Glioblastoma multiforme – A clinical case report

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Abstract

Glioblastoma multiforme is the most common primary brain tumor in adults. Despite research efforts and progress in neuroimaging, neurosurgery, radiation and chemotherapy, the overall survival of patients with this disease has changed little over the past 30 years. Presenting a clinical case, the authors make a short revision of the literature.

Key words: glioblastoma multiforme, primary brain tumor.

Introduction

Around 18,000 cases of malignant primary brain cancer are diagnosed in the USA every year. Approximately, 40 to 50% have Glioblastoma multiforme, being this the supratentorial brain primary neoplasm more frequent in adults. Glioblastoma multiforme is classified as Grade IV astrocytoma and occurs more frequently after 50 years of age reaching a peak in the sixth decade. It is rare in childhood, but when it occurs, it reaches children in the first decade of life. There is a slight predominance in the male gender, with a 1,5:1 ratio, being also higher in Caucasians.1,2,3

Etiology and risk factors

These tumors etiology is unknown. However, it is thought that genetic and environmental factors can contribute to its development. Hereditary causes have a minor role in its origin. Less than 5% of glioma patients present a family history of brain cancer.

Individuals with several genetic conditions such as neurofibromatosis, Turcot syndrome, Li-Fraumeni syndrome and tuberous sclerosis, are predisposed to develop malignant gliomas. In these cases, tumors tend to occur in children and young adults.

A previous cranial irradiation is the only well established risk. The prophylactic cranial radiation, in cases of acute lymphocytic leukemia increases 21 fold the incidence of primary brain tumors.[1,4]

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There are several reports in literature whereas low grade gliomas, i.e., grade I and II, can become overtime, high grade glioma. This transition is followed by a marked increase on the lesion malignant behavior.[2,4]

At least two different molecular ways lead to the development of glioblastoma multiforme. When the tumor derives from a pre-existing low grade astrocytoma, it is called a secondary glioblastoma. Often low grade astrocytomas have mutations of the tumoral suppressing gene p53 and an exaggerated expression of the growing factor derived from platelets (PDGF – platelet-derived growth factor). The transformation of these tumors into anaplastic astrocytomas is preceded by the loss of suppressing genes at chromosomes 9q, 13q or 19q. The progression to glioblastoma multiforme is associated with the epidermal growth factor receptor amplification or the genes MDM2. By contrast, primary glioblastomas show the loss of the suppressor gene PTEN (phosphatase and tensin homolog) or an exaggerated expression by the epidermal growth receptor, without a p53 [1] mutation.

Clinic presentation

Overall, the signs and symptoms presented are the result of the infiltration or compression by the tumor on the normal brain tissue, on the peritumoral edema and sometimes, the hemorrhage.

Vascularization and cerebrospinal fluid might also be committed, leading to progressing neurologic deficits and an increase in the intracranial pressure.[1]

Symptoms can be divided in specific and non-specific.

Specific symptoms are caused by intracranial tumor location. It is shown by neurological lateral signs as paresis, aphasia and visual deficits. Seizures

are a common symptom, occurring in about 25% of high grade glioma and can be partial or generalized. In general, tumoral hemorrhage is associated with high grade gliomas, occurring in 5-8% of glioblastoma multiforme patients. Hemorrhage can present itself as a stroke. Changes in awareness associated with headaches suggest an intracranial hemorrhage and not a cerebral infarction.

Non-specific symptoms express themselves as headaches, nausea and vomiting which are caused by intracranial pressure. As CT (Computerized Tomography) and NMR (Nuclear Magnetic Resonance) are available, pappillaedema is, at present, seen in less than 10% of the cases, even when the symptoms of intracranial pressure are present.[4]

Diagnosis

NMI is the preferred diagnosis approach to be used in signs and symptoms suggesting intracranial mass, which must be performed with and without contrast (gadolinium).

Contrast CT can be used, if NMR is not available or if there is some contraindication when performing the latter (for example: pacemaker carrier).[4]

Topographically, glioblastomas multiforme are predominant in the supratentorial region. They occur more often at the temporal (32%), frontal (31%), fronto-parietal (11%), parietal (10%), temporal-parietal (7%) lobes and in the occipital-parietal regions (5%). They are not very common in the third ventricle and seldom occur in the posterior fossae [3].

Tests show lesions appearing in the white matter, presenting a necrotic central region, surrounded by a contrast enhanced fine ring, a lengthy peritumoral edema and mass effect. These tumors tend to spread through the white matter bundles, and often, cross the corpus callosum. They are highly invasive tumors with tumor cells found over 4 cm (1,5 inch) away of the primary tumoral mass. Spontaneous hemorrhage can be seen, but calcification occurs only when the glioblastoma derides from low grade tumors.[1,2,4]

At present, there are NMR advanced techniques namely perfusion and diffusion of protons spectroscopy, to evaluate gliomas pre- and post therapy, which are a supplementary method to traditional NMR. These exams enable a better detection of gliomas malignity in an earlier stage and in a less invasive way. Besides, they are useful to determine tumoral areas with higher malignity, preferential targets to stereotactic and therapeutic biopsy. They are also particularly useful to differentiate a residual tumor, a tumoral recurrence, and radiation necrosis.[5]

The most frequent differential diagnosis includes cerebral metastases, central nervous system primary lymphomas, low grade gliomas capturing contrast and non-neoplasic diseases, as abscessus, multiple sclerosis, progressive multifocal leukoencephalopathy, cerebral infarction and vascular malformations.[1]

The definite diagnosis can only be declared histologically. As they are heterogenous tumors, a single vacuum-assisted biopsy may not be representative of the total tumor. Histological findings include: false "picket fence", necrosis, increased cellularity, pleomorphism, mitosis and vascular endothelial proliferation.[1]

Prognosis

Glioblastoma multiforme patients survive in average 9 to 12 months. Most die within 2 years and less than 5% survive 5 years.

The prognosis factors, identified as the most relevant, were the youngest ages and a good KFS (Karnofsky performance status). KPS enables to classify patients according to their functional incapacity *(Table I)*. It can be used to compare the efficacy of different therapies and evaluate the individual prognosis. Smaller the KPS, worst will be the survival.

The survival rates, at 18th months, were less than 50% in patients aged less than 40 years old; 20% between 40 and 60 years old and 10 % above 60 years old. Similarly, survival rate at 18th months was 34% for patients with KPS above 70 and 13% for those with KPS less than 70.[1]

Treatment

Therapy for these tumors has a double approach: support and definitive.[4]

Support therapy aims the symptomatic relief and an improvement on the neurologic function. First line drugs are the anticonvulsivants and corticosteroids.

Anticonvulsivants are given to those patients having fits with the neoplasm.

Phenytoin (300 to 400 mg/day) it is the most common drug used at present, but carbamazepine (600 to 1000 mg/day), phenobarbitol (90 to 150 mg/day) and valproic acid (750 to 1500 mg/day) have similar efficacy. Dosages of these drugs should be titrated until one gets the serial levels achieving maximum

TABLE I

Karnofsky performance status (%)

%	
100	Normal, no complaints, no evidence of the disease
90	Normal activity, few signs
80	Normal activity with some effort, some symptoms
70	The patient looks after himself, incapable of doing basic tasks
60	He needs occasional care and help with most tasks
50	He needs considerable assistance and frequent medical care
40	Disabled, needs special care and assistance
30	Very disabled, there is an indication for hospital admission, but death is not imminent
20	Very ill, need hospital care and support treatment
10	Dying, lethal progress rapidly progressive
0	Death

protection.

New drugs as gabapentin, lamotrigine and topiramate, are also effective. However, the therapeutic serial levels remain to be established.

Prophylactic anticonvulsivants should not be given to patients who had no fits. However, phenytoin and carbamazepine are used in general at the perioperative period, in the sense of reducing the incidence of post operatives fits.

Corticosteroids reduce the peritumoral edema, the mass effect and the intracranial pressure. These effects produce an immediate effect on headaches and improve neurological signs.

Dexamethasone is the choice corticoid, due to its minimal mineralocorticoid activity. The initial dosage is 15 mg/day, and should be adjusted to the minimum dosage necessary to control neurologic alterations.

Many patients can stop corticoids at the time of completing the total cranial irradiation.

All patients taking corticoids, over 6 weeks, should be under antibiotic prophylaxis for pneumonia by *Pneumocystis carinii,* which should be kept for a month, after suspending corticotherapy.[4]

Definite treatment includes surgery, radiotherapy and chemotherapy.

Early spread of the glioblastoma multiforme malignant cells makes this neoplasm incurable, surgically. However, surgery has a crucial role approaching patients suspected of having this neoplasm. Neurosurgery enables to get brain tissue to establish a correct diagnosis, it relieves the resulting symptoms of mass effect and reduces the need for corticotherapy. Besides an aggressive surgery, where most part of the tumor is removed, reduces the number of cancer cells in need of treatment and, many times, removes the hypoxic tumor nucleus, which is relatively resistant to radiation and inaccessible to chemotherapy.

There are some controversy regarding the surgery dimension and these patients survival. However, it is thought that the best treatment consists on the widest possible excision of the tumoral mass without causing neurological damage.

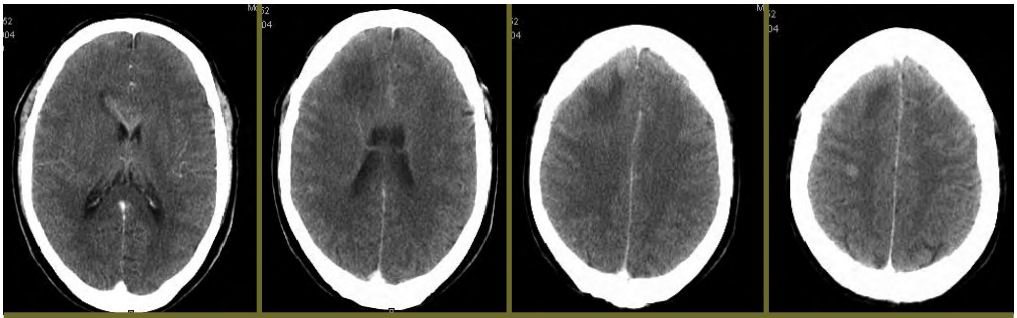
Stereotactic biopsies are, in general, reserved for tumors located in deeper regions, in important cerebral areas or in patients with extensive lesions, where a total excision is not be possible.[1]

Radiotherapy keeps being an effective non-surgical and post-operative therapy to these patients. Cerebral irradiation may be total or partial. A total one is reserved for multi-focal lesions with subependymal or leptomeningeal involvement. For most patients, with unifocal disease, a limited treatment cause less morbidity and it seems to produce the same overall survival.[4]

Based upon available date, the standard regimen consists of 60 Gy given in 30 fractions. Only 25% of cases show some X ray response, being rare a complete response.[4] However, in patients over 60 years old, there is a study which points to similar results in terms of survival, using shortened courses of radiotherapy (40 Gy in 15 fractions).[6]

In order to improve radiotherapy efficacy, new approaches have been tried: hyperfractionated radiotherapy, interstitial brachytherapy, stereotactic techniques and radiosurgery, but whose results, in random studies have not shown yet, any additional benefit.[1]

Until a few years ago, the glioblastoma multiforme standard treatment was made excising, in the first place, the widest possible extension of the tumor, followed by radiotherapy. Chemotherapy had a limited benefit on treating malignant gliomas and did not increase significantly the average survival[7]. At present, using Temozolomide and other more recent



CE CT scan Images.

FIG. 1

chemotherapy agents, acting inhibiting kynase tirosine, at the level of the EGFR – epidermal growth factor receptor and the VEGF – vascular endothelial growth factor, among others, seems to increase a bit these patients survival.

Temozolomide was approved in 1999, by the FDA (Food and Drugs Administration) on the treatment of recurrent anaplastic astrocytoma and in 2005, on the newly diagnosed glioblastoma multiforme.[8] It is an alkylating agent to be taken orally. It crosses the blood brain barrier presenting CSF concentrations 20% to 40% of the plasmatic. This drug potential, taken on its own or associated to radiotherapy has been evaluated in random trials, with results suggesting a significant survival increase.[7,8,9]

Recent chemotherapy drugs have been evaluated to treat recurrent glioma. Irinotecam, a topoisomerase I inhibitor, which crosses quickly the blood brain barrier has been extensively investigated. However, few patients present objective responses. An attractive target is the EGFR, which is often amplified and excessively expressed in the malignant glioma. EGFR kynase tirosine inhibitors, Gefitinib e Erlotinib, have been studied on the treatment of malignant glioma. Without any objective answers, some limited antitumoral activity seems to have to do with Gefitinib. Objective answers were seen in Phase I and II trials with Erlotinib in the recurrent glioma. VEGF, which increases permeability and stimulates endothelial proliferation and migration, is often over-expressed in solid tumors, including glioblastoma. A preliminary report suggests Bevacizumab has an antitumoral activity, a monoclonal antibody anti-VEGF, in combination with Irinotecam, in patients with recurring glioma.[9]

It should be emphasized that, potentially, all malignant gliomas will recur, whatever the initial treatment used. Patients can benefit from a new surgery, local radiotherapy techniques and other different chemotherapy agents.[1,2,4]

Clinical case

52 year-old patient, male, that on the 18th November 2004 went to the emergency service due sweating, vomits, parestesis on the left arm and dressing apraxia on the left hand.

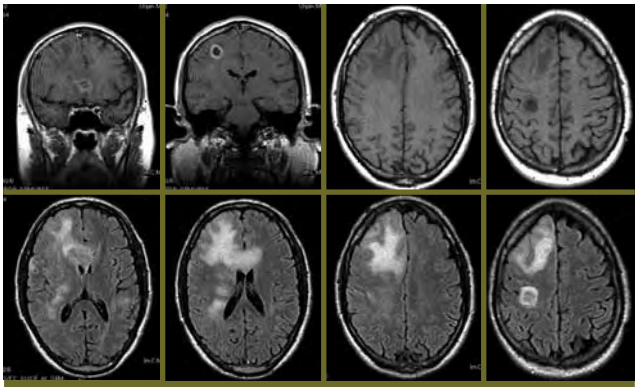
The patient objective exam did not show any other alterations. Namely, it did not show motor, sensitivity or balance deficits at a short neurologic exam. He had personal antecedents of keloid scarring in the face and arms, caused by burns. He mentioned heartburn episodes, for a long time, which would give in to the intake of dihydroxyaluminum sodium carbonate (Kompensan®) in an emergency.

A CE CT scan (*Fig. 1*) was taken at the emergency service, which revealed "small capturing lesions in the right frontal parenchyma, two in sub-cortical position and a periventricular one, with vasogenic edema suggesting metastatic etiology due to its multiplicity". The blood tests made did not show any alteration. Before this hypothesis of lesions occupying brain space, the patient was admitted to study a possible primary neoplasm and to undergo a cranial encephalic NMR, in order to evaluate better these lesions.

The patient was subsequently admitted in the Internal Medicine service, having started endovenous corticotherapy with dexamethasone 5mg every 8 hours, being progressively reduced to a 5 mg day dosage.

A CE-RMN (*Fig. 2*) showed a right frontal lobe with two capturing cortical-subcortical lesions, with capsular aspect, irregular and abundant halo of vasogenic edema, a very suggestive setting of metastatic etiology. It is still seen another lesion in the corpus callosum knee. Together with the edema, the lesions press a slight deviation to the left of the middle line structures.

In order to exclude neoplasm which most frequently would form metastasis to the encephalic tissue,



CE NMR Images.

FIG. 2

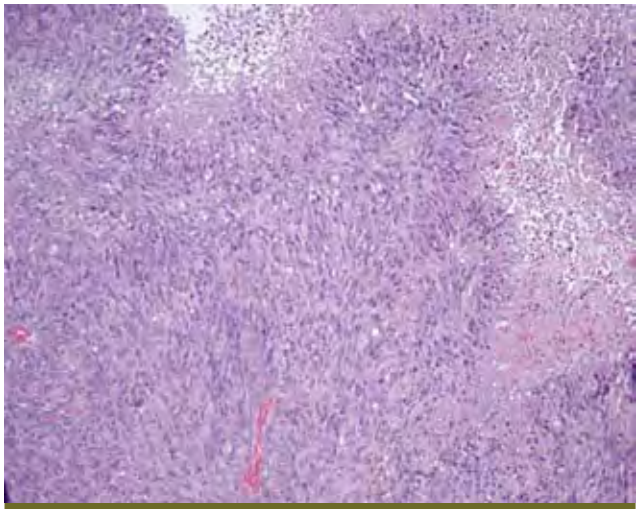
particularly the lung, the digestive tract, thyroid, testicle and cutaneous, the patient underwent thorax-abdominal-pelvic CT scan, thyroid and testicles ultrasound, digestive high endoscopy and colonoscopy and Dermatology has also requested to evaluate. All these exams showed no alterations. The serial tumor markers were also dosed and were within the normal range.

During admission, there was a deterioration of neurological deficits, with a progressive left hemiparesis and sudden frontal headaches, nausea and food vomiting.

Before the difficulty of reaching a definite diagnosis, it was requested a Neurosurgery evaluation, in order to perform a stereotactic biopsy of cerebral lesions.

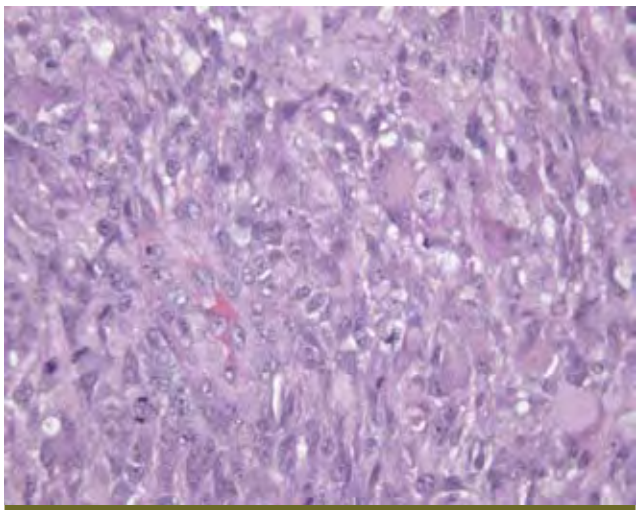
The patient started anticonvulsivant prophylaxis, before surgery, with sodium valproate and dexamethasone dosage was increased again to 5mg every 8 hours. On the 16th December 2004 the patient underwent right frontal craniotomy with removal of most cortical lesion.

The macroscopic study of the operative piece has revealed "a nodular formation around 1.2 cm (1/2 inch) diameter". The histological exam showed "a malignant neuro-epithelial neoplasm with a focal infiltration in the cortex in some areas …highly dense cell pleomorphic tumor … gemistocytic astrocyte type and there are multinucleate giant cells. The mitosis pictures are numerous and sometimes, atypical and there are vascular microproliferation phenomena. Often it is found necrosis areas surrounded by false



Tumor general aspect with cellular high density and false "picket fence" cells around areas of necrosis (Hematoxylin/eosin 100x).

FIG. 3

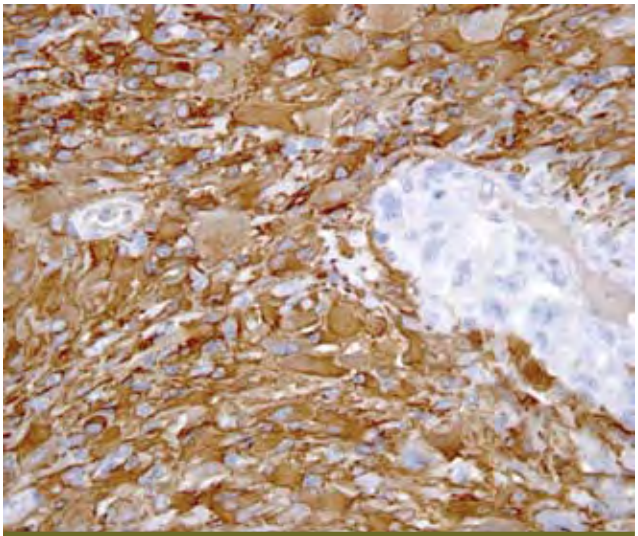


Cytonucleus atypia with multinucleate giant cells, mitosis pictures and vascular microproliferation (Hematoxylin/eosin 400x).

FIG. 4

"picket fence" cells in the periphery and there is a perivascular mononuclear inflammatory infiltrate, vascular thrombosis and hemorrhage areas. The immunocytochemical study shows an intense and diffuse mark of tumoral cells to the fibrillar acidic glial protein…it is a grade IV astrocytoma or glioblastoma multiforme (*Figs. 3-5*)".

At the time he was discharged, a support therapy with sodium valproate 500mg every 8 hours, dexame-



Tumoral cells with cytoplasmatic immunoreactivity for the fibrillar glial acidic protein (Immunohistochemistry GFAP 400x).

FIG. 5

thasone 5mg id, ranitidine 150mg id and alprazolam 0,5mg id was implemented. The patient was referred to the Oncology Portuguese Institute in Coimbra, where it was performed a cranial radiotherapy for bad tolerability.

Considering this neoplasm bad prognosis, the patient has deceased on April 2005, less than 6 months after diagnosis. ■

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