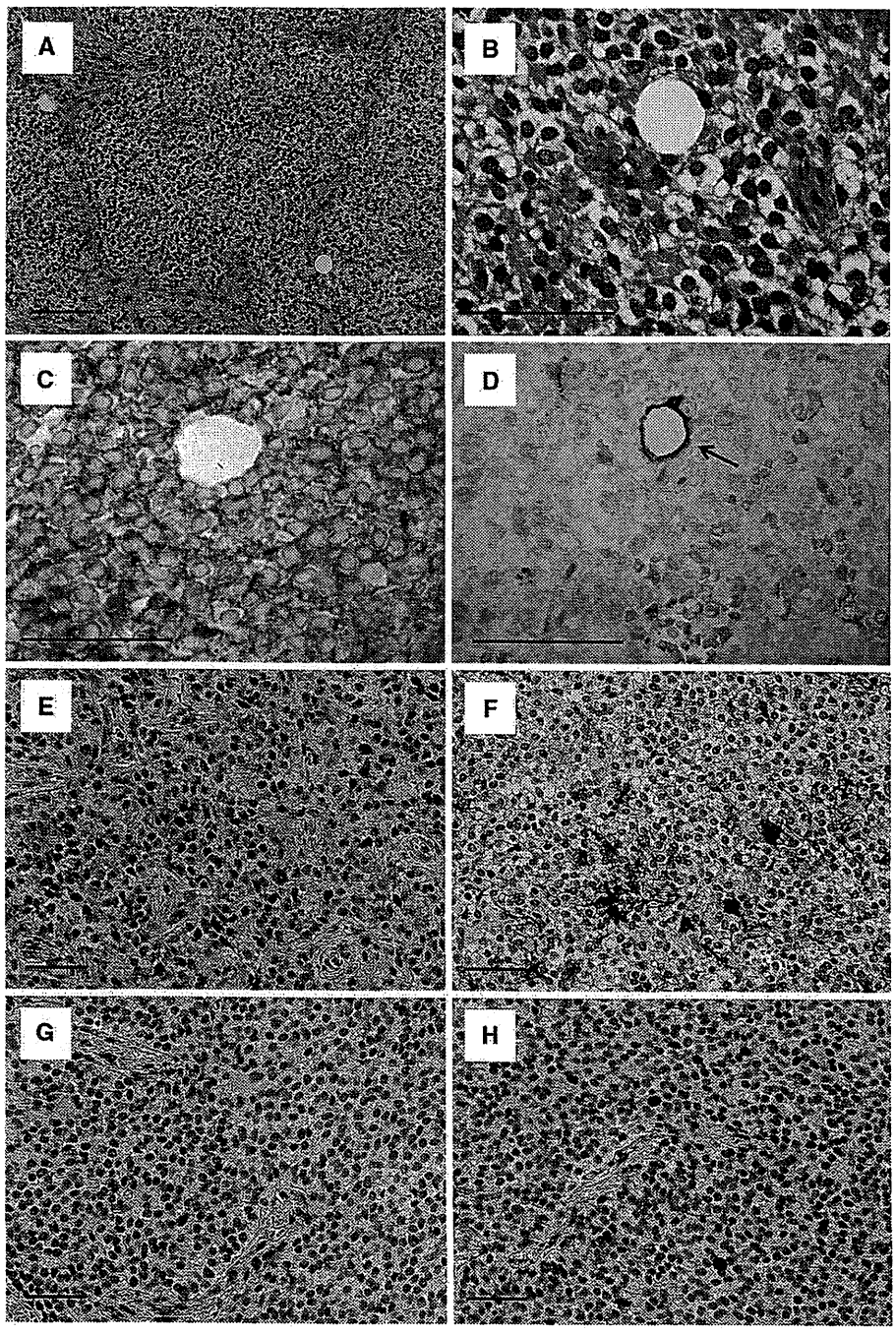

Fig. 3 Histological (**a**, **b**) and immunohistochemical (**c**–**h**) findings. **a** H&E-stained section shows sheets of relatively monomorphous cells with round nuclei and clear cytoplasm. Rare cells contain large intracytoplasmic vacuoles. **b** Tumor cells have round nuclei with indistinct nucleoli and fine chromatin on a cytology specimen (H&E). **c** Tumor cells are diffusely immunoreactive for synaptophysin. **d** A vacuolated cell is immunoreactive for perilipin (*arrow*). **e** GFAP is largely negative on tumor cells. **f** Tumor cells are completely negative for Olig2. **g** Tumor cells are moderately positive for NeuN. **h** Ki67-labeling index is 2 %. *Black bars* indicate 50 μm (**b**–**h**) or 100 μm (**a**)

that the lipomatous cells are not true adipose cells, instead representing neuroepithelial tumor cells with lipid accumulation. The pathogenesis of differentiation into lipid-producing cells in neuroepithelial tumors has not been discussed in the literature as far as we know, and remains to be elucidated.

Oligodendrogliomas occasionally demonstrate neuronal differentiation, resulting in a tumor possessing glial and neuronal characteristics. In this sense, oligodendrogliomas can show similar pathological findings to liponeurocytoma [5, 6, 12, 18, 21, 24, 26], although Olig2 immunohistochemistry is reported to show a high possibility of positive results in oligodendroglioma, while neurocytomas are mostly negative [15, 20, 23].

With genetic analysis, 50–80 % of oligodendrogliomas are known to show chromosome 1p/19q co-deletion, while neurocytoma is considered to be devoid of 1p/19q deletion [25, 30]. In addition, Capper et al. [5] reported that *IDH1* R132H mutation was negative in all of 35 central neurocytomas and 4 extraventricular neurocytomas, as well as in 2 cerebellar liponeurocytomas, while oligodendrogliomas showed a high frequency (>90 %) of *IDH1* mutation in addition to 1p/19q co-deletion [13]. We therefore propose that the absence of both chromosome 1p/19q loss and *IDH1* mutation, as observed in our case, is very useful in reaching a pathological diagnosis by eliminating the possibility of oligodendroglioma.

Conclusion

This case report suggests that cerebellar liponeurocytoma shows characteristic PET and genetic findings, including negative results for both *IDH1* mutation and chromosome 1p19q co-deletion, somewhat resembling the findings for neurocytoma. These findings will be helpful in differentiating the rare disease of cerebellar liponeurocytoma from more common neoplasms with similar pathological morphology. Further accumulation of findings from tumor investigations is necessary to definitively establish the characteristics of cerebellar liponeurocytoma.

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Cancer-specific health-related quality of life in children with brain tumors

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Abstract
Purpose To understand the influence of disease and treatment on the health-related quality of life (HRQOL) of children with brain tumors, compared to the HRQOL of children with other cancers, from the viewpoints of children and parents.
Methods A total of 133 children aged 5–18 years and 165 parents of children aged 2–18 completed questionnaires of the Pediatric Quality of Life Inventory Cancer Module (Pain and Hurt, Nausea, Procedural Anxiety, Treatment Anxiety, Worry, Cognitive Problems, Perceived Physical Appearance, and Communication scales); higher scores indicate a better HRQOL. The Cancer Module scores, weighted by age and treatment status, were compared to those obtained in a previous study of children with other cancers (mostly leukemia).
Results The weighted mean scores for Pain and Hurt (effect size $d = 0.26$) and Nausea ($d = 0.23$) from child reports and the scores for Nausea ($d = 0.28$) from parent reports were higher for children with brain tumors than scores for children with other cancers. The scores for Procedural Anxiety ($d = -0.22$) and Treatment Anxiety ($d = -0.32$) from parent reports were lower for parents of children with brain tumors than the scores for parents of children with other cancers. The child-reported Pain and Hurt score of the Cancer Module was higher ($d = 0.29$) and in less agreement (*intraclass correlation coefficient* = 0.43) with scores from the Brain Tumor Module, indicating that assessments completed with the Cancer Module misesteem pain and hurt problems in children with brain tumors.

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Conclusions The profiles of cancer-specific HRQOL in children with brain tumors differ from those of children with other cancers; we therefore suggest that these children receive specific psychological support.

Keywords Brain neoplasms · Child · Japan · Quality of life · Questionnaires

Introduction

While modern treatment methodologies have improved the outcome for pediatric cancer survival to approximately 70–80 % [1, 2], managing health-related quality of life (HRQOL) during and after treatment becomes a more important part of treatment. Brain tumors are the second most common (27 %) form of pediatric cancer after leukemia (33 %) [3]. Children with brain tumors often experience pain, nausea, lack of energy, and emotional distress [4, 5] and may also experience late effects, such as endocrinological problems, cognitive impairment, neurological (motor and sensory) disability, and posttraumatic stress symptoms [6–8]. Consequently, survivors of brain tumors who receive intensive treatment [9, 10] are at higher risk of physical, psychological, social, and developmental difficulties than survivors of other cancers [11–14]. By understanding the HRQOL profile of these children, medical practitioners can design targeted interventions to maintain and improve HRQOL in this population during and after treatment.

Global profiles of HRQOL (for example, physical, emotional, and social) in children with brain tumors are lower than those of children with other cancers or without cancer [15–18]. However, little information is available on disease-specific HRQOL profiles in children with brain tumors. Meeske et al. compared cancer-specific HRQOL between children with brain tumors and those with acute lymphoblastic leukemia (ALL) using the parent-reported Pediatric Quality of Life Inventory (PedsQL) Cancer Module [17], finding that parents of children with brain tumors and acute lymphoblastic leukemia report different experiences for their children during and after treatment. This highlights the need to understand how children with brain tumors perceive their own HRQOL.

The disease-specific HRQOL of patients with brain tumors can be measured with one of several cancer-specific tools [19–21], such as the PedsQL Cancer Module, or with a brain-tumor-specific tool [15, 22, 23], such as the PedsQL Brain Tumor Module. Different tools may provide different measures of HRQOL, as the questionnaire structure, number, and time of the questions differ among available tools. Here, we compared cancer-specific HRQOL in children with brain tumors with the HRQOL of children with other cancers, the reported views of children and their parents, and the HRQOL as measured by two PedsQL modules—the PedsQL Cancer and the PedsQL Brain Tumor Modules.

Methods

This study was conducted jointly with the development of the Japanese version of the PedsQL Brain Tumor Module [24].

Study population

Children with brain tumors and their parents were recruited from six hospitals across Japan and from the Children's Cancer Association of Japan (CCAJ) between September and December 2008. Inclusion criteria were as follows: age 5–18 years for children (the parent was included if their child was 2–18 years) and at least 1 month had passed since diagnosis. Children and parents were excluded if physicians at the hospital or social workers of the CCAJ determined that the family found the subject of the child's condition too uncomfortable to discuss.

Procedure

Researchers presented the study aims to 101 children and 122 parents at participating hospitals verbally and in writing, and the CCAJ sent a written notice to all families, inviting them to a meeting regarding brain tumors. Of 55 families from the CCAJ that provided informed consent or assent, 2 families were bereaved, 1 had an adult survivor, 6 children were aged 2–4 years, and 1 child old enough to provide his own consent opted out. A total of 98 children and 120 parents from the hospitals as well as 45 children and 52 parents contacted directly by the CCAJ agreed to participate. Questionnaires were distributed to 143 children and 172 parents.

Questionnaires for children were either self-administered or administered by an interviewer. When providing

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informed consent, parents determined whether or not their child was able to self-administer the questionnaire. In accordance with the PedsQL™ administration guidelines, children aged 5–7 years or who were otherwise determined incapable of self-administration were administered the questionnaire by either their parents or a researcher (children were allowed to decide). In both cases, the instructions and each item were read to the child. Parent report questionnaires were simultaneously self-administered.

The questionnaires were returned by 138 children and 167 parents. We excluded questionnaires from 5 children and 2 parents who did not answer any scales of the PedsQL Cancer Module, and we analyzed answers from 133 children and 165 parents. Next, we analyzed answers from 124 children and 143 parents after omitting questionnaires with missing data for any scale of the PedsQL Cancer Module. Given the lack of any significant differences between the results of the former and latter analyses, we report only the latter.

Ethical considerations

This study was approved by the review boards of all seven participating institutions. Children aged ≥12 years and the parents of all children provided written consent prior to participation. Children aged <12 years provided informed verbal assent.

Measurements

The cancer-specific HRQOL of the PedsQL Cancer Module [21, 25] has eight scales: Pain and Hurt (two items), Nausea (five items), Procedural Anxiety (three items), Treatment Anxiety (three items), Worry (three items), Cognitive Problems (five items), Perceived Physical Appearance (three items), and Communication (three items).

Respondents were asked to describe the extent to which each item troubled them over the past month. Although the PedsQL Cancer Module comprises the standard (covering the previous month) and acute versions (covering the previous 7 days), we used the standard version, because it served as a historical control (described in the next section). For the child reports for ages 8–18 and all parent reports, a 5-point Likert response scale was used (0 = never a problem; 1 = almost never; 2 = sometimes; 3 = often; 4 = almost always). For the child report for children ages 5–7, a 3-point face scale was used. Items were reverse scored and linearly transformed to a 0–100 scale, with higher scores indicating a better HRQOL. To account for missing data, scale scores were computed as the sum of the items divided by the number of items answered. If more than 50 % of the items were missing or incomplete, the scale score was not computed.

Table 1 Characteristics of participants

	This study				Tsuji et al. [25] ($N = 245$)	
	All participants ($N = 165$)		Complete participants ($N = 143$)[a]			
	n	%	*n*	%	*n*	%
Gender						
Male	91	55.5	84	59.2	135	55.1
Female	73	44.5	58	40.8	110	44.9
Age (years)						
2–4	25	15.2	23	16.1	41	16.7
5–7	31	18.8	21	14.7	62	25.3
8–12	56	33.9	48	33.6	75	30.6
13–18	53	32.1	51	35.7	67	27.3
Tumor pathology						
Embryonal tumors	47	29.2	39	27.9	–	–
Germ cell tumors	36	22.4	34	24.3	–	–
High-grade glioma	24	14.9	19	13.6	–	–
Low-grade glioma	39	24.2	33	23.6	–	–
Other tumors	15	9.3	15	10.7	–	–
Treatment status						
On-treatment	63	39.4	56	39.2	88	35.9
Off-treatment ≤ 12 months	23	14.4	21	14.7	33	13.5
Off-treatment > 12 months	74	46.3	66	46.2	124	50.6
Age of guardian (years)						
21–28	7	4.3	4	2.8	5	2.1
29–34	23	14.0	18	12.7	40	16.9
35–39	47	28.7	41	28.9	72	30.4
40–60	86	52.4	78	54.9	120	50.6
≥61	1	0.6	1	0.7	0	0.0
Relationship to patient						
Mother	152	92.1	133	93.0	230	96.2
Father	10	6.1	8	5.6	9	3.8
Other guardian	3	1.8	2	1.4	0	0.0
Guardian's academic background						
Junior high school	3	1.9	2	1.4	4	1.7
High school	63	38.9	49	35.0	87	36.6
Vocational school	28	17.3	27	19.3	44	18.5
Junior college	29	17.9	28	20.0	48	20.2
University	36	22.2	32	22.9	52	21.8
Graduate school	3	1.9	2	1.4	1	0.4
Other	0	0.0	0	0.0	2	0.8

Missing data were excluded

[a] Sample without missing data for any scale of the PedsQL Cancer Module

The PedsQL Brain Tumor Module [15, 24] has six scales. Questions about Nausea, Procedural Anxiety, and Worry scales are identical to those in the PedsQL Cancer Module, whereas questions on the Pain and Hurt scale (three items) and Cognitive Problems scale (seven items)

differ from those in the PedsQL Cancer Module. The parent report for toddlers (ages 2–4) does not include the Cognitive Problems scale. The Movement and Balance scale is not reported here. Agreement between the parent and child reports (intraclass correlation coefficient [ICC]) was described previously as follows: 0.41 (Pain and Hurt), 0.65 (Nausea), 0.62 (Procedural Anxiety), 0.18 (Worry), and 0.49 (Cognitive Problems) [24].

Respondents were asked to describe the extent to which each item troubled them over the previous 7 days. Although the recall period of the questionnaire differed from that of the Cancer Module, no published studies using the Brain Tumor Module as the standard (1 month) version were available when the present study was planned and designed. Because the PedsQL Brain Tumor Module adopts the acute version (covering the previous 7 days) as a standard, we employed the acute version. The respondents, response scale, and scoring method were identical to the PedsQL Cancer Module. Parents were also asked to record their child's gender, date of birth, age, tumor pathology, date of diagnosis, and date of therapy completion.

Historical control

We used data reported by Tsuji et al. [25] as a control. This study reported scores from for Japanese children with cancer (67.8 % had leukemia, 9.0 % had malignant lymphoma, followed by neuroblastoma, Wilm's tumor, rhabdomyosarcoma, and hepatoblastoma) using the Japanese version of the PedsQL Cancer Module. Children with brain tumors were excluded in that study.

The average age of children with cancer was 10.5 years (standard deviation [SD] = 3.9 years), and 55.1 % of patients were boys (Table 1). Mothers answered 93.9 % of the questionnaires, and parents' ages ranged between 40 and 60 years.

Statistical analysis

Statistics were calculated using IBM SPSS software, version 19 (SPSS, Inc., Chicago, IL, USA), and the level of significance was defined as 0.05. We calculated the sample characteristics as follows: age distribution, disease, and treatment characteristics; and scale characteristics as follows: mean, SD, minimum and maximum scores. The internal consistency of each subscale was estimated using Cronbach's alpha coefficient [26] (good consistency > 0.70). The agreement between the child and parent reports was estimated using ICC in a two-way mixed effects model [27] (ICC value of 0.20 indicates fair agreement, 0.40 moderate, 0.60 good, and 0.80 high agreement).

The cancer-specific HRQOL of children with brain tumors was compared to the HRQOL of children with other cancers. We compensated for the effect of age (toddler, young child, school child, or adolescent) and treatment status (on-treatment, soon after treatment, or off-treatment) differences using the weighted means and SDs of the PedsQL Cancer Module scale scores, adjusted for age and treatment status. The age distribution of leukemia and brain-tumor onset differs [29, 30], and previous reports have found that treatment status affects the PedsQL Cancer Module score [21, 25]. We also found in this study that the treatment status affected the PedsQL Cancer Module score (see electronic Supplementary Table 1).

These values were calculated by dividing the total sample into different groups based on age and treatment status. The control study sample size (Nc_{total}) was 245, and the brain-tumor sample size (N_{total}) was 165 if all respondents completed the PedsQL Cancer Module scale. The control and study populations were divided into groups (Nc_{ij} and N_{ij}) separated by treatment status (on-treatment, off-treatment ≤12 months, or off-treatment >12 months; $i = 1$–3) and by age (2–4, 5–7, 8–12, or 13–18 years; $j = 1$–4). The weighted means [31] were calculated as follows:

$$\text{Weighted mean}(\bar{X}) = \sum_{k=1}^{N_{total}} W_k X_k / \sum_{k=1}^{N_{total}} W_k.$$

$$\left(\text{The common mean} = \sum_{k=1}^{N_{total}} X_k / N_{total}\right).$$

$$W_k = \left(\frac{Nc_{ij}}{Nc_{total}}\right) / \left(\frac{N_{ij}}{N_{total}}\right).$$

where X_k was the PedsQL Cancer Module scale score of each respondent that belonged to treatment status i and age j; the weights for each respondent (W_k) were calculated from the ratio of the age and treatment status of the standard population, divided by the proportion of the age and treatment status in this study.

The weighted SDs were calculated using the same weight (W_k) as follows:

$$\text{Weighted SD} = \sqrt{\sum_{k=1}^{N_{total}} W_k (X_k - \bar{X})^2 / \left(\sum_{k=1}^{N_{total}} W_k - 1\right)}.$$

$$\left(\text{The common SD} = \sqrt{\sum_{k=1}^{N_{total}} (X_k - \bar{X})^2 / (N_{total} - 1)}.\right)$$

We compared the cancer-specific HRQOL using Welch's t test and calculated the effect size d from the difference between the two means divided by the pooled SD of both samples.

Table 2 PedsQL Cancer Module scores of children with brain tumors ($N = 143$)

	Mean	SD	Min.	Max.	Alpha[a]	ICC[b]
Child report (n = 124)						
Pain and Hurt	90.4	17.6	0	100	0.62	0.20
Nausea	87.5	20.6	15.0	100	0.86	0.68
Procedural Anxiety	74.5	30.8	0	100	0.88	0.70
Treatment Anxiety	92.8	19.0	0	100	0.88	0.41
Worry	81.9	23.4	0	100	0.76	0.27
Cognitive Problems	73.6	22.4	0	100	0.78	0.44
Perceived Physical Appearance	73.8	26.3	0	100	0.71	0.28
Communication	68.5	29.9	0	100	0.77	0.45
Parent report (n = 143)						
Pain and Hurt	84.5	20.0	0	100	0.83	
Nausea	84.7	22.6	15.0	100	0.93	
Procedural Anxiety	59.8	35.4	0	100	0.96	
Treatment Anxiety	79.7	23.1	0	100	0.93	
Worry	78.3	22.3	0	100	0.86	
Cognitive Problems	66.0	23.8	0	100	0.89	
Perceived Physical Appearance	70.6	24.6	0	100	0.81	
Communication	59.5	29.6	0	100	0.89	

ICC intraclass correlation coefficient, *Max.* maximum, *Min.* minimum, *SD* standard deviation

[a] Cronbach's alpha coefficient

[b] ICC values for child and parent reports in the two-way mixed effects model ($n = 124$)

The agreement of the two modules was evaluated using paired t tests; the effect size d (the mean score difference divided by SD of the mean score difference) [28] designated as small (0.20), medium (0.50), and large (0.80) in magnitude and by the ICC calculated from a one-way random effects model [27].

Results

Sample characteristics

The median age of the children with brain tumors was 10.0 years (range: 2–18) (Table 1), and the sample was heterogeneous for tumor pathology. Most children presented with embryonal tumors, low-grade gliomas, and germ cell tumors. Median age at diagnosis was 6.0 years; 63 children (39.4 %) were still receiving treatment, while 97 (60.6 %) had completed treatment, and the interval from completion of treatment to the survey ranged from 0.1 to 13.3 years. Most children on treatment were younger than the children who had completed treatment.

With the exceptions noted below, no significant differences were observed between the characteristics of the children and their parents and those of the historical control (Table 1). The differences were as follows: The present study enrolled fewer children between the ages of 5 and 7 years and more between the ages of 13 and 18 years ($P = 0.069$, Chi-square test).

Scale descriptions

The child-reported scores were higher than parent-reported scores on all scales of the PedsQL Cancer Module and were internally consistent for all scales except for the Pain and Hurt scale (Cronbach's alpha coefficient = 0.62); parent-reported scores were internally consistent for all scales (Table 2). Agreement between the child and parent reports was good for the Nausea and Procedural Anxiety scales, moderate for the Treatment Anxiety, Cognitive Problems, and Communication scales, and fair for the Pain and Hurt, and Perceived Physical Appearance scales.

Cancer-specific HRQOL in children with brain tumors compared with the HRQOL of children with other cancers

We noted small but significant differences between the children's reports for Pain and Hurt ($d = 0.26$) and Nausea ($d = 0.23$) and the parents' reports for Nausea ($d = 0.28$), Procedural Anxiety ($d = -0.22$), and Treatment Anxiety ($d = -0.32$) (Table 3). The scores for Pain and Hurt and Nausea were higher for children with brain tumors than for children with other cancers, indicating better HRQOL. However, the scores for Procedural Anxiety and Treatment Anxiety were lower for children with brain tumors than for children with other cancers, indicating worse HRQOL. The direction of the effects was the same for the scales reported by parents and children.

Table 3 Comparison of cancer-specific HRQOL in children with brain tumors and those with other cancers

	This study[a]		Tsuji et al. [25][b]			P^c	Effect size d^d
	Mean	SD	*n*	Mean	SD		
$N = 143$							
Child report ($n = 124$)							
Pain and Hurt	89.8	19.3	202	84.7	19.7	0.024	0.26
Nausea	88.0	20.0	199	83.0	24.0	0.044	0.23
Procedural Anxiety	72.5	32.8	203	72.9	31.0	0.910	−0.01
Treatment Anxiety	90.7	22.8	203	93.1	17.0	0.302	−0.12
Worry	81.0	25.8	202	76.6	25.9	0.140	0.17
Cognitive Problems	72.3	23.8	200	71.5	22.1	0.775	0.03
Perceived Physical Appearance	71.9	28.7	204	70.3	28.6	0.639	0.05
Communication	65.5	32.6	204	67.0	27.0	0.656	−0.05
Parent report ($n = 143$)							
Pain and Hurt	84.9	20.9	242	82.9	22.0	0.367	0.09
Nausea	87.0	20.8	233	80.5	25.7	0.008	0.28
Procedural Anxiety	55.7	36.6	242	63.2	31.8	0.043	−0.22
Treatment Anxiety	77.9	24.4	241	84.9	19.0	0.004	−0.32
Worry	79.0	23.6	242	81.4	21.9	0.334	−0.10
Cognitive Problems	65.8	24.9	243	69.4	21.6	0.151	−0.15
Perceived Physical Appearance	71.7	25.3	243	73.8	24.9	0.437	−0.08
Communication	60.1	31.1	241	62.2	25.4	0.496	−0.07

HRQOL health-related quality of life, *SD* standard deviation

[a] Means and SDs of the PedsQL Cancer Module score in children with brain tumors adjusted for age and treatment status to subjects reported by Tsuji et al. [25]

[b] Previously reported data in children with the other cancers

[c] *P* value from the Welch *t* test

[d] Effect size *d* defined by Cohen [28] is the difference between two means divided by a pooled SD with two samples. A positive value indicates that children with brain tumors have higher HRQOL scores compared with children with other cancers

Agreement between the PedsQL cancer and the PedsQL Brain Tumor Modules of the PedsQL

Children and parents reported higher Pain and Hurt scores ($d = 0.29$, $P = 0.001$ and $d = 0.22$, $P = 0.010$, respectively) on the Cancer than on the Brain Tumor Module (Table 4). Children reported higher Procedural Anxiety ($d = 0.31$, $P = 0.001$) and Cognitive Problems scores ($d = 0.28$, $P = 0.003$) on the Cancer Module. The agreement between the PedsQL Cancer and the PedsQL Brain Tumor Modules was very high (ICC > 0.80) except for the Pain and Hurt scale for the child report where the agreement was moderate (ICC = 0.43). The agreement according to treatment status is shown in Supplementary Table 2.

Discussion

We report here that children with brain tumors perceive their HRQOL differently from children with other cancers. Several aspects of HRQOL were more difficult (for example, procedural and treatment anxiety) for patients with brain tumors, while other aspects (nausea, pain and hurt) were less difficult, and a number of factors may be responsible for these differences. In particular, the brain is the center of multiple functions. The brain integrates the information received from, and coordinates the physical and mental activity of, the whole body. Thus, the unique HRQOL of children with brain tumors likely reflects the vast complexity of brain function. Knowledge of these differences should help medical practitioners design-specific support and care strategies for these children.

A total of 29 % of children in this study suffered from embryonal tumors (mainly medulloblastomas), and treatment for these tumors requires surgery, radiation, and chemotherapy [32, 33]. The main treatments for children with germ cell tumors (mainly germinomas) include surgery, radiation, and chemotherapy [34], with chemotherapy representing the main treatment for children with leukemia (controls). Each treatment method will affect a child's HRQOL differently.

Table 4 Comparison of cancer-specific HRQOL using the PedsQL cancer and PedsQL Brain Tumor Modules

	n	Dif.[a]	95 % CI of the Dif.		*P*[b]	Effect size *d*[c]	ICC (5–18 years)[d]	ICC (2–18 years)[e]
			Lower	Upper				
$N = 143$								
Child report ($n = 124$)								
Pain and Hurt	124	5.41	2.12	8.70	0.001	0.29	0.43	–
Nausea	124	0.91	−0.91	2.72	0.325	0.09	0.88	–
Procedural Anxiety	123[f]	4.34	1.80	6.87	0.001	0.31	0.89	–
Worry	124	1.95	−0.39	4.30	0.102	0.15	0.84	–
Cognitive Problems	124	3.64	1.29	5.99	0.003	0.28	0.81	–
Parent report ($n = 143$)								
Pain and Hurt	143	2.50	0.60	4.40	0.010	0.22	0.82	0.91
Nausea	143	0.59	−1.20	2.39	0.515	0.05	0.91	0.89
Procedural Anxiety	142[f]	2.14	−0.77	5.05	0.148	0.12	0.88	0.87
Worry	143	1.46	−0.20	3.11	0.084	0.15	0.90	0.90
Cognitive Problems	124[g]	−0.99	−2.89	0.91	0.304	−0.09	0.89	–

CI confidence interval, *Dif.* difference, *HRQOL* health-related quality of life, *ICC* intraclass correlation coefficients, *PedsQL* pediatric quality of life inventory, *SD* standard deviation

[a] Mean score differences (PedsQL Cancer Module—PedsQL Brain Tumor Module). A positive value indicates that participants (children with brain tumors or parents of children with brain tumors) have higher scores in the PedsQL Cancer Module (fewer problems) than in the PedsQL Brain Tumor Module

[b] *P* value from the paired *t* test

[c] Effect size *d* defined by Cohen [28] is the mean score difference divided by SD of the mean score difference. A positive value indicates that participants (children with brain tumors or parents of children with brain tumors) scored higher in the PedsQL Cancer Module (fewer problems) than the PedsQL Brain Tumor Module

[d] ICC values for the PedsQL Cancer Module and the PedsQL Brain Tumor Module in the one-way random effects model among children aged 5–18 years

[e] ICC values for the PedsQL Cancer Module and the PedsQL Brain Tumor Module in the one-way random effects model among children aged 2–18 years

[f] Missing data for the Brain Tumor Module ($n = 1$) were excluded

[g] The PedsQL Brain Tumor Module parent report for toddlers (ages 2–4) does not include the Cognitive Problems scale

Children with brain tumors reported less difficulty with pain and hurt than children with other cancers; however, we believe it unlikely that these children actually experienced less pain, as here and in a previous study [17], parents reported similar difficulty with pain and hurt irrespective of cancer type. Children with brain tumors reported pain and hurt more frequently than children with lymphoma at a similar frequency to children with leukemia and less frequently than children with solid tumors [4]. These inconsistencies may arise due to scale characteristics. The agreement between Pain and Hurt scores in the Cancer and Brain Tumor Modules was moderate, while the agreement on other scales was high. These findings suggest that the Pain and Hurt scale of the PedsQL Cancer Module may not consider problems for children with brain tumors compared with the Brain Tumor Module.

The Pain and Hurt scale of the Cancer Module asks about generalized body pain but does not localize the pain. For example, "I ache or hurt in my joints and/or muscles," versus "I hurt a lot." Further, the Brain Tumor Module measures two items present in the Cancer Module and, uniquely, "I get headaches." Thus, the Brain Tumor Module includes a question about headaches, which are frequent in patients and survivors of brain tumors [35]. Headache is the most frequently reported initial symptom of pediatric brain tumors in children aged ≥2 years and may be interpreted with particular meaning for these children [36]. Headache would remind the children and parents of the first brain tumor and induce worry about a relapse. Such headaches cause physical distress and psychosocial concern. Therefore, we prefer to use the Brain Tumor to the Cancer Module to measure disease-specific HRQOL for these children.

Children with brain tumors and their parents reported less difficulty with nausea than children with other cancers. Causes of nausea may include side effects of chemotherapy, radiation sickness, postoperative reactions, tumors close to the area postrema, intracranial hypertension, gastrointestinal pathology, and anxiety [37, 38]. Here, at least 1 month had passed since diagnosis, and factors such as

postoperative reaction, brain-tumor activity, and intracranial hypertension would have been controlled, resulting in less difficulty with nausea [39, 40].

Patients may experience strong nausea and vomiting at the onset of brain tumors as well as in the perioperative period; therefore, pediatric patients may evaluate their experience with treatment-induced nausea and vomiting as less trying than that experienced perioperatively. In contrast, children with ALL (control group majority) are treated at the first remission-induction phase using moderately emetogenic chemotherapy (i.e., vincristine, daunorubicin, L-asparaginase) [41], and severe emetogenic chemotherapy (i.e., cyclophosphamide, ifosfamide) is added during the intensification phase. Treatment type and course will affect a child's experience, so a longitudinal study will be required to assess how the experience of children with brain tumors changes after diagnosis and treatment.

Parents of children with brain tumors reported more procedural and treatment anxiety for their children than did the parents of children with other cancers. The PedsQL Cancer Module evaluates children's and parents' perception of a child's anxiety about needle sticks, blood tests, seeing a doctor, and hospitalization, which relate to trauma and stressor-related symptoms that are classified as anxiety disorders. Perceived life threat and treatment intensity are directly associated with posttraumatic stress disorder [42]. We assume that intensive symptoms and the treatment of pediatric brain tumors increase anxiety.

Our findings here of increased anxiety in children with brain tumors differ from those of a previous study conducted in the United States [17]. Although we cannot explain the reason for this discrepancy, pediatric oncology practice differs between the United States and Japan [43], and patients in Japan may not be fully informed of the diagnosis, which affects posttraumatic stress disorder [44]. Cognitive problems of children with brain tumors might also limit their understanding of disease and treatment course. Each child's psychological readiness for each stage of the diagnosis and treatment may be affected by the information provided and by the child's cognitive ability.

Several limitations of the present study warrant mention. First, the study and controls were heterogeneous and included various pathologies. All children in this study suffered central nervous system damage from invasion, compression, or hydrocephalus as well as from therapy. Further investigations of tumor types and treatment should reveal how HRQOL differs between children with brain tumors and those with other cancers.

Second, data obtained from children and parents were not completely equivalent; the ages of self-reporting children ranged between 5 and 18 years, whereas parental-reporting included children 2–18 years of age. Further, the varying degrees of patients' impairments prevented optimum accuracy of reporting [17]. However, the number of children participating in the present study (133) was similar to that of participating parents of children aged 5–18 years (140) because of assisted administration. Further, HRQOL reporting by children is not significantly influenced by the administration technique [24, 45].

Third, the PedsQL Cancer and Brain Tumor Modules employ different recall periods, as described above [15, 25]. This difference must be taken into account when interpreting data. Although the items on the Procedural Anxiety subscale are identical in both modules, children with brain tumors studied here reported less difficulty with procedural anxiety using the Cancer than with the Brain Tumor Module. The recall period may alter a child's perception of procedural anxiety. Further research is required to determine why children reported less anxiety over the past month than over the previous 7 days.

Fourth, our ability to generalize the data is limited. For example, at the CCAJ, several hundred families, including those not eligible to participate, were notified of this study; therefore, the true response rate is unknown. Families were excluded if doctors or social workers determined that the family found the child's condition too uncomfortable to discuss. Although the number of such excluded families was not recorded, this exclusion may have limited data collection.

Fifth, when comparing children with brain tumors to those with other cancers, certain parental characteristics could not be taken into account, as Tsuji et al. [25] did not report them. Parental reports might have been influenced by factors such as parental mental health, which may limit comparability. However, all child and parent characteristics reported here, except for age and tumor pathology, were similar.

Conclusion

Here, we found that children with brain tumors reported less difficulty with the categories of pain and hurt and nausea than children with other cancers that included mostly leukemia. Parents of the children with brain tumors reported more procedural and treatment anxiety. The information will help medical professionals and researchers to understand the influence of the disease and treatment on the HRQOL of children with brain tumors regardless of age and treatment status.

This study is the only comparison, to our knowledge, of the PedsQL Cancer and Brain Tumor Modules. The PedsQL Cancer Module compares cancer-specific HRQOL of children with brain tumors and those with other cancers. However, the PedsQL Brain Tumor Module is more

sensitive for brain-tumor-specific aspects of the HRQOL and should be used to assess HRQOL in children with brain tumors.

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Original Article

Intraoperative rapid diagnosis of primary central nervous system lymphomas: Advantages and pitfalls

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To study the advantages and pitfalls of intraoperative rapid diagnosis (IRD) of primary central nervous system lymphomas (PCNSL), pathology reports and frozen sections in our institution were reviewed. We examined 27 cases of PCNSL, one case of anaplastic glioma, and one case of metastatic brain tumor that were diagnosed on neuroimaging. Fifteen cases of intraoperative cytological preparations were also reviewed in a correlative manner. Among the 27 cases initially diagnosed as PCNSL, 18 were also diagnosed as PCNSL by IRD. However, IRD identified four of the 27 cases as gliosis, two as demyelination, one as atypical epithelial cells, one as malignant glioma and anaplastic astrocytoma. In addition, the case identified as metastatic brain tumor on neuroimaging was corrected to a diagnosis of PCNSL based on IRD. The final accuracy of IRD in the present study was 89.6% (26/29). After postoperative definitive diagnosis, two cases of anaplastic astrocytoma and one case of PCNSL by IRD were corrected to PCNSL, anaplastic oligodendroglioma and demyelination, respectively. PCNSL were sometimes histologically indistinguishable from malignant gliomas or demyelinating diseases in the present study, particularly in frozen sections. Notably, all cases for which both intraoperative cytology and frozen section were performed concomitantly were correctly diagnosed in the present study. In particular, lymphoglandular bodies were highly characteristic cytological findings of PCNSL. Both intraoperative cytology and frozen sections should therefore be performed concomitantly when PCNSL are suspected.

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Key words: cytological diagnosis, demyelination disease, intraoperative rapid diagnosis, lymphoglandular bodies, primary central nervous system lymphoma.

INTRODUCTION

In general, intraoperative rapid diagnosis (IRD) of the CNS requires both clinicopathological knowledge and closer cooperation between neurosurgeons and pathologists. In particular, neuroimaging provides the intraoperative pathologist with key information about primary central nervous system lymphomas (PCNSL).[1] However, only the actual histological pattern can confirm the diagnosis of PCNSL. Careful intraoperative assessment of pathological samples should thus enable the pathologist to suggest the possibility of PCNSL and minimize the risk of unnecessary resection. However, pathologists are generally required to make neurosurgical diagnoses with very small, poor-quality frozen sections, so differentiation between PCNSL and other brain lesions, including malignant gliomas, infarctions, metastatic brain tumors, demyelinating diseases and inflammatory diseases, is often difficult. In addition, as the incidence of PCNSL has long been low,[2–5] few pathologists expert in the intraoperative diagnosis of PCNSL are available. Some investigators have therefore recommended performing intraoperative cytology and frozen sections concomitantly, to help pathologists and provide correlative information.[6–9]

The present study focused on the experience with PCNSL in our institution and examined the advantages and pitfalls of IRD for identifying PCNSL.

MATERIALS AND METHODS

Twenty-nine cases in 27 patients were examined in the present study (Table 1). All samples were from the

Table 1 Summary of cases

Case	Age (years)/sex	Tumor localization	Surgical procedures	Preoperative diagnosis	Intraoperative rapid diagnosis	Definitive diagnosis
1	56/F	Splenium	Biopsy	PCNSL	Gliosis	Gliosis
2	59/M	Rt. cerebellar hemisphere	Biopsy	PCNSL	Atypical epithelial cells	Metastatic carcinoma
3	62/F	Lt. frontal lobe	Biopsy	PCNSL	PCNSL	PCNSL
4	66/F	Lt. frontal lobe	Resection	PCNSL	Malignant glioma	GB
5	66/M	Rt. frontal	Resection	PCNSL	PCNSL	PCNSL
6	50/F	Bil. basal ganglia	Biopsy	PCNSL	Gliosis	Gliosis
7	60/F	Rt. basal ganglia	Biopsy	PCNSL	PCNSL	PCNSL
8	54/M	Unknown	Biopsy	PCNSL	PCNSL	PCNSL
9	60/F	Lt. temporal lobe	Resection	AA	AA	PCNSL
10	74/F	Splenium	Biopsy	PCNSL	PCNSL	PCNSL
11	45/F	Lt. lateral ventricle; Rt. frontal & occipital lobe	Biopsy	PCNSL	PCNSL	PCNSL
12	71/M	1st: lt. temporal lobe	Biopsy	PCNSL	Gliosis	Gliosis
13	71/M	2nd: rt. frontal lobe	Biopsy	PCNSL	PCNSL	PCNSL
*14	56/F	Lt. temporal lobe; rt. Cp angle	Biopsy	PCNSL	Gliosis	Gliosis
*15	61/M	Rt. cerebellar hemisphere	Biopsy	PCNSL	PCNSL	PCNSL
*16	68/F	Cerebellar vermis	Biopsy	PCNSL	PCNSL	PCNSL
*17	64/M	Bil. paraventricle	Biopsy	PCNSL	PCNSL	PCNSL
*18	69/M	Lt. frontal lobe	Biopsy	PCNSL	AA	AO
*19	61/M	Lt. temporal lobe	Biopsy	PCNSL	PCNSL	PCNSL
*20	51/F	Lt. occipital lobe	Biopsy	PCNSL	PCNSL	PCNSL
*21	83/F	Rt. Frontal lobe	Biopsy	PCNSL	PCNSL	PCNSL
*22	44/M	Bil. occipital lobe	Biopsy	PCNSL	Demyelination	Adrenoleukodystrophy
*23	76/M	1st: lt. temporal lobe	Biopsy	1st: PCNSL	1st: demyelination	1st: demyelination
*24	76/M	2nd: rt. frontal lobe; lt. thalamus	Biopsy	2nd: PCNSL	2nd: PCNSL	2nd: PCNSL
*25	62/M	Lt. parietal lobe	Biopsy	PCNSL	PCNSL	Demyelination
*26	64/M	Rt. occipital lobe	Resection	Metastatic brain tumor	PCNSL	PCNSL
*27	60/M	Rt. parietal lobe; rt. Cerebellar hemisphere	Resection	PCNSL	PCNSL	PCNSL
*28	48/F	Rt. frontal lobe	Biopsy	PCNSL	PCNSL	PCNSL
*29	75/F	Splenium; lt. frontal lobe	Biopsy	PCNSL	PCNSL	PCNSL

*Cases of intraoperative cytological preparations examined in a correlative manner. Cases 12 and 13 represented the same patient, and Cases 23 and 24 represented the same patient. AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; bil., bilateral; CP angle, cerebellopontine angle; GB, glioblastoma; lt., left.; PCNSL, primary central nervous system lymphoma; rt., right.

Department of Surgical Pathology at Kurume University Hospital, Japan, from surgeries performed between 2002 and 2013. Frozen section forms were assessed, pathology reports were read and frozen section slides were reviewed. In addition, 15 intraoperative cytological preparations were reviewed for correlation purposes. This study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee of Kurume University School of Medicine.

Histological, cytological and immunohistochemical studies

To prepare frozen sections, the surgical specimen was placed on a metal tissue disc, the sample embedded in optimal cutting temperature compound medium (Sakura Finetek, Torrance, CA, USA), and immersed in acetone. Subsequently, the sample was cut frozen with the microtome portion of the cryostat, and sections (6–8 μm thick) were immediately fixed with Cytokeep II (Nippon Shoji, Osaka, Japan) and stained with HE. Touch smears were also intraoperatively prepared. Some slides were fixed with Cytokeep II and stained with HE and Papanicolaou stain. Residual slides were air-dried and stained with Giemsa stain. Cytological studies were evaluated as follows: no cell clusters with lymphoglandular bodies (LGB), 0; 0–10% cell clusters with LGB, 1+; 10–50% cell clusters with LGB, 2+; >50% cell clusters with LGB, 3+.

Postoperatively, residual tissue samples were fixed in 10% buffered formalin, embedded in paraffin, and processed conventionally for histology and immunohistochemistry. Sections (5 mm) were stained using HE for histological confirmation. The remaining unstained serial sections were used for immunohistochemistry. All specimens were then histologically diagnosed according to World Health Organization criteria for tumors of the CNS.[5] Paraffin-embedded sections were immunostained using monoclonal antibodies against CD3, CD20 and CD79a (DakoCytomation, Glostrup, Denmark) following heat-induced antigen retrieval.

Statistical analysis

To gain a better understanding of the advantages of IRD of PCNSL, statistical analyses among the relevant groups were performed. All statistics were calculated using SAS version 9.4 software (SAS Institute, Cary, NC, USA). Comparisons between groups were assessed using the chi-square test. All tests of significance were two-sided, with values of $P < 0.05$ considered significant.

RESULTS

Clinical features

Clinical features of study participants are summarized in Table 1. Twenty-seven cases from 25 patients were initially diagnosed as PCNSL based on MRI and clinical data. Two other cases were initially diagnosed as anaplastic astrocytoma (Case 9) and metastatic brain tumor (Case 26, Fig. 1a) based on MRI and clinical data. Patients ranged in age from 44 to 83 years (mean, 62 years) and comprised 13 men and 14 women. Tumor localization was listed in 28 of the 29 cases. A solitary lesion was found in 19 patients (68%), while the other nine patients showed multiple lesions on presentation (32%). Regarding surgical procedures, biopsy was performed in 24 cases and resection in five. In Case 27, the patient had been pretreated with steroids in another hospital prior to biopsy and MRI on admission showed an enhancing band-like lesion in the right parietal lobe. However, most lesions showed no enhancement (Fig. 1b). In Case 12, initial MRI showed a left temporal lesion (Fig. 1c), but that lesion disappeared spontaneously without treatment during the 2 months after biopsy. However, 3 months later a newly formed tumor was found on serial MRI (Fig. 1d).

Intraoperative rapid diagnosis

Among the 27 cases of PCNSL diagnosed based on MRI and clinical data, 18 were diagnosed as PCNSL, while the diagnosis of four cases was corrected to gliosis (Cases 1, 6, 12 and 14), and two of the 27 cases were corrected to demyelination (Cases 22, 23) following examination of frozen sections or cytological preparations. Three of the 27 cases were corrected to atypical epithelial cells (Case 2), malignant glioma (Case 4) and anaplastic astrocytoma (Case 18). In most cases of PCNSL, frozen sections showed angiocentricity and angioinvasion of tumor cells. From these perivascular cuffs, tumor cells invaded the neural parenchyma, either with compact cellular aggregates and a well-delineated invasion front, or with single, diffusely infiltrating tumor cells. In addition, cells from PCNSL did not adhere to each other. In the present study, diagnosis of PCNSL was difficult in Cases 26 and 27 due to extensive apoptosis and necrosis (Fig. 2a,c). However, characteristic LGB were easily observed, and neoplastic cells of PCNSL were also seen in the cytological preparations of these cases (Fig. 2b,d).

Based on cytological preparations and frozen sections, these cases were diagnosed as PCNSL. In Case 22, frozen sections showed angiocentricity of lymphocytes and gliosis, but no lymphocytic invasion of the neural parenchyma in these perivascular cuffs. In addition, cytological

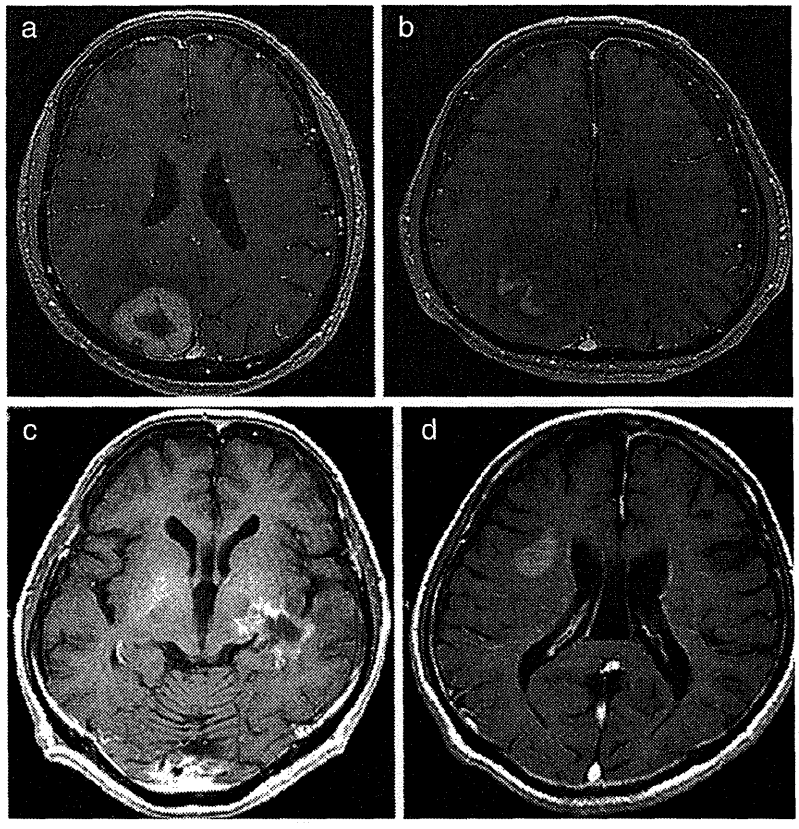

Fig. 1 (a) T1-weighted MRI after contrast administration. The lesion has a central, non-enhancing core and possible necrosis in the right occipital lobe (Case 26). (b) T1-weighted MRI after contrast administration. Note the enhancing band-like lesion in the right parietal lobe (Case 27). (c) The initial T1-weighted MRI after contrast administration showing a left temporal lesion (Case 12). (d) Three months later, a newly formed tumor is found in the right frontal lobe on serial MRI (Case 12).

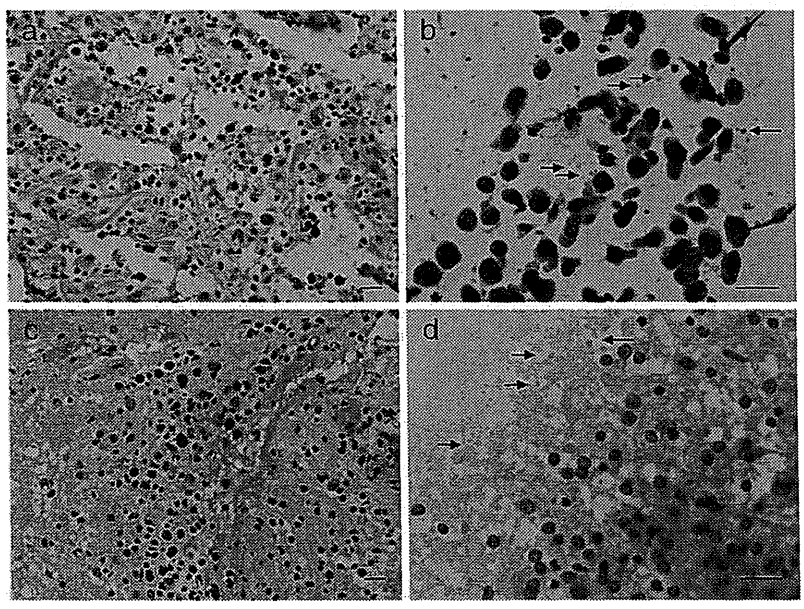

Fig. 2 (a) Frozen section showing lymphoma cells. Note the background of extensive apoptosis and necrosis (Case 26) (HE, bar: 20 μm). (b) Note the characteristic lymphoglandular bodies (LGB) (arrows) and the morphology of the neoplastic cells of the lymphoma in a portion of the cytological preparation (Case 26) (Papanicolaou stain, original magnification, bar: 20 μm). (c) Frozen section showing lymphoma cells. Note the background of extensive apoptosis and necrosis (Case 27) (HE, original magnification, bar: 20 μm). (d) Cytological preparation showing the characteristic LGB (arrows) and the morphology of the lymphoma cells (Case 27) (HE, bar: 20 μm).

preparations did not show LGB or the neoplastic cells of PCNSL. Based on both cytological preparations and frozen sections, this case was diagnosed as demyelination. In 10 of 15 cases, LGB were detected using intraoperative cytological preparations; of these, seven were scored as 3+, two as 2+, and one as 1+. All cases with LGB were diagnosed correctly as PCNSL using IRD (Tables 1,2).

Table 2 Semi-quantitative amounts of lymphoglandular bodies (LGB) in cases

Case No.	Age (years)/sex	Semi-quantitative amounts of LGB
14.	56/F	0
15.	61/M	2+
16.	68/F	1+
17.	64/M	1+
18.	69/M	0
19.	61/M	3+
20.	51/F	3+
21.	83/F	3+
22.	44/M	0
23.	76/M 1st	0
24	76/M 2nd	Cytodiagnosis not performed
25.	62/M	0
26.	64/M	3+
27.	60/M	3+
28.	48/F	3+
29.	75/F	3+

No LGB, 0; 0–10% cell clusters with LGB, 1+; 10–50% cell clusters with LGB, 2+; >50% cell clusters with LGB, 3+. Cases 23 and 24 represent the same patient.

Postoperative definitive diagnosis

Seventeen cases that were diagnosed as PCNSL from frozen sections were confirmed with examination of permanent sections. In addition, the case of anaplastic astrocytoma that was diagnosed with both MRI and frozen sections (Fig. 3a) was corrected to PCNSL after examination of a permanent section (Fig. 3b) (Case 9).

On the other hand, a case diagnosed as PCNSL from frozen sections (Fig. 3c) was corrected to demyelination (Case 25). This case was misdiagnosed as PCNSL due to angiocentricity of lymphocytes. However, these lymphocytes did not show significant atypia or monoclonality in permanent sections and retrospective analysis of cytological preparations showed no LGB (Fig. 3d, Table 2).

Immunohistochemically, all cases were positive for CD20 and negative for CD3. Histologically, the 19 PCNSL were all characterized as diffuse large B-cell type. One of the two cases of demyelination (Case 22) was confirmed as representing adult-type adrenoleukodystrophy following examination of a permanent paraffin section and biochemical analysis. One of the four gliosis cases (Case 12) and one of the two demyelination cases (Case 23) were not confirmed following pathological examination of permanent sections, but were confirmed as PCNSL during a second operation (Cases 13, 24). Finally, etiologies of the other cases of gliosis and demyelination were unknown (Cases 1, 6, 14 and 25). Follow-up of these cases has shown no recurrence as of the time of writing. A case diagnosed as anaplastic astrocytoma from frozen sections was corrected to anaplastic oligodendroglioma (Case 18). The final accu-

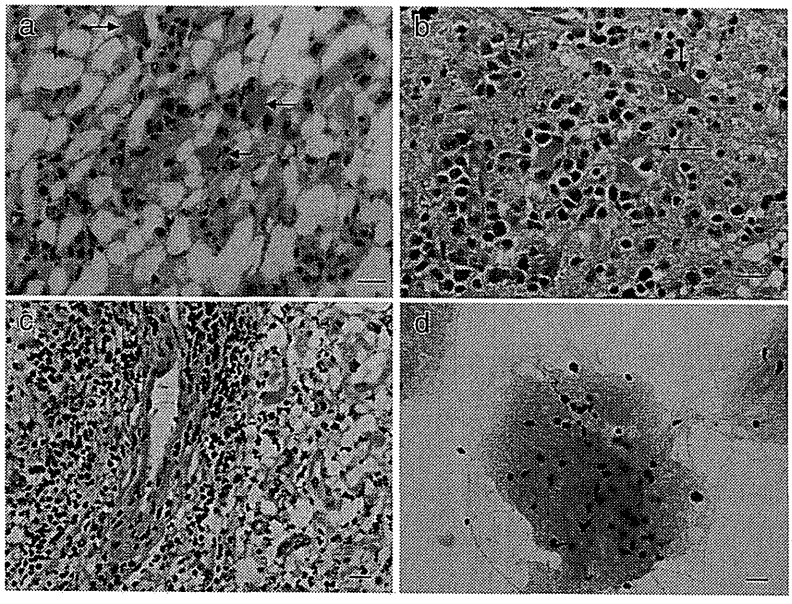

Fig. 3 (a) Frozen section showing small undifferentiated cells with abundant astrocytes simulating astrocytoma cells (arrows) (Case 9) (HE, bar: 20 μm). (b) Permanent section of Case 9. Note the characteristic lymphoma cells with abundant reactive gemistocytic astrocytes (arrows) (HE, bar: 20 μm). (c) Frozen section of Case 25, showing prominent perivascular inflammatory cells. (d) Cytological preparation of Case 25, showing no cell clusters with lymphoglandular bodies (LGB) on retrospective analysis (Papanicolaou stain, original magnification, bar: 20 μm).

racy of IRD in the present study was therefore 89.6% (26/29). In addition, all cases for which both intraoperative cytology and frozen section were performed concomitantly were correctly diagnosed in the present study (Table 2).

Statistical analysis

No correlation was seen between preoperative and definitive diagnoses ($P = 1.0000$). However, a significant correlation was evident between IRD and definitive diagnosis ($P < 0.0001$). The accuracy of IRD should therefore be significantly higher than that of preoperative diagnosis.

DISCUSSION

Recent advances in neuroimaging, particularly MRI, have revolutionized the diagnosis and treatment of CNS diseases. Small, slowly growing, minimally invasive tumors are increasingly being diagnosed in association with such advances. Regarding PCNSL, MRI can detect the typical features of these tumors, including intra-axial homogeneous single- or multiple-contrast enhancing lesions with marked surrounding edema and restricted diffusion, usually in contact with a surface exposed to cerebrospinal fluid.[10–12] Ring enhancement lesions that are usually associated with necrosis on MRI are thus uncommon in cases of immunocompetent patients with PCNSL, and other diagnoses should be considered for such lesions. On the other hand, cases with necrosis comprised 4–11% of PCNSL in recent reports.[10,11] In addition, MRI underestimates the tumor burden of PCNSL.[13] Bulky disease is seen as a contrast-enhancing lesion, but areas of microscopic tumor infiltration may appear radiographically normal. Neuroimaging thus provides crucial information to the pathologist, but PCNSL should be considered in cases showing diverse neuroimaging results. In reality, the accuracy of the clinical diagnosis of PCNSL in the present study was not high, but the IRD rate was high (89.6%). The level of agreement of IRD and postoperative definitive diagnosis has been reported as 83–95.6% in neurosurgical specimens.[7,9,12,14] Although the present study was limited regarding PCNSL, the rate of IRD in the present study corresponded to findings from the past reports. We also performed statistical analyses among the relevant groups to gain a better understanding of the advantages of intraoperative diagnosis of PCNSL. As a result, the accuracy of intraoperative diagnosis was significantly higher than that of neuroimaging diagnosis. In general, the primary treatment for PCNSL includes a combination of chemotherapies containing high-dose methotrexate followed by radiotherapy.[2–4,12] IRD is therefore important for avoiding unnecessary surgery for PCNSL. For example, in Case 26, we were able to reach a final decision regarding the extent of surgical resection according to the appropriate IRD, even though MRI suggested metastatic brain tumor.

Histologically, PCNSL are typically patchy, poorly demarcated and angiocentric at low magnification. Angiocentricity and angioinvasion, although most apparent in less cellular regions, are also present in dense cellular portions of the lesion. From these perivascular cuffs, tumor cells invade the neural parenchyma, either with compact cellular aggregates and a well-delineated invasion front or with single, diffusely infiltrating tumor cells resembling encephalitis.[15,16] In addition, when examining intraoperative preparations, pathologists should note the key feature that cells from PCNSL do not adhere to each other. In general, PCNSL cells fragment and die easily, leaving behind cellular debris comprising apoptotic cells and LGB.[1,6] These LGB are small, membrane-delimited fragments of cytoplasm that often contain a slightly more basophilic core. These bodies are highly characteristic of high-grade lymphoma.[1,6] In Case 26 of the present study, diagnosis of PCNSL from frozen sections was difficult due to extensive necrosis. However, characteristic LGB were readily apparent, and the morphology of neoplastic cells in PCNSL was readily seen in cytological preparations. Early in the course of steroid administration, many diagnostic lymphoma cells undergo apoptosis. In Case 27, a physician unfamiliar with the management of PCNSL treated the patient with steroids before the patient was transferred to our hospital. Fortunately, we were able to identify diagnostic lymphoma cells in the background tissue of apoptotic cells. In that case, the presence of noncohesive cells with scant cytoplasm and prominent nuclei against the background of dispersed LGB in the cytological preparation suggested PCNSL. Sharma *et al.* also demonstrated that the presence of relatively monotonous large, noncohesive cells with scant cytoplasm and prominent nuclei against a background of dispersed LGB suggests PCNSL.

PCNSL are sometimes histologically indistinguishable from malignant gliomas or demyelinating diseases, particularly in the frozen sections used in IRD, because the edge of the lesion often contains demyelination, gliosis, macrophages and small non-neoplastic perivascular lymphocytes.[1] In the present series, in Case 9, we misdiagnosed lymphoma as anaplastic astrocytoma based on IRD in the same situation (Fig. 3a). In addition, Ohe *et al.* reported a case of PCNSL that was initially diagnosed as tumefactive multiple sclerosis after brain biopsy.[17] This case demonstrated that PCNSL can mimic multiple sclerosis both clinically and radiologically. Sharma *et al.* demonstrated that PCNSL have an accompanying component of demyelination that may increase following corticosteroid-induced tumor regression.[6] Indeed, pathologists should

notice the opposite situation in which demyelinating diseases mimic PCNSL both clinically and histologically, as seen in Cases 22 and 25 of the present series. In Case 25, we misdiagnosed a case of demyelinating disease as PCNSL because of prominent perivascular lymphocytes and other inflammatory cells in the frozen section without using cytological preparations (Fig. 3c). However, these lymphocytes did not show significant atypia or monoclonality in permanent sections and retrospective analysis of cytological preparations showed no LGB (Fig. 3d, Table 2). These results indicate that when abundant tissue is available, preparation of both smears and frozen sections will yield the maximum diagnostic information.

In Case 12 of the present study, initial MRI showed a right occipital lesion, but that lesion disappeared spontaneously without treatment during the 2 months after biopsy. The first histological examination included intraoperative frozen and permanent sections, which showed only nonspecific inflammation, gliosis and demyelination. However, 3 months later a newly formed tumor was found on serial MRI. Repeated histological examination confirmed this case as PCNSL.

Similarly, cases of spontaneous regression of PCNSL without steroid administration have been reported.[18-21] In such cases, histopathological findings showed nonspecific lymphocytic inflammatory changes in the first biopsy. Therefore, even in cases that cannot be diagnosed as PCNSL from histological examinations that include intraoperative rapid and postoperative definitive diagnosis, the possible influences of steroids, spontaneous regression or incorrect diagnosis of multiple sclerosis should be considered.

In summary, the present study indicated that neuroimaging provided crucial information to the pathologist, but PCNSL should be considered in cases showing diverse neuroimaging results. In addition, PCNSL are sometimes histologically indistinguishable from malignant gliomas or demyelinating diseases, particularly in the frozen sections used in IRD. However, all cases with LGB were diagnosed correctly as PCNSL using intraoperative cytology in the present study. Both intraoperative cytology and frozen sections should therefore be performed concomitantly when PCNSL are suspected.

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