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## **Extracranial Metastasis of Anaplastic Oligodendroglioma With 1p19q Loss of Heterozygosity**

**—Case Report—**

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### **Abstract**

**We report a rare case of anaplastic oligodendroglioma with extracranial metastasis, showing 1p19q co-deletion in both the brain tissue and the metastatic site. A 53-year-old man first presented with a left frontal tumor. The tumor was subtotally removed and irradiation was performed for the residual tumor and tumor bed. Two years after the initial treatment, several tumors appeared on his neck and one was resected. Histological examination revealed anaplastic oligodendroglioma, proved to be the same as the previous brain tumor. The patient refused further treatment, and died 30 months after the initial treatment. Autopsy demonstrated multiple extracranial metastases in the vertebrae, lymph nodes, spinal dura mater, thymus gland, and chest wall. We confirmed 1p19q loss of heterozygosity in both lesions, suggesting that 1p19q co-deletion might important to extracranial metastasis of oligodendroglioma.**

Key words: oligodendroglioma, extracranial metastasis, autopsy, 1p19q, loss of heterozygosity

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## Introduction

Primary brain tumors rarely metastasize outside the central nervous system. A review of 8000 tumors involving the central nervous system identified only 35 cases of extracranial metastasis, including one oligodendroglioma.<sup>16)</sup> A review of 116 cases of extracranial metastasis found that the most common primary tumor was glioblastoma (41.4%), followed by medulloblastoma (26.7%), ependymoma (16.4%), astrocytoma (10.3%), and oligodendroglioma (5.25%).<sup>10)</sup> More than 30 cases of extracranial metastatic oligodendroglioma have been reported.<sup>8,9,12,18,19,23)</sup> The number of cases has increased recently, possibly because survival times have been prolonged due to improved treatment.<sup>12,19)</sup>

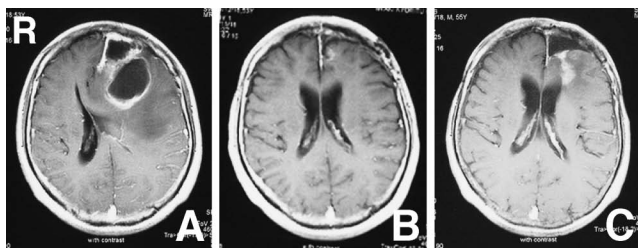
Oligodendroglioma is characterized by loss of heterozygosity (LOH) in chromosomes 1p and 19q (1p19q). Sometimes, the presence of 1p and 19q co-deletion can be proof of oligodendroglioma. However, the molecular and genetic alterations have been evaluated in only a few cases of oligodendroglioma with extracranial metastasis.

We describe a case of oligodendroglioma with multiple extracranial metastases, including the vertebrae, lymph nodes, spinal dura mater, thymus gland, and chest wall, in which 1p and 19q co-deletion was found in both intracranial and extracranial lesions, suggesting that 1p19q LOH might be involved in the extracranial metastasis of oligodendroglioma.

## Case Report

A 53-year-old man was admitted to our clinic in 2004, complaining of gait disturbance and aphasia. Computed tomography and magnetic resonance (MR) imaging demonstrated a left frontal tumor (Fig. 1A). A craniotomy was performed and the frontal tumor was subtotally removed (Fig. 1B). The diagnosis was glioblastoma, and irradiation therapy (total 80 Gy) was performed. After the treatment, he was discharged with no neurological deficits.

Two years later, several tumors appeared on his neck. Resection of a cervical tumor was performed. The histological findings of anaplastic oligodendroglioma (World



**Fig. 1** T<sub>1</sub>-weighted magnetic resonance images with gadolinium, (A) before the operation showing a left frontal tumor with irregular ring enhancement, (B) at 4 months after the operation showing no residual tumor, and (C) at 2 years after surgery showing no conspicuous recurrence despite the presence of multiple extracranial metastatic lesions.

Health Organization grade III) suggested that the tumor originated from the intracranial lesion. Review of the previous brain tumor revealed anaplastic oligodendroglioma (Fig. 2). Fluorescent in situ hybridization (FISH) assay was performed for both the brain tumor and cervical tumor, finding 1p19q LOH in both lesions (Fig. 3).

Thereafter he complained of back pain and MR imaging of the spinal cord disclosed an epidural mass at the T5 level. Brain MR imaging did not show evident progression of the intracranial lesion (Fig. 1C). He refused further treatment, and died after aggravation of his general condition 30 months after the initial treatment. Autopsy demonstrated multiple extracranial metastases in the vertebrae, lymph nodes, spinal dura mater, thymus gland, and chest wall (Fig. 4).

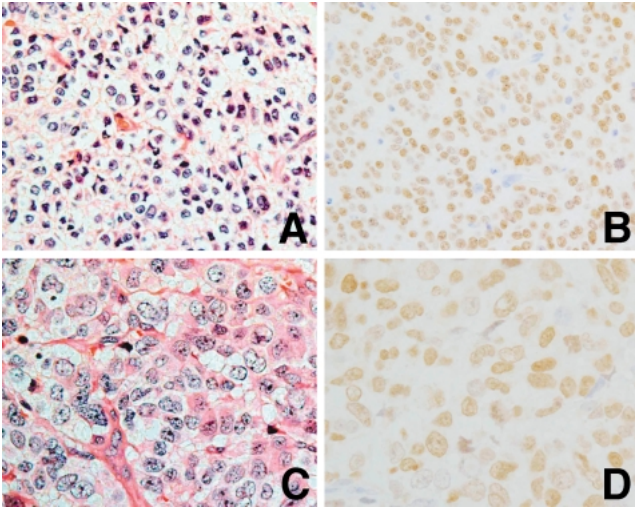
## Discussion

The bone is the most common site of metastasis from oligodendroglioma.<sup>1,11-14,18)</sup> A recent review of 33 cases of extracranial metastatic oligodendroglioma showed that the most frequent metastatic site was the bone and bone marrow (97%), followed by the lymph nodes (33%), lungs and pleura (18%), scalp (12%), other soft tissue (9%), parotid gland (3%), adrenal (3%), spleen (3%), and pancreas (3%).<sup>23)</sup> In our case, postmortem examination found multiple extracranial metastases, including the vertebrae, lymph nodes, spinal dura mater, thymus gland, and chest wall. Metastases in the bone and lymph nodes suggest that the tumor was delivered via the vascular channels and lymphatic system.

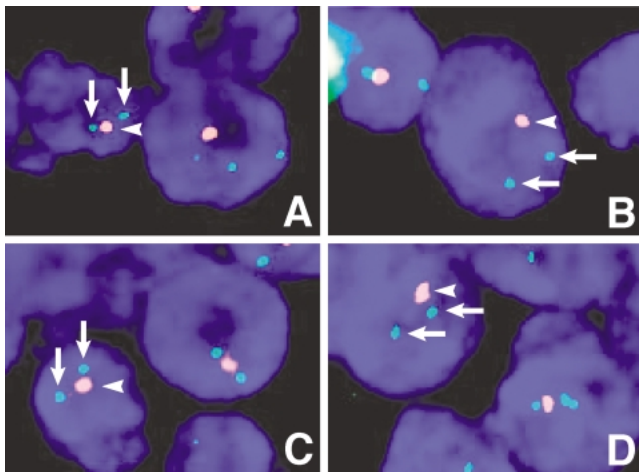
Primary tumor in the brain is thought to spread in three ways: local invasion, seeding via the cerebrospinal fluid pathways, and remotely through the lymphatic and vascular channels.<sup>5)</sup> The brain and spinal cord contain no lymphatic pathways,<sup>21,22)</sup> but once the tumor cells invade the dura mater, extracranial metastasis via the lymphatic system becomes possible, and could especially occur after craniotomy. Surgical procedures can increase the risk of metastasis outside the nervous system via the lymphatic system as well as the vascular channel.

Multiple craniotomies, shunt operations, and long-term survival are considered to be critical factors predisposing to extracranial metastasis.<sup>3,7,11,15,19)</sup> Extracranial metastasis without previous surgical intervention is rare, with only 24 (8.5%) cases of spontaneous metastasis among 282 reported cases of extracranial spread.<sup>6)</sup> Another study showed that most cases of extraneural metastasis occurred after surgical excision of the primary tumor.<sup>7)</sup> Shunt operation is also a critical factor for seeding via cerebrospinal fluid to extracranial spaces. In addition, the prolonged survival times related to the recent improvement of therapy has increased the number of extracranial metastases.<sup>12,19)</sup> In our case, craniotomy was an important factor in the occurrence of the extracranial metastases.

Therapy for the metastatic site of oligodendroglioma achieved marked response in the bone metastasis of anaplastic oligodendroglioma using temozolomide,<sup>11)</sup> and marked reduction of spinal epidural metastasis of oligodendroglioma by radiation therapy.<sup>18)</sup> In the present



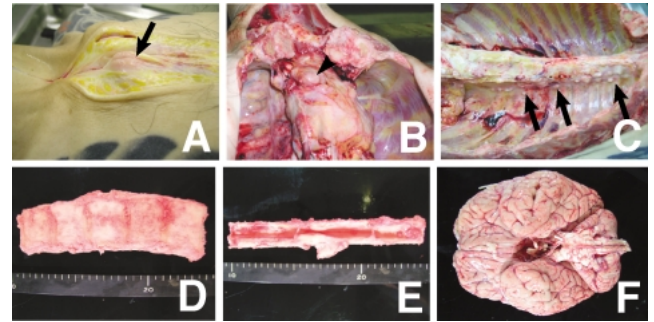
**Fig. 2** Photomicrographs of the cerebral lesion showing a highly cellular tumor with rounded hyperchromatic nuclei and perinuclear halos, with vascular endothelial proliferation, mitotic figures, and cellular anaplasia suggesting anaplastic oligodendroglioma (A), and olig2 immunohistochemistry demonstrating a high ratio of positive cells (B). Photomicrographs of tissues from the cervical lymph node (C, D) showing metastatic oligodendroglial cells. A, C: hematoxylin-eosin stain,  $\times 400$ ; B, D: olig2 immunostain,  $\times 400$ .



**Fig. 3** Representative hybridizations from the brain tumor and the cervical lymph node. Some signals are missing due to nuclear truncation: 1p deletion with 1 orange (1p, arrowhead) and 2 green (1q, arrows) signals are observed in the nuclei of the brain tumor (A) and the cervical lymph node (B). Similarly, 19q deletion with 1 orange (19q, arrowhead) and 2 green signals (19p, arrows) are observed in the brain tumor (C) and the cervical lymph node (D), suggesting 1p19q loss of heterozygosity.

case, we did not perform further treatment because of the patient's refusal. Adjuvant therapy to the metastatic site should be considered, depending on the general condition of the patients.

Oligodendroglioma is characterized by 1p19q LOH,



**Fig. 4** Representative photographs of the metastatic lesions in the lymph nodes (A, arrow), thymus gland (B, arrowhead), chest wall (C, arrows), vertebrae (D), and dura mater of the spine (E). No remarkable sign of recurrence was observed in the brain (F).

which is unique to oligodendroglioma and not seen in other low-grade gliomas.<sup>4</sup>) Deletions of chromosomes 1p and 19q are correlated with longer survival in oligodendroglioma, as well as better response to the chemotherapy.<sup>2,17</sup> 1p19q LOH may be closely connected to classic oligodendroglial morphology, longer survival, and sensitivity to alkylating chemotherapeutic agents and radiation.<sup>12</sup> The presence of 1p19q LOH may provide proof of oligodendroglioma, as 1p19q LOH has been reported to occur in over 85%<sup>19</sup> and 68% of oligodendrogliomas,<sup>20</sup> suggesting the presence of 1p19q LOH is strongly correlated with the histological diagnosis corresponding to oligodendroglioma.

Evaluation of the molecular and genetic alterations in previous cases of oligodendroglioma with extracranial metastasis showed 1p19q LOH in both brain tumor and parotid gland by capillary electropherograms using deoxyribonucleic acid (DNA) extract,<sup>19</sup> LOH of 1p, but not 19q, in the original tumor and bone metastasis by genetic analysis of DNA,<sup>4</sup> and 1p19q LOH and 1p LOH in the brain lesion and extracranial metastasis, respectively.<sup>12,13</sup> In the present case, we demonstrated 1p19q LOH in both the intracranial tumor and cervical tumor by FISH. Therefore, deletion of 1p and 19q might be relevant to extracranial metastasis of oligodendroglioma, possibility as longer survival led by 1p19q LOH might increase the chance for metastasis. Another possibility is that 1p19q LOH might be more prone to metastasis.

The present case of metastatic oligodendroglioma showed that 1p19q LOH was present in both the primary and metastatic tumors, suggesting that 1p19q LOH is related to extracranial metastasis. Extracranial metastasis occurred despite absence of marked enlargement of the brain lesion after the treatment, so the possibility of extracranial metastasis of oligodendroglioma should be considered, especially if 1p19q LOH is found in the primary tumor.

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