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. Citology 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 metastatization of anaplastic oligodendroglioma that had a good response to temozolomide in the metastatic setting.

Keywords: Anaplastic oligodendroglioma. Brain tumors. Metastasis.

Case Report
Here we present a rare case of a patient with confirmed metachronous metastatization to the bone presenting with spinal cord compression and pleural effusion. Metastasis from a brain primary tumor is a rare event. Smith et al, described an incidence of 0.4% in 8000 patients analysed4. 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 process5,6. 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 invasion7.

Discussion
The event of metastatization of primary brain malignancies is a rare event. Smith et al, described an incidence of 0.4% in 8000 patients analysed4. 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 process5,6. 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 invasion7.

There have been proposed three main pathways for metastatization: local invasion, seeding through hematogeneous or lymphatic pathways or through the cerebrospinal fluid (CSF) pathways. Even though the cerebral tissue does not have...
lymphatics once coverage membranes are compromised the lymphatic spread becomes possible\(^5\). It has been also postulated that surgery could open the vascular channels by leading to seeding. It is also possible that the proliferation of cappilaires as part of the reparative process give access to metastization\(^5\). Multiples craniotomies, the presence of shunt and long survival are indeed identified risk factors for metastization\(^9\). Eventhough, most patients seem to metas-tatize 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 oligodendrogloma is extremelly rare. Li et al, 2014, reviewed the metastized oligodendrogloma cases to date and have idddentified 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 Mollecule (NCAM) that is expressed in both glioma cells and osteo-blasts and might promote NCAM-NCAM connections\(^15\).

The presence of oligodendrogloma cells in the CSF was present in up to 14 % of the patients, but the metastization was a rare event\(^3\). Ozisik and co-workers, identified 16 patients in the literature with symptomatic spinal metastization\(^13\).

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 heterogeneous\(^6\). 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 unknow. 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 disease\(^10\).

Molecularly there have been some attempts to iddentify partic-ular alterations that can predispose to metastasis. The codeletion of 1p/19q has been related with more incidence of me-tastasis which may be related with the long survival associated with this deletion\(^11\). In the WHO 2016 revision the codeletion of 1p/19q has been incorporated in the definition of oligoden-droglioma this relation might be outdated\(^8\). In our patient, the codeletion of 1p19q was found in the metastasis which is a strong indicator of the oligodendrogloma origin. Giordana and co-workers described a molecular analysis of a brain metastasis from oligodendrogloma identified the presence of a deletion on CDKN2A that leads to lack of p16 which could be important.
in the process of metastization. There has also been postulated that PTEN loss might also make patients more prone to extracranial metastization, but the data are still insufficient.

In conclusion, metastization in oligodendroglioma 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 these situations.

References