Received: 05.09.2011 / **Accepted:** 07.10.2011
DOI: 10.5137/1019-5149.JTN.5198-11.1

Case Report

A Case of Adult Onset Medulloblastoma During Maintenance Chemotherapy for Anaplastic Astrocytoma One Year After Radiotherapy

Anaplastik Astrositom için Radyoterapiden Bir Yıl Sonra İdame Kemoterapisi Sırasında Yetişkin Başlangıçlı Medülloblastom Vakası

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ABSTRACT

Multiple primitive intracranial tumors with different histological characteristics are uncommon. Although coexistence of a medulloblastoma with glial tumors has been reported in children, medulloblastoma is rarely found in adults, especially those older than 40 years of age. We present an extremely rare case of a medulloblastoma developing in a 40-year-old male undergoing maintenance chemotherapy for anaplastic astrocytoma for 21 months after radiotherapy. Initially, he complained of intractable epilepsy characterized by complex partial seizures. Magnetic resonance imaging (MRI) revealed a slightly enhanced mass lesion in the left insula region. He underwent subtotal removal of the tumor and it was histologically diagnosed as anaplastic astrocytoma. After 19 months of treatment with temozolomide (TMZ) and radiotherapy, he presented with vertigo and headache. A homogeneously enhanced mass had developed in the left cerebellar hemisphere. He received gross total resection of the second tumor, pathologically diagnosed as medulloblastoma. In conclusion, this is the first case report of an adult medulloblastoma coexisting with anaplastic astrocytoma.

KEYWORDS: Adult medulloblastoma, Anaplastic oligoastrocytoma, Coexistence

ÖZ

Farklı histolojik özelliklere sahip birden fazla primitif intrakraniyal tümör nadirdir. Medülloblastomun glial tümörlerle birlikte bulunması çocuklarda bildirilmiş olsa da medülloblastoma yetişkinlerde ve özellikle 40 yaşın üzerinde olanlarda nadiren görülür. Anaplastik astrositom için radyoterapiden 21 ay sonra idame kemoterapisi yapılan 40 yaşında bir erkekte gelişen çok nadir bir medülloblastom vakası sunuyoruz. Başlangıçta, kompleks parsiyal havalelerle karakterize iyileşmeyen epilepsi yakınmasıyla geldi. Manyetik rezonans görüntüleme (MRG) sol insüla bölgesinde hafif kontrast madde tutan bir kitle lezyonu gösterdi. Tümöre subtotal rezeksiyon yapıldı ve histolojik olarak anaplastik anstrositom tanısı kondu. Temozolomid (TMZ) ve radyoterapi ile 19 ay tedaviden sonra başdönmesi ve başağrısıyla geldi. Sol serebellar hemisferde homojen kontrast tutan bir kitle gelişmişti. İkinci tümöre gross total rezeksiyon yapıldı ve patolojik olarak medülloblastom tanısı kondu. Sonuç olarak, bu vaka anaplastik astrositomla birlikte görülen ilk yetişkin medülloblastom vakasıdır.

ANAHTAR SÖZCÜKLER: Yetişkin medülloblastomu, Anaplastik oligoastrositom, Birlikte bulunma

INTRODUCTION

Multiple primitive intracranial tumors with different histological characteristics are rare, and only two cases of medulloblastoma coexisting with glial tumors (both consisting of medulloblastoma and juvenile pilocytic astrocytoma) have so far been reported in the pediatric departments (2, 13). Medulloblastoma is rare in adults, and is even more rare in patients older than 40 years of age (1, 5, 14, 16). We encountered a case where a medulloblastoma developed in an adult patient at the age of 40 while he was undergoing maintenance chemotherapy for anaplastic astrocytoma in the brain 19 months after radiotherapy. This is the first case report of an adult showing a medulloblastoma coexisting with an anaplastic astrocytoma in the brain.

CASE REPORT

A 38-year-old male was referred to our department in August 2006 for intractable epilepsy characterized by complex partial seizures. Computed tomography (CT) and magnetic resonance imaging (MRI) with prior gadolinium (Gd) treatment revealed a slightly enhanced mass lesion in the left insula region (Figure 1A-C). The tumor was subtotally removed using intracranial electrodes for functional mapping, because the tumor was located in an anatomical site with limited accessibility. Pathological findings revealed the tumor to be an anaplastic astrocytoma (Figure 2A,B). We administered radiotherapy plus continuous daily temozolomide orally (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy) (Figure 3A-

C), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle) (Figure 4A-C) (18). The patient subsequently complained of headache and vertigo in August 2008. Between October 2006 and August 2008, follow-up MRI was done periodically every 2-3 months. Follow-up MRI of the left cerebellum in May portrayed a heterogeneously enhanced mass manifesting as a high-intensity spot in a T2-weighted image inside the previous radiotherapy-targeted field (Figure 5A-D). After total tumor removal from the cerebellum, pathological examination identified the specimen as a medulloblastoma (Figure 6A,B). He received additional craniospinal irradiation (whole brain: 18 Gy; whole spine: 27 Gy; total: 54 Gy extended locally to the posterior fossa) with oncovin, followed up by periodic chemotherapy (etoposide, cisplatine) at our hospital without any neurological deficit. Follow-up MRI was performed after every chemotherapy course (every 8 weeks). Six months later (after three courses of chemotherapy), follow-up MRI revealed a newly developed homogeneously enhanced mass that extended in the right frontal lobe and right posteotemporal lobe with a perifocal edema (Figure 7A,B). Removal of tumor followed by specimen examination revealed the specimen as an anaplastic oligoastrocytoma. When all available versions of effective adjuvant therapies were exhausted, the patient died in November 2009.

DISCUSSION

This case report is extremely rare in terms of the coexistence

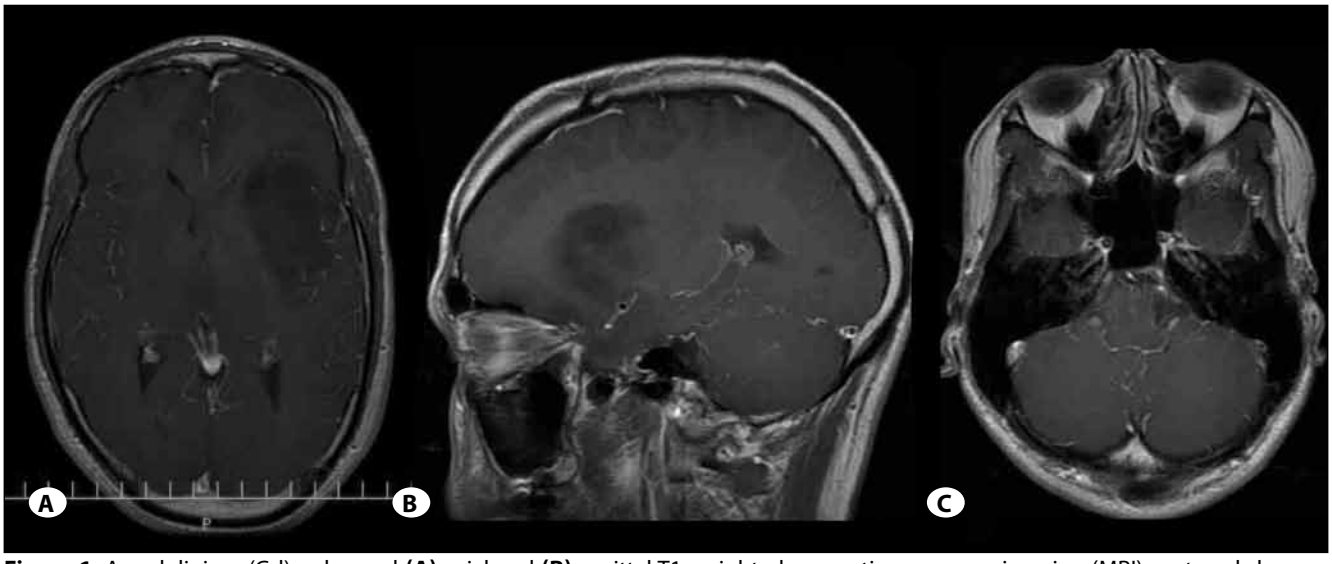

Figure 1: A gadolinium (Gd)-enhanced **(A)** axial and **(B)** sagittal T1-weighted magnetic resonance imaging (MRI) portrayal shows a slightly enhanced mass lesion in the left insula region. **(C)** There was no mass in the posterior fossa at the initial surgery.

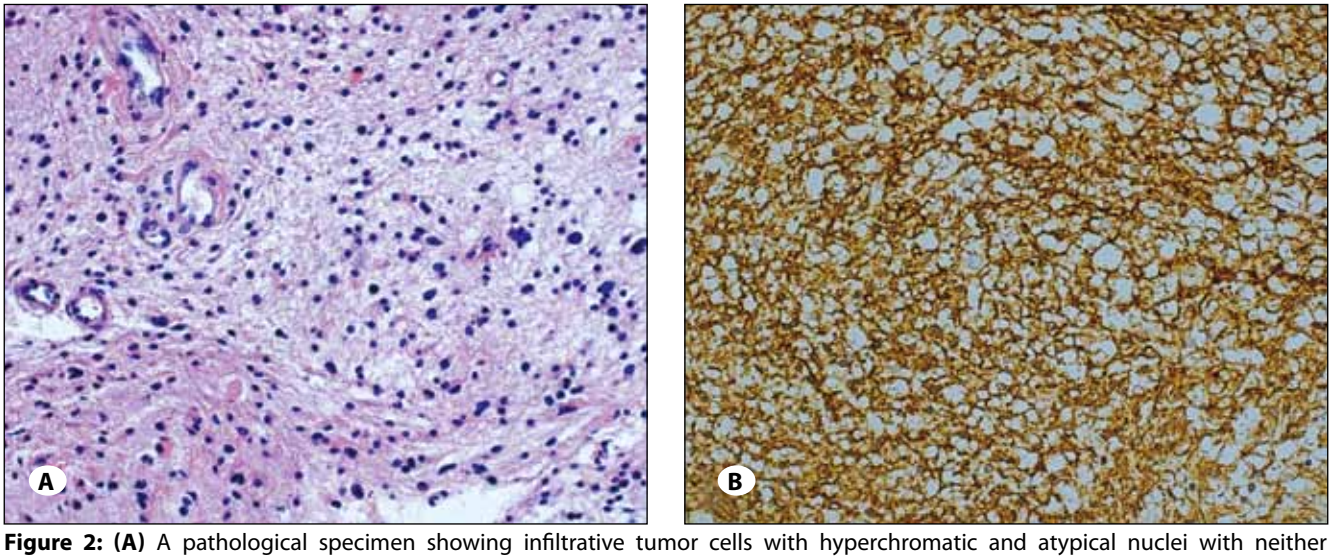

Figure 2: (A) A pathological specimen showing infiltrative tumor cells with hyperchromatic and atypical nuclei with neither microvascular proliferation nor necrosis (hematoxylin & eosin =staining, X100). **(B)** Tumor cells stained positive with antibodies against glial fibrillary acid protein (GFAP, X100).

of two different tumors (medulloblastoma and astrocytoma), the age at onset of the medulloblastoma, and malignancy in the astrocytoma. Clinical features as well as pathological and molecular studies can discriminate medulloblastoma from astrocytoma, as these tumors are clearly different in terms of their origin, typical features and common characteristics (including proliferation/growth) (3, 8, 9, 19). Additionally, microarray gene-expression studies also differentiate medulloblastomas from other brain tumors, including astrocytoma (3). A medulloblastoma coexisting with glial tumors has been documented in only two cases to date. Bhangui et al. (1977) have reported on a 12-year-old girl with multiple primary brain tumors that included a right optic nerve glioma, a pilocytic astrocytoma in the right globus pallidus, a ganglioglioma in the left globus palidus, and a medulloblastoma in the cerebellum. Moreover, Jea et al. (2010) have observed an 8-year-old boy with a juvenile pilocytic astrocytoma and a medulloblastoma in the left cerebellar hemisphere parenchyma and in the cerebellar superior vermis respectively. Contrary to our present case where the medulloblastoma was in an adult and the astrocytoma was malignant, the medulloblastomas and all gliomas were benign astrocytomas in the two pediatric cases. Medulloblastoma accounts for 30% of brain tumors in pediatric studies; however, only fewer than 3% of all primary central nervous system neoplasms have been encountered in adults (1, 5, 14, 16). Available literature has documented medulloblastomas as primarily pediatric tumors, with 80% occurring in adolescents below 15 years of age. Therefore, adult medulloblastoma is defined as onset in human subjects

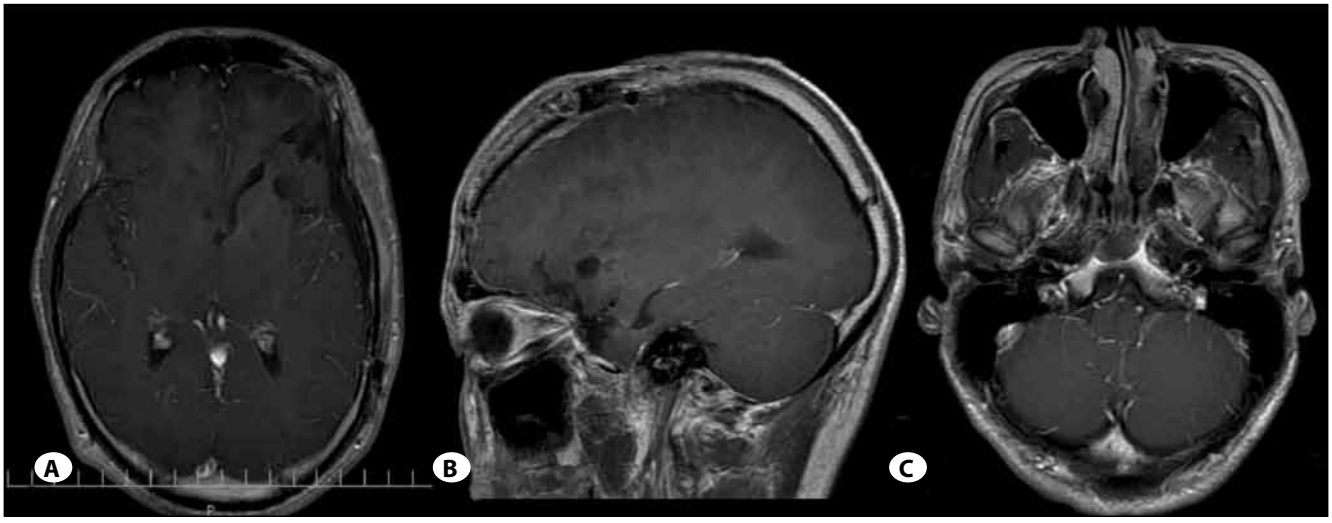

Figure 3: A Gd-enhanced **(A)** axial and **(B)** sagittal T1-weighted MRI portrayal after radiotherapy and chemotherapy indicates no residual tumor (refer to Figure 1 for abbreviations). **(C)** There was no mass in the posterior fossa after treatment with chemotherapy and radiotherapy.

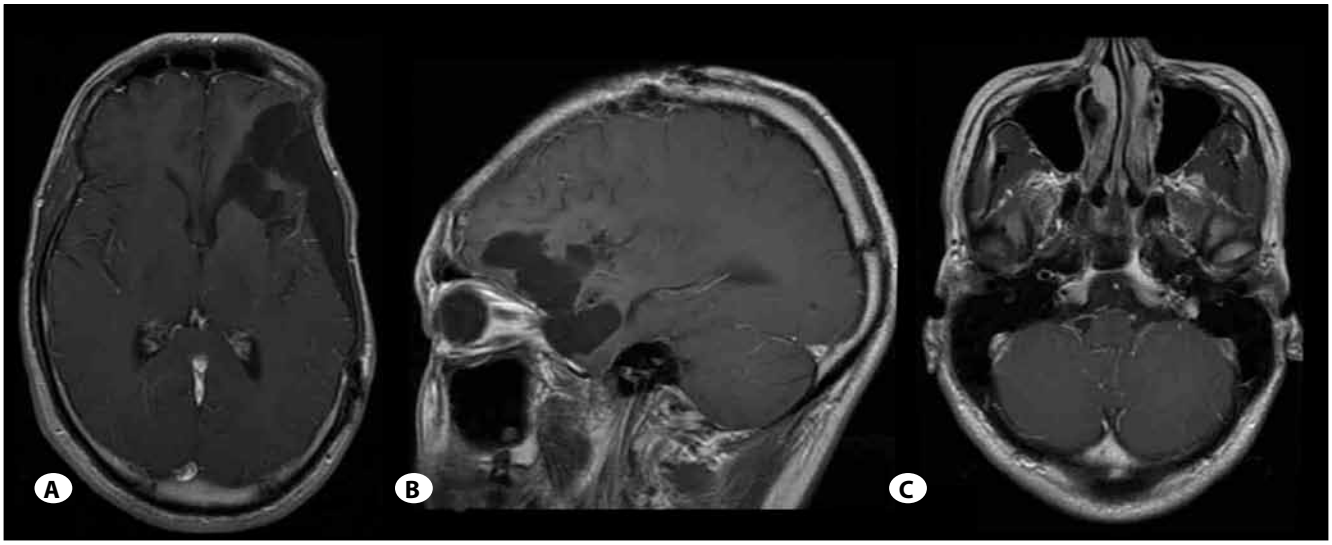

Figure 4. Periodical follow-up MRI portrayal with Gd enhance indicates no residual tumor during maintenance therapy for anaplastic astrocytoma (**A**; axial, b; sagittal). **(B, C)** There was no mass in the posterior fossa during maintenance therapy for anaplastic astrocytoma.

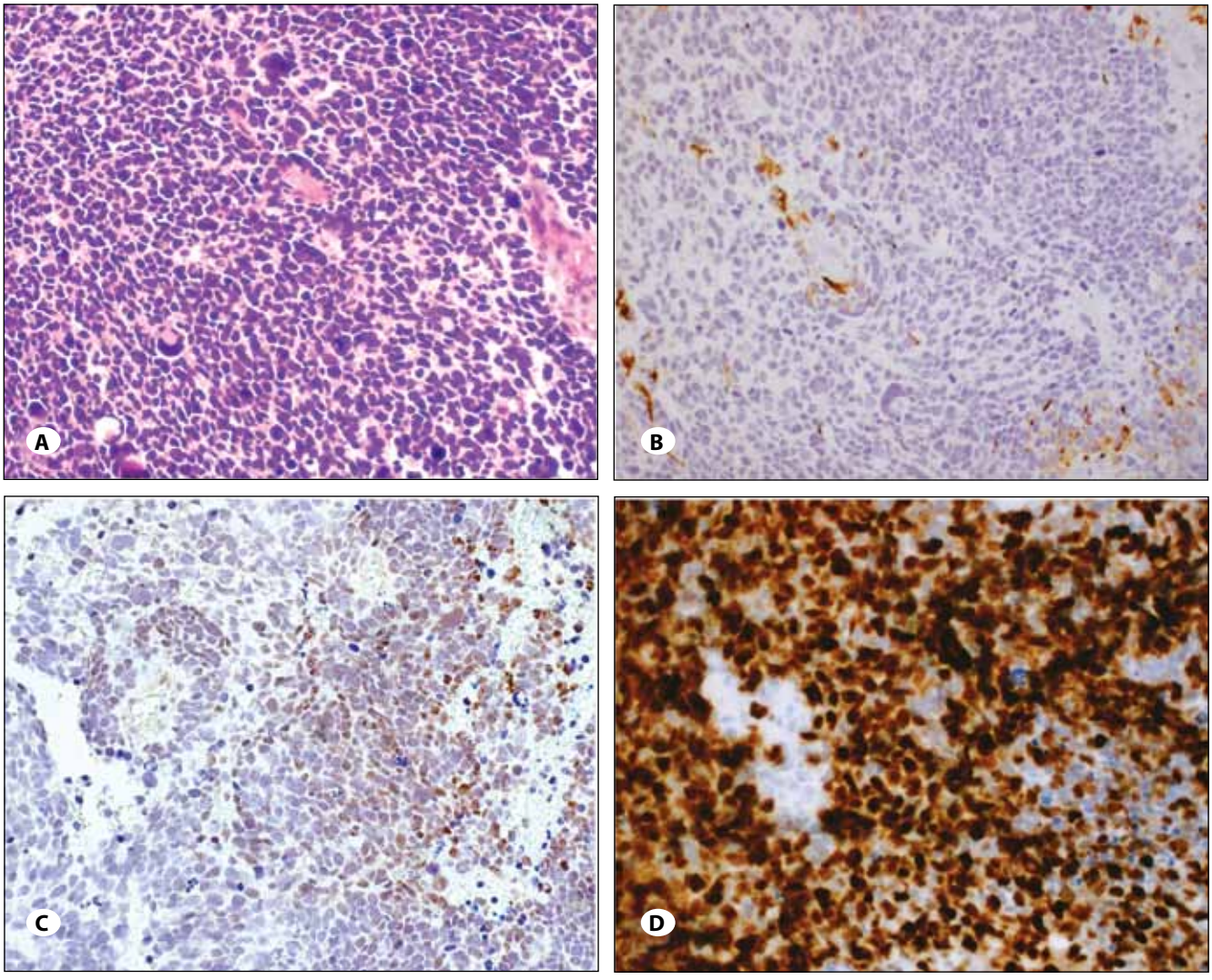

Figure 5: (A) A pathological specimen exhibiting highly cellular diffuse small cells having hyperchromatic round to slightly elongated nuclei and scant cytoplasm (hematoxylin & eosin =staining, x100). **(B, C)** Immunohistochemically, tumor cells were immunoreactive with GFAP and synaptophisin (GFAP, synaptophysin, x100). **(D)** The MIB-1 labeling index was 90% (Ki-67 immunostaining, x100).

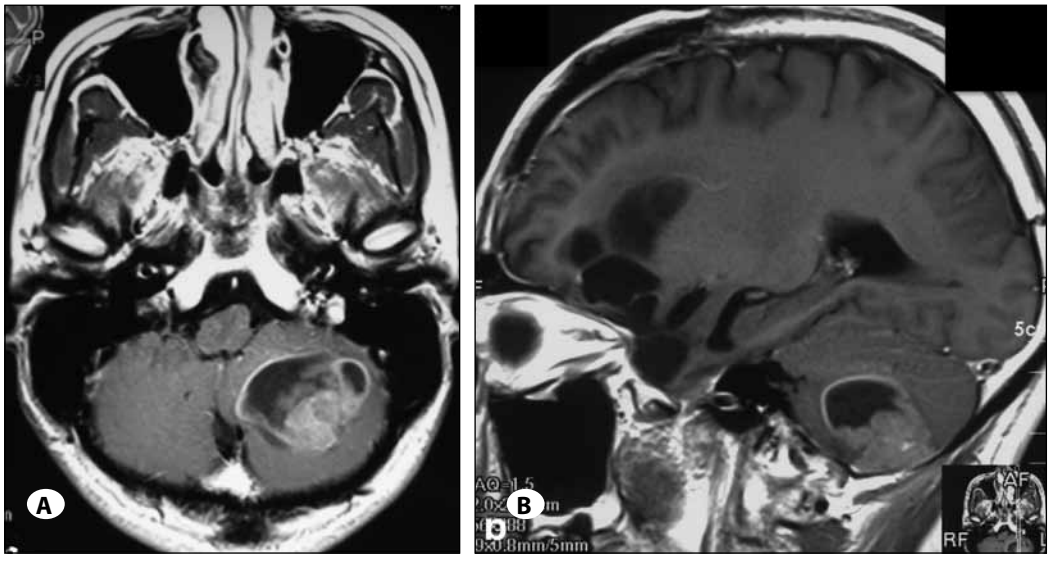

Figure 6: (A) Gd-enhanced axial T1-weighted MRI portrayals show (A) a homogeneously enhanced mass developing in the right frontal lobe with perifocal edema, and **(B)** a homogeneously enhanced mass similar to (A) in the right posterior temporal region (refer to Figure 1 for abbreviations).

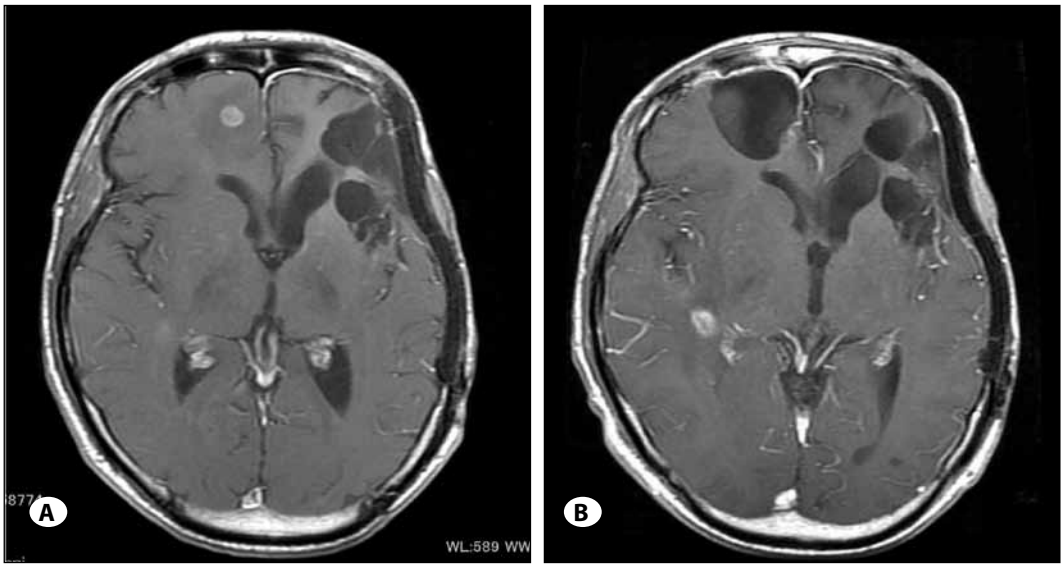

Figure 7: (A) Gd-enhanced axial T1-weighted MRI portrayals show (A) a homogeneously enhanced mass developing in the right frontal lobe with a perifocal edema,. and **(B)** a homogeneously enhanced mass similar to (A) in the right posterior tempotal region. (refer to Figure 1 for abbreviations).

older than 16-18 years of age (1, 5, 14, 16). Among the defined adult medulloblastoma patients, only 20% of the cases are more than 40 years of age (14). Adult medulloblastoma itself is quite rare, and coexistence of adult medulloblastoma with glioma is even more or extremely rare. Moreover, anaplastic astrocytoma is far more malignant than piloctic astrocytoma, and the present patient in fact died of uncontrollable anaplastic astrocytoma.

The possible explanations for occurrence of multiple diverse primary brain tumors in this extremely rare case include: (I) secondary brain tumor induction by radiation; (II) tumorigenetic activities of certain oncogenes; and (III) defects in tumor suppressor genes. Hitherto, there are only six reported rare cases of radiation-induced medulloblastoma compared to the many radiation-induced glioma cases documented (6, 10, 11, 12, 17). According to the modified Cahan's criteria for radiation-induced tumors: (i) The onset of secondary tumors is sited in the previously irradiated field; (ii) both the primary and secondary tumors are histologically different from each other; and (iii) a sufficiently long latency period (ca. 5 years) exists from the point of irradiation termination to the onset of a secondary tumor (7). The latency period of the secondary tumor onset (ca. 5 years) is attributable to the underlying mechanism of carcinogenesis triggered by irradiation-induced partial DNA injury (i.e. to the degree of not killing the cell but inducing abnormalities in DNA strands with defects in tumor-suppressor genes or oncogenes controlling the cell replication cycle) (4, 15). In previously reported second malignant brain tumors, the onsets of glioblastomas and sarcomas range respectively within 5 to 15 and 4 to 15 years after the initial exposure to radiation (4, 15). All the three previously documented cases of radiation-induced medulloblastoma indicated a post-irradiation latency period of 8 to 41 years (average 22.0 years); a finding that shows the marked discrepancy with our present case of 19 months. In our case, the medulloblastoma was not considered to be a radiation-induced tumor, because of discrepancies in the diagnosis criteria and features when compared with previously reported cases, although the secondary tumor (medulloblastoma) was sited inside the previously irradiated field. Molecular abnormalities, oncogenes or defective tumor-suppressor genes of medulloblastomas and astrocytomas patients have recently been investigated; however, corresponding molecular data of the present patient are not known. The potential factors responsible for the development of multiple primary brain tumors remain unknown, further studies in elucidating the relevant factors are warranted. In addition, the more complex multi-factors inducing tumorigenesis have to be clarified in order to resolve the mechanism(s) of multiple primary brain tumors.

CONCLUSIONS

To our knowledge, this is the first case report of a medulloblastoma coexisting with a malignant astrocytoma in a 40-year-old patient who has undergone maintenance chemotherapy for anaplastic astrocytoma 19 months after radiotherapy. Complex multi-factors inducing tumorigenesis have to be clarified in order to understand the mechanism and treatment of multiple primary brain tumors.

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