

## GLIOBLASTOMA MULTIFORME AND BREAST CANCER: REPORT ON 11 CASES AND CLINICO-PATHOLOGICAL REMARKS

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The association between breast cancer and glioblastoma multiforme has not been amply analyzed in the literature. We describe 11 female patients with a diagnosis of glioblastoma multiforme who were treated when younger for breast cancer. We believe that this association is not due to chance but rather to genetic changes in hormone status and in particular to sex hor-

mones. Another important point of view is represented by the chemotherapy treatment of breast cancer, which could have a carcinogenic effect and explain the growth of glioblastoma. This consideration, in our opinion, is important, because more effort should be made to understand the pathogenesis of glioblastoma multiforme and to improve the therapeutic approaches.

**Key words:** breast cancer, chemotherapy, glioblastoma multiforme, radiotherapy, secondary malignancies, surgery.

### Introduction

In Italy, 7 of 100 women have during their life a breast cancer (BC), and the neoplasm is responsible for 18% of female mortality<sup>1,2</sup>. The incidence of BC in Italy is 60-80 new cases per year over 100,000 women<sup>3,4</sup>.

Glioblastoma multiforme (GBM) incidence in Europe and in North America countries is in the range of 2-3 new cases per 100,000 per year<sup>5</sup>. Glioblastoma may manifest at any age, with a peak of incidence between 45 and 70 years (mean, 53) and a predominance for males (M : F ratio, 1.5 : 1)<sup>5</sup>.

According to the literature, the association between BC and GBM is not as common as the association between BC and other primary malignant tumors or intracranial tumors as well as meningiomas<sup>6</sup>. In contrast, we observed a series of 11 patients with positive anamnesis for BC and in whom a GBM was diagnosed.

### Case reports

Between November 1995 and December 2001, 11 females were admitted to the Neurosurgery Section of the Department of Neurological Sciences of "La Sapienza" University of Rome, Policlinico Umberto I, with a diagnosis of GBM. The average age was 61 years. They all had been previously treated for BC at a younger age (Table 1). The mean age at BC diagnosis was 42.9 years, and the average time between the BC diagnosis and the clinical onset of GBM was 18 years.

Glioblastoma treatment has had a multimodality nature, based on cytoreductive surgery followed by adjuvant radiotherapy and chemotherapy (CMF). Cytoreductive surgery was obtained by the use of microsurgi-

cal methods and tools, and the extent of surgical resection was defined by the neurosurgeon's impression and, above all, by magnetic resonance imaging performed within 72 hrs of surgery.

Radiotherapy was administered using a Linac unit. Treatment fields were confined to the tumor plus a 2 cm margin over the neoplastic edema. The average length of the radiotherapy was 6 weeks, for a total dose of 60 Gy (average value).

Temozolomide was the chemotherapy drug administered to the patients. Temozolomide, among all the chemotherapy drugs, has the most favorable toxicity profile and its bioavailability after oral administration is about 100%<sup>7-10</sup>. It was administered concomitantly (1 h before radiotherapy, 75 mg/m<sup>2</sup> per day, 5 days/week) for 5-6 weeks and as adjuvant chemotherapy (200 mg/m<sup>2</sup> per day, 5 days/week, every 28 days for six cycles) after radiotherapy.

*Case 1.* The patient was a 47-year-old woman who had had BC 13 years before. The staging was T1N0M0. She was operated on with a quadrantectomy, followed by local radiotherapy (50 Gy). The patient also underwent chemotherapy based on a CMF schedule: cyclophosphamide (100 mg/m<sup>2</sup> per os from the 1<sup>st</sup> to the 14<sup>th</sup> day of each month), methotrexate (40 mg/m<sup>2</sup> iv, the 1<sup>st</sup> and the 8<sup>th</sup> day of each month), and fluorouracil (600 mg/m<sup>2</sup> iv the 1<sup>st</sup> and the 8<sup>th</sup> day of each month) for 12 months. The clinical evidence of GBM was characterized by the presence of seizures. The GBM was in the left frontal lobe. The patient had a multimodality approach, based on cytoreductive surgery (total removal), followed by radiotherapy and concomitant and adjuvant temozolomide. Exitus was 13 months after the surgical approach for a myocardial infarction.

**Table 1 - Characteristics of our series of patients with glioblastoma multiforme**

Patient no.	Breast cancer age (yr)	GBM age (yr)	Interval	GBM localization	GBM clinical evidence	GBM treatment	Survival (mo) after first surgery	Breast cancer staging	BC treatment
1	34	47	13	Left frontal lobe	Seizures	Surgery Radiotherapy Chemotherapy	13	T1N0M0	Quadrantectomy, radiotherapy, chemotherapy
2	45	56	11	Right frontal lobe	Seizures	Surgery, radiotherapy, chemotherapy	11	T1N0M0	Quadrantectomy, radiotherapy, chemotherapy
3	40	57	17	Right frontal lobe	Endocranial hypertension	Surgery*, radiotherapy, chemotherapy*	18	No data	Mastectomy, radiotherapy, chemotherapy
4	36	53	17	Right temporal lobe	Temporal seizures	Surgery	Lost to follow-up	T2N1M0	Mastectomy, radiotherapy, chemotherapy
5	49	60	11	Left frontal lobe	Change in character	Surgery, radiotherapy, chemotherapy	13	TisN0M0	Tumorectomy, radiotherapy
6	52	71	19	Posterior part left frontal lobe	Apathy, sopor	Biopsy	5	No data	Mastectomy
7	40	58	18	Left occipital lobe & splenium	Drowsiness	Biopsy	4	T2N1M0	Mastectomy, radiotherapy, chemotherapy
8	55	77	22	Right frontal lobe	Drowsiness, apathy	Surgery, radiotherapy, chemotherapy	13	No data	Mastectomy, radiotherapy, chemotherapy
9	37	55	18	Right frontal lobe	Seizures	Surgery*, radiotherapy, chemotherapy*	23	No data	Mastectomy, radiotherapy, chemotherapy
10	32	51	19	Right frontal lobe	Seizures	Surgery**, radiotherapy, chemotherapy*	27	T1N0M0	Quadrantectomy, radiotherapy, chemotherapy
11	52	86	34	Thalamus	Hemiplegia, hemianesthesia	Biopsy	4	No data	Mastectomy

Surgery\*: the patient underwent a second cytoreductive surgery for a relapse of the GBM; surgery\*\*: the patient underwent a third cytoreductive surgery for a relapse of the GBM; chemotherapy\*, the patient had a new treatment with temodal after the second surgical approach.

*Case 2.* The patient was a 56-year-old woman who had had BC (stage T1N0M0) 11 years before. The BC treatment was the same as that of case 1, with quadrantectomy, local radiotherapy and CMF. The GBM, which was in the right frontal lobe and had a clinical manifestation with seizures and loss of consciousness, was treated with a multimodality approach, and death occurred after 11 months for a diffuse relapse of the neoplasm.

*Case 3.* A 57-year-old woman treated for BC 17 years before. No data was available about TNM. Treatment was based on mastectomy plus local radiotherapy (50 Gy) and CMF for 12 months. The GBM, which was in the right frontal lobe, had a clinical manifestation with endocranial hypertension. The patient underwent a first surgical approach plus radiotherapy (60 Gy) and CMF (concomitant and adjuvant temodal). After 13 months there was a clinical and radiological relapse of the neoplasm, which was treated by a new cytoreductive surgery (subtotal removal) and adjuvant CMF (temodal). Exitus occurred after 18 months.

*Case 4.* A 53-year-old woman treated for BC (T2N1M0) 17 years before. She had undergone mastectomy and received local radiotherapy (50 Gy) and CMF for 12 months. The GBM was in the right temporal lobe and the clinical manifestation was characterized by temporal seizures. The patient underwent a surgical ap-

proach, with a total removal of the GBM, and was then lost to follow-up.

*Case 5.* A 60-year-old woman who had had a BC (TisN0M0) 11 years before. She had undergone tumorectomy and received local radiotherapy (50 Gy) but not CMF. The GBM was in the left frontal lobe, and the clinical manifestation was an important change in character. She received a multimodality treatment based on cytoreductive surgery (total removal) plus radiotherapy (60 Gy) and chemotherapy (concomitant and adjuvant temodal). Clinical and radiological relapse occurred 11 months later. The patient refused other therapy. Exitus occurred 13 months after surgery.

*Case 6.* A 71-year-old woman treated by mastectomy for BC 19 years before. No data were available on the staging of the neoplasm. The GBM was located in the posterior part of the left frontal lobe, and the clinical manifestation was based on apathy and sopor. The patient underwent a biopsy and refused other therapy. Exitus occurred 5 months later.

*Case 7.* A 58-year-old woman who had had a BC (T2N1M0) 18 years before. She had been treated by as-tectomy plus local radiotherapy (50 Gy) and CMF. The GBM was in the left occipital lobe with invasion of the splenium. The patient suffered from drowsiness. She underwent a biopsy without other therapy. Exitus occurred 4 months later.

*Case 8.* A 77-year-old woman who had had a BC 22 years before. No data were available on the staging of the neoplasm. She had undergone mastectomy plus local radiotherapy (50 Gy) and CMF. The GBM was in the right frontal lobe. The clinical manifestation was drowsiness and apathy. She underwent a surgical approach (total removal) followed by radiotherapy (60 Gy) and chemotherapy (concomitant and adjuvant temozolomide). After 12 months the patient had flue, and 10 days later there was a radiological and pseudoencephalitic relapse. Exitus occurred 13 months after surgery.

*Case 9.* A 55-year-old woman who had had a BC 18 years before. No data were available on the staging of the neoplasm. She had undergone mastectomy plus radiotherapy (no data available) and CMF. The GBM was in the right frontal lobe, clinically evidenced by seizures. The patient underwent a first surgical approach (total removal) plus radiotherapy (60 Gy over 6 weeks) and chemotherapy (concomitant and adjuvant temozolomide). After 13 months there was clinical and radiological relapse of the neoplasm, which was treated by a new cytoreductive surgery (total removal) and chemotherapy (temozolomide). Exitus for a lung embolus occurred 23 months after the first surgical approach. There was no clinical or radiological evidence of a relapse of the neoplasm.

*Case 10.* A 51-year-old woman who had had a BC (T1N0M0) 19 years before. She had undergone quadrantectomy and received local radiotherapy (50 Gy) and CMF. The clinical evidence of GBM was characterized by the presence of seizures. The GBM was in the right frontal lobe. The patient underwent a first surgical approach (total removal) followed by radiotherapy (60 Gy over 6 weeks) and chemotherapy (concomitant and adjuvant temozolomide). There was a clinical and radiological relapse of the disease after 11 months. The patient underwent a second operation after 12 months (total removal), followed by temodal therapy. There was a new radiological relapse of the disease after 7 months. The patient underwent a third cytoreductive surgery (total removal) after 8 months. Exitus occurred 27 months after the first surgery. The GBM had spread over the deep encephalic structures.

*Case 11.* An 86-year-old woman who had undergone a mastectomy for BC 34 years before. No data were available on the staging of the neoplasm. The GBM was in the left thalamus. The patient had a contralateral hemiplegia and hemianesthesia. She underwent biopsy of the lesion. Exitus occurred 4 months later.

## Discussion

There are only a few reports in the literature about the association between BC and GBM<sup>11,12</sup>. In contrast, there are several clinical reports on patients who have had BC and meningioma<sup>6</sup>.

Although it is true that the association between BC and GBM is not as common as the association between

BC and meningioma, we observed 11 patients, treated when younger for BC, with a histologically proven diagnosis of GBM. We believe that the association is not due to chance<sup>12</sup>.

An important aspect that should be analyzed is the genetic one. The most important genes, BC predisposing, are BRCA1, BRCA2 and p53. BRCA1 mutations are associated with familial breast and/or ovarian cancer, whereas BCRA2 deals with familial site-specific BC<sup>13</sup>. p53 mutations generally predispose to the Li-Fraumeni syndrome, specific of children and young adults, in which there is the association between breast, brain, adrenocortical, hematological cancer and sarcoma<sup>14</sup>.

Another important tumor suppressor gene, located on the 10q23 chromosomal region, is the PTEN. This gene could be an important example of a possible common genetic origin of BC and GBM. PTEN mutations are responsible for Cowden's disease, a dominantly inherited syndrome characterized by an increased risk for breast and thyroid cancer and multiple hamartomas of the skin, intestine, breast and thyroid<sup>15</sup>. However, PTEN mutations have also been found in glioblastomas and to a lesser extent in meningiomas and medulloblastomas<sup>16,17</sup>.

Tran *et al.*<sup>18</sup> pointed out the presence of one or more tumor suppressor genes on the short arm of chromosome 18, which could be involved, after a loss of heterozygosity, in non-small-cell lung cancer, GMB and BC.

The other important aspect that could explain the association between BC and GBM is endocrinological. The presence of specific steroid hormone receptors has been pointed out in a number of different neoplasms, including breast and prostate cancer. Thus, hormone therapy in those tumors is based on the concept that specific antagonists and agonists may allow modulation of the growth of the neoplasm. We believe that hormone status is also important in the growth of GBM<sup>19</sup>.

Li *et al.*<sup>20</sup> demonstrated how the increasing incidence of BC (0.5%/year between 1992 and 1998 in the USA) seems to be a result of an increasing incidence of hormone receptor-positive BC.

A study conducted on nude rats, implanted with human GBM cell lines, demonstrated that female nude rats have a survival advantage over male rats. According to the authors, the advantage was provided by hormonal status, and most of all by estrogens<sup>21</sup>.

McKinley *et al.*<sup>22</sup>, analyzing the incidence of GBM in New York State between 1976 and 1995, showed how females had a lower risk of developing glioblastoma than males. The protective effect of the sex was greater at the approximate age of menopause and decreased in postmenopausal age. Thus, gender and sex hormones play an important role in the pathogenesis of GBM.

Progesterone is also involved in regulation of the growth of brain tumors<sup>23</sup>. One study<sup>24</sup> demonstrated how the presence of progesterone receptors was high in GBM and anaplastic astrocytomas but was lower in low-grade astrocytomas.

In our study, the treatment of GBM was multimodal, based on cytoreductive surgery followed by chemotherapy (temozolomide) and radiotherapy. The chemotherapy drug was, in our schedule, temozolomide, first used concomitantly 1 h before radiotherapy (75 mg/m<sup>2</sup> per day for 5 days a week) and adjuvantly after radiotherapy (200 mg/m<sup>2</sup> for 5 days a week, every 28 days for six cycles). The recommended treatment is therefore the same as for patients with a prior GBM diagnosis. Three patients underwent cerebral biopsy and refused other therapy. One patient after cytoreductive surgery was lost to follow-up. The average survival of the 10 patients was 13.1 months, which is comparable with the mean survival of patients with glioblastoma as the first neoplasm. The average interval between BC and GBM was 18 years, which, in our opinion, is important.

There is no an absolute evidence in the literature that adjuvant CMF could be the cause of an increased risk for a second malignancy. Valagussa *et al.*<sup>25</sup> carried out a prospective study, with a mean follow-up of 12 years, on 2465 patients who received a CMF schedule for BC. They reported a relative risk of developing a second malignancy following CMF-based chemotherapy of 1.29 compared to the general female population. Breast irradiation did not increase the risk of developing a new malignancy. The authors considered the CMF schedule as a short-term effective adjuvant chemotherapy with no evidence of a significantly increased risk of developing a second malignancy, so the conclusion was that the CMF schedule, in patients with BC, should not be omitted.

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Maluf *et al.*<sup>26</sup> studied 21 patients with a diagnosis of high-grade glioma and with had a prior diagnosis of a solid tumor or hematological malignancy and concluded that the association could be due to chance. Moreover, they pointed out that the treatment of the glioma had to be the same as for a prior glioma (multimodality treatment), and the mean survival was also the same (14 months).

It should be noted that the follow-up of the patients with BC in the prospective studies, conducted to evaluate the long-term effect of adjuvant chemotherapy, was not as long as the mean interval of 18 years we observed in our study. We thus believe that further epidemiological studies, with a longer follow-up, should be carried out to improve the knowledge of BC and GBM pathogenesis and to define a better therapeutic approach.

## Conclusions

In the light of our clinical experience and according to literature data, we believe that the association between BC and GBM in our 11 case reports cannot easily be explained as a coincidence. The genetic substratum is important for predisposition to BC and GBM. Hormone status and, most importantly, sex hormones are important in the growth of BC and are also important to determine the development of GBM.

Another important aspect is the chemotherapeutic treatment of prior malignancies, in this case BC. Adjuvant chemotherapy could play an important role, even though it has not been clarified, in the genesis of a new malignant neoplasm such as glioblastoma.

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