Contralateral Crossrecurrence of a Malignant Glioma: A Case With Long-Term Survival

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Abstract

In surgically treated glioblastomas a recurrence of the primitive tumour with subsequent infiltration of the surrounding parenchyma is the commonest cause of death.

In the vast majority of the cases it occurs within or nearby the tumour site. However, in a few patients the recurrence is located far from the primary tumour site and radiological heralding signs may even not be visible.

This paper illustrates the clinical and radiological patterns of a 56 year old woman with a right occipital glioblastoma and a late contralateral cross recurrence in the left frontal lobe.

After a complete surgical removal, the patient experienced an high quality 6 year-survival period. The tumour was expressing the promoter to methylation but was wild type for IDH mutation. It was treated with radiotherapy plus Temozolamide.

Lately she developed a very unusual contralateral cross-recurrence with these cond tumour genetically similar to the original one (MGMT promoter and IDH wild type) but rapidly and relentlessly fatal.

As a peculiar event we have an MRI, in course of a routine control done 4 months before the second hospitalization, which shows no sign of recurrence.

This casts a further light on the speed and modality of growth of an high grade glioma.

Introduction

Despite advances in several oncological fields, the prognosis of patients affected by glioblastoma is still poor and the median survival remains very short (15 months).

The general features for glioblastomas quote a 3-5% survival rate at three years and 2-3% at 5 years [1,2]. In the patients receiving the Stupp protocol we find a 16% rate at 3 years and 10% at 5 years [3,4].

Some patients survive even more. The features that allow to live longer are not completely understood but the progress achieved in neurosurgical techniques, focal radiotherapy and chemotherapy with temozolomide have certainly helped. They are referred to as long-term survivors and their number seems to be strictly dependent on the molecular pattern of the glioblastoma, namely the MGMT promoter methylation, the IDH status and the combination of the two, as it has been recently stated in the paper by Molenaar et al. [5].

In some cases the cause of death reportedly has no correlation with the original glioblastoma nor with complications or sequelae of its treatment [6,1]. However, the majority of patients die from one or more relapses of the original glioblastoma. Most occur in the original surgical site or adjacent to it, but 5%-20% of recurrences are found to emerge distant in the ipsilateral hemisphere or even in the contralateral one [7]. Very often, these cases lack of signal abnormalities in T2 MRI and no leptomeningeal involvement is visible, neither in the brain parenchyma adjacent to the original glioblastoma nor in the contralateral area of relapse.

A deeper understanding of such cases may be helpful to gain in sights into the entire development of the glioblastoma both concerning the bulk and the surrounding parenchyma.
Case Presentation

A 56-year-old women was admitted, at the end of November 2006, because of generalized seizures. She showed apathy, mild disorientation, sensorial disphasia and had been complaining about visual disturbances for a few days before admission. At neurological examination a right homonimous lateral hemianopsia was present. The MRI revealed a right parieto-occipital contrast enhancing tumor (Figure 1). Spectroscopy also suggested the presence of an high grade glioma.

The patient was operated on and the tumour completely removed. The postoperative follow-up was uneventful. Histopathological examination revealed a WHO grade IV glioma. The proliferation index was 22% and the MGMT-promoter methylated. The IDH status was wild type, as it usually happens in the newly diagnosed glioblastomas [8]. The patient was treated according to Stupp’s protocol [4] with conformal radiotherapy and adjuvant chemotherapy. The total dose delivered with linear accelerator was 60 Gy in 30 fractions of 2 Gy 5 days a week during a 6 week period.

Daily temozolomide, 75 mg per square meter of body-surface area, was administered during radiotherapy. After a 4-week break, six monthly cycles of adjuvant temozolomide, at daily dose of 200 mg for square meter, 5 days per week, were added.

The patient was regularly examined and remained in good health. An MRI done at the end of September 2011 (5 years after surgery) still showed no signs of relapse (Figure 2 and 3). Then the patient was re-admitted in our department at the beginning of February 2012. She showed disorientation and uncertain walking during the last week. A CT scan displayed a space occupying lesion surrounded by edema in the left frontal region. MRI (Figure 4) and spectroscopy again oriented for a high grade glioma. T2 MRI contrast enhanced scan still did not show any connection between the left frontal lesion and the primary right parieto-occipital glioblastoma removed in 2006 (Figure 5). The patient underwent a new surgery in February 2012 and the postoperative follow-up was good.

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The histopathological examination confirmed a WHO grade IV glioma, Ki-67-positive cells at 17% rate, the MGMT-promoter methylated and IDH wild-type [9,10]. The molecular pattern was so the same of the original tumour.

Being the new lesion in the contralateral hemisphere, the patient was enrolled once more for Stupp’s protocol with conformal radiotherapy and adjuvant temozolomide. Finally, she died at the end of 2012, approximately one year after the second surgery, due to a local recurrence (Figure 6) and subsequent diffusion of the disease.

Discussion

The long-term survival of patients diagnosed with glioblastoma multiforme is a rare but possible event [11]. Their number has slightly increased in the last years compared to the past [1,2,12]. The clinical and molecular features that allow some patients to live longer are under debate. To date, the more relevant factor (present in 74% of patients evaluated) contributing to a prolonged survival is the methylation of the MGMT promoter, particularly in those patients receiving focal radiotherapy and adjuvant temozolomide [10].

In particular, this turns to be true in young patients with a good Karnofsky personal score (KPS) at the time of the diagnosis.

Socioeconomic, environmental and occupational factors had no relevance at all [13]. In this case a new tumor, with a second stem cell giving origin to a second glioblastoma, cannot be excluded. Also, a malignancy associated with the radiotherapy could also be the case but the simpler, and probably most obvious solution, is a relapse caused by one of the cancer stem cells settled in the whole parenchyma from the site of the primary glioblastoma since its onset [14]. The identical molecular patterns of the two tumours, even after years, strongly favour this hypothesis. Recently, researchers have documented that a hierarchical model with the cancer stem cells at the top of the pyramid [15,16,17] exist in the glioblastoma and in other tumor types. It is highly probable that they remain quiescent in the brain until when, for some reasons, reactive. In histological brain sections of mice transplanted with glioblastoma cells, a gradient of invasive tumor cells is documented. This means that outside the macroscopic bulk of the glioblastoma, there may be a decreasing number of micro infiltrating CSCs which settle quiescent in the parenchymal niche. Indirect evidence of this is drawn from the early unsuccessful attempts made by neurosurgeons to remove an entire right emisphere affected by a glioblastoma. Their efforts failed due to relapse in the contralateral hemisphere.

In our patient, however, the absolute absence of any sign of recurrence in the original tumour bed until only 4 months before, confirmed by an MRI with contrast enhancement and a spectroscopy, sounds extremely peculiar and has motivated the case illustration. It seems unbelievable, in fact, that no signs of recurrence have been observed in the contrast enhanced MRI along the white interconnecting fibers.

Conclusion

This case emphasizes once more the importance of the surgical act and that, probably, the recurrences originate in two different ways.

The first and more common modality, derives from active Cancer Stem Cells (CSCs) of the bulk tumor not completely removed at time of first surgery. The second, and less frequent, probably stems from quiescent CSCs settled in the parenchymal niche. The identification of membrane antigens or receptors identifying these stray cells located along these called glial fields or “Gliarasen” of the German neuropathologists, could be of utmost importance for the development of new therapeutic agents against the glioblastoma.

References