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Pineal germinomas with granulomatous inflammation

Report of two cases and review of the literature

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The authors report on two cases of pineal germinomas with granulomatous inflammation (granulomatous germinomas). Macroscopically, both tumors were relatively hard and grayish in color. Histological examination revealed a germinoma with multinucleated giant cells and Schaumann bodies in one case, and a germinoma with the background of acellular fibrillated matrix in the other. On immunohistochemical analysis, the granulomatous germinomas were shown to contain many macrophages, T- and B-lymphocytes, and glial fibrillary acid protein-positive cells infiltrating the specimens, compared to nongranulomatous germinomas. Analysis of Masson's trichrome staining tests showed that large areas of the granulomatous germinomas were occupied by a collagenous component; this was not the case in cases of nongranulomatous germinomas. Analysis of monoclonal anti-human Ki-67 results showed that the granulomatous germinomas had a lower score than nongranulomatous germinomas ($p < 0.05$, unpaired t-test), indicating that germinomas with granulomatous inflammation may have a better prognosis.

Key Words * cerebral germinoma * granulomatous inflammation * MIB-1

The incidence of cerebral germinomas accounts for 2.3% of all brain tumors in Japan.[4] Histologically, they exhibit a characteristic two-cell pattern consisting of large neoplastic cells and small lymphoid cells. In addition to lymphocytic infiltration, there is occasionally granulomatous inflammation. Gonadal germinomas are known to have a relatively high incidence of granulomatous inflammation,[13,16] whereas cerebral germinomas with granulomatous inflammation are rare. To our knowledge, only 14 cerebral germinomas with granulomatous inflammation have been reported.[1,3,7,9,10,12,14] Examination of biopsy samples obtained using stereotactic methods led to an erroneous diagnosis of granuloma or gliosis in some of the cases.[3,10,12,14] We present two patients with cerebral germinomas with granulomatous inflammation (granulomatous germinomas), and we further discuss their prognosis based on cell proliferation index, monoclonal anti-human Ki-67 (MIB-1).

CASE REPORTS

Case 1

This 15-year-old boy sustained an eye injury during a handball game. A plain computerized tomography (CT) scan showed a slightly high density mass with calcification in the pineal region. Magnetic resonance (MR) imaging revealed a tumor mass with cystic lesions (Fig. 1 left). The tumor displayed homogeneous enhancement on CT and MR imaging after addition of contrast medium. The results of laboratory examinations showed no alpha-fetoprotein or human chorionic gonadotropin-beta in the serum. The mass spontaneously regressed during a 3-month follow-up period. The patient did not receive radiation therapy nor chemotherapy before surgical treatment. A biopsy sample of the mass was obtained via the occipital-transtentorial approach. It was relatively hard and grayish in color; on histological examination, it was identified as a germinoma with granulomatous inflammation.

Fig. 1. Left: Gadolinium-enhanced MR image showing a tumor mass with cystic lesions in the pineal area, producing ventricular dilation (Case 1). Right: Gadolinium-enhanced MR image revealing a tumor mass with good enhancement at the rim, producing ventricular dilation (Case 2).

Case 2

This 15-year-old boy experienced a seizure and increased intracranial hypertension. A plain CT scan showed a slightly high density mass with calcification in the pineal region. The mass enhanced at the rim on contrast-enhanced MR imaging (Fig. 1 right). The results of laboratory tests showed no alpha-fetoprotein or human chorionic gonadotropin-beta in the serum. A biopsy sample of the mass was obtained via the occipital-transtentorial approach and showed only fibrous tissue. It was subsequently totally removed because teratoma or mixed germ cell tumor was suspected. The tumor was relatively hard and grayish in color; on histological examination, it was identified as germinoma with granulomatous inflammation.

Description of Histopathological Studies

We examined 10% formalin-fixed and paraffin-embedded thin sections (4 μm) from the surgical specimens. For immunocytochemical study, monoclonal anti-human macrophage antibody (1:50) (Dako, Copenhagen, Denmark), monoclonal anti-human T-lymphocyte subset (1:40) (Bio-Science Product, Emmenbrücke, Switzerland), monoclonal anti-human B-lymphocyte subset (1:40) (Bio-Science Product), polyclonal anti-cow glial fibrillary acidic protein ([GFAP] 1:500) (Dako), polyclonal anti-human placental alkaline phosphatase ([PALP] 1:200) (Biomedica Corp., Foster, CA), and

monoclonal anti-human Ki-67 ([MIB-1] 1:50) (Immunotech, Marseille, France) were used. The avidin-biotin complex procedure was used to detect the immunoreactive products. Masson's trichrome staining was used to detect the collagenous component in the specimens. Eight other germinomas without granulomatous inflammation (nongranulomatous germinomas) represented the controls. To evaluate the immunostaining results, the staining patterns were classified into four groups, depending on the relative ratio of the immunoreactive cells: ++ indicated many; + an intermediate number; +- a few; and - no immunoreactive cells were present. To evaluate the collagenous component in the specimens, Masson's trichrome staining patterns were classified into three groups depending on the ratio of the collagenous component: ++ indicated more than 50%; + 10 to 50%; and +- indicated less than 10% of the tumor was composed of a collagenous component.

TABLE 1								
SUMMARY OF RESULTS OF HISTOPATHOLOGICAL ANALYSES*								
Case No.	Age (yrs), Sex	Immunocytochemical Study						MIB-1 (%)†
		CD-68	MT-1	MB-1	GFAP	PALP	Col-lagen	
1	15, M	++	++	++	++	+	++	28.0
2‡	15, M	++	++	++	++	+	++	25.4
3	10, M	+-	++	+	+	+	+-	62.5
4	16, F	+	++	-	+	+	+-	48.6
5	20, F	-	+	+	-	+	+-	30.2
6	16, F	-	+	+-	+-	+	+-	51.7
7	16, M	++	++	+-	+-	+-	+-	46.7
8	17, F	-	++	+	++	+-	+-	44.0
9	39, M	-	++	-	+	+	+-	30.9
10	16, M	++	++	+	++	+	+-	55.0
* See Clinical Material and Methods section for explanation of positivity ratings. Abbreviations: CD-68 = monoclonal anti-human macrophage antibody; MB-1 = monoclonal anti-human B lymphocyte; MT-1 = monoclonal anti-human T lymphocyte. † There was a statistically significant difference between patients with granulomatous (Case 1 and 2) and nongranulomatous (Cases 3–10) germinoma; p < 0.05. Unpaired t-test. ‡ Case 2 showed giant cells and Schaumann body on immunocytochemical analysis.								

RESULTS

The results of our histopathological studies of two granulomatous and eight nongranulomatous germinomas are summarized in Table 1. Routine hematoxylin and eosin study showed that in Case 1, there was a relatively marked acellular fibrillated matrix (Fig. 2 upper left); in Case 2, many multinucleated giant cells were observed (Fig. 2 upper right). The cytoplasm of the giant cells contained shell-like materials, the so-called Schaumann bodies (Fig. 2 lower).

Fig. 2. Photomicrographs. Upper: The two-cell pattern is seen in the background of a relatively large area of the acellular fibrillated matrix (Case 1). H&E, original magnification X 100. Lower Left: Numerous multinucleated giant cells are seen in addition to the two-cell pattern (Case 2). H&E, original magnification X 100. Lower Right: The cytoplasm of the giant cells contains shell-like material, the so-called Schaumann bodies (Case 2). H&E, original magnification X 400.

Both granulomatous germinomas were infiltrated by many macrophages (Fig. 3 upper). Among the eight nongranulomatous (control) germinomas, only two exhibited infiltration by a high number of macrophages, whereas the other six were infiltrated by an intermediate number or no macrophages. To assess lymphocyte infiltration we examined T and B subsets by using antibodies. Both granulomatous germinomas showed evidence of infiltration by not only T-lymphocyte (Fig. 3 lower left) but also B-lymphocyte subsets (Fig. 3 lower right).

Fig. 3. Photomicrographs showing the results of immunohistochemical studies. Upper: Infiltration of many macrophages (CD68-positive cells) into the granulomatous germinomas. Original magnification X 400. Lower Left and Right: Not only many T-lymphocyte (left), but also B-lymphocyte subsets (right) have infiltrated the granulomatous germinomas. Original magnification X 200.

In four of the eight nongranulomatous germinomas, not only T- but also B-lymphocyte subsets were infiltrated. However, the ratio of B-lymphocyte subsets was smaller than that of T-lymphocyte subsets. The other four cases showed few or no B-lymphocyte subsets, although there was pronounced infiltration by T-lymphocyte subsets. Both granulomatous germinomas showed high infiltration by GFAP-positive cells (Fig. 4 left). Among the nongranulomatous germinomas, two showed many, three an intermediate number, and the remaining three showed few or no GFAP-positive cells. There was no significant difference in the number of PALP-positive cells between the granulomatous and nongranulomatous germinomas (Fig. 4 right).

Fig. 4. Photomicrographs showing the results of immunohistochemical studies. Left: Many GFAP-positive cells have infiltrated the granulomatous germinoma. Right: The

PALP-positive cells are seen in a granulomatous germinoma, showing a membranous staining pattern. Original magnification X 200.

The membranous PALP staining pattern was characteristic. Masson's trichrome staining showed that more than 50% of both granulomatous germinomas consisted of a collagenous area (Fig. 5 left). All eight nongranulomatous germinomas contained less than 10% collagenous area (Fig. 5 right).

Fig. 5. Photomicrographs. More than 50% of the granulomatous germinoma consists of a collagenous area (blue) (left). Less than 10% of the total area is collagenous in the nongranulomatous germinomas (right). Masson's trichrome staining, original magnification X 100.

Staining with MIB-1 (Ki-67) revealed that the granulomatous germinomas contained a low percentage of MIB-1-positive cells. The average score for the granulomatous germinomas was 26.7% (Fig. 6 left). In contrast, the average score for the nongranulomatous germinomas was 46.2% (Fig. 6 right); this difference was statistically significant by unpaired t-test ($p < 0.05$).

Fig. 6. Photomicrographs. A low percentage of MIB-1-positive cells is seen in the granulomatous germinomas (left), whereas a high percentage of MIB-1-positive cells is seen in the nongranulomatous germinomas (right). MIB-1 staining, original magnification X 200. There is statistical difference between the two groups ($p < 0.05$, unpaired t-test).

The follow-up period for the two patients with granulomatous germinomas and the eight patients with nongranulomatous germinomas ranged from 3 to 60 months; all patients were responsive to chemotherapy and radiation therapy. There was no statistical difference in the survival times between these two groups (Table 2).

Case No.	Diagnosis	Tumor Location	Treatment	Recurrence	Survival (mos)
1	germinoma	pineal	chem & rad	no	11
2	germinoma	pineal	chem & rad	no	13
3	germinoma	pineal	chem	no	13
4	germinoma + STGC	corpus callosum	chem & rad	no	10
5	germinoma	suprasellar	chem & rad	no	24
6	germinoma	suprasellar	rad & chem	no	38
7	germinoma	suprasellar + pineal	rad & chem	yes	64
8	germinoma	suprasellar	rad & chem	no	45
9	germinoma	suprasellar	rad & chem	no	46
10	germinoma	basal ganglia	chem	no	7

* Alpha-feto protein and human chorionic gonadotropin-beta results were negative for all cases. Abbreviations: chem = chemotherapy, rad = radiation therapy, STGC = syncytiotrophoblastic giant cell.

DISCUSSION

In 1947, Friedman[7] first reported a patient with germinoma with granulomatous inflammation in the pineal region.[5] Since then, only 13 other cases of cerebral germinoma with granulomatous inflammation have been reported (Table 3).[1,3,7,9,10,12,14] In gonadal germinomas, granulomatous inflammation is relatively frequent (20%),[13,16] whereas in intracranial germinomas it appears to be rare.[15] The incidence of granulomatous inflammation in cerebral germinomas was examined in two large series: in one of these series,[7] one (4.3%) of 23 cases with intracranial germinoma manifested granulomatous inflammation; in the other series,[1] this was the case in two (4.7%) of 43 cases.

Authors & Year	Age (yrs), Sex	Duration	Symptom	Site	Surgery	Misdiagnosed
Friedman, 1947	—	—	—	—	—	no
Kasper, et al., 1983	22, M	—	polyuria headache	suprasellar	open	yes
Bjornsson, et al., 1985	—	—	—	—	—	no
Kraichoke, et al., 1988	19, M	2 wks	headache visual defect	pineal	stereotactic	yes
	28, M	3 wks	headache visual defect	pineal	stereotactic	yes
	22, M	1 mo	headache visual defect	pineal	stereotactic	yes
	17, M	1 yr	headache visual defect	thalamus	stereotactic	yes
Chandrasoma, et al., 1989	—	—	—	—	—	yes
Okuno, et al., 1992	20, M	2 mos	hemiparesis	corona radiata	open	yes
Gotoda, et al., 1996	21, M	5 yrs	visual defect	suprasellar	open	no
	21, M	2 yrs	visual defect	suprasellar	open	no
	14, M	3 wks	convulsion	temporal lobe	open	no
	16, F	4 yrs	visual defect	suprasellar	open	no
Current report						
Case 1	15, M	5 mos	seizure	pineal	open	no
Case 2	15, M	—	incidental	pineal	open	no

* — = not described.

Germinoma with granulomatous inflammation may be difficult to diagnose: seven such cases have been reported. Kraichoke, et al.,[12] reported that four pineal germinomas with granulomatous inflammation were misdiagnosed as being gliosis or granuloma on first examination of a biopsy sample. Chandrasoma, et al.,[3] documented a case in which the initial misdiagnosis by stereotactic biopsy sample resulted in 1-year delay in correctly diagnosing granulomatous germinoma and thus delayed treatment. Okuno, et al.,[14] also reported a case of intracerebral germinoma with granulomatous inflammation that was misdiagnosed as being a granuloma because of fungal infection at the first craniotomy. Recently, Gotoda, et al.,[9] reported identification of four cases of cerebral germinomas with granulomatous inflammation by using immunohistochemical methods.

We compared our histochemical and immunohistochemical findings in two pineal germinomas with granulomatous inflammation (granulomatous germinomas) with eight nongranulomatous cerebral germinomas. Macroscopically, the granulomatous germinomas were different in color and texture from nongranulomatous tumors: the former were grayish and hard. Microscopically, routine hematoxylin and eosin staining showed that in our Case 1 there was a relatively marked acellular fibrillated matrix; in Case 2 we noted many multinucleated giant cells, and most of these giant cells contained a shell-like material, the so-called Schaumann bodies, which are often seen in sarcoid granuloma.[11,17] Immunohistochemically, the granulomatous germinomas tended to exhibit many macrophages, T and B lymphocytes, and infiltration by GFAP-positive cells; the latter cells are thought to be reactive astrocytes. The most striking difference between granulomatous and nongranulomatous germinomas was related to collagen component, which was histochemically determined by Masson's trichrome staining. In the former, more than 50% of the tumor was composed of this collagenous component, whereas only small portions of the nongranulomatous germinomas exhibited a collagenous component. Another difference in the two types of germinomas was related to MIB-1 positivity, which is an accepted marker of cell proliferation and a good prognostic indicator.[2,5,8] There have been no reports of MIB-1 positivity in granulomatous germinomas, especially regarding its difference between these two groups. In our study, the MIB-1 score for granulomatous germinomas was 26.7%, for the nongranulomatous germinomas it was 46.2%, and the difference was statistically significant ($p < 0.05$, unpaired t-test). Clinically, the tumors in both patient groups were very sensitive to chemo- and radiation therapy, and there was no statistical difference in clinical outcome, although the follow-up periods (3 months-5 years) were relatively short. In Case 7 (Table 3), whose MIB-1 score was 46.7%, there was tumor recurrence during the 5-year follow-up period. In testis, seminomas with a lymphoid-granulomatous stromal response were associated with a good prognosis.[6] Based on our MIB-1 study, we suggest that the granulomatous germinomas in brains may grow more slowly than the other tumors. Yamashiro, et al.,[18] transplanted malignant fibrous histiocytoma transfected with monocyte chemoattractant protein-1 into rats and found that the degree of monocyte-macrophage infiltration into the tumor areas paralleled the biologically slow growth of the tumor. We posit that granulomatous inflammation may affect tumor growth, and we will continue to study cerebral germinomas to test this hypothesis.

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