Extracranial Skeletal Metastasis in Anaplastic Oligodendroglioma: Case Report and Review of the Literature

Y Wu¹, B Liu¹, L Qu² and H Tao¹

¹Department of Orthopaedics, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China; ²Clinical Laboratory Centre, Binjiang Hospital of Hangzhou, Hangzhou, Zhejiang, China

A case of anaplastic oligodendroglioma with femoral metastasis is presented in a 37-year old male with a 2-year history of progressive headaches and dizziness associated with a 2-month history of epilepsy and right hemiparesis. Magnetic resonance imaging (MRI) demonstrated a solid temporoparietal tumour and the patient underwent a left temporal craniotomy and subtotal resection followed by limited-field radiation therapy. The pathological diagnosis was anaplastic oligodendroglioma. The patient presented with left hip pain 3 years later. Radiography and computed tomography demonstrated osteosclerosis of the left proximal femur, and MRI revealed an intramedullary metastatic lesion. Total body ⁹⁹mTc-methylene diphosphonate bone scan showed hyperactivity in the lesion and open biopsy confirmed it was a metastasis from the cerebral oligodendroglioma. The patient was treated with temozolomide and, to date, there is no sign of recurrence or progression in either the brain or the femur. Seven previously reported cases of extracranial skeletal metastasis from anaplastic oligodendroglioma are reviewed. Co-deletion of chromosome arms 1p and 19q and O⁶-methylguanine DNA methyltransferase status remain the most important prognostic and predictive markers.

KEY WORDS: ANAPLASTIC OLIGODENDROGLIOMA; METASTASIS; GENETIC ANALYSIS; CHEMOTHERAPY

Introduction

Gliomas, the most frequent tumours of the central nervous system, are categorized as astrocytomas, oligodendrogliomas or mixed gliomas. In the World Health Organization (WHO) classification, tumours with oligodendrocytic elements can be further subdivided into oligodendrogliomas WHO grade II, anaplastic oligodendrogliomas WHO grade III, oligoastrocytomas WHO grade II, anaplastic oligoastrocytomas WHO grade III or glioblastomas with an oligodendroglialoma component WHO grade IV.¹ The biological behaviour of oligodendrogliomas is characterized by multiple recurrences.² Extracranial spread is, however, exceptional, with distant skeletal metastases being particularly rare. The present study reports a case of anaplastic oligodendroglioma with femoral metastasis.
Case report
A 37-year old man was admitted to the Department of Orthopaedics, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China, in November 2005 with a 2-year history of progressive headaches and dizziness associated with a 2-month history of epilepsy and right hemiparesis. His past medical history and systems review were unremarkable. On physical examination the patient was fully conscious; muscle power was grade V on the left side and grade IV on the right. Magnetic resonance imaging (MRI) demonstrated a solid temporoparietal tumour (Fig. 1A). The patient underwent a left temporal craniotomy and subtotal resection. He made a good postoperative recovery and had no neurological deficit at the time of discharge. The pathological diagnosis was anaplastic oligodendroglioma WHO grade III. Limited-field radiation therapy was then administered to a total dose of 60 Gy in 30 fractions.

In December 2008, the patient presented with left hip pain. A craniospinal MRI was performed: no recurrence of the primary tumour was seen (Fig. 1B). Radiography (Fig. 2A) and computed tomography scan (Fig. 2B) of the hip demonstrated osteosclerosis of the left proximal femur. An MRI of the hip revealed an intramedullary metastatic lesion with low signal intensity on T1-weighted images (Fig. 2C) and increased signal intensity on T2-weighted images (Fig. 2D). A total body 99mTc-methylene diphosphonate bone scan showed hyperactivity in the left proximal femur (Fig. 2E). An open biopsy of the lesion confirmed it was a metastasis from the cerebral oligodendroglioma (Fig. 3A). Immunohistochemical studies for glial fibrillary acidic protein (Fig. 3B) and S100 protein (Fig. 3C) were positive, whereas those for cytokeratin AE1/AE3, epithelial membrane antigen, leucocyte common antigen, CD68 and p53 were negative. The patient was given temozolomide (TMZ) at a dose of 200 mg/m² per day for 5 days, repeated every 28 days. Treatment continued for a total of six cycles. To date (September...
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2010), there is no sign of recurrence or progression in either the brain or the left proximal femur (Fig. 4).

Discussion

Malignant gliomas are the most frequent primary brain tumours in adults. They are categorized into astrocytomas, oligodendrogliomas and mixed gliomas. Oligodendrogliomas are rare neoplasms, with an incidence of 2 – 5% of all primary brain tumours. The proportion of anaplastic tumours among oligodendrogliomas varies between 20% and 51%.

Extracranial metastasis of primary brain tumours is a rare occurrence. A Medline search of the English literature using the subject heading ‘bone metastasis AND anaplastic oligodendroglioma’ revealed seven previously reported cases of extracranial skeletal metastasis from anaplastic oligodendrogliomas (Table 1). Different theories have been proposed for the rarity of this event, including the absence of intracranial lymphatic vessels and the collapse of intracerebral veins ahead of the advancing tumour, the inability of the intracerebral environment to select metastatic malignant clones, and the critical role of the relative integrity of the blood–brain barrier.

In 1979, Liwnicz and Rubinstein analysed 116 cases of extracranial spread and found that the presence of metastasis...
was most frequently detected in patients with glioblastoma (41.4%), followed by medulloblastoma (26.7%), ependymoma (16.4%), astrocytoma (10.3%) and, lastly, oligodendroglioma (5.25%). The prolonged survival of oligodendroglialoma patients associated with the enhanced chemosensitivity of these tumours may be a


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is 2 – 3 years for those without the 1p/19q co-deletion compared with 6 – 7 years in those with 1p/19q loss.24,25 The 1p/19q co-deletion is mediated by an unbalanced translocation of 19p to 1q:der (1;19) (p10;q10), which occurs during the tumorigenesis of oligodendroglioma.26 Fallon et al.27 found that co-deletions of 1p/19q were conserved in 100% of oligodendroglial tumours at diagnosis and recurrence. Campbell et al.28 investigated 24 patients with oligodendroglial neoplasms and 53 tumour specimens and also reported that 100% of those with 1p/19q co-deletions demonstrated persistent 1p/19q co-deletions in progressive disease and recurrences. Thus, progression of these tumours does not appear to be due to a proliferating subpopulation of treatment-resistant cells.

Phosphatase and tensin homologue (PTEN) mutations occur in only about half of the cases with 10q loss, suggesting that there might be another progression-related target gene in this region.29,30 PTEN mutations and 10q deletions are more common in anaplastic oligodendrogliomas without 1p and 19q losses.31 Rarely anaplastic oligodendrogliomas carry activating mutations in the PIK3CA gene.29

### TABLE 1:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Location of metastasis</th>
<th>Time between presentation of primary tumour and metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al.6</td>
<td>64</td>
<td>Female</td>
<td>Right humerus and femur</td>
<td>7 years</td>
</tr>
<tr>
<td>Merrell et al.7</td>
<td>32</td>
<td>Male</td>
<td>Spine and sacrum</td>
<td>10 years</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>Female</td>
<td>Ribs</td>
<td>1 year</td>
</tr>
<tr>
<td>Noshita et al.8</td>
<td>53</td>
<td>Male</td>
<td>Thoracic vertebrae and chest wall</td>
<td>2 years</td>
</tr>
<tr>
<td>Jellinger et al.9</td>
<td>58</td>
<td>Female</td>
<td>Lumbar vertebrae</td>
<td>3 years</td>
</tr>
<tr>
<td>Schuster et al.10</td>
<td>58</td>
<td>Female</td>
<td>Vertebrae</td>
<td>30 months</td>
</tr>
<tr>
<td>Volavsek et al.11</td>
<td>30</td>
<td>Female</td>
<td>Sacrum and femur</td>
<td>7 months</td>
</tr>
<tr>
<td>Present case</td>
<td>37</td>
<td>Male</td>
<td>Femur</td>
<td>37 months</td>
</tr>
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</table>
Anaplastic oligodendrogliomas are chemosensitive tumours that respond to combined treatment with procarbazine, lomustine (also known as CCNU) and vincristine (PCV therapy) in 60 – 70% of patients.\textsuperscript{32} Studies have demonstrated that TMZ, an oral alkylating agent that inhibits DNA replication by methylating nucleotide bases, is active and particularly well tolerated in patients with anaplastic oligodendroglioma,\textsuperscript{33,34} as well as in patients with various subtypes of progressive low-grade gliomas.\textsuperscript{35} Preclinical studies have demonstrated that low concentrations of TMZ inhibit angiogenesis and enhance apoptosis.\textsuperscript{36,37} TMZ methylates guanines in DNA at the O\textsuperscript{6} position, causing base-pair mismatch.\textsuperscript{38} This O\textsuperscript{6}-methylguanine (O\textsuperscript{6}-MeG) lesion leads to DNA double-strand breaks and subsequent cell death via apoptosis and/or autophagy.\textsuperscript{39} O\textsuperscript{6}-MeG DNA methyltransferase (MGMT) is a DNA repair enzyme that repairs the O\textsuperscript{6}-MeG lesion and is induced either by environmental carcinogens or chemotherapeutic agents;\textsuperscript{40} high levels of MGMT are thought to contribute to resistance to TMZ.\textsuperscript{41} Levin et al.\textsuperscript{34} reported that TMZ was active in patients with progressive oligodendrogliomas, and that the response to treatment was associated with 1p deletion and low MGMT protein expression. Taliansky-Aronov et al.\textsuperscript{42} reported that the rate of radiographic response of newly diagnosed anaplastic oligodendroglioma to initial treatment with TMZ was 75%, similar to results obtained with PCV combination therapy in both recurrent and newly diagnosed tumours.\textsuperscript{43} 1p/19q co-deletion and MGMT status remain the most important prognostic and predictive markers.\textsuperscript{44}

In summary, extracranial metastases in anaplastic oligodendroglioma are very rare but can occur. The combined deletion of the 1p and 19q chromosomal arms is frequent in oligodendroglioma that is sensitive to chemotherapy and this co-deletion and MGMT status remain the most important prognostic and predictive markers. Patients with anaplastic oligodendroglioma receive either radiotherapy or chemotherapy, or a combination of both, after surgery as standard treatment. With the combination of surgery and TMZ chemoirradiation, the outcome of oligodendroglioma has been improved.

Conflicts of interest
The authors had no conflicts of interest to declare in relation to this article.
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Author’s address for correspondence

Dr Huimin Tao

Department of Orthopaedics, Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jie Fang Road, Hangzhou 310009, Zhejiang, China.

E-mail: zrspine@gmail.com