Glioblastoma Multiforme with Atypical Appearance

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We present the case of a 68-year-old patient who is hospitalized in our clinic for cognitive and attention disorders, progressively progressing over the past three months. The neurological examination revealed, besides cognitive decline, a motor deficit in the right limbs, and mild swallowing disorders for liquids. Although both CT and MRI were performed, the images obtained from the investigations were inconclusive, raising differential diagnosis problems. The patient was subjected to additional investigations, but the diagnosis of certainty was established by performing sterotactic biopsy and histological examination. Although cerebral MRI is the investigation of choice in the diagnosis of glioblastoma, in our patient's case, the diagnosis of certainty was determined by stereotactic biopsy and subsequent histological examination.

Keywords: glioblastoma multiforme, cerebral metastasis, cerebral toxoplasmosis

Glioblastoma multiforme (GM) is the most aggressive form of brain tumor. Together, with anaplastic astrocytoma, the two high-grade gliomas represent 20% of the intracranial tumors [1, 2] and 80% of the tumors located at the cerebral hemispheres. The incidence of GM is in the middle adulthood (predominantly in the 6th decade of life), but every age group can be affected. The vital prognosis of patients with glioblastoma multiform is influenced by a variety of factors such as patient age, tumor location and size, the posibility of surgical resection. Despite the advances in surgery, radiotherapy and chemotherapy of brain tumors, the overall survival of glioblastoma patients remains very low (less than 20% of patients survive more than 1 year and less than 3% survive for more than 3 years[3].

Symptoms of patients with glioblastoma multiforme are varied: headache (30 -50% of cases), epileptic seizures (30 -60% of cases) or focal neurologic signs (40 to 60% of patients have motor deficits) [4].

The usual CT appearance of glioblastoma is lesion with thick, irregular, iso or hyperdense (due to hypercellularity), surrounded by a hypodensal area due to tumor infiltration and vasogenic edema with marked mass effect. Intratumoral haemorrhage can also be observed, and calcifications may occasionally be observed. By contrast CT it is possible to highlight a hypodense center due to intratumoral necrosis. The capture of intense and irregular contrast by the edges of the lesion is almost always present [5]. Cerebral MRI is the most important non-invasive diagnostic and assessment tool for glioblastoma [6]. This investigation highlights the physical properties of the affected tissue, but the images are not always specific. In the MRI, almost all glioblastomas capture gadolinium, thus revealing one or more non-homogeneous lesions with a hypointense center, with an irregular contour, which captures contrast (due to the presence of hypercellularity and neovascularization), surrounded by edematous brain tissue without contrast. Intratumoral haemorrhage, which may complicate glioblastoma, visualises hypointense in T2 and iso or hyperintense in T1 sequences [5]. Thus, in the T1 sequences, hipo or isointense lesions are highlighted, with heterogeneous central signal (due to necrosis or haemorrhage), in T1 with contrast, the lesions capture irregular contrast at the periphery (surrounding the necrosis area), and in T2 / FLAIR the lesions are hyperintense, surrounded by vasogenic edema. Weighted T1 and T2 sequences can be complemented by functional measurements, such as diffusion and perfusion MRI, that provide additional physiopathological information [6].

Histologically, glioblastoma shows hypercellularity with pleomorphism and nuclear atypia. Hypercellularity, high mitotic activity and vascular proliferation are characteristic. GM is characterized imunohistochemical by the expression of GFAP (sensitive and specific marker of astrocytic differentiation in primary nervous system tumors and in diagnosis of glial tumors) and Ki-67 (both being nuclear antigen markers used to show cell proliferation), increased CD34 and CD105 expression-markers (its expression is correlated with accelerated tumor growth, tumor invasion and has an unfavorable prognosis), the S100 protein (overexpression thereof, along with GFAP, are markers of astrocytic activation), overexpression of EGFR (positive in 40-98% cases) and mutations of p53. There are no histopathological features that differentiate a multiform or multicentric glioblastoma of a solitary glioblastoma [7-9].

In this article we present the case of a 68-year-old patient who is hospitalized in our clinic for cognitive and attention disorders, progressively progressing over the past three months. The neurological examination revealed, besides cognitive decline, a motor deficit in the right limbs, and mild swallowing disorders for liquids. Although both CT and MRI were performed, the images obtained from the investigations were inconclusive, raising differential diagnosis problems. The patient was subjected to additional investigations, but the diagnosis of certainty was established by performing sterotactic biopsy and histological examination. Although cerebral MRI is the investigation of choice in the diagnosis of glioblastoma, in our patient's case, the diagnosis of certainty was determined by stereotactic biopsy and subsequent histological examination.

Experimental part

Patient P.M., female, 68 years old, is presenting in our clinic for cognitive decline that has been revealed by short-term memory impairment, attention deficit disorder and asthenia, which has been in direct decline over the past

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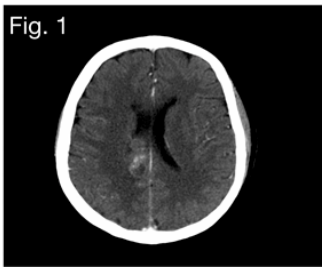
three months. From family affirmations, the patient was indifferent to common household and social practices, had emotional lability, progressively accentuated symptoms over the past month. Patient is known with magaloblastic anemia for which is treated with vitamin B12.

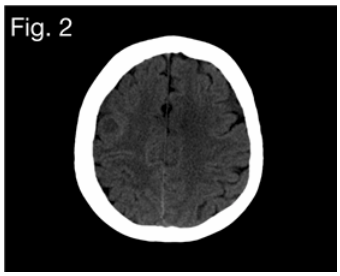
The neurologic examination reveals normal oculomotricity, mild facial asymmetry (right central facial paresis), bilateral lateral nystagmus, swallowing disorder for liquids, walking possible with support, paretic motor deficit of right limbs, equally distributed, segmental muscular force of right limbs was 4/5, mild hypertonia of the right limbs, brachial, stiloradial, rotulian, and achilian refelxesof the right limbs hyperactive, plantar refelexes in extension billateral, without superficial or deep sensitivity disorder, without sphincter disorder, spontaneous language affected by difficulty in finding words, bradypsychia, apathy.

The blood tests reveal blood glucose level 135.1mg/dL and total cholesterol 241mg/dL, vitamin B12 in normal limits (862 pg/mL), no changes in CBC, biologically inflammatory syndrome absent, HIV serology, negative VRDL, negative ag HBS, negative HBS. Lumbar puncture show clear, hypertensive CSF, with 0 elements/mmc, PANDY negative, glycogen, proteinuria and lactic acid within normal range (lactic acid 15mg / dL, glucose 65mg / dL, protein 34mg / dL).

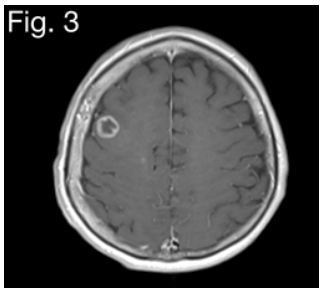
EEG is performed and indicates a diffuse irritative zones.

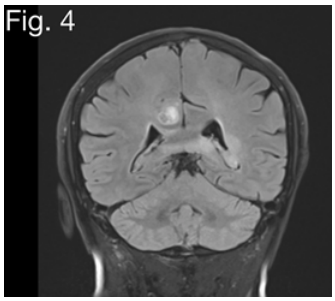
Cerebral CT with contrast reveals, both in native and post-contrast, at the splenium of corpus callosum a heterodense zone with calcifications measuring 27 mm, with a hyperdense area with subacute hemorrhagic aspect, without excluding a tumoral process (fig.1). In the right parietal zone is seen a rounded oval-shaped lesion measuring 1.2cm with thin wall without perilesional edema (fig. 2).





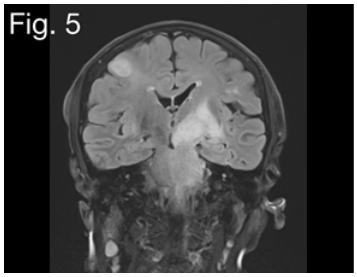
Cerebral MRI shows supra and infratentoral polymorphic focal lesions, usually with cortico-subcortical topography, heterogeneous, some with a cystic appearance, with an annular peripheral contrast capturing, partially with restriction of diffusion and some lesions with SWI hyposignal (intralesional haemorrhagic necrosis or calcifications), lesions with gadolinophilic periphery without diffusion restrictioncan be seen in the right superolateral frontal zone (fig.3-5) and in the posterior part of the cingulate gyrus (fig. 4), all associating perilesional edema;There is also an area of diffuse edema, which slightly expands the left capsulo-thalamic region, the ipsilateral cerebellar peduncle, the pons (fig. 5-6) and the left-side of midbrain (fig. 5); It is also seen a mass effect on the lateral left ventricle, slight narrowing of the of the IV ventricle and discreet deviations of the median line to the right (fig. 4-5).

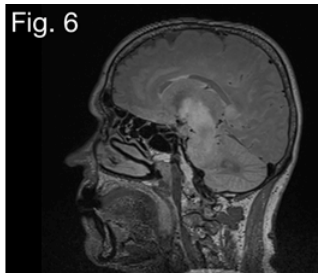




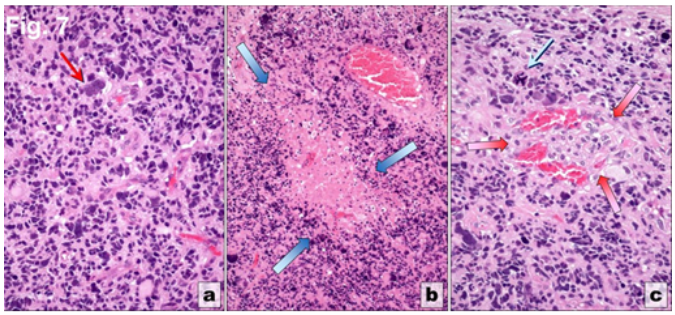
The MRI aspect may correspond to infectious lesions, in different evolutionary stages, parasitic or fungal lesions(toxoplasmosis, cysticercosis, tuberculosis)but a tumor aspect can not be excluded.

A thoracic-abdomen-pelvis CT was performed with contrast substance and it didn't detect any CT-detectable tumor masses at the thoraco-abdominal-pelvic zones or supra or infradiaphragmatic adenopathies.





Cerebral biopsy was performed and the anatomo-pathological result describes astrocytic infiltrative glial proliferation, with pleomorphism, nuclear atypia (fig. 7a), important microvascular proliferation (fig. 7c), and pseudopalisading necrosis (fig. 7b). Immunohisto-chemical testing revealed - Ki67 positive antibodies with a 55% nuclear index, positive vimentin, positive GFAP, CD34 positive in vascular structures, p53 positive with a 10% nuclear index. Conclusion: Glioblastoma NOS.



Results and discussions

In current medical practice, due to nonspecific sympathology and inconclusive results obtained by CT and MRI examination, the diagnosis of multiform glioblastoma may be misleading or late, thus influencing the patient's vital prognosis. In the present case, both contrast CT and contrast MRI, were inconclusive for the diagnosis of glioblastoma. Although cerebral MRI is the investigation of choice in the diagnosis of glioblastoma, in our patient's case, the diagnosis of certainty was determined by stereotactic biopsy and subsequent histological examination.

Nonspecific clinical symptomatology, largely expressed by cognitive decline and lack of interest in daily activities, the absence of intracranial hypertension or epileptic seizures, and the multiple polimorphic lesions, disseminated both supra and infratentorial(cystic, nodular, the presence of calcifications), and the presence of small proportions of cerebral edema, raised issues of differential diagnosis, without being able to exclude a infectious disease, tumoral pathology or cerebral metastasis.

Thus, in our case, the problem was the differentiation of the multiform glioblastoma from the cerebral metastasis and primary central nervous lymphoma (PCNSL), which may have a similar appearance in the MRI, but the

therapeutic approach is different (GBM standard treatment and cerebral metastasis are surgical resection, radiotherapy and chemotherapy, whereas PCNSL should not be subjected to surgical resection but chemotherapy only)[10,11].

PCNSL is a rare and aggressive cerebral neoplasm that may involve brain, spinal cord, cerebrospinal fluid, and intraocular structures, representing 2-6% of primary cerebral tumors [12]. PCNSL is typically large diffuse B cell lymphoma, and rarely other types, such as Burkitt lymphoma, T-cell lymphoma or Hodgkin's lymphoma [13]. In immunocompetent patients, PCNSL has an increased incidence after the 6th decade of life, with a slight male predilection[14]. Immunosuppressed patients, especially those with AIDS, are at an increased risk of developing PCNSL. The choice of treatment for PCNSL is radiotherapy and/or chemotherapy [15]. For the diagnosis of PCNSL, there are no characteristic serological tests, but HIV determination is required, given that it is predominantly present in immunosuppressed patients. The CSF study may point to a PCNLS by increasing the elements above 10/ mmc, the increase of CSF proteins, and the decrease of CSF glocose levels [15]. CT images in PCNSL, the lesions are hyperdense and capture contrast, and in MRI, in T1 the lesions are hypointense, in T2 are iso or hypointense and they capture homogeneous contrast, and have diffusion restriction. They are located supratentorial in almost 80% of cases, and appear either as single lesions or as multiple lesions (in 11-50% of cases); in case of large lesions the mass effect is reduced and the perilesional edema is limited [16]. Characteristic of these lesions is the homogeneous capture of contrast. The diagnosis is determined by cerebral biopsy, which highlights the malignant cells specific to the type of lymphoma involved. Sterotactic biopsy is preferred, tumor resection being undesirable due to increased morbidity due to the intense infiltrative nature of the tumor. Immunohistochemistry in PCNLS reveals CD20(present in most B cell neoplasms), CD79a (is involved in the development and function of B cells), BCL6 (is present exclusively in B cells, both in healthy and malignant cells), Bcl2 (orientates patient prognosis), MYC (involved in growth, proliferation of cellular apoptosis has B cell proliferation effect), MUM-1 (involved in B cell differentiation), Ki-67 (marker of cell proliferation) [17].

In our case, MRI sequences do not provide sufficient data for diagnosing PCNSL. Although IRM showed multiple supra and infratentoriallesions, surrounded by edema and reduced mass effect, and lesions capturing contrast non-homogeneous, necrotic and haemorrhagic lesions, also, the patient being immunocompetent, as evidenced by negative HIV serology, and the normal biological profile, the CSF with 0 elements / mm3, CSF glucose and protein levels within normal limits, PANDY negative contributes to the exclusion of a PCNSL. Histological and immunohisto-chemical examination of fragments obtained by cerebral biopsy have definitely eliminated a PCNSL by describing glial cell proliferation, microvascular proliferation, necrosis and palisade beaches, and positivity of GFAP (specific marker of glial tumors), thus establishing the diagnosis of glioblastoma. The only common marker of the two pathologies is Ki-67, but this is nonspecific, being an indicator of cellular proliferation.

As mentioned above, the differential diagnosis of multiple brain lesions that capture contrast, highlighted by MRI, mainly includes neoplastic and infectious processes, so in our patient's case, the problem of the presence of a neoplasm cerebral metastasis has arisen.

In the adult population, cerebral metastasis and glioblastoma are the most common causes of brain cancer [18]. Differentiation of the two pathologies is important from the point of view of therapeutic management. In most cases, brain metastasis are symptomatic at the time of diagnosis. These can be manifested by epileptic seizures, motor deficits, language or headache disorders[19]. The most common primary tumors that give brain metastasis are lung (20% incidence), kidney (in 6.8% of cases), skin (in 6.5% of cases) breast (in 5% of cases) and gastrointestinal tract (in 1.8% of cases). However, in many cases, the first signs of malignancy may be the symptoms of cerebral metastasis, such cases accounting for up to 16% of central nervous system metastasis (most of them have a pulmonary starting point) (20).

The most sensitive method of diagnosing these tumors is MRI, but the specificity of this investigation is limited. The lesions produced by a GM and the lesions produced by brain metastasis capture both contrast in the T1 sequences and appear hyperintense in T2 and FLAIR, but more commonly cerebral metastasis occur mainly at the cortical junction of the gray-white substance, the lesion being nodular and capturing contrast. Despite these characteristics, GM and metastasis differentiation is all the more difficult when the primary tumor is not known, thus requiring microscopic evaluation of the lesions obtained either by surgical resection or by cerebral biopsy. Most cerebral metastasis have the same histological characteristics as the primary tumor and are clearly delimited by the surrounding tissue, with obvious gliosis and neovascularization (expressed imagistically by the presence of vasogenic edema). Unlike metastasis, glioblastomas usually have an invasive area in the brain parenchyma around the lesions. However, similar appearance can also be observed in the case of cerebral metastasis, especially those caused by small cell lung cancer, melanoma or lymphoma. In metastatic lesions, perilesional cerebral parenchyma exhibits reactive astrocytosis, microglial proliferation and vascular proliferation, all of which may be misinterpreted as a glioblastoma, especially in the absence of primary tumor knowledge [19,20]. In such cases, the immunohisto-chemical examination is useful, when GFAP, S100, CD34 and CD105 protein determine the diagnosis of glioblastoma.Thus, in our case, when the presence of multiple brain, polymorphic, contrast-sensitive brain lesions raised suspicion of the presence of a neoplasm with secondary cerebral determinations. The lack of a history of neoplasia required a thorax-abdomen-pelvis CT. As the images offered by it did not indicate the presence of a primary tumor, the diagnosis of certainty was established after the histological and immunohistochemical examination. Although the presence of glial, microvascular and reactive astrocytosis, did not certainly differentiate a glioblastoma from brain metastasis, expression of GFAP, CD34, vimentin, and Ki-67 determined the glioblastoma assurance diagnosis.

Since imaging investigations have posed the problem of infectious substrate lesions, we also considered the presence of cerebral abscesses of various etiologies or toxoplasmosis.Most commonly, besides direct inoculation through external contact (skull fractures, surgery, wounds), cerebral abscess occurs secondary to a bacterial or fungal septic outbreak from other parts of the body. Cerebral abscesses have, for the most part, a pulmonary or pleural starting point, a cord starting point (through infectious endocarditis), when cerebral dissemination is haemathogenic, or paranasal sinuses, mastoids or middle ear starting point. Occasionally, it can also be a consequence of an infection of the pelvic organs and skin.

In about 20% of cases, the starting point can not be identified. The most common microorganisms involved in the cerebral abscess are streptococci, especially those anaerobic (starting with a septic pulmonary or paranasal focus), staphylococci (accidental or surgical trauma, infectious endocarditis), enterococci (frequently in otic infections) pneumococci, meningococci, and less frequently Gram-positive bacteria Actinomyces, Nocardia and fungi such as Candida Mucor and Aspergillus. In immunosuppressed patients most involved are fungal infectiones and parasites (Toxoplasma gondii)[5]. The symptoms of patients with cerebral abscess are nonspecific: headaches, seizures, signs of intracranial hypertension. There may have mild fever, except when the abscess is encapsulated, when the temperature and the number of leukocytes can be normal, VSH is usually increased and the LCR has moderate pressure with mild to moderate pleiocytosis, with neutrophilia between 10-80%, slightly increased proteinorhea (rarely up to 100mg/dL). The CSF is sterile, unless a bacterial meningitisis associated [5]. CT and MRI examinations are the most important investigations for the diagnosis of cerebral abscess, diffusion sequences (DWI) has a 96% sensitivity in the differentiation of cerebral abscesses from necrotic or cerebral cystic tumors [21]. The CT exam reveals the abscess capsule that captures contrast and the center of the abscess and the white matter appear hypodense. At examination of MRI, in T1 sequences, the capsule captures the contrast substance, and the center of the abscess is hypointense, with diffusion restriction. In T2, peripheral edema is highlighted, the capsule is hypointense and there is diffusion restriction inside the lesion, which causes hyperintes aspect on DWI and hypointense in ADC [22].Along with imaging investigations, for the identification of the primary septic outbreak, pulmonary X-ray, VSH, haemocultures are required, cerebral biopsy being the only one that can confirm the diagnosis.

Though the patient is immunocompetent, with no history of infectious history, and the biological and CSF profiles are within normal limits, the non-specific aspect of MRI examination could not definitely exclude the presence of multiple cerebral abscesses, the diagnoseis of certainty was estabilished only after the anatomopathological examination of the fragments obtained by cerebral biopsy.

Cerebral toxoplasmosis is a zoonosis caused by Toxoplasma Gondii, the most affected being immunocompromised patients (such as those infected with HIV) who have a high mortality rate. The incidence of cerebral toxoplasmosis in immunocompetent individuals is extremely rare, with few reported cases in the literature [23]. T. Gondii mainly affects the gray-white junction, basal ganglia and thalamus, but can also appear in the callous body and in the cerebral trunk. Infestation with T. gondii can be done either by eating infected meat or by ingestion of contaminated water or vegetables by contacting cat litter (the natural host of T. gondii) or by mother-to-fetus transmission in infected congenital [5].Diagnosing cerebral Toxoplasmosis in immunocompetent individuals is all the more difficult because symptoms and imagistic lesions are uncharacteristic and can easily be confused with another infectious disease (cerebral abscesses, tuberculomas) or a central nervous system tumor such as primary cerebral lymphoma or brain metastasis[24-27].By CT imaging, the lesions appear hypo or isodens, surrounded by vasogenic edema and mass effect, the lesions can be single or multiple, solid, nodular, or contrast-capturing.MRI plays an important role in differential diagnosis. It is reported in the literature the appearance of a *sign to target* (hypointense center, surrounded by a hyperintense intermediate area, followed by a hypointense area delimited by perilesional edema), obtained post-contrast in the T1 and FLAIR sequences, a sign considered patognomonic. Because the characteristic imaging aspect is not present in all cases, diagnosis is made by the presence of anti-T. Gondii antibodies in serum and cerebrospinal fluid and by biopsy and consecutive microscopic evaluation. In our case, negative HIV serology and the non-specific aspect of lesions observed by imaging examination was clarified by the result of histological and immunohistochemical examination of cerebral biopsy.

Conclusions

In this article, we presented the case of a patient with poor clinical symptoms, in which imaging investigations provided nonspecific images, thus raising differential diagnostic problems. The diagnosis of certainty was established only after the sterotactic biopsy and the histological and immunohistochemistry examination.

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