

Metastatic anaplastic oligodendroglioma

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Abstract

Metastization from a brain primary tumor is a rare event. The mechanisms of metastization and the best treatment approach are still unknown. Knowledge is, so far, mostly based on case reports.

We report a case of a patient with the diagnosis of an anaplastic oligodendroglioma, presenting, 9 months after the brain surgery, with spinal cord compression and pleural effusion. The patient underwent surgery for decompression and local radiotherapy to D12-L5, 30 Gy, 10 fractions and the histology confirmed metastasis of oligodendroglioma. Cytology of

pleural liquid confirmed the same origin. The patient started temozolomide with good clinical response and stabilization of the disease for 9 months.

This is an uncommon case of bone and pleural metastization of anaplastic oligodendroglioma that had a good response to temozolomide in the metastatic setting.

Keywords: Anaplastic oligodendroglioma. Brain tumors. Metastasis.

Palabras clave: oligodendroglioma anaplásico. Tumores cerebrales. Metástasis.

Introduction

Oligodendroglioma is a rare tumour with an incidence of 0.35/100.000 per year, representing about 4% of the malignant brain primary malignancies¹². Although brain tumours were believed not to be capable of metastasize, there have been throughout the years various case reports showing extracranial metastization of a brain primary^{1,7}. Liwnicz et al, reviewed 116 cases of extraneural metastization of brain tumours. In this review, the most common primary was glioblastoma multiforme (41.4%) followed by medulloblastoma (26.7%) and ependymoma⁷. Oligodendroglioma was reported as the primary in only about 4.2% of the patients⁷. Due to its rarity the diagnosis is commonly difficult and the best treatment approach is currently unknown.

Here we present a rare case of a patient with confirmed metachronous metastization to the bone presenting with spinal cord compression and pleural effusion.

Case Report

We report the case of a patient 58 years old, without relevant past medical or familiar history, presented with headaches and behaviour changes in March 2011. The MRI (magnetic resonance imaging) showed a frontal lesion with 70 mm, suggestive of a glioma (fig. 1). The patient was submitted to a craniotomy with removal of the lesion May 2011.

The final histologic diagnosis was of an anaplastic oligodendroglioma (WHO grade III). Post-surgery he was submitted to whole brain radiotherapy with 60Gy in 30 fractions with IMRT (intensity modulated radiotherapy), that he completed in July 2011.

In December 2012, the patient developed headache and emesis. The MRI was repeated and did not show signs of recurrence. Three months later, he presented sciatic pain and gait claudication. A CT (computed tomography) scan was performed that showed diffuse bone metastasis with a soft tissue mass pressing the spinal cord in L3, L4 and the cauda equina (fig. 2). Subsequently, in March 2013, he underwent surgery for decompression and subtotal excision of

the mass. The histologic results showed metastasis of previous diagnosed oligodendroglioma, with the co-deletion of 1p/19q (fig. 3). The repeated MRI persisted without signs of cerebral recurrence. Staging PET-CT (positron emission tomography-CT) scan showed a bilateral pleural effusion, bone lesions without significant captation and mediastinal lymph nodes. The cytology of the pleural effusion showed the presence of glial cells. After surgery, radiotherapy to D12-L5 was delivered with 30 Gy/10 fractions with 3DRT.

In June 2013, post-surgery and radiotherapy, his performance status was ECOG (Eastern Cooperative Oncology Group) 2 and described uncontrolled pain. He started paliative temozolomide 150 mg/m² from D1-D5 with improvement of the clinical status and stabilization of the disease. In April 2014, after 10 cycles of treatment there was clinical progression with re-accumulation of the pleural effusion and temozolomide was suspended. He died 3 months later.

Discussion

The event of metastization of primary brain malignancies is a rare event. Smith et al, described an incidence of 0.4% in 8000 patients analysed¹⁴.

The reasons for this low incidence of metastasis are unclear. Initial theories reported as possible contributor factors: the presence of blood brain barrier, difficulty of neural cells to grow outside the central nervous system (CNS), the absence of lymphatic vessels in the brain tissue, the thin walled veins easily collapsed by tumour growth, and the relative short survival not allowing time for the metastatic process^{5,6}. Another theory is that the brain environment is not hostile enough to give a selective advantage to metastatic clones. As the brain has a relative low quantity of connective tissue, cells are not selected based on their capacity of invasion⁵.

There have been proposed three main pathways for metastization: local invasion, seeding through hematogeneous or lymphatic pathways or through the cerebrospinal fluid (CSF) pathways². Even though the cerebral tissue does not have

Figure 1. Initial MRI showing an expansive cortico-subcortical frontal lesion.

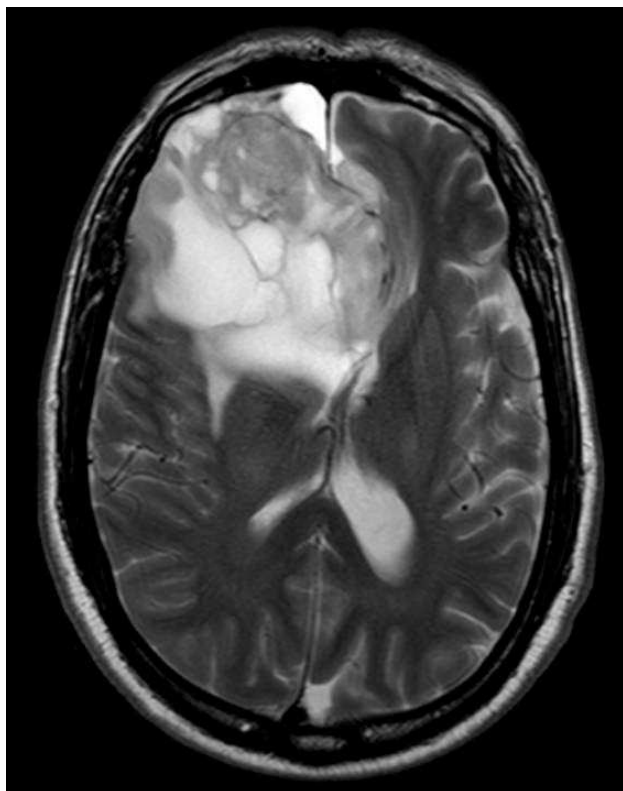


Figure 2. Spinal MRI showing bone metastasis and signs of a soft tissue mass causing cord compression in L3, L4 and cauda equine.



lymphatics once coverage membranes are compromised the lymphatic spread becomes possible⁵. It has been also postulated that surgery could open the vascular channels by leading to seeding. It is also possible that the proliferation of capillaries as part of the reparative process give access to metastization⁵. Multiples craniotomies, the presence of shunt and long survival are indeed identified risk factors for metastization⁹. Eventhough, most patients seem to metastatize after surgery, it is unlikely surgery is the main contributive factor, as if so, the incidence of metastasis would be significantly higher.

If metastization from brain primary is uncommon, metastization from oligodendroglioma is extremelly rare. Li et al, 2014, reviewed the metastized oligodendroglioma cases to date and have iddentified 61 cases, 35 male (54.1%) and 17 (27.9) female, with a median age of 40 years. The most frequent metastatic site was bone and bone marrow (n=47; 42.7%), followed by lymph nodes (n=22, 20%). Pleural metastasis were found in 4 patients (3.6%). The overall survival was 38 months (3-288 months)⁶.

Zustovich and co-workers, explained this predilection for the bone might be related to the Neural Cell Adhesion Molecule (NCAM) that is expressed in both glioma cells and osteoblasts and might promote NCAM-NCAM connections¹⁵.

The presence of oligodendroglioma cells in the CSF was present in up to 14 % of the patients, but the metastization was a rare event³. Ozisik and co-workers, identified 16 patients in the literature with symptomatic spinal metastization¹³.

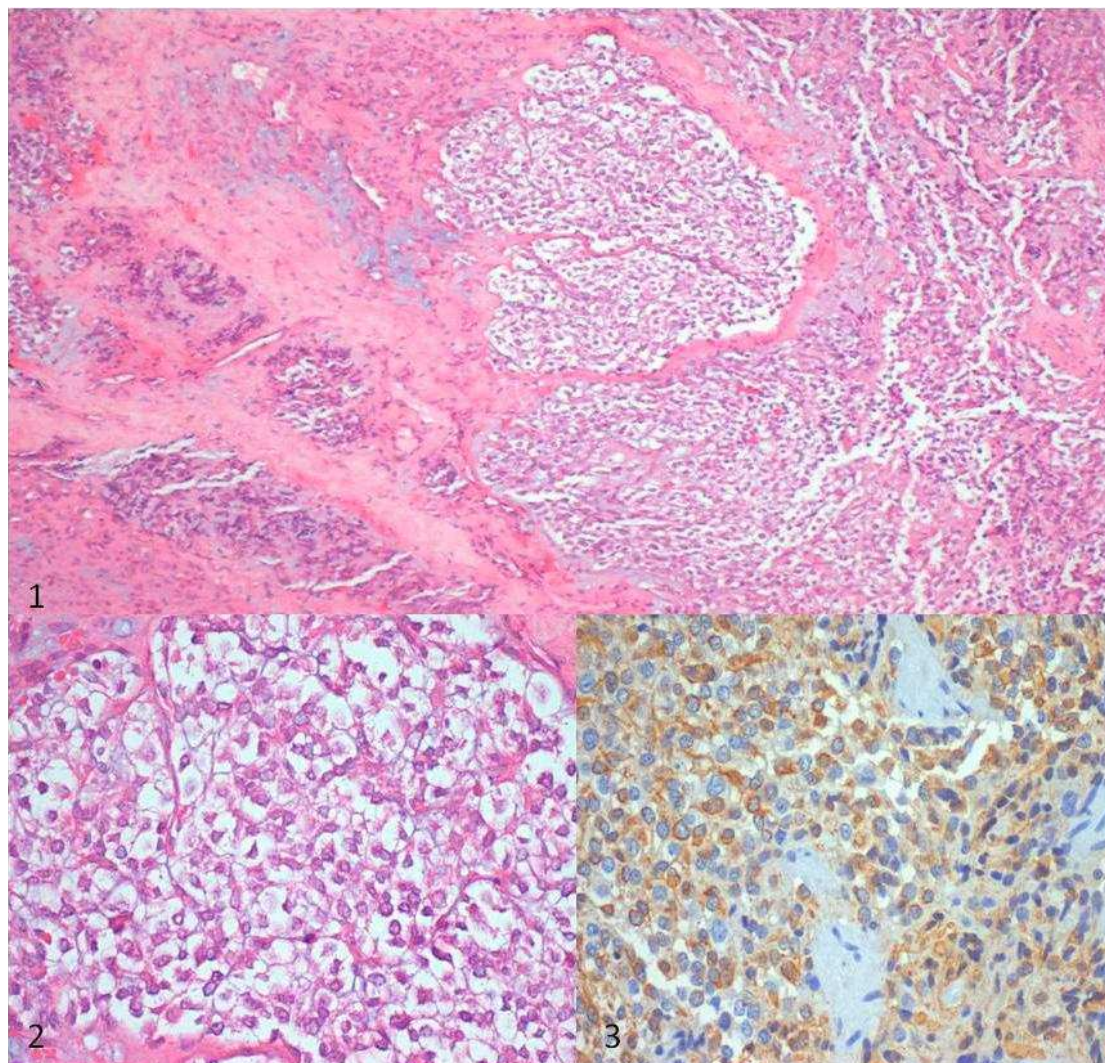
Our patient was diagnosed with metastasis after 9 months after resection of the primary tumour and had an overall survival of 17 months post-diagnosis of metastasis which is inferior to the median reported in Li and co-workers, however the population was quite heterogeneous⁶. As the patient presented with both pleural and diffuse spinal metastasis the hematogenous dissemination was probably the cause, even though invasion of CSF can not be excluded.

The best treatment in the case of metastasis is still unknown. Our patient was treated with temozolomide 10 cycles with stabilization of the disease and significant improvement of the pain and clinical status.

Maloney and co-workers, describe a case of another patient with bone metastasis with similar response. Temozolamide might be a good treatment not only for local recurrence but also in the rare event of metastatic disease¹⁰.

Molecularly there have been some attempts to iddentify particular alterations that can predispose to metastasis. The codeletion of 1p/19q has been related with more incidence of metastasis which may be related with the long survival associated with this deletion¹¹. In the WHO 2016 revision the codeletion of 1p/19q has been incorporated in the definition of oligodendroglioma this relation might be outdated⁸. In our patient, the codeletion of 1p19q was found in the metastasis which is a strong indicator of the oligodendroglioma origin. Giordana and co-workers described a molecular analysis of a brain metastasis from oligodendroglioma identified the presence of a deletion on CDKN2A that leads to lack of p16 which could be important

Figure 3. (1) Histology of the spinal cord metastasis Hematoxylin & eosin, 100x ampliation; (2) Histology of the spinal cord metastasis Hematoxylin & eosin, 400x ampliation; (3) Immunohistochemistry for Glial fibrillary acid protein (GFAP).



in the processe of metastization⁴. There has also been postulated that PTEN loss might also make patients more prone to extracranial metastization, but the data are still insufficient¹⁵. In conclusion, metastization in oligodendrogloma patients is a rare event and the diagnosis and best management are still unclear. It is important to be aware of the possibility of metastization and investigate symptomatic patients. Further investigation is needed to identify clinical and molecular biomarkers that can predict a metastatic pattern of disease. Temozolamide might be useful to control disease and symptoms also in this situations.

References

- Bailey P, Cushing P: A classification of the tumors of the glioma group on histogenetic basis with correlated study of prognosis. Philadelphia J.B. Lippincott: 1926. p. 175.
- Carlsen JG, Tietze A, Lassen YA, Rosendal F: Paraplegia due to drop metastases from anaplastic oligodendrogloma. *British Journal of Neurosurgery* 26(1): 94-95, 2012
- Engelhard HH. Current diagnosis and treatment of oligodendrogloma. *Neurosurg Focus*. 12(2): 1-7, 2002.
- Giordana MT, Ghimentì C, Leonardo E, Balteri I, Ludicell M, Duó D: Molecular genetic study of a metastatic oligodendrogloma. *J Neurooncol* 66(3): 265-71, 2004.
- Kim JG, Park CO, Hyun KD, Ha YS: Spinal Epidural Metastasis of Cerebral Oligodendrogloma. *Yonsei Medical Journal* 44:340-346, 2003.
- Li G, Zhang Z, Zhang J, Jin T, Liang H, Gong L, Cui G, Yang H, He S, Zhang Y, Gao G: Occipital anaplastic oligodendrogloma with multiple organ metastases after a short clinical course: a case report and literature review. *Diagnostic Pathology* 9:17, 2014.
- Liwnicz BH, Rubinstein LJ: The pathways of extraneural spread in metastasizing glioma. A report of three cases and critical review of the literature. *Hum Pathol* 10: 453-67, 1979.
- Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW: The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 31(6):803-202016.
- Macdonald DR, O'Brien RA, Gilbert JJ, Cairncross JG: Metastatic anaplastic oligodendrogloma. *Neurology* 39: 1593-1596, 1989.
- Maloney PR, Yamaki VN, Kumar R, Johnson D, Hunt C, Jentoft ME, Clarke M: Osteosclerosis secondary to metastatic oligodendrogloma. *Rare tumours* 9: 6837, 2017.
- Noshita N, Mashiyama S, Fukawa O, Asano S, Watanabe M, Tominaga T: Extracranial metastasis of anaplastic oligodendrogloma with 1p19q loss of heterozygosity. *Neurol Med Chir* 50:161-614, 2010.
- Ostrom QT, Gittleman H, Xu J, Kromer C, Wollinsky Y, Kruchko C, Barnholtz-Sloan JS: CBRTUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2009-2013. *Neuro-Oncology* 18: v1-v75, 2016.
- Ozişik PA, Işikay I, Oruçkaptan H, Söylemezoğlu F, Özcan OE: Unusual Massive spinal metastasis of an intracranial oligodendrogloma. *Turkish Neurosurgery* 18(3): 276-280, 2008.
- Smith DR, Hardman JM, Earl KM: Metastasizing neuroectodermal tumors of the central nervous system. *J Neurosurg* 31:50-8, 1969.
- Zustovich F, Puppa AD, Scienza R, Anselmi P, Furlan C, Cartei G: Metastatic oligodendroglomas: a review of the literature and case report. *Acta Neurochirurgica* 150:699-703, 2008.