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Case report

Malignant transformation of diffuse infiltrating glial neoplasm after prolonged stable period initially discovered with hypothalamic hamartoma

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ABSTRACT

We present a case of malignant transformation of diffuse infiltrating glial neoplasm after a prolonged stable period on magnetic resonance imaging (MRI) and spectroscopy (MRS) initially discovered with a hypothalamic hamartoma. Although MRI and MRS suggest the possibility of malignant transformation in future, they cannot precisely predict the timing of rapid growth.

1. Introduction

Diffuse astrocytoma is characterized by a high degree of cellular differentiation and slow growth corresponds to WHO grade II which may be located in any region of central nervous system including the region of junction of the three cerebral lobes. Gliomatosis cerebri (GC) is a rare, diffusely infiltrating glial neoplasm with little mass effect that is usually associated with a poor prognosis [1]. Hypothalamic hamartoma (HH) is a benign congenital malformation of the brain containing heterotopic nervous tissue. Magnetic resonance imaging (MRI) of HH reveals a sessile hypothalamic mass suspended from the floor of the third ventricle, isointense in T1-weighted images (T1WI) and iso or hyperintense in T2-weighted images (T2WI) to gray matter [2].

Here we present a case of an intra-axial diffuse infiltrating glial neoplasm whose MR spectroscopy (MRS) appearance was consistent with a GC but revealed a prolonged stable or slow growing course followed by sudden symptomatic development of a high grade glioma combined with an HH compatible mass.

This study was performed with the approval of the institutional ethics committee of our university, and after informed consent was obtained from the patient.

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2. Case report

An 8-year-old male patient without any history of remarkable neurological disorders from birth was evaluated at a pediatric endocrinology department because of signs of precocious puberty (enlarged penis and muscular build). His family history was not contributory. MRI revealed a hypothalamic mass involving the mammillary body and showing isointensity in all the MR pulse sequence images that was diagnosed as hypothalamic hamartoma. Simultaneously, an abnormal signal lesion showing homogeneous hyperintensity on fluid attenuated inversion recovery (FLAIR) images, and T2WI, and hypointensity on T1WI with no contrast enhancement was noted to spread in the right temporal, parietal and occipital lobes. Although GC or a diffuse astrocytoma accompanying HH

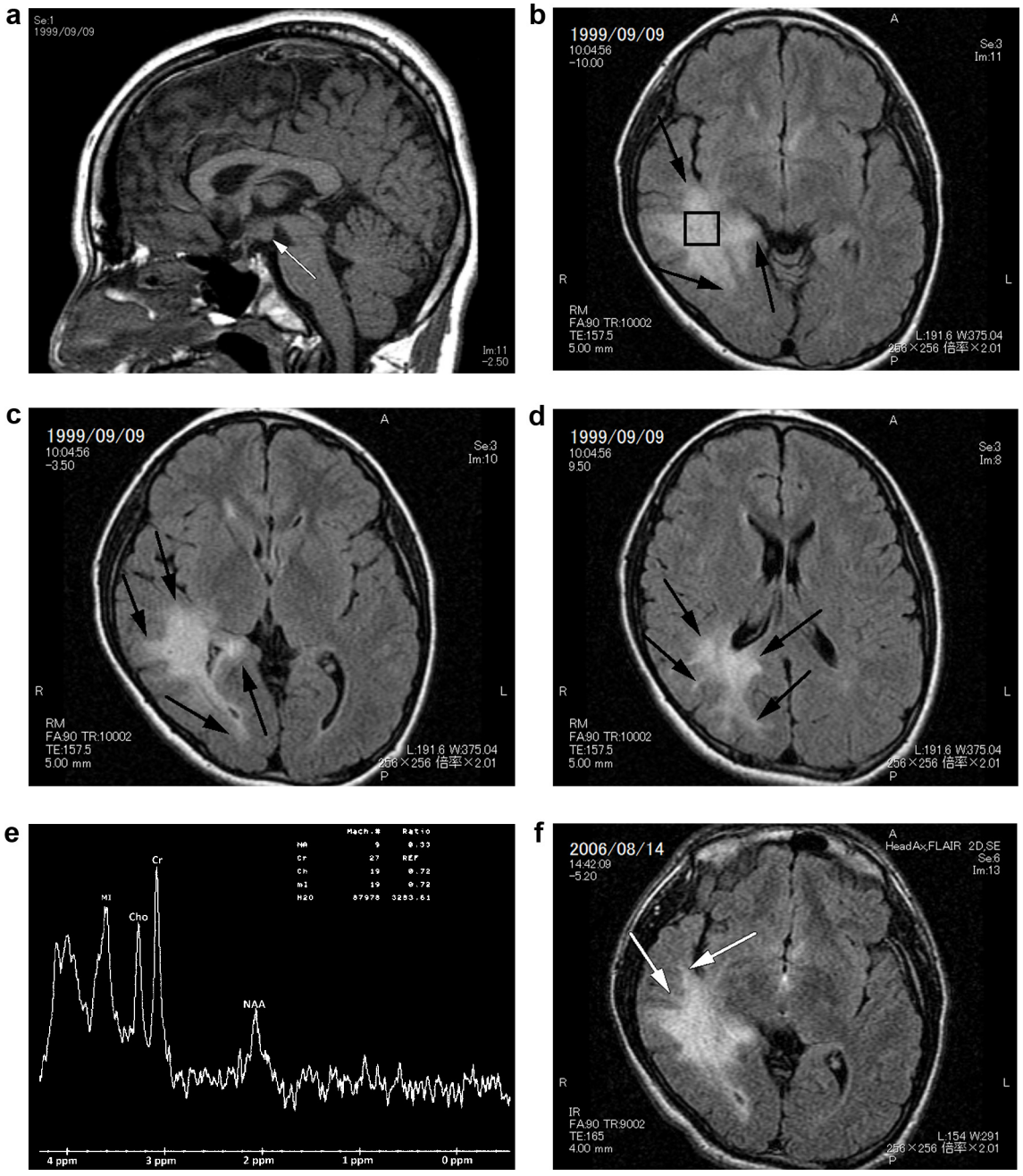

Fig. 1 – Magnetic resonance imaging and spectroscopy (MRS) examined at ages 15 and 21 years. (a). Sagittal T1 weighted image shows a sessile isointense hypothalamic mass with gray matter that was suspended from the floor of the third ventricle (arrow). (b)–(d). Axial fluid attenuated inversion recovery (FLAIR) images show extensive white matter hyperintensity of the right temporal, parietal and occipital lobes surrounding the trigon and posterior horn of right lateral ventricle (black arrows). Voxel indicates sampling area of MRS. (e). MRS reveals reduction of N-acetylaspartate, and elevation of myoinositol without choline elevation. (f). Axial FLAIR image examined when the patient was 21 years reveals anterior extension of the hyperintensity (arrows).

Table 1 – Time course of MR spectroscopic ratio.

Age	NAA/Cr	Cho/Cr	MI/Cr
11	0.38	0.76	0.66
13	0.30	0.79	0.53
15	0.33	0.72	0.72
17	0.48	0.73	0.69
19	0.41	0.71	0.64
21	0.34	0.77	0.61

NAA indicates N-acetylaspartate; Cr, creatine; Cho, choline; MI, myoinositol.

was suggested by these MRI findings, brain biopsy was refused by his parents. The precocious puberty was well treated by hormone therapy. Annual MRI examinations were started as follow up. When he was 11 years, MRS was first performed at the same time as the MRI examination. From this time to age 21 years, annual MRI and biannual MRS were performed. The digital data of the MRI performed from age 8 to 14 years were lost but image interpretation reports revealed no particular change during this follow-up period. MRI and MRS at age 15 years are shown in Fig. 1(a)–(e).

MRI and MRS were performed using a 1.5T scanner [SIGNA; General Electric (GE) Healthcare, Milwaukee, WI, USA]. Automated single voxel MRS examination was performed with the following parameters, 1500/35/128 (repetition time/echo time/number of excitations), obtained from voxels located within the FLAIR hyperintensity region at almost the same voxel position as in the previous measurements. MRS showed 4 major peak resonances at 2.02, 3.03, 3.22, and 3.56 ppm, which corresponded to N-acetylaspartate (NAA), creatine (Cr), choline (Cho), and myoinositol (MI), respectively. Normal NAA/Cr, Cho/Cr, and MI/Cr ratios of teenagers in our institution are 1.68 ± 0.11, 0.79 ± 0.09, and 0.55 ± 0.13, respectively. Automatically calculated peak ratios correlated with Cr were demonstrated in Table 1.

Although the hypothalamic mass showed no marked change during the follow up period, the right hemispheric FLAIR hyperintensity revealed slight anterior extension (Fig. 1 (f)). We considered that the slice angle of MRI was not

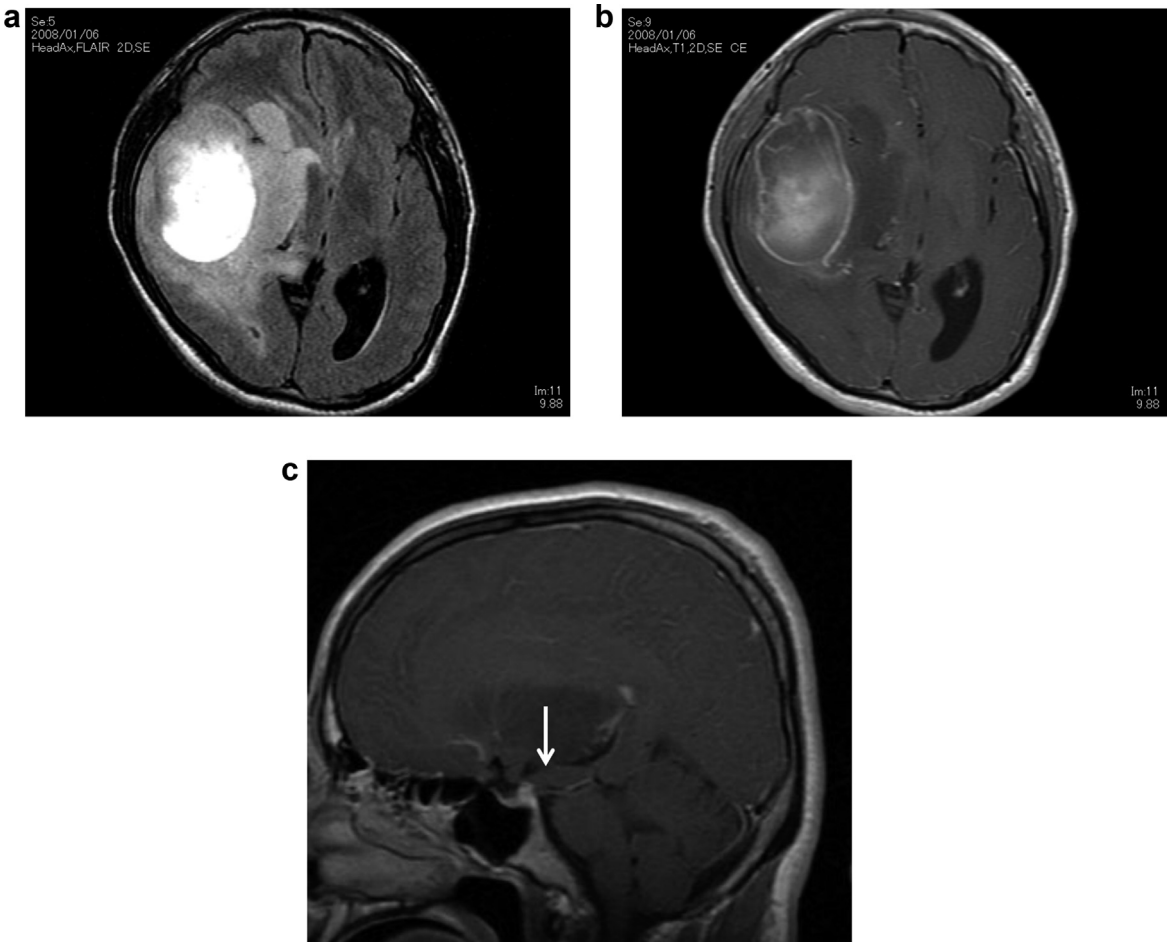

Fig. 2 – Magnetic resonance imaging at 23 years that is 15 months after the findings shown in Fig. 1(f), when the patient was emergently transferred to our hospital. (a). Axial fluid attenuated inversion recovery image reveals a right temporal markedly hyperintense mass surrounded by a homogeneously hyperintense area. (b). Post-contrast enhanced T1 weighted image showed a ring enhanced mass surrounded by a hypointense area. (c). Post-contrast enhanced T1 weighted sagittal image revealed a non-enhanced and markedly deformed mass deviating to the left (c, arrow). This is the same lesion as that originally characterized as sessile, isointense, and hypothalamic with gray matter suspended from the floor of the third ventricle (Fig. 1(a)).

completely the same as that of the previous imaging study, thereby possibly inducing pseudo-extension. The MRS appearance with slightly increased MI/Cr, no definite Cho/Cr increase or NAA/Cr decrease was almost stable from age 11 to 21 years (Fig. 1(e)) (Table 1). No neurological symptoms appeared during the follow-up period.

His follow-up MRI examination at 22 years was canceled at the patient's request. Fifteen months after the time when the findings shown in Fig. 1(f), he suddenly complained of a severe headache and was transferred on an emergency basis to our hospital. MRI revealed a markedly FLAIR hyperintense lesion within a ring enhanced mass surrounded by a homogeneous FLAIR hyperintensity area with midline shift (Fig. 2(a) and (b)). Although the hypothalamic mass showed marked deformity no definite enhancement or volume progression was evident (Fig. 2(c)). Emergent surgery was performed. A hemorrhagic fluid containing mass was resected to the extent possible.

Histopathologically, nuclear atypia, increased cellularity, cellular pleomorphism, microvascular proliferation, and necrosis were seen in a hemorrhagic cyst wall. Mitotic features were evident. Ki 67 MIB-1 labeling index was 34%. High grade (WHO grade III or IV) glioma was evident. Diffuse infiltration of well differentiated neoplastic astrocytes but with moderately increased cellularity corresponding to WHO grade II was seen at the area showing homogeneous FLAIR hyperintensity surrounding the high grade glial neoplasm. A histopathological specimen of the hypothalamic mass was not obtained.

3. Discussion

GC considered in the classical sense is defined as a diffuse glioma growth consisting of exceptionally extensive infiltration of a large region on the central nervous system, with involvement of at least three cerebral lobes, usually with bilateral involvement of the cerebral hemispheres. GC considered in the strict sense would exclude diffuse gliomas in the region of junction of the three cerebral lobes but are relatively localized, so in the strict sense our case may be considered as diffuse astrocytoma on imaging findings. But the reported MRS appearance of GC was similar to that of our case, namely increased MI peak with NAA decrease with or without Cho elevation [3,4]. Castillo et al. reported that histological down-grading of glioma results in an increase of MI [5]. And Galanaud et al. found that MRS can differentiate GC from low-grade glioma by the combination of the peak heights of NAA, Cr, Cho, and MI [6].

Determination of the precise histological grade of GC is difficult. When biopsies are taken from contrast-enhancing areas, they show histological features of anaplasia corresponding to WHO grade III or IV, whereas when taken from non-contrast lesions they may show a diffuse pathology with a low density of infiltrating neoplastic cells and no mitotic activity corresponding to WHO grade II. The natural course of GC is considered progressive and is usually associated with a poor outcome [1]. The imaging findings of GC are similarly progressive and usually parallel the progression of the clinical symptoms. MRS was reported as a useful modality to estimate the length of survival in cases with GC depending on the degree of Cho elevation [7]. In our case, the MRS measured biannually between the ages of 11 and 21 years showed no definite elevation of Cho/Cr, with this finding thought useful in predicting the stability of the MRI findings observed. We considered that it would be difficult to detect the spatial difference of tissue metabolites without using multivoxel MRS, but even multivoxel MRS has occasionally shown a normal spectrum at 6 months before malignant transformation [8].

Although an association of HH with other congenital abnormalities has been noted, the combination with glial neoplasm has yet to be reported to the best of our knowledge. A hypothalamic astrocytoma which followed as HH that showed no significant change from age 8–17 years has been reported [9]. In our case, because histological proof of a HH like lesion had not been obtained, the possibility of multicentric glioma with little mass progression in the hypothalamic mass remained. Elucidation of the histopathological and/or genetic relation with the right hemispheric signal abnormality and HH like lesion might have been possible if an intensive histopathological investigation had been performed at the time of the initial detection, but it was not, precluding any intensive investigation of the right hemispheric lesion and HH like lesion at this time. And clinically, we think that it would need an impossible frequency of care to detect his right hemispheric mass in a curable stage.

4. Conclusion

In conclusion, we report a rare case of rapid maliganant transformation of GC or diffuse astrocytoma after a prolonged stable period initially discovered with HH. It is still difficult to make a conclusive histopathological diagnosis of a pre-existing abnormal MRI and MRS region even after histological evaluation of a surgical specimen of a subsequently occurring glioma.

Conflict of interest

The authors declare that they have no conflict of interest.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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