Glioblastoma Multiforme Associated With Klinefelter Syndrome
—Case Report—

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Abstract
A 54-year-old man with Klinefelter syndrome presented with glioblastoma multiforme manifesting as a 2-week history of motor weakness of the bilateral extremities. Magnetic resonance imaging showed multiple heterogeneously enhanced tumors in the bilateral frontal lobes. Angiography showed no tumor stain or arteriovenous shunt. The tumor was partially removed through a right craniotomy. The histological diagnosis was glioblastoma. Immunohistochemical examination showed no O6-methylguanine-deoxyribonucleic acid methyltransferase protein expression. Postoperative local radiotherapy (60 Gy/30 fractions) combined with temozolomide (75 mg/m² × 42 days) and interferon-beta (3,000,000 U, 3 times/week) was performed. The patient’s clinical status rapidly deteriorated during chemoradiotherapy, and he died of tumor progression 3.5 months after the surgery. Postmortem examination revealed widespread glioblastoma infiltrating the basal ganglia and thalamus. Klinefelter syndrome is associated with increased cancer predisposition, especially for male breast cancer and germ cell tumors, but glioma is extremely rare. The abnormal genetic constitution of this patient may have been directly responsible for the poor outcome.

Key words: glioblastoma, Klinefelter syndrome, temozolomide, radiation, prognosis

Introduction
Klinefelter syndrome was first described in 1942 and is characterized by hypogonadism and gynecomastia.14) Klinefelter syndrome involves an excess number of X chromosomes, and is the most common sex chromosome disorder occurring in about one of 660 men.22) Various tumors, such as breast cancer, germ cell tumors, and hematological malignancies, are associated with Klinefelter syndrome.3,8,10–12) Several cases of primary central nervous system tumor, mostly intracranial germ cell tumors, have been associated with Klinefelter syndrome.1,2,5,7,13–25) Glioma associated with Klinefelter syndrome is extremely rare, with only three previously reported cases, a pilocytic astrocytoma in the left cerebellar hemisphere28) and two ependymomas.6)

We treated a patient with Klinefelter syndrome for glioblastoma multiforme (GBM) of the cerebrum by partial tumor resection followed by adjuvant radiotherapy with temozolomide (TMZ) administration. Although O6-methylguanine-deoxyribonucleic acid methyltransferase (MGMT) protein expression was negative in tumor cells, he died of tumor progression 3.5 months after the operation.

Case Report
A 54-year-old man was admitted to our neurosurgical clinic with a 2-week history of motor weakness of the bilateral arms and legs in November 2006. He had a history of hypertension and diabetes mellitus. Moreover, Klinefelter syndrome was diagnosed at the age of 44 years, but intramuscular injections of testosterone enanthate once a month allowed total testosterone levels to be consistently normalized through dose adjustment over the following 10 years.

On admission, the patient was 174.0 cm tall and weighed 86 kg. The bilateral testes were small and soft without palpable tumor, and no genital malformation or gynecomastia was seen. The serum lactic dehydrogenase level was elevated to 268 U/l (normal, 115–217 U/l). Serum alpha-fetoprotein was within normal limits. Serum luteinizing hormone and follicle-stimulating hormone levels were elevated to 22.4 mIU/ml (normal, 0.79–5.72 mIU/ml) and 54.5 mIU/ml (normal, 2.00–8.30 mIU/ml), respectively. Chromosomal analysis revealed a 47, XXY karyotype, which confirmed the diagnosis of Klinefelter syndrome (Fig. 1).
Neurological examination disclosed reduced attention span and short memory deficit. The mini-mental state examination score was 12 of 30 points. Cranial nerve functions were intact, but mild motor weakness in the bilateral extremities was observed, although there were no signs of increased intracranial pressure. Computed tomography demonstrated multiple mass lesions with perifocal edema in the bilateral frontal lobes. Magnetic resonance (MR) imaging showed multiple tumors in the white matter of the bilateral frontal lobes, which appeared hypointense on T₁-weighted images and hyperintense on T₂-weighted images, with strong and heterogeneous enhancement after administration of gadolinium-diethylenetriaminepenta-acetic acid (Fig. 2A, B). Carotid angiography showed no tumor stain or arteriovenous shunt, and fluorine-18-fluorodeoxyglucose positron emission tomography showed no abnormal uptake, except for the brain lesion (Fig. 2C).

Right frontal craniotomy resulted in partial removal of the soft and vascular tumor. Histological examination showed increased cellularity of atypical astrocytes with high nuclear/cytoplasmatic ratio, pleomorphism, and microvascular proliferation, with necrosis and many mitotic shapes (Fig. 3A). The MIB-1 labeling index was 23.0% (Fig. 3D). Immunohistochemical findings showed that most tumor cells were positive for glial fibrillary acidic protein (Fig. 3B) and S-100 protein, but negative for oligodendrocyte lineage transcription factor 2 (Olig-2), synaptophysin, and neuron-specific enolase. Based on these findings, the histological diagnosis was GBM. Immunohistological staining showed that p53, a known tumor suppressor, was not expressed in most tumor cells, and MGMT, which affects the chemosensitivity of TMZ in glioma, was negative (Fig. 3C).

Two weeks postoperatively, treatment was started with standard external beam radiotherapy (60 Gy/30 fractions) with daily oral administration of TMZ (75 mg/m² × 42 days) and interferon-beta (3,000,000 U) 3 times a week. Despite combined chemoradiotherapy, his consciousness gradually declined. MR imaging demonstrated tumor infiltration into the white matter of the parietal lobes and basal ganglia with severe perifocal edema and shift 1 month after chemoradiotherapy. The patient died 3.5 months after the initial diagnosis.

Postmortem examination showed that the tumor was located in the bilateral frontal lobes, and extended to the corpus callosum, white matter in the bilateral parietal lobes, bilateral basal ganglia, thalamus, and the wall of the lateral ventricle. The tumor mass consisted of multiple white soft nodules and yellow-brown necrotic foci. Histological examination demonstrated the presence of pleomorphic astrocytes and small round, polygonal, and fusiform cells in...
the neoplastic lesion. Multinucleated cells and giant cells with bizarre nuclei and pseudopalisading were also observed. Cellularity was enhanced and the nuclei were hyperchromatic with variable pleomorphisms. Microvascular proliferation was seen. No differences were found in histological findings between the various lesions.

**Discussion**

Fifteen previous cases of intracranial brain tumor in association with Klinefelter syndrome have been reported: 10 germ cell tumors, 2 ependymomas, and one each of lymphoma, pilocytic astrocytoma, and polar spongiosoblastoma (Table 1).1,2,4-7,13,15,17,23-26,28) Most central nervous system tumors associated with Klinefelter syndrome are germ cell tumors, whereas intracranial germ cell tumors are generally rare, accounting for only approximately 3% of all primary intracranial tumors.17,26) Gliomas associated with Klinefelter syndrome are quite infrequent, with only three previously reported cases (Table 1). A 13-year-old boy had pilocytic astrocytoma in the left cerebellar hemisphere close to the midline, which recurred after total resection and the patient died 5 years after the initial operation.26) One patient was diagnosed with Klinefelter syndrome during gestation and was treated for a grade II ependymoma of the fourth ventricle by surgery followed by oral chemotherapy and stereotactic radiotherapy at age one year, but developed local recurrence and died after 15 months.6) Another patient had a myxopapillary ependymoma of the cauda equina and underwent surgery and radiotherapy.6)

Our patient was diagnosed with Klinefelter syndrome at age 44 years, and GBM developed at age 54 years. MR imaging on admission showed multifocal tumors in the bilateral frontal lobes. His chromosomal abnormality may have contributed to this multifocal tumor development. The histological findings were typical of GBM, including necrosis, microvascular proliferation, many mitotic cells, and high MIB-1 labeling index, and the tumor seemed to be primary GBM. Immunohistochemical analysis revealed low or no expression of MGMT protein. MGMT expression is correlated with the prognosis in GBMs. MGMT promoter methylation is an independent favorable prognostic factor, as median survival of patients with GBM and methylated MGMT promoter was 21.7 months, compared with 15.3 months with unmethylated MGMT promoter.9) MGMT expression detected by immunohistochemistry is a significant prognostic factor for the overall survival of patients with GBM, and median overall survival of the patients with negative MGMT expression was 65.5 weeks.21) The present tumor was negative for MGMT and was treated with chemoradiotherapy using TMZ after surgery, but rapidly progressed and overall survival time was very short. Postmortem histological examination revealed tumor extension to the corpus callosum, white matter in the bilateral parietal lobes, bilateral basal ganglia, and thalamus.

The reasons for the dismal outcome in our patient remain unclear, but may have involved the chromosomal abnormalities of Klinefelter syndrome. Patients with Klinefelter syndrome have a high risk of cancer, but the true mechanism of carcinogenesis is not clear. One possible reason for the high relative risk in men with Klinefelter syndrome is the elevated estradiol-testosterone ratio or increased peripheral conversion of testosterone to estradiol compared with normal karyotype men.27) Another possibility is that the presence of two X chromosomes might increase the genetic risk of cancer in men with Klinefelter syndrome or might cause overexpression of an unknown oncogene on the X chromosome that escapes X inactivation. Cells from a cancer patient with Klinefelter syndrome and XY/XXY sex chromosome mosaicism showed susceptibility to in vitro transformation by Simian virus 40 (SV40).20) In fact, latent infection of SV40 was detected in several patients with primary GBM.16) SV40 infection was not examined in our patient, but may be implicated in the gliomagenesis. Testosterone replacement therapy might also affect tumorigenesis, because testosterone stimulated

Table 1  Reported cases of central nervous system tumor associated with Klinefelter syndrome

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Author (Year)</th>
<th>Age (yrs)</th>
<th>Histology</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Coley et al. (1971)</td>
<td>38</td>
<td>spongiosoblastoma</td>
<td>rt temporoparietal lobe</td>
</tr>
<tr>
<td>2</td>
<td>Rubinstein (1972)</td>
<td>16</td>
<td>germinoma</td>
<td>pineal body</td>
</tr>
<tr>
<td>3</td>
<td>Ahagon et al. (1983)</td>
<td>20</td>
<td>germinoma</td>
<td>suprasellar</td>
</tr>
<tr>
<td>4</td>
<td>Ellis et al. (1986)</td>
<td>12</td>
<td>germinoma</td>
<td>suprasellar</td>
</tr>
<tr>
<td>5</td>
<td>Oki et al. (1987)</td>
<td>17</td>
<td>malignant germ cell tumor</td>
<td>pineal body-suprasellar</td>
</tr>
<tr>
<td>6</td>
<td>Arens et al. (1988)</td>
<td>15</td>
<td>germinoma</td>
<td>pineal body</td>
</tr>
<tr>
<td>7</td>
<td>König et al. (1990)</td>
<td>8</td>
<td>germinoma</td>
<td>suprasellar</td>
</tr>
<tr>
<td>8</td>
<td>Liang et al. (1990)</td>
<td>40</td>
<td>malignant lymphoma</td>
<td>rt frontoparietal lobe</td>
</tr>
<tr>
<td>9</td>
<td>Hashimoto et al. (1992)</td>
<td>19</td>
<td>germinoma</td>
<td>medulla oblongata</td>
</tr>
<tr>
<td>10</td>
<td>Prall et al. (1993)</td>
<td>12</td>
<td>malignant germ cell tumor</td>
<td>pineal body</td>
</tr>
<tr>
<td>11</td>
<td>Wysocka et al. (1996)</td>
<td>13</td>
<td>pilocytic astrocytoma</td>
<td>cerebellum</td>
</tr>
<tr>
<td>12</td>
<td>Kaido et al. (2003)</td>
<td>19</td>
<td>germinoma</td>
<td>lt temporal lobe</td>
</tr>
<tr>
<td>13</td>
<td>Phowthongkum (2006)</td>
<td>29</td>
<td>germinoma</td>
<td>suprasellar</td>
</tr>
<tr>
<td>14</td>
<td>Garrett et al. (2007)</td>
<td>2.8</td>
<td>ependymoma</td>
<td>fourth ventricle</td>
</tr>
<tr>
<td>15</td>
<td>Present case</td>
<td>54</td>
<td>glioblastoma</td>
<td>bilateral lobes</td>
</tr>
</tbody>
</table>

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proliferation in T98G glioma cells in vitro. Since our patient had received testosterone replacement therapy for about 10 years, the possibility that this therapy might have affected the development of GBM in our patient cannot be rejected.

The present case of GBM associated with Klinefelter syndrome is extremely unusual. There is little evidence for frequent gross structural abnormalities on chromosome X in high-grade glioma. However, the X chromosome may in fact be important in high-grade glioma oncogenesis, because the tumor-specific antigen, interleukin-13 receptor alpha, is located on chromosome X and is highly expressed in high-grade glioma. More clinical and basic findings are required to clarify tumorigenesis in patients with Klinefelter syndrome.

References


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