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Immune Microenvironment of Primary and Recurrent Craniopharyngiomas: A Study of the Differences and Clinical Significance

Da Lin[1], Ye Wang[2], Zhongqing Zhou[2], Zhixiong Lin[1,2]

■ OBJECTIVE: **This study explored the differences between the immune microenvironments of primary and recurrent craniopharyngiomas (CPs). In addition, we investigated the relationship between the immune microenvironment and clinical characteristics of CP.**

■ METHODS: **We collected 52 specimens from 26 patients with CPs. For each patient, specimens for both primary and recurrent CPs were obtained. We performed an immunohistochemical analysis of these specimens to determine the distributions of M2 macrophages, CD8+ T cells, programmed cell death 1 ligand 1 (PD-L1), and Ki67.**

■ RESULTS: **In recurrent CP specimens, the distributions of M2 macrophages, Ki67, and PD-L1 increased compared with primary CP specimens ($P = 0.019$, $P = 0.0084$, and $P = 0.0319$, respectively). Moreover, the distributions of M2 macrophages, CD8+ T cells, and PD-L1 in papillary CPs were higher than those observed in adamantinomatous craniopharyngiomas (ACPs) ($P = 0.0317$, $P = 0.0359$, and $P < 0.0001$, respectively). In the adult ACP group, M2 macrophages, CD8+ T cells, and PD-L1 were more abundant/expressed than in the child ACP group ($P = 0.0159$, $P = 0.0215$, and $P < 0.0088$, respectively). A positive correlation was found between M2 macrophages and CD8+ T cells ($r = 0.4079$; $P = 0.0027$). Correspondingly, M2 macrophages and CD8+ T cells were both positively correlated with PD-L1 ($r = 0.4564$; $P = 0.0007$ and $r = 0.3987$; $P = 0.0034$, respectively). The observed high expression of M2 macrophages in primary CPs suggests a shortened time for tumor recurrence ($P = 0.0131$).**

■ CONCLUSIONS: **The microenvironment of recurrent CP varies from that of primary CP. The abundance of M2 macrophages in primary CP may indicate a risk of early recurrence. Therefore, it is recommended to increase the frequency of follow-up examinations in these patients.**

INTRODUCTION

Craniopharyngioma (CP) occurs mainly in the 5- to 14-year and 50- to 74-year age groups, accounting for 2% to 5% of primary intracranial tumors and more than half of saddle area tumors in children.[1,2] The histological subtypes of CP include adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP). ACP may be diagnosed in all ages, whereas PCP invariably occurs in adults and is rarely observed in children. Although CP is a benign tumor, it is adjacent to the pituitary, hypothalamus, optic nerve, and internal carotid artery. In addition, its clinical manifestations are complicated and it is associated with a high rate of relapse. Studies investigating CP involved various aspects, such as molecular pathology, cancer stem cells, patient-derived xenografts, and molecular targeted therapy.[3] Using new-generation sequencing, it was confirmed that ACP primarily carries *CTNNB1* mutations, whereas PCP mainly carries *BRAF* mutations. Use of a BRAF inhibitor achieved positive results in the treatment of PCP and it is currently under investigation in clinical trials.[4,5]

The proliferation of tumors is based on changes in its molecular biology. More recent studies also indicated that the tumor microenvironment plays a key regulatory role in the progression

Key words
- CD8+ T cell
- Craniopharyngioma
- Immune microenvironment
- Ki67
- M2 macrophages
- Programmed cell death 1 ligand 1

Abbreviations and Acronyms
ACP: Adamantinomatous craniopharyngioma
CP: Craniopharyngioma
PBS: Phosphate buffered saline
PCP: Papillary craniopharyngioma
PD-1: Programmed cell death 1
PD-L1: Programmed cell death 1 ligand 1

From the [1]Department of Neurosurgery, the First Affiliated Hospital, Fujian Medical University, Fuzhou; and [2]Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, China

To whom correspondence should be addressed: Zhixiong Lin, M.D., Ph.D. [E-mail: LIN_ZX1967@163.com]

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of intracranial malignant tumors, and that targeted therapy against the components of the microenvironment may be performed to achieve certain clinical effects.[6] Nevertheless, studies investigating the immune microenvironment of CP are currently limited. In this study, we collected specimens obtained from patients with CPs. For each patient, specimens for both primary and recurrent CPs were collected. We analyzed the distributions of M2 macrophages (main cells of tumor tissue), CD8+ T cells (immune killer cells), programmed cell death 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) (immune checkpoint), and Ki67 (proliferation marker), to understand the differences between the immune microenvironments of primary and recurrent CPs. In addition, we investigated the relationship of immune microenvironmental indicators with clinical characteristics.

MATERIALS AND METHODS

Patients

This study retrospectively analyzed a total of 52 tumor specimens of primary and recurrent CPs (26 specimens each) and clinical data of 26 patients from September 2008 to February 2017. Clinical data included demographics, clinical symptoms, imaging, surgical conditions, pathological types, and recurrence time (Table 1, Figures 1 and 2). The patients were treated only with surgical resection and did not receive other treatments such as radiation therapy or intracapsular interventions. Recurrent CP was defined by the occurrence of new clinical symptoms or follow-up findings of tumor recurrence using magnetic resonance imaging. Radical total resection was defined by the intraoperative confirmation of total resection and postoperative imaging without the presence of residual tumor. All patients provided written informed consent.

Table 1. Demographic and Baseline Disease Characteristics

Gender	
Males	21 (80.7%)
Females	5 (19.2%)
Mean age at primary CP (years)	21.4
Mean age at recurrent CP (years)	24.1
Mean recurrence time (months)	31.2
Resection degree of primary CP	
Radical resection	20 (76.9%)
Partial resection	6 (23%)
Pathological subtype*	
ACP	21 (80.7%)
PCP	5 (19.2%)

Data are n (%), unless otherwise indicated.
ACP, adamantinomatous craniopharyngioma; CP, craniopharyngioma; PCP, papillary craniopharyngioma.
*The pathological subtypes of primary and recurrent CPs were consistent.

Immunohistochemistry

The distributions of M2 macrophages, CD8+ T cells, Ki67, and PD-L1 in the specimens were analyzed through immunohistochemistry. Immunohistochemical staining was performed using streptavidin-peroxidase SP. Specimens were sliced (4 μm) after formalin fixation and paraffin embedding. The specimens were deparaffinized in xylene and dehydrated in graded alcohol. Endogenous peroxidase was inactivated using 3% H_2O_2 and the specimens were rinsed with phosphate buffered saline (PBS). Antigen retrieval was performed using citrate buffer (pH 6.0). Sheep serum was added dropwise. The specimens were incubated with a primary antibody at 4°Covernight and rinsed with PBS. Horseradish peroxidase-labeled secondary antibody was added dropwise, incubated at 37°C for 30 minutes, and rinsed with PBS. The specimens were set inside diaminobenzidine and rinsed with PBS. The film was sealed after dehydration and drying. The antibodies CD206 (ab64693, Abcam, Cambridge, United Kingdom; 1:5000), CD8 (ab4055, Abcam; 1:100), Ki67 (clone Mib1, Dako, Glostrup, Denmark; 1:100), and PD-L1 (13684, Cell Signaling Technology, Boston, USA; 1:200) were mainly used. M2 macrophages were labeled using the CD206 antibody.

Evaluation of the Specimens

The immune indicators were assessed by 2 investigators (D.L. and Y.W.) in a blinded fashion under the supervision of an experienced pathologist. For M2 macrophages and CD8+ T cells, 5 fields were randomly selected from the tumor stroma and the average value was obtained through manual counting of positive cells. Ki67-positive cells referred to tumor cells with brown-stained cell nuclei. Five fields of dense areas with Ki67-positive cells were selected, and the mean percentage of Ki67-positive cells was calculated. For PD-L1, the positivity was divided into 4 levels and the final quantitative data were obtained using scoring software (Analytical Instruments: PerkinElmer, software: Vectra2.0.8 inForm2.1.1).[7]

Statistical Analysis

Comparisons of each immune indicator in primary and recurrence CPs and between groups (after grouping) were performed using the nonparametric Mann-Whitney U test. Correlation analysis was conducted using the nonparametric Spearman test. The Kaplan-Meier analysis and log-rank test were adopted to assess the risk of the early recurrence of CP. A $P < 0.05$ denoted statistical significance.

RESULTS

Characteristics of Immune Microenvironments in Primary and Recurrent CPs

M2 macrophages were mainly found in the stroma and significantly distributed around the perivascular areas and close to tumor cells. Compared with primary CPs, the abundance of M2 macrophages in recurrent CPs was significantly increased. In contrast, the number of CD8+ T cells in recurrent CPs was not significantly different from that observed in primary CPs. Ki67-positive cells were mainly distributed in basal cells and in whorls of tumor epithelium. Moreover, concerning the expression of Ki67, the proliferation of tumor cells in recurrent CPs was more pronounced than that reported in primary CPs. Based on the comparison with

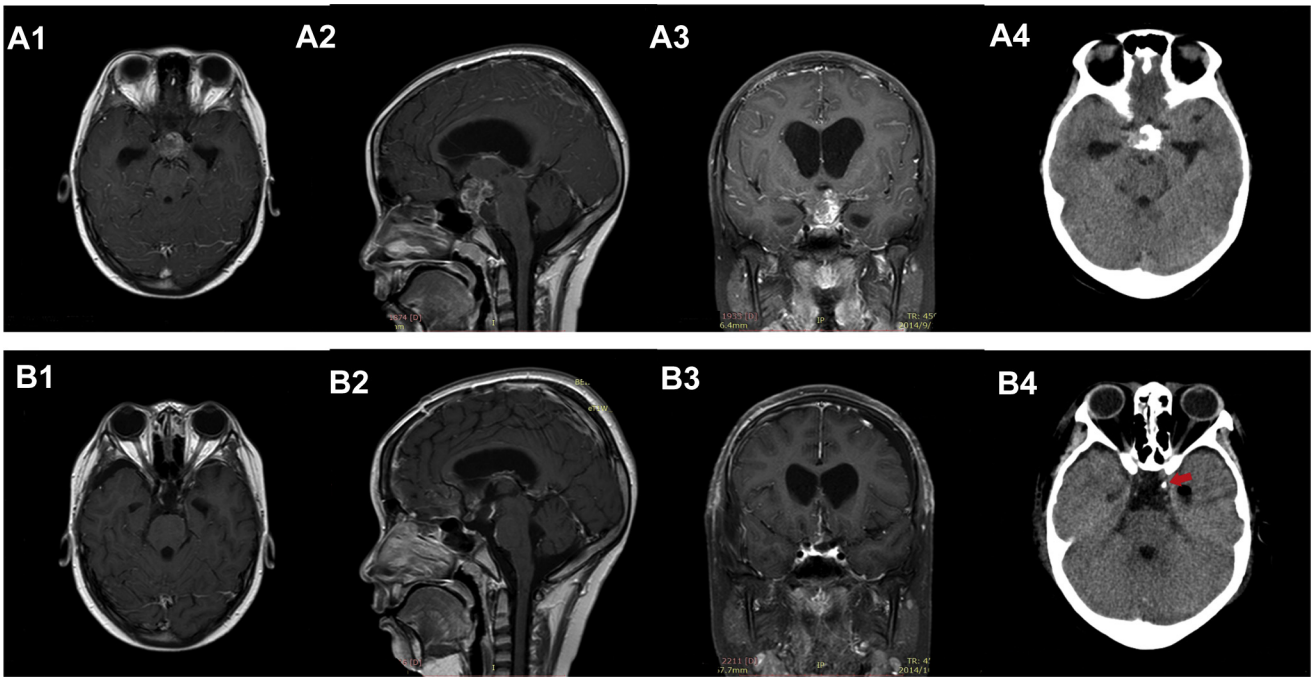

Figure 1. A 9-year-old girl presented with right-eye blurred vision lasting for 20 days. Magnetic resonance imaging revealed the presence of a cystic and solid tumor localized in the intrasellar, suprasellar, third ventricle, and pontine cistern area. The tumor slightly oppressed the brain stem and invaded the pituitary stalk, leading to obstructive hydrocephalus (**A1**–**A3**). Computed tomography showed obvious calcification (**A4**). Unifrontal basal interhemispheric approach was applied and radical resection of the tumor was achieved (**B1**–**B3**). The computed tomography high-density shadow observed in the operation area was the bone clinoid process rather than residual calcified tumor (*red arrows*) (**B4**).

positive control staining results, PD-1 did not exhibit color development during staining on lymphocytes in the tumor stroma. The staining results of PD-1 were negative in all specimens. PD-L1 was expressed only on the membrane of tumor cells and was not found in tumor-associated macrophages or immune cells. In PCPs, PD-L1 was mainly expressed in basal cells that circumferentially surrounded the fibrovascular stromal. Close proximity to the fibrovascular stromal indicated strong expression. Furthermore, continuous expression of PD-L1 was exhibited in basal cells in regions of flat epithelium. In ACPs, the expression of PD-L1 was primarily localized in the cyst-lining epithelium. PD-L1 was distributed more diffusely in PCPs than in ACPs. The expression of PD-L1 in recurrent CPs was higher than that observed in primary CPs (Table 2, Figure 3).

Correlation Between the Immune Microenvironment and Clinical Characteristics of CP

In this study, all patients were classified based on their clinical data (Table 3). In the adult group, the expressions of M2 macrophages, CD8+ T cells, and PD-L1 were higher than those observed in the child group. Notably, these expressions were higher in the PCP group than the ACP group. Considering that the age of onset for PCP is typically more than 18 years, we further divided the ACP specimens into adult and child groups based on the age of onset. We found that the expressions of the aforementioned indicators were higher in the adult ACP group than the child ACP group. There was no correlation between the indicators of the immune microenvironment and the occurrence of diabetes insipidus or intraoperative adhesion (Table 3).

Correlation Analysis of Immune Microenvironment Indicators in CP

Correlation analysis of M2 macrophages, CD8+ T cells, Ki67, and PD-L1 revealed a positive correlation between M2 macrophages and CD8+ T cells. Correspondingly, a positive correlation was found between M2 macrophages and PD-L1. Moreover, CD8+ T cells were positively correlated with PD-L1. There was no correlation between Ki67 and PD-L1 (Figure 4).

The Effects of the Immune Microenvironment of CP on the Risk of Early Recurrence

A total of 26 patients underwent primary surgery, including 20 cases of radical total resection and 6 cases of subtotal resection. For recurrent CPs, 25 patients underwent radical total resection, and 1 patient had intraoperative confirmation of total resection; however, postoperative magnetic resonance imaging re-examination of the patient revealed enhanced signals in the left ambient cistern region, which was considered as tumor residue. For patients who were primarily unable to have radical total resection, our strategy is to increase the frequency of follow-up

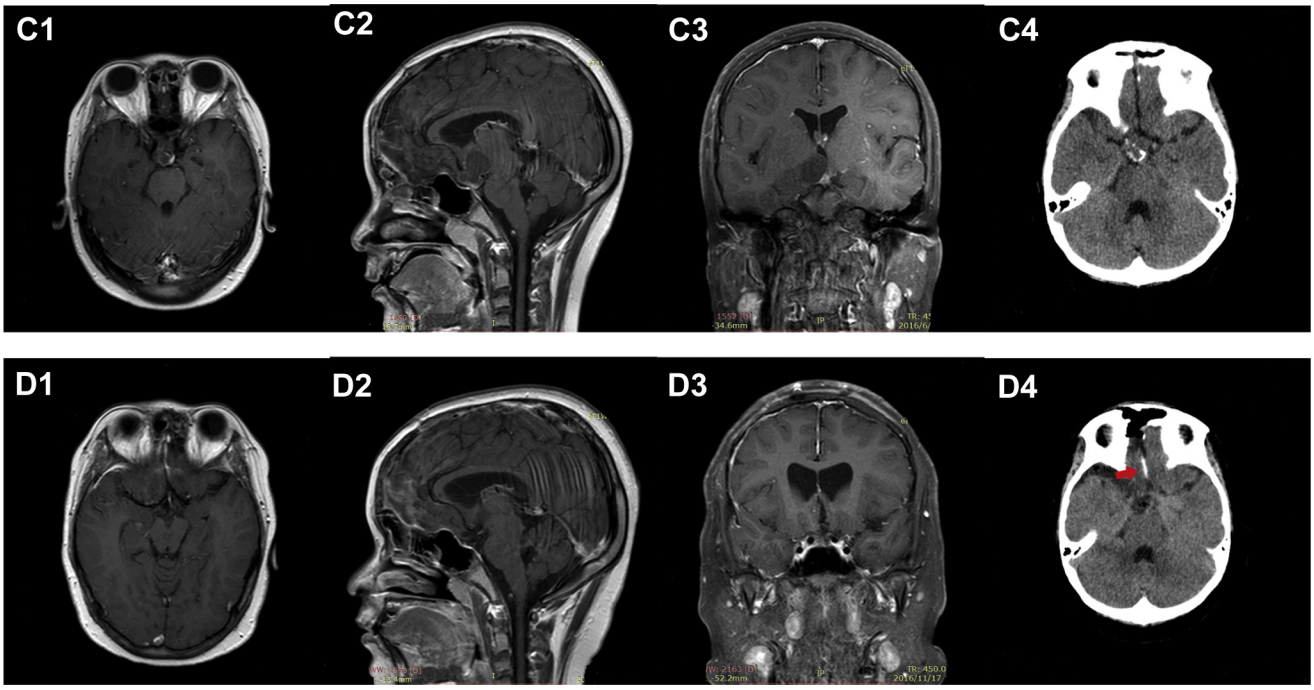

Figure 2. Follow-up magnetic resonance imaging revealed recurrence of the tumor 9 months after primary surgery. Magnetic resonance imaging showed that the lesion was mainly localized in the suprasellar. Part of the tumor invaded into the third ventricle and the obstructive hydrocephalus had disappeared (**C1**–**C3**). Calcification was found in the original location (**C4**). Magnetic resonance imaging features after radical resection of the tumor using the original surgical approach (**D1**–**D3**). The computed tomography high-density shadow observed in the longitudinal fissure was the postoperative drainage tube (*red arrows*) (**D4**).

and closely observe whether there are new clinical manifestations. Radical total resection under the premise of protecting hypothalamus function is our principle for the treatment of CP.[8]

The main causes of CP recurrence are partial resection or the presence of residual tumor.[9,10] In this study, 20 patients with primary radical resection were included to explore the effect of immune indicators on the risk of CP recurrence. Of note, 6 patients who were primarily unable to have radical excision were excluded. The medians for M2 macrophages, CD8+ T cells, Ki67, and PD-L1 (54.4, 28, 0.448%, and 51.1, respectively) in 20 primary CPs were obtained and divided into high- and low-expression groups. This study found that the high-expression group of M2 macrophages had a shorter recurrence time, suggesting a risk of early tumor recurrence (**Figure 5**).

DISCUSSION

The tumor microenvironment is composed of tumor cells, extracellular matrix components, immune cells, and the tumor vascular system. It plays an important role in tumor progression and metastasis of intracranial primary and metastatic tumors.[11] Tumor-associated macrophages are derived from monocytes in the blood, which are recruited into tumor tissues by various signals, cytokines of tumor cells, and cytokines of tumor microenvironment, polarizing into M1 and M2 types with different functions and phenotypes. Studies investigating human tumors have confirmed that M2 macrophages and their derived factors promote remodeling of the tumor stroma, tumor angiogenesis, anti-immune response, and tumor progression. Therefore, an abundance of M2 macrophage tumors is closely related to poor

Table 2. Immune Differences Between Primary and Recurrent CPs

	M2	CD8+ T	Ki67	PD-L1
PRI	9.6–117.4; 53.1*	5.4–229.2; 28	0.04–1.9; 0.44	0.06–295.9; 26.1
RECUR	14.8–217.4; 76	7–201; 26.2	0.21–2.9; 0.66	1.9–286.7; 73.8
P value	0.019	0.95	0.008	0.031

CP, craniopharyngioma; PRI, primary CP; RECUR, recurrent CP.
*Range; median.

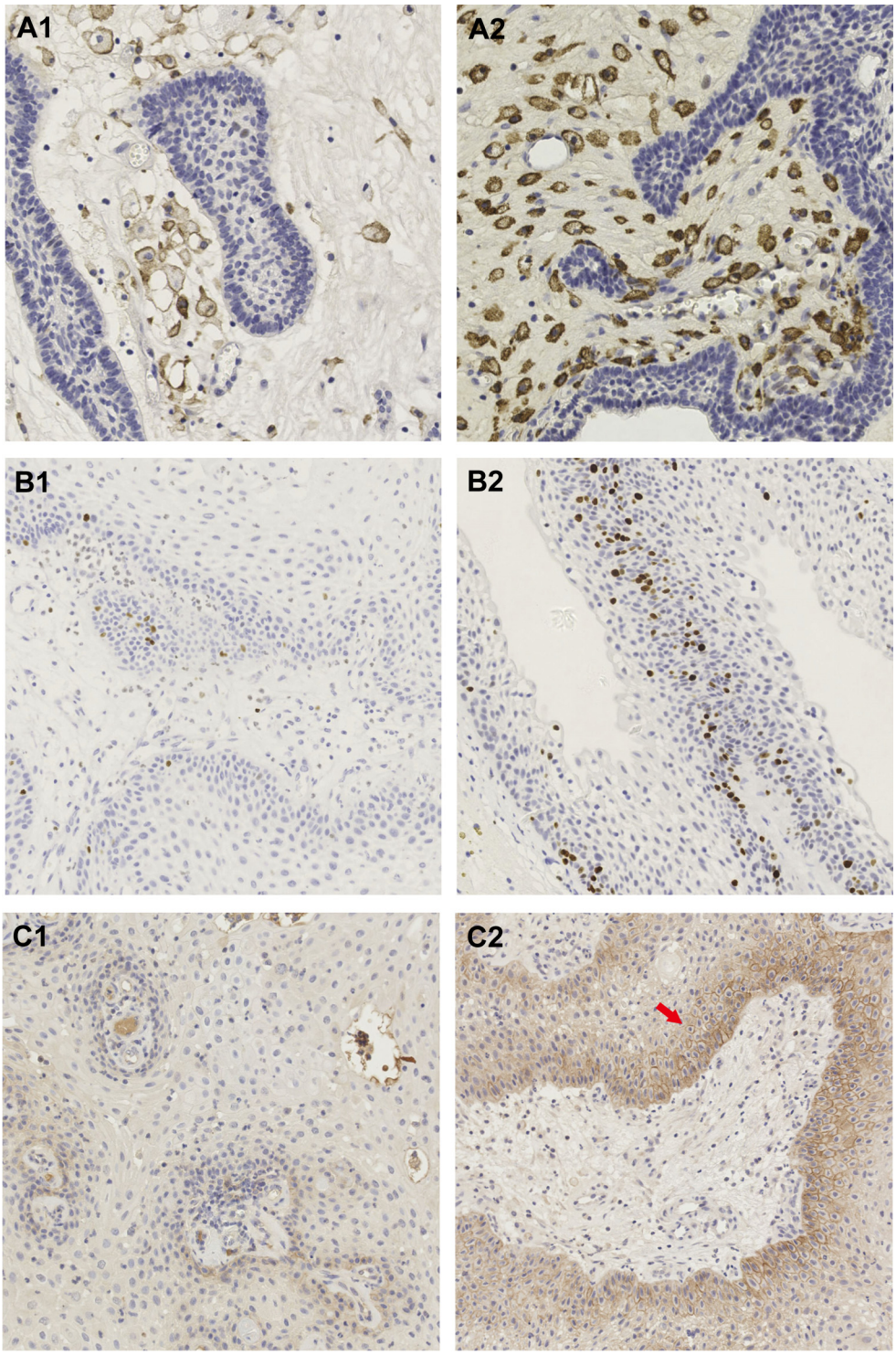

Figure 3. Comparisons of M2 macrophages (**A1, A2**), Ki67 cells (**B1, B2**), and PD-L1 (PCP **C1, C2**; ACP **D1, D2**) in primary and recurrent CPs of the same patients. In PCPs, PD-L1 was mainly expressed in basal cells that circumferentially surrounded the fibrovascular stroma. Close proximity to the fibrovascular stroma indicated strong expression (*red arrows*, **C2**). In ACPs, the expression of PD-L1 was primarily localized in cyst-lining epithelium (*red arrows*, **D2**). The staining results of PD-1 were negative in the stroma of PCP (E1), whereas the staining results of PD-1 indicated positive expression in the tonsil (positive control, brown). Scale bars: **A1**–**D2**, 100 μm; **E1**–**E2**, 250 μm. ACP, adamantinomatous craniopharyngioma; PCP, papillary craniopharyngioma; PD-L1, programmed cell death 1 ligand 1. (Continues)

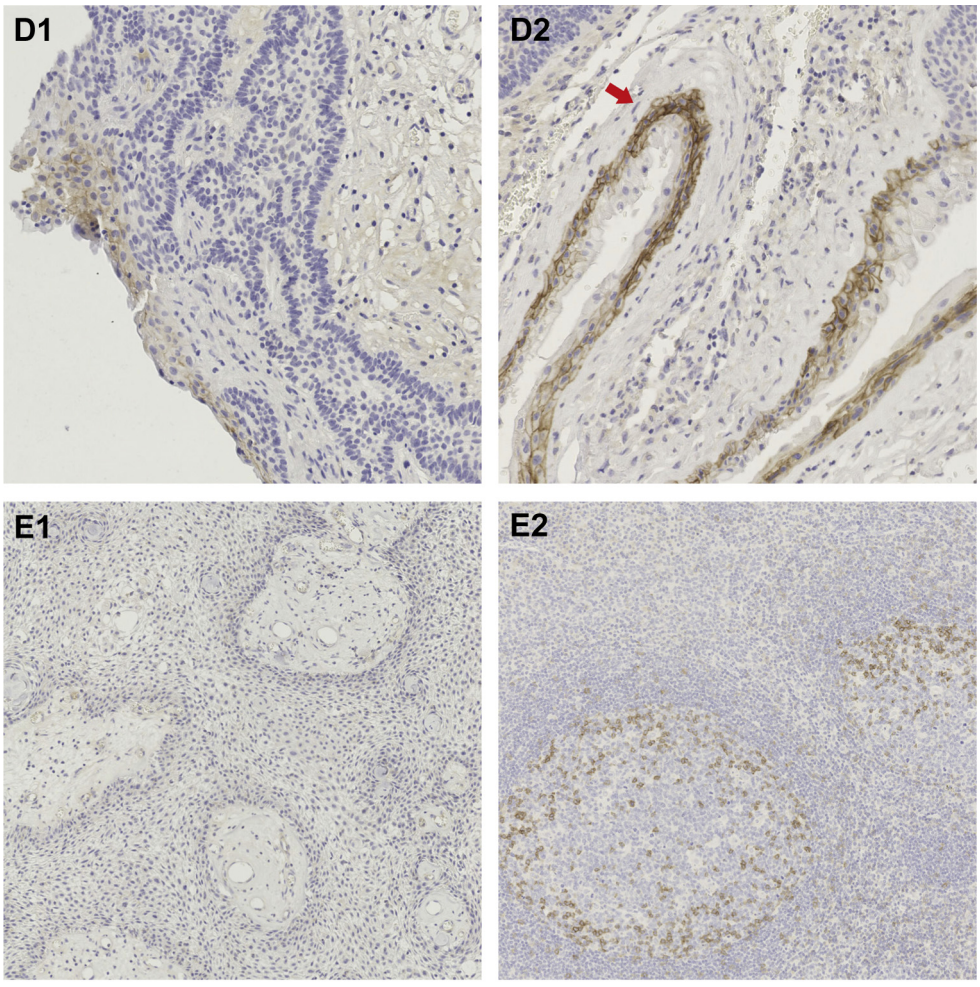

Figure 3. Continued.

prognosis.[12,13] We found an increased number of M2 macrophages in recurrent CP compared with that observed in primary CP. This finding suggests that the accumulation or polarization of M2 macrophages into tumor tissues is more obvious in recurrent CP. We conducted an analysis of the relationship between the abundance of M2 macrophages and risk of early recurrence. This analysis showed that patients with more M2 macrophages in the primary CP specimens were exposed to a higher risk of early recurrence. This further supports that M2 macrophages may constitute a risk factor for the promotion of CP recurrence. Therefore, it is recommended to increase the frequency of follow-up examinations in patients with high expression of M2 macrophages in primary CP.

The results of this study showed that the expression of PD-L1 in tumor cells of recurrent CP was higher than that reported in primary CP. Moreover, PCP exhibited higher expression of PD-L1 than ACP. In ACP, the adult group demonstrated higher expression of PD-L1 than the child group. Furthermore, in ACP, PD-L1 was mainly expressed in cyst-lining epithelial cells. The increased expression of PD-L1 may be related to the presence of a large number of inflammatory mediators in the tumor cyst fluid.[14] In non–small-cell lung cancer, activation of the epidermal growth factor receptor pathway may induce the expression of PD-L1 in tumor cells, and this expression may be elevated by type I interferon.[15] Paracrine signals of the epidermal growth factor receptor and sonic hedgehog cellular pathways were activated, leading to an increase in the expression of PD-L1 in ACP.[16] In addition, PD-L1 in tumor cells may induce apoptosis of CD8+ T cells and immune escape.[17] Moreover, the expression of PD-L1 was negatively correlated with the abundance of CD8+ T cells. Consequently, the expression of PD-L1 was shown to be closely related to the overall survival rate, linking the increased expression of PD-L1 with worse prognosis.[18] However, this finding is inconsistent with the results of the present study, in which we found that the expression of PD-L1 was positively correlated with the abundance of CD8+ T cells ($r = 0.3987$, $P = 0034$). In PCP, the abundances of CD8+ T cells and PD-L1 were significantly larger compared with ACP. This

Table 3. Factors Influencing the Immune Microenvironment of CPs

			M2	CD8+ T	Ki67 (%)	PD-L1
Clinical Characteristics	**Group**		***P* Value**			
Sex	Males	n = 42	0.8610	0.7967	0.938	0.1412
	Females	n = 10				
Adult*	Yes	n = 25	0.0031	0.0025	0.1190	<0.0001
	No	n = 27				
Adult ACP	Yes	n = 15	0.0159	0.0215	0.0609	0.0088
	No	n = 27				
Subtype	ACP	n = 42	0.0317	0.0359	0.7532	<0.0001
	PCP	n = 10				
Diabetes insipidus†	Yes	n = 20	0.0577	0.6444	0.6311	0.0811
	No	n = 32				
Adhesion‡	Yes	n = 31	0.8643	0.7150	0.9595	0.9962
	No	n = 21				
Tumor size	≤3 cm	n = 19	0.6410	0.2711	0.0575	0.9437
	>3 cm	n = 33				

ACP, adamantinomatous craniopharyngioma; CP, craniopharyngioma; PCP, papillary craniopharyngioma.
*Patients aged >18 years.
†Occurrence of diabetes insipidus before operation.
‡Intraoperative detection of tumor adhesion to peripheral structures by the surgeon.

finding does not directly support the hypothesis that PD-L1 inhibits CD8+ T cells in CP and, therefore, promotes tumor proliferation or immune escape. In addition, studies revealed that B lymphocytes play a dominant role in the immunomodulation of CP and their abundance was also greater than that reported for T lymphocytes.[16] Moreover, it was reported that PCP is associated with a lower overall recurrence rate and better prognosis versus ACP.[19] This further confirms that the degree of involvement of PD-L1 in tumor immune escape varies among different organs or tumor types.[18]

In CPs, Ki67-positive nuclei do not show a uniform distribution and Ki67 levels exhibit a wide range (0.1% to 49%).[20] The role of Ki67 in tumor recurrence and poor prognosis remains controversial. Nishi et al[21] demonstrated that Ki67 may be used as a predictor of CP recurrence, whereas a Ki67 >7% may be used as a predictive value of tumor recurrence. These predictors indicate that further radiotherapy or chemotherapy is warranted after surgery.[21] In contrast, other studies showed that Ki67 was not correlated with tumor recurrence.[22,23] We compared the expressions of Ki67 in primary and recurrent CPs in the same patient, showing higher Ki67 expression in the latter. This finding indicates that tumor proliferation in recurrent CP is more obvious than that observed in primary CP. Therefore, it is suspected that the abundance of Ki67 may increase further as the times of tumor recurrence increase. Although the Ki67 high-expression group was not associated with a risk of early recurrence in this study, we suggest that Ki67 may be taken into consideration as a factor related to the poor prognosis of CP, based on the overexpression of Ki67 in malignant transformed CP tumors.[24]

A deep understanding of the tumor microenvironment is the premise and basis for the implementation of molecular targeted therapy. In glioblastoma, targeted therapy of tumor-associated macrophage using CSF-1 inhibitors is currently being investigated in clinical trials.[25,26] Use of PD-1/PD-L1 as a therapeutic target in the treatment of melanoma, non–small-cell lung cancer, and other solid tumors has demonstrated positive response.[27-30]

The present study was conducted to examine primary and recurrent CPs in the same patients and determine the distribution of certain immune indicators in the microenvironment. The results demonstrated that the abundances/expressions of M2 macrophages, Ki67, and PD-L1 were clearly enhanced in recurrent CP, suggesting that the tumor microenvironment in recurrent CP was significantly altered compared with that observed in primary CP. Considering that these immune indicators are associated with poor prognosis, greater immune escape may occur in recurrent CP. This study provides clues for immunotherapy and targeted therapy for recurrent or refractory CP. In addition, the disappearance of the arachnoid interface and the glial reaction that occurred after primary surgery may lead to difficulties in the resection of recurrent tumors and increase the risk of damage to important nerves/vascular structures and residual tumor.[31] It is reasonable to consider that greater recurrence times may be linked to lower rates of total resection and worse prognosis. Currently, controlling the tumor volume or striving for "tumor-bearing" survival is not the optimal way to treat CP. The present

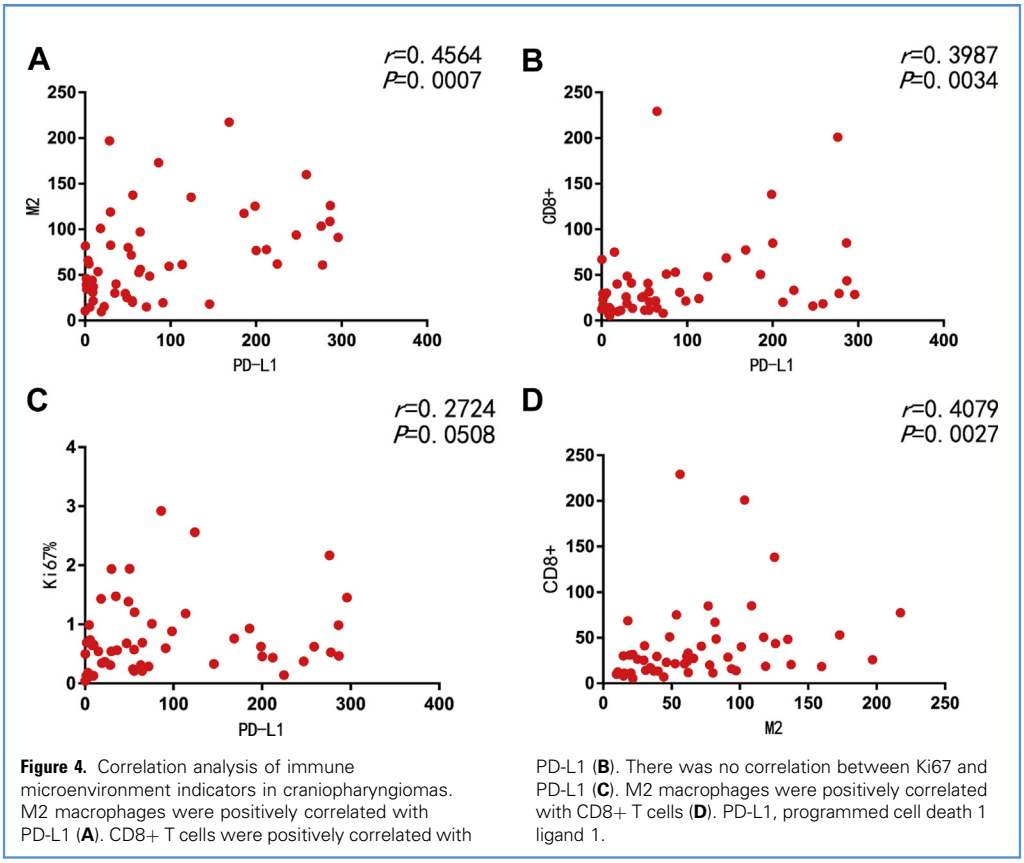

Figure 4. Correlation analysis of immune microenvironment indicators in craniopharyngiomas. M2 macrophages were positively correlated with PD-L1 (**A**). CD8+ T cells were positively correlated with PD-L1 (**B**). There was no correlation between Ki67 and PD-L1 (**C**). M2 macrophages were positively correlated with CD8+ T cells (**D**). PD-L1, programmed cell death 1 ligand 1.

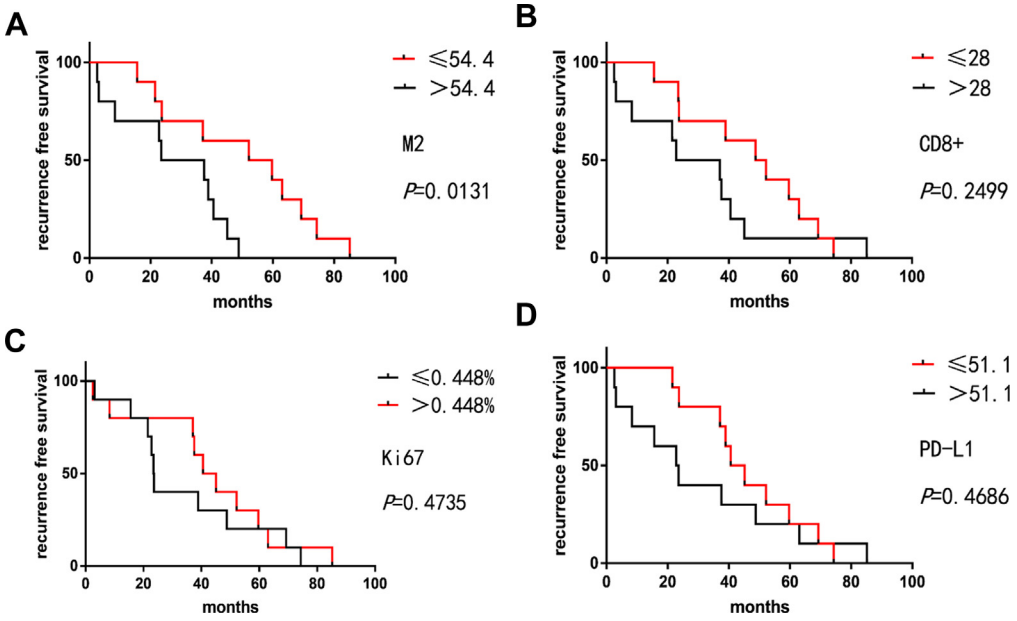

Figure 5. Effects of high or low expressions of M2 macrophage (**A**), CD8+ T cell (**B**), Ki67 (**C**), and programmed death-ligand 1 (**D**) on the risk of early recurrence of craniopharyngiomas based on the Kaplan-Meier curves analysis. PD-L1, programmed cell death 1 ligand 1.

research has certain guiding significance for the clinical treatment of this disease. We should perform radical resection of primary tumor as extensively as possible.

CONCLUSIONS

Comparisons between primary and recurrent CPs in the same patients indicated that the immune microenvironment of recurrent CPs was significantly changed. The abundance of M2 macrophages in primary CP may suggest a shortened time for tumor recurrence. Consequently, the frequency of follow-up examinations in these patients should be increased. In recurrent tumors, the microenvironment indicators with increased expressions are correlated with poor prognosis, higher chance of immune escape, and increased difficulty in surgical resection. Therefore, we should perform radical resection of primary tumors as extensively as possible.

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