Practice of Interferon Therapy
—Brain tumor—

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Abstract: This paper outlines the current clinical application of interferon-β for treating brain tumor. Since approved as a therapeutic drug for brain tumor, IFN-β has been reported to be effective when it was used alone, in combination with chemo-radiation therapy (IAR therapy), and as a maintenance therapy. Recently, the regimens with IFN-β have been improved to obtain a higher efficacy rate. For example, liposome is used as a drug delivery system (DDS) to administer IFN-β protein or genes. Although much remains to be examined about administration methods for DDS, it is expected that new developments in the field of gene therapy will improve the therapeutic results of antitumor therapies by cytokines including interferon.

Key words: Brain tumor; Interferon-β; IAR therapy; Gene therapy

Introduction

Interferon (IFN) was discovered in the 1950's during research on viral interference, and its antitumor and other effects were reported from the 1960's. During the 1970's, attention was paid to IFN as an anti-cancer drug because its antitumor effect was reported in clinical studies. Now, it is clinically used to treat Type C hepatitis, multiple sclerosis, and various tumors including renal tumor, malignant melanoma, and brain tumor.

IFN is classified by its properties into 3 types: IFN-α, IFN-β, and IFN-γ. IFN-α and IFN-β code common gene loci and have common cellular surface receptors, while IFN-γ has different dynamics. Therefore, the former and latter are called Types I and II IFN, respectively. In the clinical application of IFN for brain tumor, IFN-α is mainly used in Western countries, while IFN-β was approved by the Ministry of Health, Labor, and Welfare and has been clinically used in Japan.

This paper describes the history of the clinical application of different types of IFN for brain tumor, current issues, and prospects for

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new therapeutic techniques.

Interferon Single Therapy

In studies of the antitumor effect of IFN-α and IFN-β using brain tumor cells, Lundblad[1] and Wakabayashi[2] reported a direct inhibitory effect on brain tumor, and Otsuka *et al.*[3] reported an indirect inhibitory effect through immunocompetent cells. Nakagawa and Ueda reported the clinical effect of IFN-α on malignant brain tumor: they achieved partial response in patients with glioblastoma and medulloblastoma by the systemic and local administration, respectively, of IFN-α. Subsequent phase II studies on the use of recombinant IFN-α for malignant glioma showed a response rate of 10.3 to 20%.

Nagai *et al.*, who performed the systemic and local administration of IFN-β, reported an overall response rate of 22.2% in 54 evaluable patients, and the response rates of 16.7% and 42.9% in patients with glioblastoma and medulloblastoma, respectively.[4] In 10 patients with malignant glioma, Yoshida *et al.* systemically administered 3×10^5 to 3×10^6 units of IFN-β for 16 to 50 days continuously via an intravenous route or locally administered 5×10^4 to 3×10^6 units into the tumors for 7 to 73 days continuously via an Ommaya reservoir implanted when a tumor was removed. The result showed the size of the tumor was reduced by 50% or higher in 2 of 7 systemically treated patients and 1 of 3 locally treated patients.

However, it was reported that, in any case, the antitumor effect after the administration period lasted for only a short period, and that the administration of IFN alone would not eventually prolong survival, although it might provide remission during the administration period. Therefore, investigators started to attempt various regimens with IFN.

Interferon Combination Therapy

To improve the therapeutic results of the interferon single therapies for brain tumor, combinations with other therapies or drugs were attempted. So far, the following combinations have been examined.

1. Combination with radiotherapy

For the combination with radiotherapy, which has been the most effective adjuvant therapy for malignant brain tumor, Miyoshi *et al.*[5] and Korosue *et al.*[6] performed basic research with IFN-α and IFN-β, respectively. The following hypotheses were obtained: partially synchronized radiotherapy with IFN in relation to the DNA synthesis inhibiting effect of IFN might be effective; IFN might play a role by sensitizing patients to radiation; and there might be an interaction between sublethal damage by radiation and the direct antitumor effect of IFN.

Regarding clinical applications, Mahaley *et al.* reported that the combination of radiotherapy and IFN significantly prolonged the median survival time in patients with malignant glioma, and that the combination provided better results than the combination of radiotherapy and BCNU (carmustine), which was previously the standard therapy for brain tumor patients in the institution.[7]

2. Combination with chemotherapy

Various combinations of IFN and anticancer agents have been examined. The Mayo Clinic reported that the combination of BCNU and IFN-α caused a significantly higher synergistic effect than that with other drugs in 35 patients with recurrent glioma: the combination achieved an efficacy rate of 29% and a period of 10.1 months, and blocked the progression of the disease for 6 months or longer in 37% of the patients. Nitrosourea anticancer drugs, such as ACNU (nimustine hydrochloride) and MCNU (ranimustine), are available in Japan, but single therapy with any of the drugs has been effective for only 30 to 50% of patients with brain tumor.

Examination of the combination of IFN-β and ACNU with 13 human glioma cell lines showed the combination 5 mg of ACNU and

1×10^3 IU of IFN-β provided a tumor proliferation inhibiting effect of at least 2 log cell kill, and that the effect was obtained in 9 cell lines, as compared with 2 and 1 cell line by the single therapy with ACNU and IFN, respectively. Further, the effect was higher than that of at least 2 log cell kill observed in 7 cell lines treated with 10 mg of ACNU alone.[8] When ACNU is clinically applied at a usual dose of 2 to 3 mg/kg body weight, the concentration obtained in brain tumors is approximately 1 to 5 mg. It is practically impossible to increase the dose because of possible adverse effects, such as bone marrow suppression. Therefore, the results indicating the potentiation of the antitumor effect more than the addition of the effect of each anticancer drug and IFN at a usual dose suggest the effectiveness of the combination therapy.

3. Combination with radio-chemotherapy

Since the combination of IFN-β and ACNU showed high antitumor activity in a basic experimental study with a human glioma cell line, a clinical study was started in Japan by combining the IFN-β and ACNU combination therapy with radiotherapy (IFN-β-ACNU-Radiation [IAR] therapy) as an adjuvant therapy for malignant glioma. Yoshida *et al.* reported that the prognosis as determined by the mean survival period was significantly improved with IAR therapy (25.3 months) as compared with radiation alone (15.2 months) and radiation + ACNU (19.7 months), and that the initial response rate by IAR therapy was higher than that by radiation + ACNU (60.5% vs. 35.7%). Further, Yoshida *et al.* also confirmed the efficacy of IAR therapy in 175 malignant glioma patients followed for a long time.[9] Hatano *et al.* reported that increasing the administration frequency of IFN-β to twice daily increased its antitumor effect.[10] A U.S. study on the combination of IFN-α, BCNU, and radiation for malignant brain tumor reported a median survival time of 12.7 months and a mean survival time of 16.1 months for Grade IV astro-

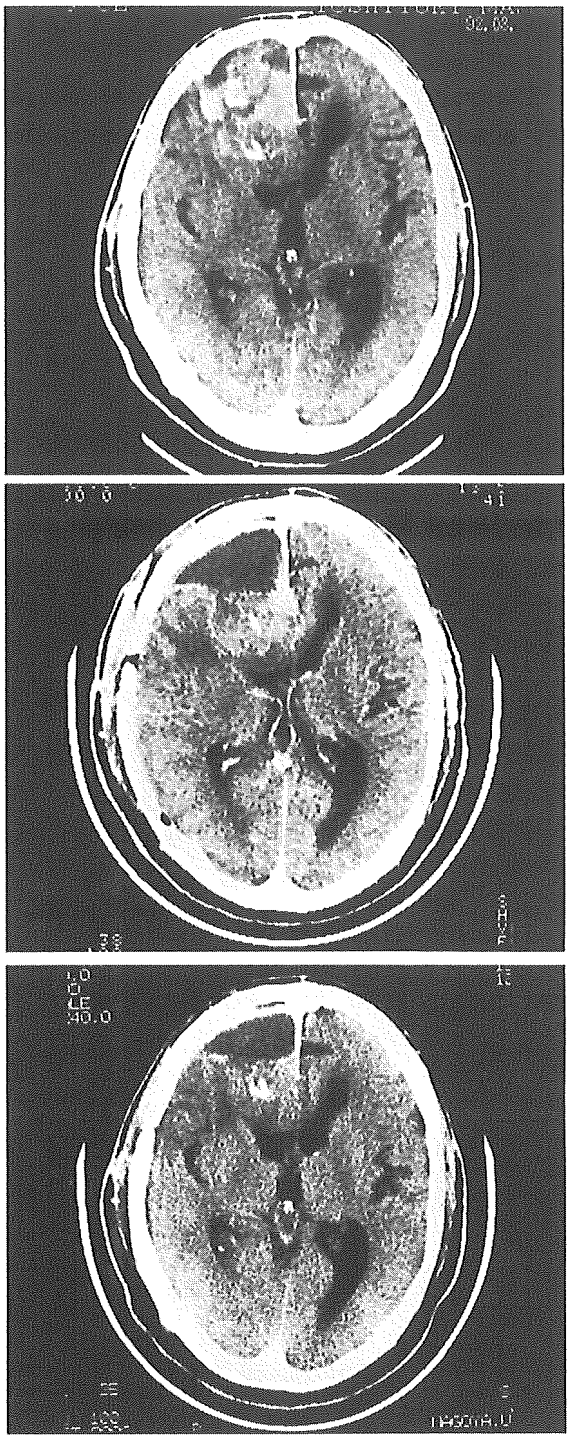

Fig. 1 54-year-old male patient: An enhanced lesion on CT scan indicating a tumor was observed in the right frontal lobe (a). It was diagnosed as glioblastoma. Since the postoperative image showed a residual tumor (b), IMR therapy was performed. A marked reduction of the tumor was observed at the end of the initial induction therapy (c). This patient received 3-month maintenance therapy, with no tumor recurrence for the subsequent 2 years.

cytoma, and 46.3 and 61.3 months for Grade III astrocytoma.

These results indicate that the inter-disciplinary combination of IFN-β, nitrosourea drug, and radiotherapy should be the first-line initial adjuvant therapy for inducing remission after an operation for malignant brain tumor (Figs. 1-a, b, and c). However, since recurrence was observed in most of the cases who responded to the combination, it is necessary to establish an appropriate maintenance therapy at an early stage after the induction of initial remission.[11]

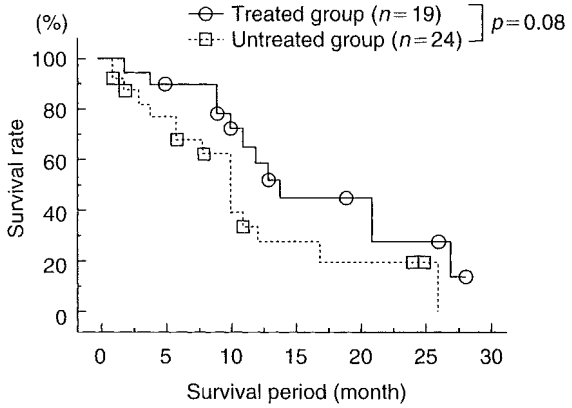

Fig. 2 Comparison between groups treated with and without IMR maintenance therapy

Interferon Maintenance Therapy

Although up to 60% of patients with malignant brain tumor could achieve remission by initial induction therapy, most of them experienced recurrence. For example, the remission and mean survival periods of patients with glioblastoma were reported to be as short as 11.2 and 13.9 months, respectively. Therefore, various maintenance therapies following initial induction therapy are being examined.

Wakabayashi *et al.* performed IFN-β-MCNU-Radiation (IMR) therapy as an initial induction therapy in patients who developed malignant glioma for the first time, and compared the remission period between those treated with a maintenance therapy consisting of 1×10^6 units of IFN-β every 2 weeks and 80 mg/m^2 of MCNU every 6 weeks for at least 3 months after the end of the induction therapy and those not treated with it. The patients registered into the initial induction therapy were randomly divided into 2 groups with and without the maintenance therapy, and they were compared for time to tumor progression (TTP) and total survival period. The results showed a significantly prolonged survival period in the maintenance therapy group (Fig. 2). Particularly, the patients who achieved complete remission by the initial induction therapy appeared to achieve a significantly prolonged remission period by receiving the maintenance therapy. It was also suggested that a certain therapeutic effect could be expected from the maintenance therapy in patients who developed the disease for the first time at 47 years or younger, or who achieved a partial response or a better response with the initial induction therapy. These results suggest that both initial induction and maintenance therapies may be important for the treatment of malignant glioma.[12]

New Developments in Interferon Therapy

1. Drug delivery system (DDS)-combined interferon (liposome)

Although IFN-β has been clinically applied for treating brain tumor, the clinical efficacy of IFN-β alone is less than expected when it was introduced in an uncombined form. It seems necessary to combine it with other therapies or drugs to fully realize its potential. In fact, IFN-β shows a marked antitumor effect at as low as 100 units *in vitro*, while it has been reported to produce tumor reduction by 50% or higher only in 15% of clinical cases, even at 10 million units. This difference in the efficacy of IFN may be explained by the pharmacokinetics of IFN, its stability in blood or tissue, or the blood brain barrier.

In an effort to overcome the problem of the

low *in vivo* effect of IFN, liposome has been examined as a drug delivery system (DDS). Epstein *et al.* examined the embedding of IFN in liposome and successfully changed the biological activities and pharmacokinetics of IFN. Kato *et al.* added sulfatide to liposome as a component to deliver IFN through the blood brain barrier into the cerebral parenchyma, and compared the stability, pharmacokinetics, intraorgan distribution, and antitumor effect between the embedded and free IFN. The result showed the blood titer of the free IFN became undetectable as early as 2 hours after intravenous administration, while the liposome-embedded IFN was detected at as high as 10^3IU/m*l* or higher even 8 hours after administration. Further, an IFN titer of 100IU/g tissue or higher was confirmed in the brain and subcutaneously implanted brain tumor tissue where no IFN was detected after the intravenous administration of the free IFN. It is expected that the clinical application of DDS will progress to increase the effectiveness of IFN for brain tumor.[13]

2. Interferon gene therapy

Larsson *et al.* reported that endogenous IFN-β was produced from glioma cells using a super-induction technique. This glioma-derived endogenous IFN-β has an antitumor effect on human glioma cells. We have been developing IFN gene therapy in which human IFN-β genes are embedded in the liposome with an affinity for glioma cells to selectively introduce the liposome into glioma cells and locally generate a large amount of endogenous IFN-β, thereby causing an antitumor effect on glioma. Since this technique ensures the secretion and maintenance of a much higher local concentration of IFN than administration from outside, the so-called paracrine effect can be expected. Further, the technique has been reported to cause phenomena that have not been observed with exogenous IFN, such as the induction of apoptosis of transgenic glioma cells. Finally, we expect an association with the immune system to indirectly enhance the antitumor effect.[14]

A clinical study on the gene therapy for brain tumor (malignant glioma) using this positively-charged liposome embedded-human IFN-β gene (local injection of the IFN-β gene-embedding liposome into brain tumor) was started on April 3, 2000 at the Nagoya University Hospital. So far, 5 patients have been registered and examined for the safety and efficacy of the therapy. The results of the study will be reported soon.

Conclusions

This paper outlines the current clinical application of interferon to brain tumor. There remains much to be examined about the use of IFN, such as appropriate administration regimens and the importance of maintenance therapy. However, together with the new developments in IFN therapy including the use of DDS and gene therapy, it is expected that the therapeutic results of antitumor therapies with cytokines including IFN will be improved.

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Management and Survival of Pineoblastoma: An Analysis of 34 Adults From the Brain Tumor Registry of Japan

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Abstract

Pineoblastoma is a rare tumor in adults, and factors influencing survival are poorly understood. Data from the Brain Tumor Registry of Japan (BTRJ) was analyzed to examine patient, tumor, and treatment characteristics associated with increased survival in adults with pineoblastomas. All pineoblastoma cases in adults aged 16 years or older were identified in the BTRJ. Data were extracted on demographics, presentation, tumor characteristics, treatments, and outcomes. Kaplan-Meier plots, the log rank method, and p value <0.15 was used to screen variables for inclusion in a multivariate Cox regression estimating survival. In the final Cox multivariate model, all variables with p values <0.05 were considered significant predictors of survival, and all variables with p values 0.05–0.099 were considered trends. The BTRJ contained 34 adults with pineoblastomas diagnosed from 1969–1998. The patients were predominantly male (22 patients), with a median age of 35 years (range 16–66 years). Median survival from diagnosis was 25.7 months, with a median follow up of 20.5 months. Median surgical resection was 75–94%, and five of the 34 patients had gross total resection. Twenty-nine of the 34 patients received cranial irradiation therapy with a median dose of 50 Gy (range 30–70 Gy). In the final multivariate model, cranial irradiation ≥ 40 Gy ($p = 0.014$) and gross total resection ($p = 0.034$) were associated with improved survival. There was a trend towards improved survival for women ($p = 0.099$). Adult pineoblastoma patients have poor survival prognosis. Cranial irradiation therapy using at least 40 Gy and complete surgical resection are associated with improved survival.

Key words: brain tumor, pineoblastoma, radiotherapy, surgery, survival, adult

Introduction

Pineoblastomas are rare, representing less than 0.1% of all primary brain tumors.[6,20] Pineoblastomas usually occur in children, whereas adults account for less than 10% of cases in published series,[19] and there are no adult pineoblastoma clinical series larger than 25 patients.[4,9] The systematic study of pineoblastomas in adults is hindered by their extreme rarity, incomplete staging, and the lack of a patient registry containing data on patient and tumor characteristics, treatments, and outcomes. In most series, treatments include chemotherapeutic and craniospinal irradiation, but the optimal regimen remains unclear.

The Brain Tumor Registry of Japan (BTRJ) is a nationwide registry of patients of all ages with primary or metastatic brain tumors. The BTRJ contains demographic, symptom, imaging, treatment, survival, functional status, and pathologic data.[6,28] An international collaborative project between the University of Pittsburgh and the Nagoya University School of Medicine provided access to the BTRJ. We queried the BTRJ to review the largest series of adults with pineoblastomas presented to date. The BTRJ is a unique source of data as almost all brain tumors in Japan are treated and recorded by the national health care system. The most recent summary report includes a statistical analysis of 81,569 patients with primary and metastatic brain tumors who were registered from 1969 to 1993.[6] The present analysis used an expanded BTRJ dataset collected from 1969–1998. Studies of extremely rare tumors such as adult pineoblastomas can only be accomplished using large databases such as the BTRJ.

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Appendix: Performance state classification of functional status

Grade	Description	Karnofsky Performance Status score equivalent
1	Normal: No complaints; No evidence of disease	90–100
2	Normal activity with effort; Some symptoms	80
3	Cares for self; Unable to carry on normal activity	70
4	Requires occasional assistance; Cares for most needs	50–60
5	Disabled; Requires special needs and assistance	40
6	Severely disabled; Hospitalized, death not imminent	20–30
7	Moribund; Fatal processes are rapidly progressing	0–10

We report the presentation, treatment, and survival of 34 adults with pineoblastoma from data deposited in the BTRJ over a 30-year interval.

Methods and Materials

I. Clinical material

We performed a retrospective analysis of the BTRJ, identifying all cases of pineoblastomas in adults 16 years of age or older at the time of original diagnosis. Brain tumors in the BTRJ are classified according to the classification of the Union International Contre Le Cancer in 1965.[38] The registry contains data on sex, date of birth, date of diagnosis, duration of symptoms prior to diagnosis, method of diagnosis (histology, cerebrospinal fluid [CSF] cytology, imaging, autopsy), surgeries (date(s), extent of tumor resection(s), extension, invasion), tumor diameter, functional status (pre- and postoperative performance state [PS]), tumor dissemination, irradiation therapy (type, dose, timing, target(s), use of a radiation sensitizer), chemotherapy (agent(s), timing of administration), date of last follow up, and death (date, cause).[6,28] Surgical tumor resection is coded as 0% (i.e., biopsy or decompressive craniectomy), 1–49%, 50–74%, 75–94%, 95–99%, and 100%. In patients with two surgeries, the value of the more complete tumor resection was used in this analysis. Tumor size was recorded as the geometric mean of two diameters (mean = square root[diameter_1 * diameter_2]). We calculated tumor volume from the diameter by assuming spherical morphology (volume = $4/3 * \Pi *$ (mean diameter/2)^3). Pre- and postoperative functional status were categorized on the PS scale,[6] a seven level classification similar to the Karnofsky Performance Status[22] ranging from 1 = "normal: no complaints; no evidence of disease" to 7 = "moribund; fatal processes are rapidly progressing" (Appendix). Irradiation therapy data included target(s) (cranial or craniospinal) and cranial dose in Gray (Gy). Chemotherapy data detailed agents and the timing of administration.

II. Statistical analysis

Medians, means, and 95% confidence intervals (CIs) were used to describe the central tendencies and dispersions of continuous variables. Median values were used to impute missing values for variables with $\leq 20\%$ missing values for the regression analysis. We did not impute missing values for variables missing $>20\%$ of values, and these variables could not be used in the regression analyses. During the screening process of the regression analyses, nominal variables were recorded as a series of dichotomous indicator variables, and continuous and ordinal variables were dichotomized on median values.

Kaplan-Meier life tables were used to determine the unadjusted survival of the entire cohort. We then built a multivariate Cox proportional hazard model to determine which patient, tumor, and treatment characteristics were independently associated with improved survival. Variables were first screened in a univariate analysis using Kaplan-Meier product-limit estimation and the log-rank test for inclusion in the multivariate model—all variables from the univariate analyses with $p < 0.15$ were candidates for inclusion in a multivariate Cox proportional hazard model. Multivariate Cox proportional hazard modeling allows the estimation of the relative rate of death, or "hazard ratio" (HR) associated with each variable while adjusting for the effects of other variables in the model.[7] In the final Cox multivariate model, p values <0.05 were considered significant, and p values 0.05–0.099 were considered trends. The appropriateness of the proportional hazard assumption for the final model was tested using Grambsch and Therneau's method.[18]

In a secondary analysis, we used multivariate ordinal logistic regression to model the predictors of postoperative functional status. Candidate predictor variables were screened for inclusion in the multivariate model using a univariate ordinal logistic regression. All variables from the univariate regression analyses with $p < 0.15$ were then included in a

stepwise multivariate ordinal logistic regression. In the final multivariate model, p values <0.05 were considered significant, and p values 0.05–0.099 were considered trends.

Table 1 Study population (n = 34)

Mean age (range)	35 (16–66) years
Male	22 (64.7%)
Presenting symptoms	
elevated intracranial pressure	16 (47.1%)
focal signs	9 (26.5%)
subjective complaints	4 (11.8%)
decreased level of consciousness	2 (5.9%)
asymptomatic (incidental)	2 (5.9%)
stupor or coma	1 (2.9%)
Tumor diameter	
median	2 cm
1 cm	2 (5.9%)
2 cm	13 (38.2%)
3 cm	5 (14.7%)
4 cm	5 (14.7%)
5 cm	2 (5.9%)
>8 cm	1 (2.9%)
unknown	6 (17.6%)
Spinal dissemination	
present	6 (17.6%)
absent	24 (70.6%)
unknown	4 (11.8%)
Tumor invasion	
none	22 (64.7%)
arachnoid	4 (11.8%)
dura	1 (2.9%)
unknown	7 (20.6%)

Results

I. Patient characteristics

The BTRJ contains 34 cases of pineoblastoma in adults aged 16 years or older diagnosed between 1969 and 1998 (Table 1). An earlier analysis of the BTRJ identified 76 cases of pineoblastoma in patients of all ages diagnosed from 1969–1993, comprising 0.19% of all primary brain tumors (an analysis of pineoblastoma incidence based on more recent BTRJ data is underway). The cohort of 34 patients contained 22 males (64.7%), with a median age at presentation of 35 years (range 16–66 years). The most common clinical presentations were signs of elevated intracranial pressure (n = 16, 47.1%), focal neurologic signs (n = 9, 26.5%), and subjective neurological complaints (n = 4, 11.8%). Two patients (5.9%) were asymptomatic at the time of diagnosis. The median tumor diameter was 2 cm (range 1–>8 cm), corresponding to a median volume of 4.2 cm^3 (range 0.5–382 cm^3). Only 30 patients had definite data documenting the presence (6 patients) or absence (24 patients) of spinal dissemination. In the remaining four patients, the presence or absence of disseminated disease could not be ascertained from the registry. The majority of patients (n = 22) had no evidence of local tumor invasion noted during surgery.

Only 23 patients had the preoperative PS recorded in the database (Table 2). Fifteen patients had PS grades of 1–2, consistent with the ability to perform normal activities.

Table 2 Performance state (PS) before and after surgery

Preoperative PS	Postoperative PS								Total
	1	2	3	4	5	6	7	Unknown	
1	4	0	2	0	1	0	0	0	7
2	4	3	0	1	0	0	0	0	8
3	1	1	1	1	0	0	0	0	4
4	0	2	1	0	0	0	0	0	3
5	0	0	0	1	0	0	0	0	1
6	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0
Unknown	2	1	1	0	1	2	3	1	11
Total	11	7	5	3	2	2	3	1	34

Twenty-three patients had both pre- and postoperative PS grades recorded in the database. The *shaded boxes* represent patients with identical pre- and postoperative grades (n = 8, 34.8%). Values above and to the right of the *shaded boxes* correspond to patients with a decline in postoperative PS (n = 5, 21.7%). Values below and to the left of the *shaded boxes* correspond to patients with improved postoperative PS grades (n = 10, 43.5%).

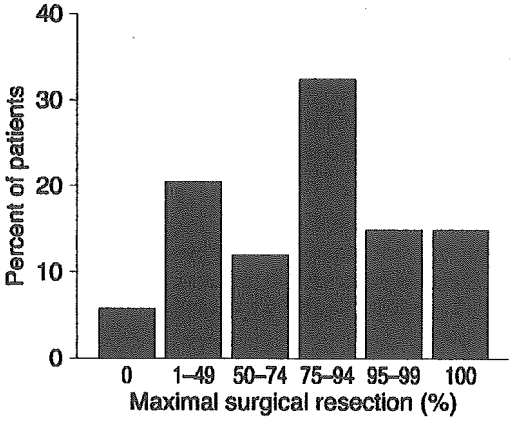

Fig. 1 Maximal extent of surgical resection in one or more procedures (n = 32).

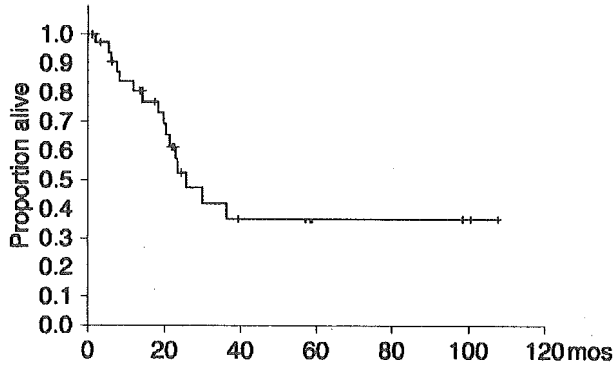

Fig. 2 Kaplan-Meier survival plot illustrating cohort survival after onset of symptoms (n = 34). Tick marks represent censoring at latest follow up. Median survival for the cohort = 25.7 months.

Table 3 Irradiation therapy cranial dose

Irradiation dose (Gy)	n (%)
0	5 (14.7%)
30	1 (2.9%)
40	3 (8.8%)
50	10 (29.4%)
60	9 (26.5%)
70	2 (5.9%)
Unknown	4 (11.8%)
Total	34 (100%)

II. Diagnosis and therapy

Thirty-two of the 34 patients underwent at least one surgical procedure to reduce tumor burden or mass effect, or to establish a diagnosis (Fig. 1). The dates of surgery ranged from April 1970 to January 1997.

Twenty-five of the 34 patients received cranial irradiation, with the tumor receiving a median dose of 50 Gy (range 30–70 Gy) (Table 3). Eleven patients received both cranial and spinal irradiation. Four of the six patients with documented disseminated disease received complete craniospinal radiation.

Ten of the 34 patients received chemotherapy, and nine of these 10 patients received multiple agents. The most common agents were VP-16 (n = 5, 50%), cisplatin (n = 4, 40%), and ACNU (n = 3, 30%). The most popular combination therapy was VP-16 combined with cisplatin (n = 3, 30%). Other agents used included vincristine (n = 2, 20%), tegafur (n = 1, 10%), methotrexate (n = 1, 10%), or bleomycin (n = 1, 10%). No patient received chemotherapy without also receiving radiation therapy. Of the 10 patients receiving chemotherapy, five received only cranial irradiation, and five received craniospinal radiation therapy.

III. Survival

At the time of the last recorded evaluation, 16 patients had died, and median follow up was 20.5 months (range 1–107.5 months). The Kaplan-Meier survival curve for the cohort demonstrates a median survival from time of presentation of 25.7 months (95% CI 16, 35.3 months) (Fig. 2).

Kaplan-Meier univariate analysis was run on the following variables: age, sex, presentation symptoms, date of surgery, maximum tumor resection, tumor size, tumor invasion, extent of intracranial tumor spread, tumor extracranial dissemination, irradiation therapy cranial dose, radiation sensitizers, spinal irradiation, and chemotherapy. Missing data in 11 patients for preoperative PS prevented the inclusion of this variable in the Kaplan-Meier or Cox regression analyses. The Kaplan-Meier univariate analysis identified seven variables that met the criteria of $p < 0.15$ for consideration of inclusion in the multivariate model: sex, maximum tumor resection, irradiation therapy cranial dose, decreased level of consciousness at presentation, focal neurological signs at presentation, extension of tumor beyond the midline, and dural invasion of tumor.

In the multivariate Cox model, two variables were independently associated with improved survival: irradiation therapy cranial dose ≥ 40 Gy (HR 3.8; 95% CI 1.3, 11.2; $p = 0.014$) and complete surgical resection (HR undefined — no deaths in gross total resection group; Kaplan-Meier $p = 0.034$) (Table 4). In addition, there was a trend towards improved

Table 4 Variables associated with increased survival in multivariate Cox model

Variable	Hazard ratio (95% CI)	p Value
Irradiation therapy cranial dose ≥ 40 Gy	3.8 (1.3, 11.2)	0.017
Gross total resection*	—	0.034
Female	3.0 (0.81, 11.4)	0.099

*No patient with gross total resection died during follow up, thus for this variable the hazard ratio is undefined and the Cox regression cannot generate a p value. The p value is derived from the Kaplan-Meier log-rank test in the univariate analysis. CI: confidence interval.

survival for females (HR 3.0; 95% CI 0.81, 11.4; p = 0.099).

Figure 3 demonstrates the Kaplan-Meier survival plots for irradiation therapy dose ≥ 40 Gy, gross total resection, and sex. In the final Cox model, Grambsch and Therneau's method showed that there was no significant deviation from the proportional hazards assumption (global test, p = 0.996), and thus a Cox regression can legitimately be used to model survival in this population. Multivariate Cox regression modeling showed no significant independent association between survival and any of the other variables: age, presentation symptoms, date of surgery, tumor size, tumor invasion, extent of intracranial tumor spread, tumor extracranial dissemination, radiation sensitizers, spinal irradiation, or chemotherapy.

IV. PS

The registry did not specify when the postoperative PS was recorded, as PS values in the registry usually indicate the most recent available annual assessment. Twenty-three of the 34 patients had both pre- and postoperative PS grades recorded in the database. Surgery had no impact on the PS grades of eight patients; postoperative grades were improved in 10 patients, but worse in five patients (Table 2).

The ordinal logistic univariate regression analysis was run on the following variables: age, sex, presentation symptoms, date of surgery, maximum tumor resection, tumor size, tumor invasion, extent of intracranial tumor spread, tumor extracranial dissemination, irradiation therapy cranial dose, radiation sensitizers, spinal irradiation, and chemotherapy. The univariate ordinal logistic analysis identified three variables that met the criteria of $p < 0.15$ for consideration of inclusion in the multivariate model: maximum tumor resection

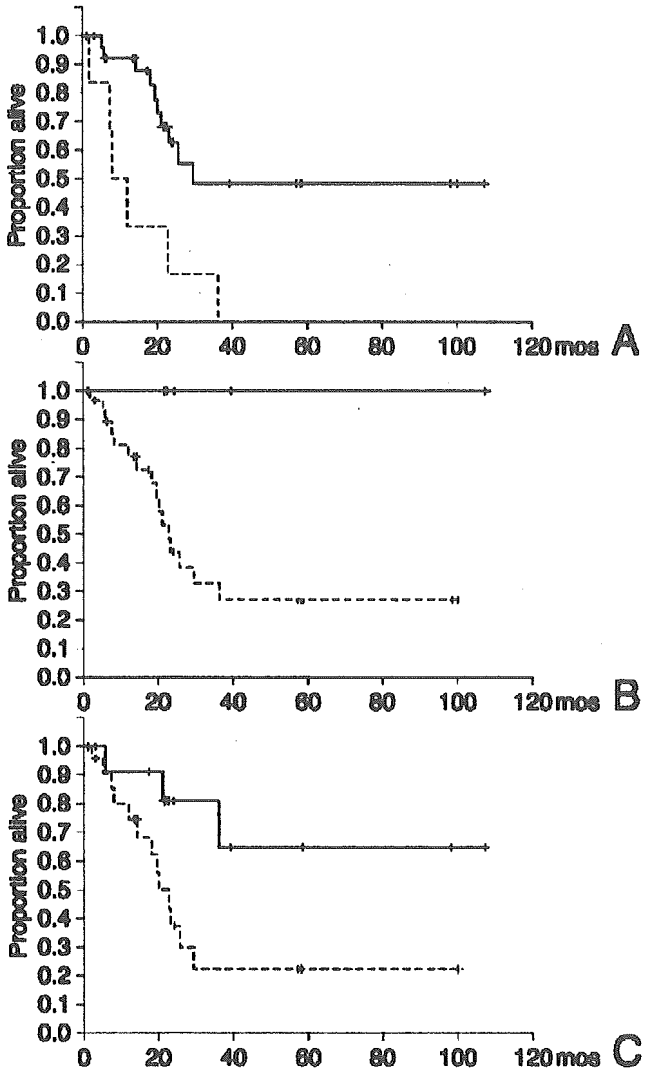

Fig. 3 Kaplan-Meier survival plots comparing cohort subgroup survival after symptom onset using the log-rank test. Tick marks represent censoring at latest follow up. A: Patients who received ≥ 40 Gy of cranial radiation (*solid line*) had significantly longer survival times (median = 29.8 months) compared to patients who received lesser doses (*dashed line*, median = 8.1 months) (p = 0.014). B: Patients who had gross total surgical resection (*solid line*) had significantly longer survival times (median > 107.5 months) compared to patients with subtotal resections (*dashed line*, median = 22.3 months) (p = 0.034). C: There was a trend towards longer survival in women (*solid line*, median > 107.5 months) compared to men (*dashed line*, median = 20.0 months) (p = 0.099).

$>50\%$, irradiation therapy cranial dose ≥ 40 Gy, and any invasion of tumor noted at surgery. In the multivariate ordinal logistic regression model, only irradiation therapy dose ≥ 40 Gy was independently associated with better postoperative PS ($p = 0.003$). The analysis showed no significant independent association between postoperative functional status and the following variables: age, sex, presentation symptoms, date of surgery, tumor size, tumor invasion, extent of intracranial tumor spread, tumor extracranial dissemination, radiation sensitizers, spinal irradiation, or chemotherapy.

Discussion

I. Histopathology

Pineoblastomas and pineocytomas are pineal parenchymal tumors that are distinct from germ cell tumors and glial tumors.[3,33] A two-tiered staging system distinguishes pineoblastomas from pineocytomas. The pineocytoma is a well-circumscribed tumor that grossly compresses the surrounding tissue. The cells appear benign and look similar to mature pineal parenchymal cells in sheets or irregular lobules. Identification of pineocytomas is facilitated with the finding of Homer-Wright rosettes and the finding of larger pineocytomatous rosettes. Pineoblastomas, in contrast, are grossly invasive with poorly defined borders and frequent leptomeningeal spread. Histologically, pineoblastoma is very similar to medulloblastoma and has been described as "medulloblastoma pineales," emphasizing its similarity to other primitive neuroectodermal tumors.[20,31] Pineoblastoma is highly cellular, with small poorly differentiated cells in pattern less sheets or aggregates. Mitosis are found along with Homer-Wright rosettes, Flexner-Wintersteiner rosettes, and areas of necrosis.[3,33]

More recently, Schild et al.[33] has divided pineal parenchymal tumors into four types: pineocytomas, intermediate tumors, mixed tumors, and pineoblastomas. The intermediate tumor is described as a transitional form between pineocytomas and pineoblastomas. The mixed tumor shows patterns of both pineocytomas and pineoblastomas. In addition to Schild's grading system, Fauchon et al.[13] have defined another scale emphasizing the number of mitoses and thereby correlating survival with mitotic activity. These grading scales are relatively recent descriptions, and most series of pineal parenchymal tumors have used the two-tiered grading system.[3,20]

Pineoblastomas are rare tumors that are sometimes simply described as supratentorial primitive neuroectodermal tumors (PNETs).[20,31] Pineoblastomas and cerebellar medulloblastomas both share the presence of Homer-Wright rosettes, which are widely accepted to represent abortive attempts at neuroblastic differentiation.[20] In addition, mononucleated and multinucleated tumor giant cells are present in pineoblastomas as in cerebellar medulloblastomas.[3] Hence, the category of PNETs has been said to include both cerebellar medulloblastomas and pineoblastomas.

The BTRJ does not require a centralized review of pathologic tissue for entry into the database, so we could not verify the classification of pineal parenchymal tumors in this series. The pathologic grading scale employed in the BTRJ is derived from Zulch[38] and describes only the two-tiered grades of pineocytoma versus pineoblastoma.

II. Survival

The overall median survival in our series of adults with pineoblastomas was 25.7 months. Chang et al.[4] reported a series of 11 adults with pineoblastomas with a median survival of 30 months. Using a grading scale for pineal parenchymal tumors based on number of mitoses, Fauchon et al.[13] reported a median survival time of 38 months and 16 months for adult and pediatric patients with the higher grade tumors (grades 3 and 4), respectively. Schild et al.[33] reported a 5-year survival rate of 58% for the 21 adult and pediatric patients with mixed, intermediate, or pure pineoblastomas. If the intermediate grade tumors are removed from Schild's or Fauchon's analysis, the survival rates remain poor.

III. Extent of resection

The most striking predictor of survival in our patient population was gross total resection. No patient in whom the surgeon was able to obtain gross total resection died during follow up ranging from 21.7 to 107.5 months (Fig. 3B). The importance of obtaining gross total resection has not been previously described for PNETs in any location or age distribution. No statistical difference between $>90\%$ resection versus $<90\%$ resection was found in children with pineoblastomas.[21] In children with cerebral PNETs, there was no correlation between extent of resection and survival in those children treated with radiation therapy.[35] However, gross total resection was associated with better local control.[35] Similarly, an adult series of medulloblastomas of the posterior fossa did not demonstrate an improvement in progression free survival with gross total resection, although complete resection was associated with a decreased rate of local recurrence.[14]

The extent of surgical resection may be influenced

by many factors: goal of surgery (biopsy, debulking, complete resection), surgeon's skill and experience, tumor invasion and involvement with adjacent structures, and physician beliefs about the effectiveness of alternative therapies (irradiation therapy, chemotherapy). While our data indicate a survival benefit from complete resection, it is unclear whether the surgeon's goal for every adult case of pineoblastoma should be the complete resection of tumor. Incomplete functional status data did not allow a comprehensive assessment of the impact of complete resection on quality of life. It is conceivable that more aggressive surgery may even reduce quality of life, resulting in a Pyrrhic victory for the surgeon and patient.

IV. Radiotherapy

We found that cranial irradiation therapy doses of at least 40 Gy were associated with improved survival in adults with pineoblastomas. Patients who received ≥ 40 Gy of cranial irradiation had a death rate 3.8 times less than that of patients who received less radiation. Median survival for the higher dose patients (29.8 months) was triple that of patients receiving lesser doses (8.1 months) (Fig. 3A).

In the pediatric pineoblastoma population, the CCG-921 report suggests that radiation therapy has a significant impact on survival with a 3-year survival of 61%.[21] However, the early delayed toxicity of radiation therapy in the pediatric population was devastating — all patients <9 years of age suffered severe neurocognitive deficits. Craniospinal radiation was "somewhat effective" as part of initial therapy in adults with pineoblastomas, but this study was not designed to evaluate the effects of radiation therapy.[4] Nevertheless, the findings in the pediatric populations have been extended to the adult population, and irradiation therapy is generally accepted as beneficial for adults with pineoblastomas. Our study supports this practice, and provides evidence for a threshold dose of >40 Gy for improved adult survival. A similar radiation dose threshold effect has been seen in children with PNETs. Several investigators have demonstrated that children with posterior fossa medulloblastomas treated with doses less than 50 Gy have poorer survival than those receiving greater than 50 Gy.[5,8,25,34] Adults with medulloblastomas of the posterior fossa show a trend towards improved survival with higher radiation doses, but no statistically significant benefit.

V. Sex

This is the first pineoblastoma series to suggest a possible survival difference between males and females. The multivariate model showed only a trend towards improved survival in women ($p = 0.099$), but the death rate in women was 3.0 times lower than that for men, and the difference in median survival was quite striking — 20.0 months in men versus >107.5 months in women (Fig. 3C). One other study of PNETs has shown a similar sex-related survival advantage. Male sex was correlated in the proportional hazards model with decreased survival ($p = 0.06$) studied 47 adults with medulloblastomas.[29] The observed survival advantage of adult females with pineoblastomas may be caused by endocrinological differences between adult females and males. This novel preliminary finding suggests that further investigations focusing on sex-specific differences in biochemistry may prove fruitful. For example, assays of hormone receptors in banked tumor samples may provide useful information, ultimately leading to hormonal strategies in the treatment of adult PNETs, including adult pineoblastomas.

VI. Age

Age was not a statistically significant predictor of survival for adults ≥ 16 years of age in our study. Nevertheless, children with pineoblastomas may have better outcomes than do adults. The 3-year progression-free survival was $61 \pm 13\%$ in a group of 17 children older than 18 months with pineoblastomas who were treated with craniospinal irradiation therapy and chemotherapy.[21] Thus, it appears that children (>18 months to 21 years of age) with pineoblastomas treated with irradiation therapy (≥ 45 Gy) and chemotherapy may fare better than do adults. Unfortunately, these two populations cannot be directly compared because of the many differences between the patient groups. The effect of age on survival may be better studied by analyzing a homogeneous group such as the BTRJ series of both adults and children.

VII. Staging

Medulloblastomas tend to metastasize through the CSF pathways, and the extent of disease dissemination through the craniospinal axis is accepted as an important prognostic factor.[14,29] Similarly, the presence of disseminated disease in patients with pineoblastomas may be a significant predictor of survival.[4] In our series of 34 patients, six patients (17.6%) were categorized as having spinal dissemination. The details and extent of staging of individual patients were not recorded in the BTRJ, and it is unclear whether every patient underwent spinal imaging and CSF cytology. For comparison, five of 11 adults with pineoblastoma had spinal dissemina-

tion.[4] Although the lack of systematic criteria for determining the presence of metastasis or dissemination suggests that our observed incidence of 17.6% is low, the incidence varies considerably within the pediatric literature on PNETs.[10,11,20,32]

Given the presumed similarity of medulloblastomas and pineoblastomas, it is advisable to stage patients with both magnetic resonance imaging and CSF cytology prior to operative resection. If magnetic resonance imaging is not available, computed tomography myelography is an appropriate substitute. Although rare reports of metastases of pineoblastomas to extraneural sites exist, the frequency is so low that further studies are not warranted.[24,30] Multivariate analysis did not find the presence of tumor dissemination to be a significant predictor of survival, but rigorous prospective staging protocols will be needed to determine the importance of staging in adults with pineoblastomas.

VIII. Functional status

Missing functional status data for 11 of the 34 patients precluded including this variable in the survival models. This is unfortunate, as functional status is a strong predictor of survival in many neurological diseases, e.g., ischemic stroke,[27] aneurysmal subarachnoid hemorrhage,[23] malignant gliomas,[36,37] and brain metastases.[1,16] Since functional status is also an important outcome measure, despite the limited number of patients with analyzable data, we searched for predictors of postoperative functional status in the subset of patients with pre- and postoperative PS data. Cranial irradiation therapy dose ≥ 40 Gy was the only factor that improved postoperative functional status as measured by the PS grade. Functional status can be used as a proxy for quality of life. The beneficial effect of irradiation therapy on PS suggests that irradiation therapy may improve both the quality of life and duration of survival.

IX. Chemotherapy

The most controversial decision in the treatment of patients with PNETs is the role of chemotherapy. Considering the biologic similarity of medulloblastomas and pineoblastomas, the effectiveness of chemotherapeutic agents in medulloblastomas has suggested a parallel role of these agents in the treatment of patients with pineoblastomas.[12,15,26] Current agents used for PNETs include cyclophosphamide, cisplatin, carboplatin, vincristine, ifosmide, and etoposide.[2,17] While our study did not show any impact of chemotherapy on survival, the power of our analysis was limited by the small number of patients who received chemotherapy (n = 10, 29.4%) and the many different regimens used in these patients. Future studies should be directed towards the determination of the best chemotherapy regimen.

X. Limitations

This retrospective study of a national centralized registry study has several limitations. The analysis was limited to variables and coding methods contained in the dataset. Some patients had missing values in some data fields, e.g., PS measurement of functional status. Nevertheless, the BTRJ is a unique resource that provides useful data for the study of rare tumors such as pineoblastomas.

XI. Conclusion

Pineoblastomas in adults are rare. A retrospective study of 34 patients identified from 30 years of BTRJ data demonstrates an overall median survival of 25.7 months. Patients with gross total resection and cranial radiation ≥ 40 Gy survive longer than do patients with subtotal resection or lower cranial radiation doses. Females had a trend towards longer survival than males. The role of chemotherapy remains unclear. Given the striking survival benefit of gross total surgical resection and higher radiation doses, the role of radiosurgery in the management of adult pineoblastomas remains to be assessed.

Acknowledgments

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Commentary

Pineoblastoma is a malignant tumor that is considered a PNET and radiosensitive. It is rare in adults and therefore, the systematic study concerning the management and survival of the tumor is hindered. In order for us to understand the factors influencing survival, the authors analyzed in detail the data from the Brain Tumor Registry of Japan (BTRJ) to examine patients, tumors and treatment characteristics associated with increased survival in 34 adults with pineoblastomas diagnosed during the 30 years from 1969 to 1998. As the authors mentioned, it is the largest clinical series up to now in the literature.

They found that patients with gross total resection and cranial radiation ≥40 Gy survive longer than do patients with subtotal resection or lower cranial radiation doses. Women also had a trend towards longer survival than men ($p = 0.099$).

This research work is well done and the results have significant value to our clinical practice. As the authors mentioned, due to limitations of the study, some of the factors influencing survival still need to be clarified. If more cases could be involved with more complete data, or an international multi-centered study could be done, the factors influencing survival such as the importance of the tumor seeding through the CSF pathways, the chemotherapy regimen, and the role of radiosurgery in the management of adult pineoblastomas would become more clear.

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This is an extremely valuable paper covering a rare tumor about which very little is known. The authors studied 34 adults with pineoblastoma and utilized the Brain Tumor Registry of Japan for initial and follow-up data. They found that the factors associated with improved prognosis for this very deadly tumor were gross total resection at the time of surgery and postoperative radiation therapy with a dose of 40 Gray or more. Unfortunately, only ten of the patients received chemotherapy and nine of these had combination chemotherapy. The data were not powerful enough to determine a significant beneficial effect of chemotherapy, primarily because of the short survivals; the overall follow-up periods were very short as well. The authors correctly recommend that a staging system similar to that utilized for medulloblastoma be utilized for pineoblastoma. They also indicate the importance of assessing the role for radiosurgery in the adjunctive management of these difficult lesions. This will be a widely quoted benchmark paper and the authors are to be congratulated for their careful and helpful review.

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The authors described an analysis of 34 adult patients with pineoplastoma from the Brain Tumor Registry of Japan. Pineoblastomas, especially of adults, are extremely rare and the treatment strategy of this disease has not been established. They evaluated the effects of various factors on the survival rate of pineoblastoma patients and concluded that cranial irradiation therapy using over 40 Gy and gross total resection are

associated with improved patient's survival rate. This study provides useful suggestions for the treatment methods of adult pineoblastomas based on an analysis of a large number of cases of the disease.

The Brain Tumor Registry of Japan does not require a centralized review on pathological information and the pathological classification of pineal parenchymal tumor comprises only pineocytoma and pineoblastoma. It must be remembered that pineoblastomas of infants are mostly PNET, whereas pineoblastomas of adults may vary in histology showing mixed type, intermediate type or pure pineoblastoma and the prognoses of patients may vary depending on the histology.

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Intraventricular chordoid meningioma presenting with Castleman disease due to overproduction of interleukin-6

Case report

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✓ A rare case of chordoid meningioma in the lateral ventricle observed in an adult is reported. The first clinical manifestation of the disease was a prolonged fever of unknown origin. Abnormalities in the patient's blood chemistry, principally polyclonal hypergammaglobulinemia (immunoglobulin [Ig]G, IgA, and markedly IgE) and an elevated serum level of C-reactive protein, were associated with the disease. The tumor was histologically confirmed to be a chordoid meningioma, and its surgical removal resulted in complete resolution of the patient's symptoms. By combining reverse transcription–polymerase chain reaction and immunohistochemical analysis, it may be shown that cytokine production, including that of interleukin (IL)-6, IL-1β, and vascular endothelial growth factor, plays a role in the pathogenesis of chordoid meningioma associated with Castleman syndrome.

KEY WORDS • **intraventricular tumor** • **chordoid meningioma** • **Castleman syndrome** • **interleukin-6** • **interleukin-1β** • **vascular endothelial growth factor**

THE primary occurrence of meningiomas in the ventricular system without dural attachment is extremely rare, with an incidence of 0.5 to 5% among all intracranial meningiomas.[6,23] Histopathologically, the fibroblastic (fibrous) subtype is predominant among intraventricular meningiomas, and both the meningothelial and transitional forms have also been encountered at this site.[1,7,9] Nevertheless, no case of intraventricular meningioma has been reported to date.

Chordoid meningioma is a rare meningioma variant named by Kepes and colleagues[12] in 1988, and has been listed in the latest classification of the World Health Organization. Several cases of this variant have been reported in the world literature. Chordoid meningioma is sometimes associated with Castleman syndrome,[3,12,14,16] which includes hematological abnormalities such as hypochromic or microcytic anemia and dysgammaglobulinemia with bone marrow plasmacytosis or other symptoms, but the pathogenesis of this disease is still unknown. Although some cytokines or tissue growth factors have been considered to play a critical role in the pathogenesis of Castleman syndrome,[8,21,26,27] the mechanism of this syndrome in conjunction with chordoid meningioma has not been elucidated. In this report we describe a rare case of intraventricular chordoid meningioma in which the patient presented with a prolonged fever and hypergammaglobulinemia, especially an elevated level of IgE.

Abbreviations used in this paper: CSF = cerebrospinal fluid; CT = computerized tomography; IFN = interferon; Ig = immunoglobulin; IL = interleukin; MR = magnetic resonance; mRNA = messenger RNA; PCR = polymerase chain reaction; RT = reverse transcription; Th1 = T helper cell Type 1; Th2 = T helper cell Type 2; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

Case Report

History. This 37-year-old woman had suffered from a remittent fever of unknown origin for a few months. Several examinations failed to detect the origin of the fever; however, MR imaging incidentally revealed a mass lesion in the anterior horn of the left lateral ventricle. The patient's medical and family histories were unremarkable, including the investigation of atopic or allergic inflammation.

Examination. On admission, the woman's body temperature was 38.2°C. Her neck did not display any meningeal signs and no lymph nodes were palpable in the anterior, posterior, and supraclavicular regions. There were no abnormalities in somatic or genital development and her menstruation cycle was uneventful. Hepatosplenomegaly was not detected in the abdomen by an echo scanner.

The neurological examination revealed no deficits, and

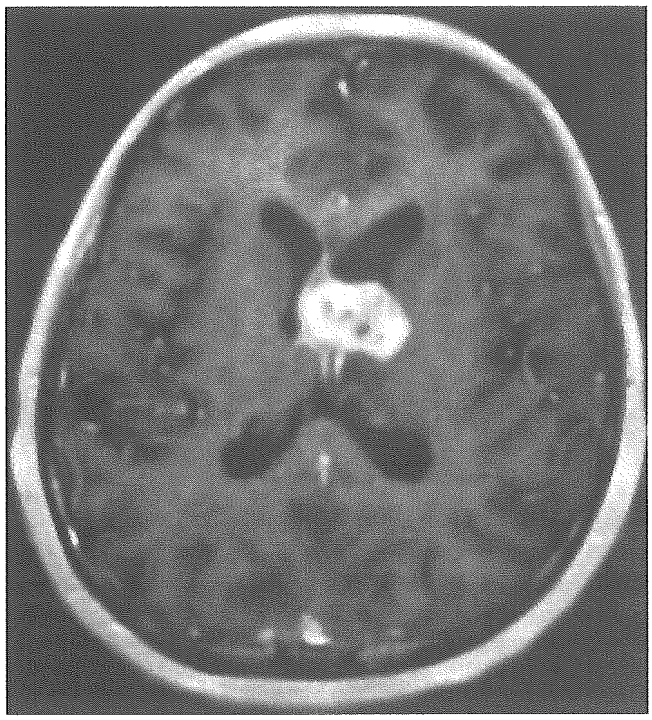

FIG. 1. Axial T_1-weighted Gd-enhanced MR image demonstrating a heterogeneously well-enhancing lesion approximately 2 cm in diameter, which is located in the anterior horn of the left lateral ventricle. The mass is attached to the colloid plexus at the foramen of Monro.

no evidence of a choked disc was found during the fundoscopic examination. Laboratory findings did not include anemia, leukocytosis, or thrombocytosis. Total plasma proteins were 7.5 g/dl (albumin, 3.5 g/dl; globulin, 4.2 g/dl), and an additional workup demonstrated that this represented a polyclonal gammopathy with high serum levels of Igs: IgG, 1740 mg/dl (normal range 870–1700 mg/dl); IgA, 579 mg/dl (normal range 110–410 mg/dl); and especially IgE, 3100 IU/ml, which was elevated approximately eightfold from the normal range. A high serum level of C-reactive protein (4.2 mg/dl) was also demonstrated in the hematological examination. Serological investigations for parasitic diseases, viruses, and an extensive search for an autoimmune disease were all nondiagnostic.

In the CSF study, elevated cell numbers (115 leukocytes, of which 88% were monocytes) and a high protein concentration, 1.16 g/L (normal range 0.15–0.45 g/L), with a normal glucose level were demonstrated. The CSF cultures were negative for virus, bacteria, and fungus, and the CSF cytology was negative for malignant cells.

Computerized tomography scans and MR images obtained at hospital admission displayed a 2-cm mass lesion located in the anterior horn of the left lateral ventricle, which enhanced homogeneously after injection of contrast medium. Sequential contrast-enhanced T_1-weighted MR images obtained 1.5 months after a previous examination demonstrated tumor growth with a central necrotic change, which was displayed heterogeneously (Fig. 1). Digital subtraction angiography did not demonstrate any marked staining of the tumor.

Operation. The patient underwent tumor resection via a left frontal craniotomy with the aid of a navigational system. The mass was found to be attached to the colloid plexus near the foramen of Monro. The tumor was rather soft and relatively vascularized. Gross-total resection was achieved by removing the lesion in a piecemeal fashion. Although temporary insertion of a ventricular drain was necessary for the control of hydrocephalus postoperatively, it was removed without any difficulty 1 week later.

Postoperative Course. After the operation, complete resolution of the prolonged fever and normalization of the C-reactive protein level were obtained within 1 week. Furthermore, all serum levels of γ-globulin, including IgE, had normalized by several months postoperatively. During the following year, all laboratory findings returned to normal and the patient experienced no fever. No recurrence of the tumor has been demonstrated on MR images.

Pathological Findings. Histopathological examination of the surgical specimen revealed that the tumor cells were arranged such that epithelial cells were in the background of a myxoid matrix with prominent infiltration of lymphoid and plasma cells (Fig. 2 *upper left*) into brain tissue around the tumor; some of the tumor cells appeared to be vacuolated. The tumor cells appeared spindly or multipolar, and formed clusters and rows in patterns that resembled a chordoma (Fig. 2 *upper center*). Furthermore, a meningothelial pattern was detected in a small portion of cells throughout the tumor (Fig. 2 *upper right*). Some nuclear pleomorphism and focal necrosis were noted. Mitoses were noted in the most active areas, but invasion of the brain parenchyma was absent. Immunohistochemically typical of meningiomas, the tumor cells exhibited membrane staining for epithelial membrane antigen in focal areas (Fig. 2 *center left*) as well as diffuse cytoplasmic staining for vimentin. Vascular endothelial growth factor was also strongly expressed in the tumor cells and in plasma cells (Fig. 2 *lower center*). None of the tumor cells expressed glial fibrillary acidic protein, cytokeratin, or S100 protein. The Ki-67 proliferative index of the tumor was 9.2%. A striking feature was the presence of several dense lymphoid and plasma cell infiltrates within the lesion. The B lymphocytes (CD20-positive and L26 positive cells) predominated within the infiltrates (Fig. 2 *lower right*), although T lymphocytes (CD3-positive cells) were also present (Fig. 2 *lower left*). The T lymphocytes were predominantly CD8-positive rather than CD4-positive T lymphocytes. A few CD56-positive natural killer cells and moderate infiltrates of plasma cells were also revealed within the tumor. Polyclonality of the plasma cells was confirmed by immunostaining for κ and λ Ig light chains. All these findings were consistent with the presence of a chordoid meningioma.

The RT-PCR Assay

Total RNA was isolated from fresh-frozen sections of the tumor by using an RNeasy Mini Kit (QIAGEN, Tokyo, Japan). Reverse transcription reactions were performed using 2 μg of total RNA and Superscript II Reverse Transcriptase (Gibco-BRL, Gaithersburg, MD) according to the manufacturer's protocol. As a positive control for each sample, β-actin complementary DNA was also amplified. The PCR was performed using Taq DNA polymerase (Life Technologies, Inc., Tokyo, Japan). Samples were incubated at 94°C for 5 minutes, followed by 40 cycles at 94°C for 30 seconds, and

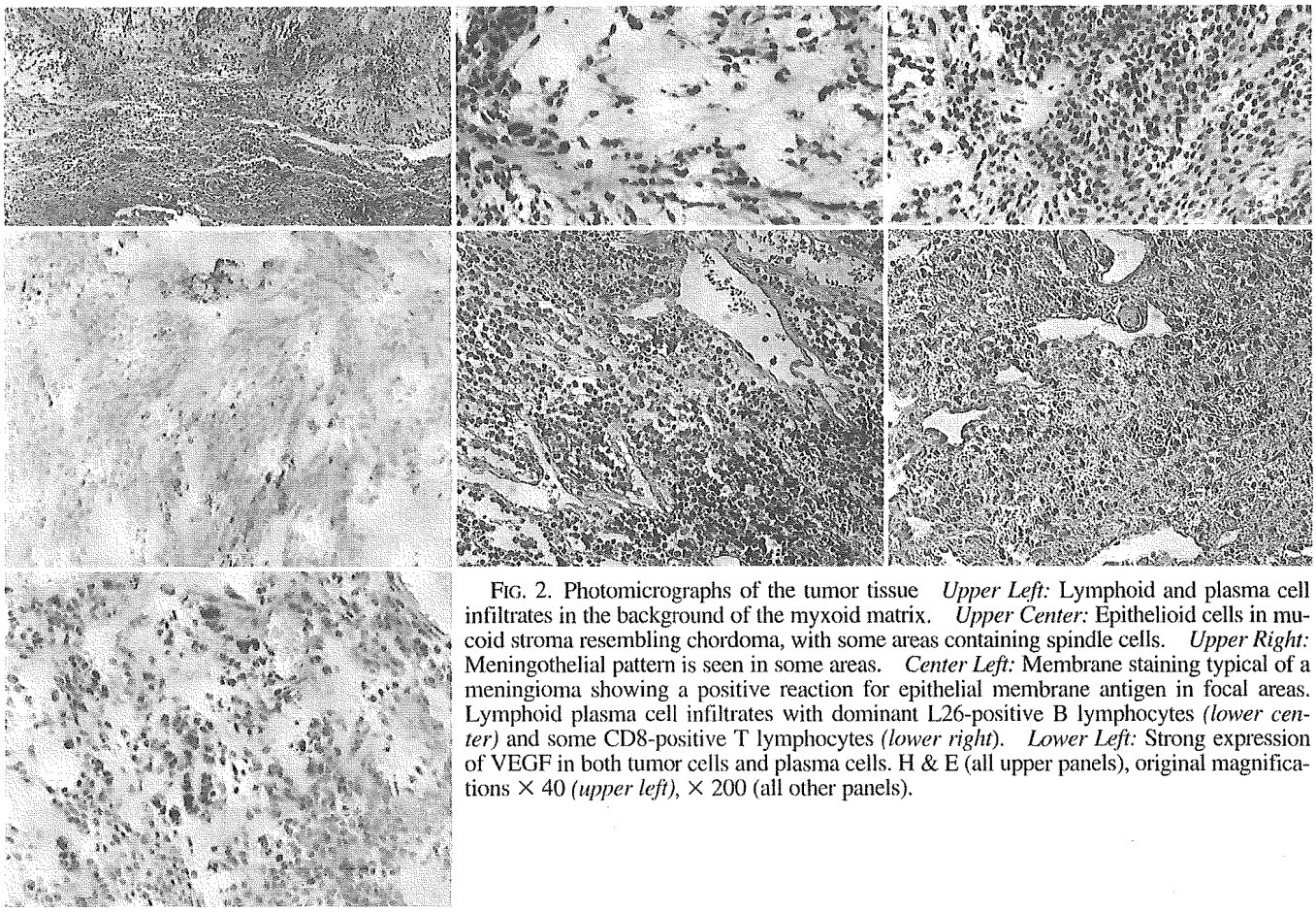

FIG. 2. Photomicrographs of the tumor tissue *Upper Left:* Lymphoid and plasma cell infiltrates in the background of the myxoid matrix. *Upper Center:* Epithelioid cells in mucoid stroma resembling chordoma, with some areas containing spindle cells. *Upper Right:* Meningothelial pattern is seen in some areas. *Center Left:* Membrane staining typical of a meningioma showing a positive reaction for epithelial membrane antigen in focal areas. Lymphoid plasma cell infiltrates with dominant L26-positive B lymphocytes *(lower center)* and some CD8-positive T lymphocytes *(lower right)*. *Lower Left:* Strong expression of VEGF in both tumor cells and plasma cells. H & E (all upper panels), original magnifications × 40 *(upper left)*, × 200 (all other panels).

72°C for 1 minute. A final extension was added at 72°C for 7 minutes. Primers for IL-1β, IL-4, IL-6, TNFα, IFNλ, and β-actin were purchased from Sigma Genomycs (Tokyo, Japan). The PCR products were electrophoresed on 2% agarose gels, visualized by ethidium bromide staining, and documented by photography. Overexpression of IL-1β mRNA and extreme overexpression of IL-6 mRNA were confirmed (Fig. 3). As a control study, an ordinary case of meningothelial meningioma with no systemic effects was also examined in the same manner; in that case there was no detected expression of cytokine mRNA, including IL-1β and IL-6, as in the present case.

Discussion

Chordoid meningioma is a rare subtype of meningioma, which is classified as World Health Organization Grade II and comprises approximately 0.5% or less of all meningiomas.[5,13] Since the first description of an intraventricular meningioma, given by Shaw[24] in 1854, 532 intraventricular meningiomas have been reported to date in the world literature.[19] Nevertheless, there have been no reported cases of chordoid meningioma in the ventricular system.

Interestingly, remittent fever was the only clinical symptom in the present case, and surgical removal of the mass resulted in complete remission. Fever is one of the most frequent clinical signs encountered in human diseases, especially during infections, but is uncommon in cases of brain tumor. The febrile response is thought to be mediated by endogenous mediators, generically called "endogenous pyrogens," which include TNFα, IL-1, IL-6, and the IFNs.[18,20,22] In our case, the RT-PCR assay confirmed the overproduction of proinflammatory cytokine mRNA, including that of IL-6 and IL-1β, within the mass, when compared with an ordinary case of meningothelial meningioma. In the clinical setting, cases of meningioma presenting with inflammatory syndrome are rarely encountered, although some investigators have revealed a certain level of cytokine production in meningiomas.[17] Thus, the combination of chronic overproduction of IL-6 and IL-1β might affect distinct, but partially overlapping, neuronal arrays in the preoptic area of the anterior hypothalamus, and therefore directly or indirectly mediate the host defense response including fever.

Since the first report of Castleman syndrome by Castleman and associates[2] in 1956, many subsequent reports of the same disease in different anatomical locations and possible causative mechanisms for this disease have been published. Interleukin-6, IL-1, and TNFβ are considered to be causative factors of Castleman syndrome,[8,26,27] but no existing evidence supports this hypothesis in the case of chordoid meningioma.

Interleukin-6 is a cytokine that is well known as one of the causative factors of the hypergammaglobulinemia associated with Castleman syndrome.[10] Interestingly, the hypergammaglobulinemia in our case consisted of IgG, IgA, and remarkably IgE, although in most reported cases IgG is pre-