REFERENCES

A Rare Case of Spontaneous Remission and Relapse of a Primary Central Nervous System Lymphoma

Caso Raro de Remissão Espontânea e Posterior Recidiva de Um Linfoma Primário do Sistema Nervoso Central

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ABSTRACT
Primary central nervous system lymphoma remission after steroid treatment is a well-known phenomenon, but remission without any type of treatment is extremely rare. We present a rare case of spontaneous remission of a diffuse large B-cell lymphoma of the central nervous system as well as its subsequent reappearance in another location. The atypical presentation misled the neurosurgeons and neurologists, delaying diagnosis and treatment. The patient underwent brain biopsy after the relapse and started radiotherapy and chemotherapy with cytarabine + methotrexate + rituximab. As of 32 months after the diagnosis, the patient remained asymptomatic, with no focal neurological deficits and the disease in complete remission. A PubMed search of the literature up to June 2017 regarding spontaneous remission central nervous system lymphoma was also carried out.

Keywords: Central Nervous System Neoplasms/drug therapy; Central Nervous System Neoplasms/radiotherapy; Lymphoma/drug therapy; Lymphoma/radiation therapy

RESUMO
É bem conhecida a remissão com corticoterapia dos linfomas primários do sistema nervoso central, mas a sua remissão sem qualquer tipo de tratamento é extremamente rara. Apresentamos um caso raro de uma remissão espontânea e posterior recidiva noutra localização de um linfoma difuso de grandes células B do sistema nervoso central. A apresentação atípica deste caso confundiu os neurocirurgiões e neurologistas, atrasando o diagnóstico e tratamento. A doente foi submetida a biópsia de uma das lesões cerebrais e, posteriormente, iniciou radioterapia e quimioterapia com citarabina + metotrexato + rituximab. Neste momento, 32 meses após o diagnóstico histológico, a doente encontra-se assintomática, sem défices neurológicos focais e com remissão completa da doença. Foi também efetuada uma pesquisa na PubMed até junho de 2017 sobre a remissão espontânea dos linfomas do sistema nervoso central.

Palavras-chave: Linfoma/quimioterapia; Linfoma/radioterapia; Neoplasias do Sistema Nervoso Central/quimioterapia; Neoplasias do Sistema Nervoso Central/radioterapia

INTRODUCTION
Malignant lymphomas can affect the central nervous system (CNS) in three ways: as primary CNS lymphoma, as a consequence of systemic lymphoma, and by intravascular lymphomatosis.1

Primary CNS lymphoma is a rare form of extranodal non-Hodgkin’s lymphoma.2,3 Its incidence has increased in both immunocompetent and immunodeficient patients, and currently accounts for about 2.2% of all intracranial tumors3,4 and 1% - 2% of all lymphomas.6 Most cases are sporadic, with a minority associated with cases of immunodeficiencies including human immunodeficiency virus (HIV) and iatrogenic immunosuppression.4

Primary CNS lymphoma can affect individuals of all ages, with a peak incidence in immunocompetent patients occurring between the fifth and seventh decades of life5 and with a mean age of 60 years.2

The clinical manifestations vary depending on the location of the lesion. The most common symptoms are psychiatric changes, headaches, seizures, ocular symptoms and other neurological focal deficits.7

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The most sensitive imaging technique is magnetic resonance imaging (MRI), and they frequently appear as a high-cellular lesion, iso- or hypo-intense in T1 weighted images, with hypersignal in T2-weighted images and intense contrast uptake. The lesions are solitary in 65% of cases and multiple in the remaining cases.

The most frequent location is in the cerebral hemispheres, followed by the basal ganglia, corpus callosum and cerebellum. However, there are no specific features that distinguish them from other primary or secondary brain neoplasms.

The most used diagnostic method is a lesion biopsy and 90% – 95% are histologically classified as diffuse large B-cell lymphoma.

Treatment of primary CNS lymphoma, as with other brain neoplasms, involves surgery, radiotherapy (RT), and chemotherapy (CT), with the latter two being the modalities of choice. The role of surgery is mainly diagnostic. However, some recent studies have reported a better prognosis in radical surgical removal of single lesions in non-eloquent brain areas. The role of RT has lost importance in recent years. Holocranial RT achieves high response rates but the duration of the effect is short and neurotoxicity is high. CT is the first therapeutic choice for newly diagnosed primary lymphomas of the CNS. It allows for high response rates and long periods without symptoms. The most commonly used drug is high-dose methotrexate alone or in combination with high-dose of cytarabine, procarbazine, vincristine and rituximab. A 2009 study reported a better response with methotrexate + cytarabine compared with methotrexate monotherapy.

In the past, primary CNS lymphoma prognoses were typically poor, but today, long-term survival of up to 10 years with certain treatment regimens is not uncommon, and cure can be achieved in some patients.

Brain lymphoma remission after corticosteroid therapy is well documented and they are the most frequent cause of “phantom tumor”. Other causes exist for the same phenomenon such as multiple sclerosis, disseminated acute encephalomyelitis, sarcoidosis and also gliomas. Theories that best explain this remission are that corticosteroids induce lymphocytic effects, repair of the blood–brain barrier, and the vasoconstriction that leads to a decrease in tumor blood supply.

When a primary CNS lymphoma is suspected, corticosteroid therapy should be postponed until histological results are reviewed because imaging and clinical remission may delay diagnosis and initiation of treatment.

Spontaneous remission of brain lymphomas without corticosteroid therapy is extremely rare. This type of remission may raise other diagnostic hypotheses, namely inflammatory and demyelinating diseases and again lead to a delay in diagnosis and treatment. The most plausible explanation for this phenomenon is based on an immune theory with changes in the host immunologic competence in which there is an increase in the body number of natural killer cells that may be caused by a concomitant viral infection. These natural killer cells then eliminate tumor lymphomatous cells.

We present a report of a tumor that vanished without corticosteroid treatment. The diagnosis and treatment of the tumor was delayed because brain lymphoma was only suspected after the second brain MRI.

CASE REPORT

A 50-year-old female patient, medicated with a serotonin reuptake inhibitor (escitalopram), bromazepam and oral contraceptive was asymptomatic until January 2014, when...
she began to complain of blurred vision. She underwent ophthalmologic evaluation and ocular correction was performed. A computed tomography (CT) scan revealed a 3 cm suprasellar hyperdense lesion (Figs. 1A and 1B). A hormonal study revealed prolactin values (PRL) of 183 ng/mL and she was referred to a pituitary disease multidisciplinary consultation for suspected macroprolactinoma.

Brain MRI was performed in May 2014 (Figs 2A to 2D), without any type of medication and after clinical improvement of the visual complaints. The MRI showed remission of the suprasellar lesion, but also showed two new nodular lesions, with the largest in the right caudate nucleus with subependymal expression, and the other in the anterior part of the third ventricle. A new hormonal study was performed, with no treatment having been given, and the prolactin levels were 76 ng/mL. The macroprolactinoma hypothesis was set aside and the patient was referred for neurologic consultation for suspected inflammatory disease.

Figure 2 – Initial MRI in May 2014. T1 axial weighted images with gadolinium enhancement demonstrate involution of the sellar / suprasellar lesion (A and B). Axial T1 weighted image with gadolinium enhancement shows nodular lesion with homogeneous contrast uptake in the head of the right caudate nucleus and with subependymal expression (C). Axial T1 weighted images with gadolinium enhancement reveals a subependymal nodule in the anterior wall of the third ventricle (D).
In August 2014, the patient again began to experience reduced visual acuity, and a new MRI was performed without any treatment given (Figs. 3A to 3D). MRI revealed regression of the lesion in the anterior portion of the third ventricle, and marked enlargement of the right caudate nucleus periventricular lesion. CNS lymphoma was hypothesized, despite some atypical features, and the patient was referred for neurosurgical consultation.

In October 2014, the patient underwent a right caudate nucleus lesion biopsy guided by neuronavigation. The histological result revealed a diffuse large B-cell lymphoma (Figs. 4A to 4D).

The patient completed the disease staging with cerebral spinal fluid analysis, bone marrow biopsy, thoraco-abdomino-pelvic CT scan, and positron emission tomography (Fig. 5). All the tests revealed that the lesion was restricted to the CNS. Viral serologies were also negative. The International Extranodal Lymphoma Study Group (IELSG) prognostic score was 2 (elevated cerebrospinal fluid proteins and elevation of serum lactate dehydrogenase, corresponding to

**Figure 3** – MRI in August 2014. Axial T1 weighted image with gadolinium enhancement shows enlargement of the right caudate nucleus periventricular lesion (A). Axial T1 weighted image with gadolinium enhancement confirms regression of the lesion in the anterior wall of the third ventricle (B). Axial diffusion (ADC map) showing restriction to diffusion in the right caudate lesion (C). Axial diffusion (b-1000 map) showing restriction to diffusion in the same lesion (D).
Chemotherapy was initiated with high-dose cytarabine + high-dose methotrexate + rituximab and radiotherapy (45 gray fractionated in 4.5 gray/day, 5 times/week). The patient was still alive at 32 months after the histological diagnosis, with the CNS lymphoma in complete remission.

**DISCUSSION**

Differential diagnosis of a vanishing sellar/suprasellar lesion should always include a demyelinating lesion. Other possible causes are inflammatory diseases such as autoimmune hypophysitis, pituitary apoplexy with interval resolution, and pituitary macroadenoma. Autoimmune hypophysitis is more frequent in young female patients, and can regress with corticosteroid treatment. Pituitary apoplexy is a clinical syndrome in which more than 80% of the cases present with sudden-onset headaches. This did not occur in our case, but is also a cause of regression in pituitary adenomas. There are two cases reported in the literature of spontaneous regression of a pituitary macroadenoma. One of these experienced regression in 3.5 months, but this patient had only one lesion and not multiple lesions as our case.

In our report, there was no histological diagnosis for the vanishing sellar/suprasellar lesion but it is highly probable that it corresponds to the same diagnosis of the caudate nucleus.
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Gender</th>
<th>Age</th>
<th>Symptoms</th>
<th>Location</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Survival</th>
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<td>Male</td>
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<td>Biopsy</td>
<td>Radiotherapy + steroids</td>
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<td>Sugita</td>
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<td>63</td>
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<td>Female, parietal lobes</td>
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<td>Autopsy</td>
<td>7 months</td>
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<td>Unconscious</td>
<td>Female, parietal lobes</td>
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<td>Unconscious</td>
<td>Female, parietal lobes</td>
<td>Diffuse large B-cell lymphoma</td>
<td>Autopsy</td>
<td>12 months</td>
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Table 1 – PubMed search regarding “spontaneous remission central nervous system lymphoma” until June 2017.
lesion.

As already mentioned, the most probable explanation for a lymphoma that vanishes without corticosteroid treat-
ment is a concomitant viral infection leading to an increased
number of body natural killer cells, which attack the tumor
cells.

To the best of our knowledge and based on a PubMed
search of the literature regarding spontaneous remission
of central nervous system lymphoma up to June 2017, there
are only 11 case reports of spontaneous remission/relaps-
ing of central nervous system lymphomas. In some of those
reports, other conditions like multiple sclerosis were sus-
ppected because of the spontaneous regression on diag-
nostic imaging and the diagnosis and treatment were also
delayed, which affected the overall survival (Table 1).

CONCLUSION

Despite being extremely rare, there are cases reported
of spontaneous remission and relapse of brain CNS lymph-

oma.

This case allows us to infer that differential diagnosis of
primary CNS lymphoma should always be considered when
a patient presents with a brain lesion that shows imaging
and clinical spontaneous remission and relapse. These pa-
patients should be followed at short intervals, and in suspi-
cious cases, a histological diagnosis must be obtained as
soon as possible to avoid delays in diagnosis and treat-
ment.

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