the surgery. She underwent a total of 55.2 Gy of adjuvant radiation following the second surgery with the two opposed portal technique. Magnetic resonance (MR) imaging demonstrated disappearance of the tumor after radiation, and the patient was regularly followed up on an outpatient basis.

The patient was admitted to our hospital with complaints of massive epistaxis in November 2009, 19 years after the initial surgery. She developed severe headache simultaneously with the onset of epistaxis. Hemostasis was achieved by nasal tampon. Computed tomography (CT) revealed SAH with slight hydrocephalus (Fig. 2A). Cerebral angiography showed a left petrous ICA aneurysm with slight stenosis of the adjacent left petrous ICA (Fig. 2B). The upper and lower parts of the aneurysm projected to the cisternal space and the sphenoid sinus, respectively (Fig. 2C). Moreover, coronal CT revealed SAH leaking into the nasal sinus through the skull base defect

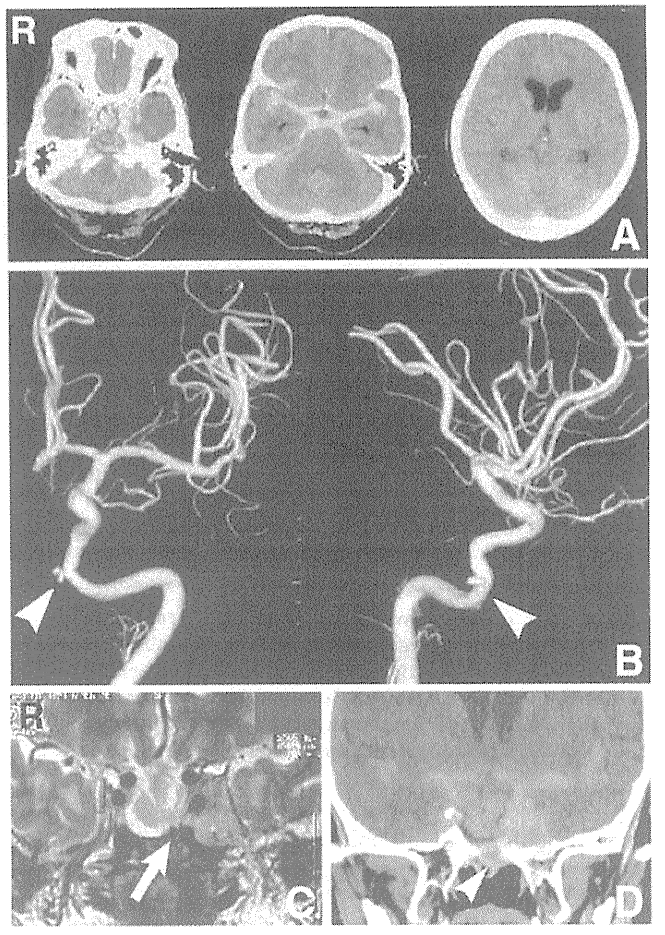

Fig. 2 Neuroradiological findings of 2009 hospitalization. A: Initial computed tomography (CT) scans demonstrating subarachnoid hemorrhage (SAH) predominantly located in the basal cistern and empty sella. B: Left internal carotid angiograms, anteroposterior (*left*) and lateral (*right*) views, demonstrating the petrous internal carotid artery (ICA) aneurysm and adjacent stenotic segment of the left petrous ICA (*arrowheads*). C: Coronal T_2-weighted magnetic resonance image showing the aneurysm (*arrow*) located at the boundary between cisternal space and sphenoid sinus. D: Coronal CT scan showing the SAH leaking into the nasal sinus through the skull base defect (*arrowhead*).

(Fig. 2D). Balloon test occlusion (BTO) of the left ICA demonstrated the presence of collateral flow via the anterior communicating artery. However, the BTO showed non-synchronous venous filling with reduced regional cerebral oxygen saturation on the occluded side. Therefore, we decided to perform bypass surgery with endovascular internal trapping of the left ICA.

Superficial temporal artery-middle cerebral artery (STA-MCA) double anastomosis was performed via left frontotemporal craniotomy. The frontal branch and the parietal branch of the STA were anastomosed to the frontal and the temporal cortical arteries (M_4), respectively. Intraoperative angiography confirmed patency of the bypass. Following the bypass surgery, the left ICA including the pseudoaneurysm and the narrowed segment was occluded by

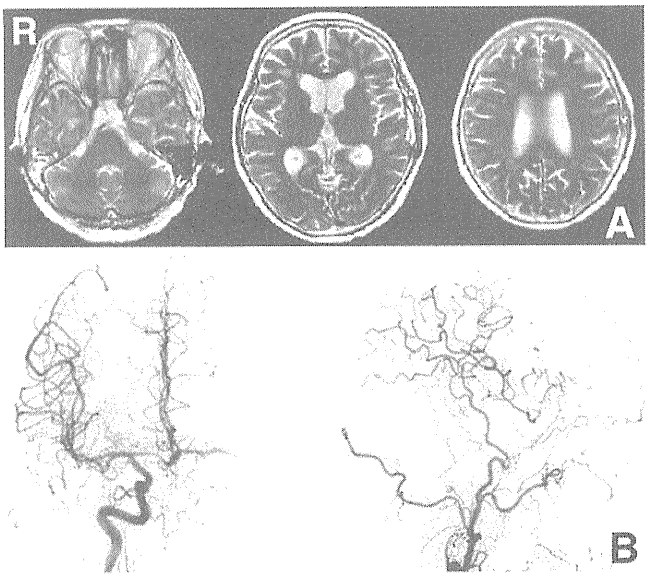

Fig. 3 A: Axial T_2-weighted magnetic resonance images one month after the surgery revealing no ischemic lesions. B: Right internal carotid angiogram, anteroposterior view (*left*) and left common carotid angiogram, lateral view (*right*) showing the patent superficial temporal artery-middle cerebral artery double bypass and disappearance of the aneurysm.

endovascular coil embolization in the same operating room. Cerebral angiography after the endovascular treatment showed complete disappearance of the pseudoaneurysm with the patent STA-MCA double bypass.

The postoperative course was uneventful. The patient did not develop symptomatic vasospasm following SAH, recurrent epistaxis, or cerebrospinal fluid rhinorrhea. Postoperative MR imaging and cerebral angiography revealed no ischemic or hemorrhagic complications with the apparently patent STA-MCA bypass (Fig. 3). The patient was discharged 2 months after surgery without neurological deficit.

Discussion

This is a very rare case of petrous ICA aneurysm presenting with simultaneous occurrence of SAH and massive epistaxis. Rupture of petrous ICA aneurysm should not result in SAH because of the extra-arachnoidal localization. In the present case, preoperative coronal MR imaging showed the aneurysm straddled the boundary between the large cisternal space arising in the empty sella and the sphenoid sinus. Furthermore, the skull base bony structure was modified by previous transsphenoidal surgeries, radiation, and tumor invasion. These factors may explain this unusual presentation of simultaneous onset of SAH and epistaxis following aneurysm rupture.

The underlying mechanisms of the aneurysm formation in the present case are unclear. The formation of ICA aneurysms is a rare surgical complication following transsphenoidal surgery.[11] Only one case of ICA aneurysm formation was included in a series of 3061 transsphenoidal operations.[8] ICA aneurysm usually develops in the cavernous portion rather than the petrous portion after transsphenoidal surgery.[5,7,11] Rupture of the aneurysm mostly occurs within 2 weeks after surgery, and is rarely delayed.[11] These aneurysms are classified as pseudoaneurysm caused by intraoperative direct injury of the arterial wall of the ICA.[5,7,11] Another possible pathogenesis of the aneurysm might be radiation therapy. Radiation-induced intracranial aneurysms are rare with only 21 reported cases.[2,4] Only 4 cases were petrous ICA aneurysms. Cerebral aneurysms usually take several years to develop after irradiation. Formation of cerebral aneurysm more than 10 years after irradiation has been reported.[2] Radiation-induced complications of large cerebral blood vessels are predominantly thrombo-occlusive in nature.[3] Aneurysm formation after radiation therapy is less common, and its pathogenesis is still speculative. Accelerated atherosclerosis may be the essential pathogenesis of radiation-induced cerebral aneurysm.[3] In the present case, transsphenoidal surgery and radiation therapy might have interacted in the formation of the petrous ICA aneurysm. The petrous ICA may have been manipulated at the second surgery, and was also included within the radiation field. Histological analysis, if possible, might be the key to reveal the pathogenesis of this lesion.

This is an extremely rare case with simultaneous onset of SAH and epistaxis caused by ruptured petrous ICA aneurysm. The previous transsphenoidal surgeries and radiation therapies might have been critical in the formation of the aneurysm and in the rare pattern of onset.

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