

GLIOMA AND MULTIPLE SCLEROSIS

Case report

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ABSTRACT – We report a case of a 44-years-old woman with relapsing-remitting and secondarily progressive form of multiple sclerosis (MS) since aged 24 years, who developed an anaplastic astrocytoma. The neurological manifestations of the tumor were misinterpreted as resulting from MS. Sequential MRI examination and seizures raised the possibility of another nature of her symptoms, besides MS. Her initial good response to high doses corticosteroids led to the initial assumption her symptoms were only exclusively due to the demyelinating process. She underwent craniotomy with radical excision of the lesion. Pathological examination disclosed anaplastic astrocytoma. Other cases of coincidental MS and primary CNS tumors are reviewed, as well as their possible relation.

KEY WORDS: multiple sclerosis, anaplastic astrocytoma, cerebral neoplasm.

Glioma e esclerose múltipla: relato de caso

RESUMO - Relatamos o caso de uma paciente de 44 anos, portadora de esclerose múltipla forma surto-remissão e progressiva secundária, que na evolução desenvolveu um astrocitoma anaplásico. Os sintomas do tumor se confundiram com os da esclerose múltipla e com a repetição de ressonâncias magnéticas foi possível suspeitar do diagnóstico. Além dos sinais neurológicos, também apresentava crises convulsivas. A melhora com os cursos de pulsoterapia mascaravam os sintomas do tumor. Submetida a craniotomia e retirado tumor com características histológicas e histoquímicas de astrocitoma anaplásico, ao lado de áreas de desmielinização típicas de esclerose múltipla. São discutidos os aspectos radiológicos, incidência e mecanismos da concomitância das duas doenças.

PALAVRAS-CHAVE: esclerose múltipla, astrocitoma anaplásico, tumor cerebral.

Multiple sclerosis (MS) may have a quite variable clinical presentation, and for that reason may simulate or masquerade other central nervous system (CNS) diseases. Before the advent of more reliable imaging methods, the diagnosis was based solely by clinical criteria and by exclusion of other diseases, and a misdiagnosis was not quite uncommon¹. Patients with MS may develop space-occupying lesions that may be mistaken as neoplasia and this form of MS is eventually called pseudo-tumor². On the other hand, neoplasia may simulate MS at its initial presentation³⁻⁵. Moreover, though uncommon, there might be a coincidence of MS and a CNS neoplasm in the same patient⁶.

We report a case of a patient with MS for many years, who developed a primary glial tumor during her clinical course.

CASE

A 44 years-old woman was diabetic since 24 years-old. On March 1987, she developed gait difficulty, lower limbs weakness, which got worse with exercise. At this time, a cranial CT-scan was done and disclosed an arachnoid cyst. She was operated on, her post-operative period was uneventful, but her symptoms did not improve and in fact worsened. A MRI was performed and showed several white matter lesions in keeping with a demyelinating disease (Fig 1). Her diagnosis was confirmed by exclusion of other diseases and beta-interferon was started. In spite of that, her clinical neurological condition progressively deteriorated. New MRI examinations showed increased number of demyelinating lesions.

On April, 1997, she developed generalized tonic-clonic seizures. She received high doses methylprednisolone (1.0 g qd, 3 days). Between August 1997 and January 1998, she developed several periods of clinical worsening and

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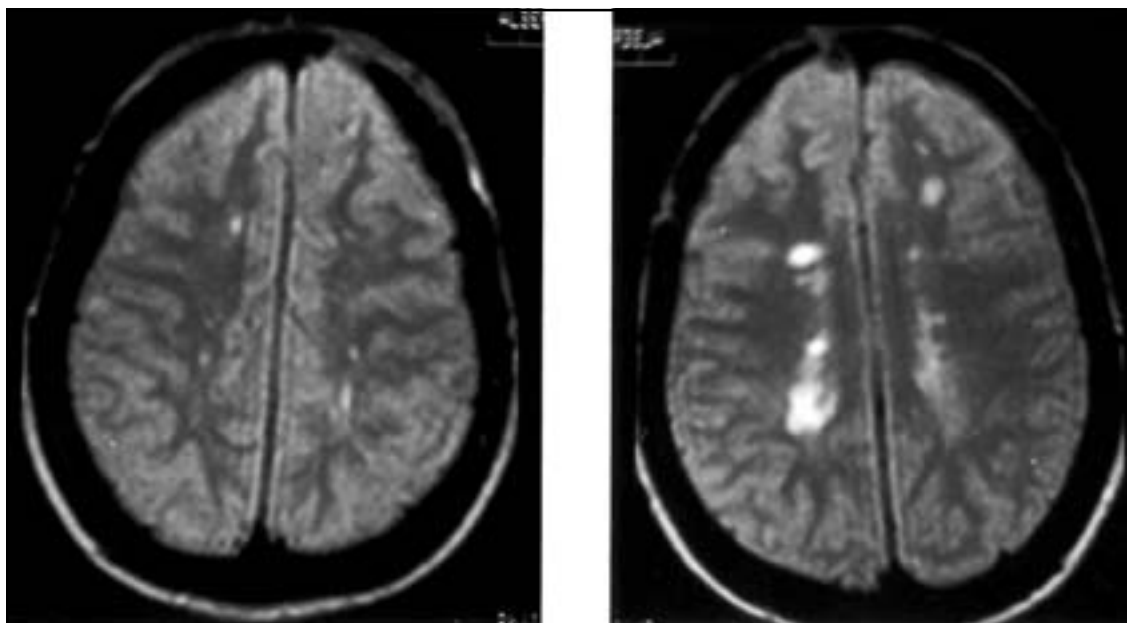


Fig 1. Magnetic resonance, May 1987.

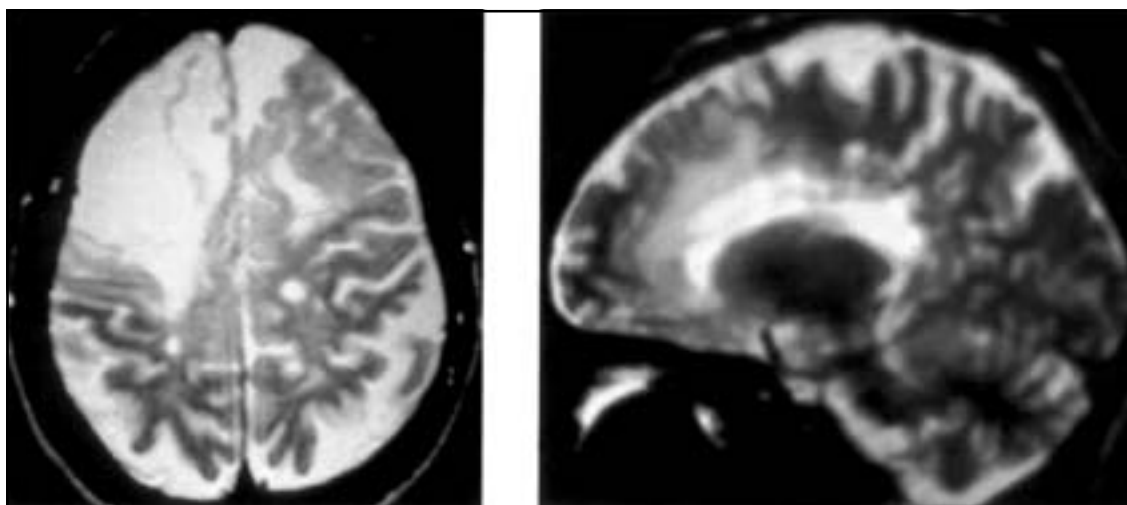


Fig 2. Magnetic resonance, May 1998.

improvement of her gait and by the end of this period she could walk only with support. She underwent several cranial MRI examinations which showed increasing number of demyelinating lesions. Beta-interferon was stopped, and several courses of high doses methylprednisolone and cyclophosphamide were done, with partial recovery.

On May 1998, she developed urinary incontinuity and urgency, lower limbs paresthesias, and feet hypoesthesia. At this time, she was admitted to our care. At examination, she was depressed, but otherwise cognitively intact. Neurological examination at this time showed normal cranial nerves, right upper limb dysmetria, and lower limbs spastic paraparesis (MRC grade 3 to 4) with tendinous hyperreflexia and bilateral Babinski sign. Her gait was paretic-spastic. A MRI showed several areas of variable

size of increased signal in T2 in the white matter involving both hemispheres. The larger was at the right frontal lobe (Fig 2). The final diagnosis was MS, diabetes mellitus and depression. Azathioprine, tizanidine, oxcarbamazepine, diabetes control and physical rehabilitation were prescribed.

Nevertheless, between June 1998 and September 1999, she developed several tonic-clonic seizures and bilateral hand weakness was noticed, as well as upper limbs incoordination, tremor, trunk ataxia, increasing lower limbs spasticity and loss of sphincter control. An uterus myoma leading to hypermenorrhea was diagnosed and a hysterectomy was performed. Oral prednisone, oxcarbamazepine and topiramate, were introduced. Beta-interferon, 8000000 IU SC was re-introduced. Her glucose blood level

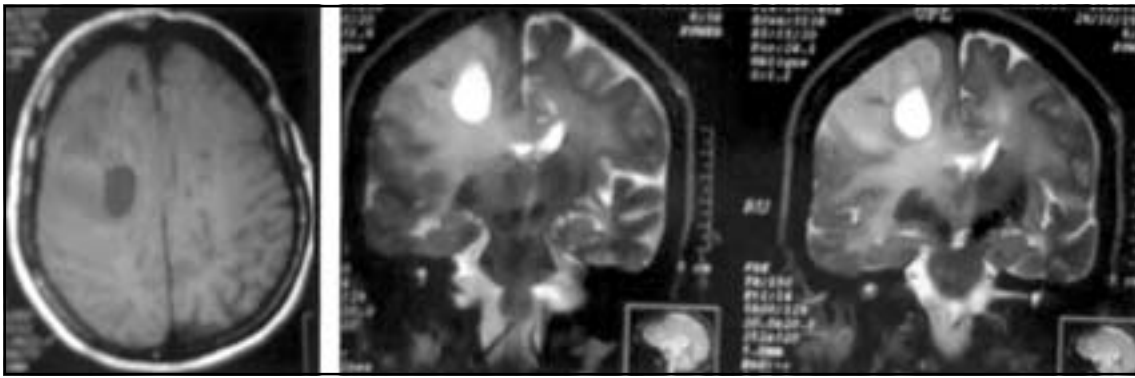


Fig 3. Magnetic resonance, October 1999.

was kept under control with regular insulin. After each episode of deterioration, she had some improvement, but at the end she progressively worsened and could not longer walk even with aid.

On September 1999, she had several seizures with head trauma, followed by mental confusion, dysarthria, left hemiplegia and thorax pain. She improved after parenteral dexamethasone. At this time, her medication was: oxcarbamazepine, topiramate, citalopram, tizanidine, and SC insulin. On October 1999, a MRI showed a space occupying lesion in the right hemisphere, with ill defined borders and a cystic component within it, about 3 cm of diameter (Fig 3 and 4).

She underwent a craniotomy (Dr. Marlus Moro) with total removal of the tumor lesion. The pathological diagnosis was anaplastic astrocytoma (Fig 5, 6 and 7). Her motor condition improved, although she had periods of mental confusion and occasional epileptic fits. The MRI one month after surgery showed edema, residual tumor and a cyst (Figure 8). She was submitted to radiotherapy and in the last evaluation she was using oral dexamethasone, oxcarbamazepine, topiramate, and regular SC insulin. After this, we lost the follow-up.

DISCUSSION

For many years, the diagnosis of MS was essentially clinical. A definite diagnosis could be obtained, in some cases, only after autopsy. One series of MS patients who underwent autopsy showed that 6% of cases diagnosed as MS were in fact cases with other diagnosis, including a small number of CNS primary neoplasms (0.57%)⁷.

There is some controversy about the incidence of brain tumors in MS patients. Some authors observed a smaller incidence when compared to general population⁶, whereas other series showed and increased prevalence^{8,9}. In our experience with more than 400 MS patients over the last 20 years, this is our first observation of coincidental primary CNS tumor and MS. One reason that may account for these dif-

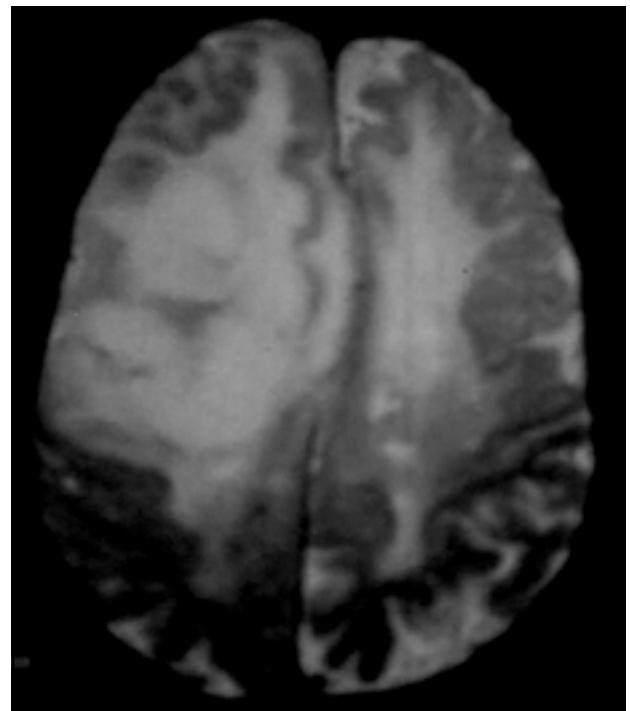


Fig 4. Magnetic resonance, November 1999.

ferent frequencies is the advent of new methods of neuroimage and their increasing availability to investigate neurological patients who already have a clinical neurological diagnosis. With MRI, the diagnosis of MS has dramatically increased, but at the same extent other CNS diseases are diagnosed at earlier stages and with more accuracy^{10,11}. Nevertheless, MS is still and ultimately a clinical diagnosis, taking in account history, clinical neurological findings, complementary tests results, and exclusion of diseases simulating MS.

Low grade astrocytomas may be sometimes a difficult diagnosis based only on neuroimaging techniques and may be only established by biopsy or radical removal^{2,10,12}. More recently, MR spectroscopy

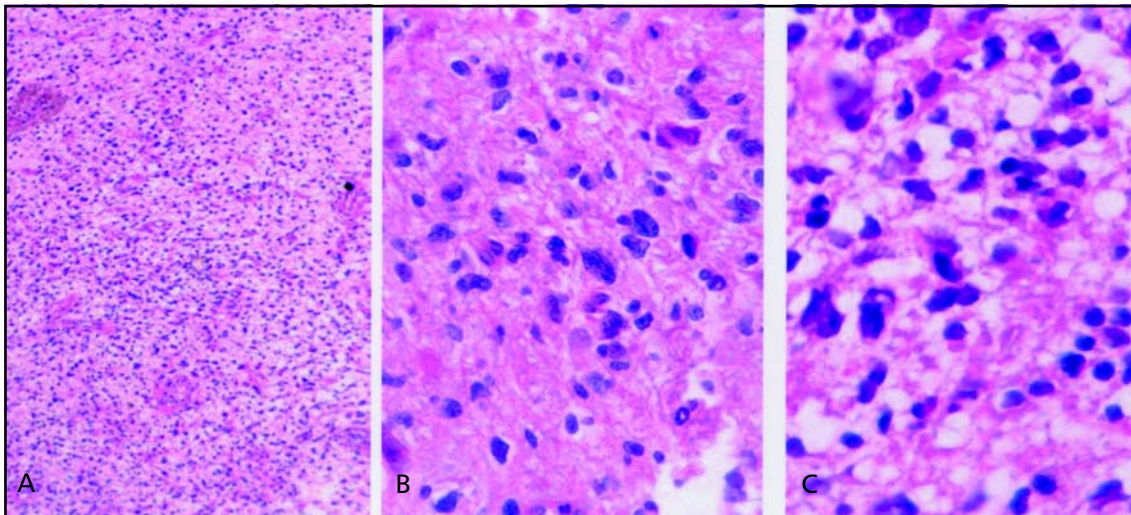


Fig 5. Anaplastic astrocytoma showing high cellularity (A) and pleomorphism of tumors cells (B and C). A: Hematoxyline-Eosine, x100; B and C Hematoxyline-Eosine x400.

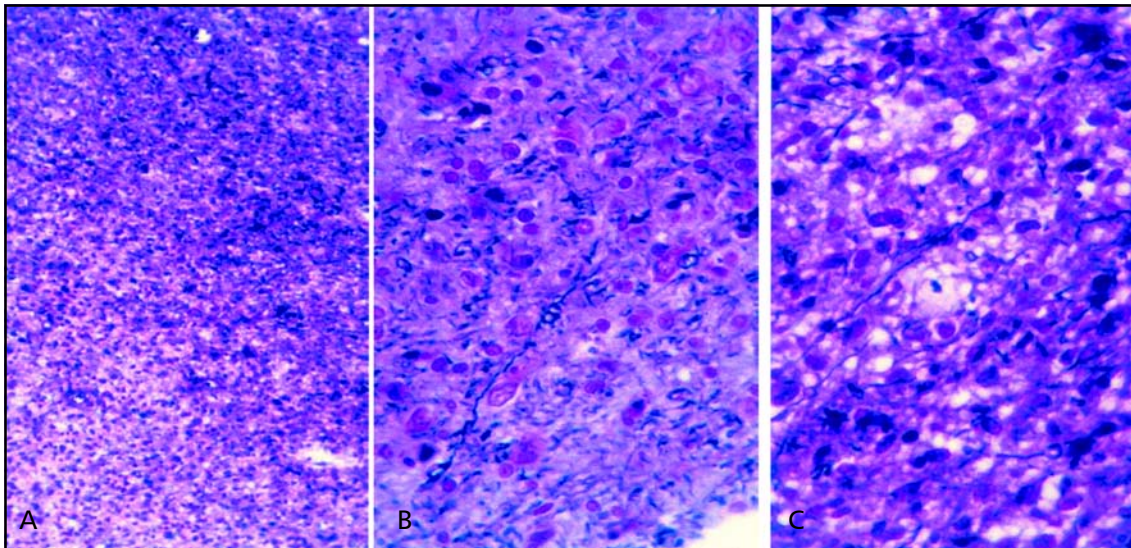


Fig 6. Myelin staining of anaplastic astrocytoma and peripheric brain tissue (A). Loss of myelin within the tumor (B) and better preservation in the periphery (C). Luxol Fast blue/Nissl. A: x100; B and C: x400.

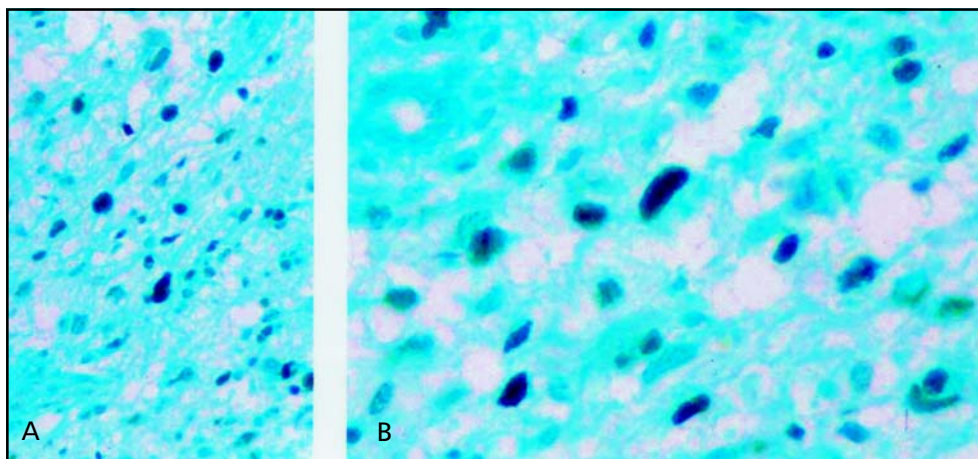


Fig 7. Anaplastic astrocytoma showing mutation of P53 protein. ABC DAKO/DAB. A: x100, B: x400. Immunohistochemistry for antibody P53.

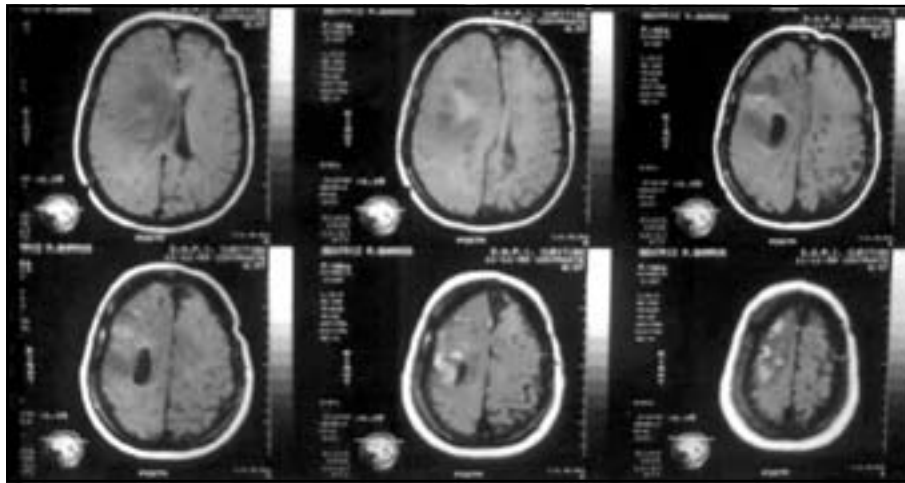


Fig 8. Magnetic resonance, December 1999 (Post surgery).

has shown to be a helpful tool in differentiating astrocytic tumors from demyelinating lesions *in vivo*¹³. On the other hand, MS may present as a mass lesion, and brain biopsy is generally necessary to confirm the diagnosis¹⁴.

The coincidence of brain tumors and MS was first described by Bosch, in 1912⁹. Twenty-four additional cases were reported till 1984¹⁵, and after that only a few sporadic cases appeared in the literature^{8,9,12}. The following histological types have been reported: oligodendroglioma^{7,9,16}, astrocytoma^{7,12,17,18} and glioblastoma^{6,8}. Besides primary glial CNS tumors, a few cases of metastatical lesions from lung and stomach primary sites have been reported, as well as two cases of meningioma and one of spinal cord ependymoma^{19,20}.

The coincidence of glioma and MS rekindles a debate that began in 1938, when Scherer²¹ described the pathological findings in a 29-year-old woman who died after a seven-month progressive neurological illness. He found periventricular gliomatosis with marked atypical and multiple demyelinating plaques with perivascular and periventricular foci of inflammatory cells, findings characteristic of acute multiple sclerosis²². The plaques and tumor were grossly contiguous, with focal transitions between reactive glial cells in plaques and neoplastic cells. Scherer²¹ hypothesized that the glioma resulted from neoplastic transformation of reactive glial cells in plaques, which he called *glioblastomatoses en plaque*.

Opinion is divided about whether the rare concurrence of multiple sclerosis and glioma is explained by cause and effect or coincidence^{15,23}. If gliomas in patients with multiple sclerosis are more likely to be

multicentric, then the hypothesis of cause and effect could be supported. However, the frequency of multicentric gliomas in patients with MS remains uncertain because serial sections of brain tissue must be examined to establish this fact and rule out microscopic glioma tracks connect foci¹⁵. It is also uncertain whether patients with multiple sclerosis are at increased risk for the development of gliomas.

Finally, the use of beta-interferon in our patient is unlikely to be related to the development of the glioma, taking in fact what is known about immunobiology of gliomas (glioma cells express both interferon- α/β receptors and interferon γ receptors). Interferon β suppresses MHC class II expression and inhibit the growth of glioma cells, but there are not current evidence of a therapeutic potential use in gliomas¹⁰.

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