



A Case of Secondary Brain Lymphoma Initially Followed Up as Multiple Sclerosis

Multipl Skleroz Tanısı ile Takip Edilmiş Sekonder Beyin Lenfoma Tanısı Alan Olgu

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Summary

Secondary brain lymphomas are more common than the primary brain lymphomas, and often present with leptomeningeal lesions. Parenchymal infiltration of the brain is a rare finding. Brain metastases, including secondary brain lymphomas, are occasionally confused with multiple sclerosis (MS) due to their localization and clinical presentation. The patient who is the subject of this manuscript had been followed-up with a diagnosis of MS for a while, until she presented to our clinic with symptoms of cerebellar syndrome. Signs of nephrotic syndrome were identified at this presentation, a year after the onset of symptoms, and the patient was diagnosed as having B-cell non-Hodgkin's lymphoma owing to the results of renal biopsy. The cranial lesions were subsequently interpreted as secondary brain lymphoma and these regressed with chemotherapy (CT). The case was deemed notable for underlining the probability of confusing secondary brain lymphomas with MS and the good response to CT.

Keywords: Non-Hodgkin's lymphoma, multiple sclerosis, nephrotic syndrome

Öz

Sekonder beyin lenfomaları primer beyin lenfomalarından daha sık görülmekte ve genellikle leptomeningeal tutulum ile prezente olmaktadır. Beyin parankim infiltrasyonu nadir olup tutulum yeri ve klinik prezentasyon nedeni ile sekonder beyin lenfoması gibi beyin metastazları nadiren de olsa multipl skleroz (MS) hastalığı ile karışabilmektedir. MS tanısı ile bir süre takip edilen ve şikayetlerinin başlamasından 1 sene sonra serebellar sendrom bulguları ile tarafımıza başvuran ve nefrotik sendrom bulguları tespit edilen hastaya yapılan renal biyopsi sonucu B hücreli non-Hodgkin lenfoma tanısı konuldu ve kranyal lezyonları sekonder beyin lenfoması olarak değerlendirildi. Kemoterapi (KT) sonrası lezyonları geriledi. MS tanısı ile karışabilmesi ve KT'ye iyi yanıtı nedeni ile olgu sunuma değer bulunmuştur.

Anahtar kelimeler: Non-Hodgkin lenfoma, multipl skleroz, nefrotik sendrom

Introduction

Lymphomas are primary tumors of the lymphoreticular system and are classified into two categories as Hodgkin's and non-Hodgkin's lymphomas. Hodgkin's lymphoma often presents with lymph node involvement, whereas extranodal involvement is more common in non-Hodgkin's lymphomas (NHL) (1).

Central nervous system (CNS) lymphomas are grouped into two: primary and secondary lymphomas. Lymphomas that stem

from the brain, medulla spinalis, and meninges are termed primary brain lymphomas, whereas CNS extensions of systemic lymphomas are termed secondary brain lymphomas. As per the definition, primary brain lymphomas exclude any systemic involvements outside the CNS. Primary brain lymphomas constitute 1-15% of all CNS tumors (1,2). Leptomeningeal involvement is the common form of presentation in brain lymphomas, and parenchymal brain infiltration is a rare presentation that is characteristic of advanced stages.

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Among extranodal lymphomas that might develop during immunosuppressive drug use due to organ transplantation or autoimmune diseases, or immune deficiencies due to AIDS, congenital immune deficiencies or treatment of Hodgkin's lymphoma, primary brain lymphomas are the second most common type following gastrointestinal system lymphomas. The majority of primary brain lymphomas are non-Hodgkin's B-cell lymphomas, which are characterized with worse prognosis compared with other system involvements (3).

Brain metastases are seen in about one third of all patients with systemic cancer, holding a 10 times greater place compared with primary brain tumors among intracranial lesions. In adults, these lesions originate from the lung, breast, skin (particularly melanoma), and gastrointestinal system, in order of frequency. Brain lymphomas secondary to a systemic lymphoma are seen less frequently (4). Although prognosis is poor in metastatic brain tumors, despite proper treatment, prolonged survival might be seen in radiosensitive tumors such as lymphomas, certain types of breast cancer, testicular tumors, and choriocarcinomas (5).

Multiple sclerosis (MS) might rarely be confused with brain metastases. A patient's disease might be misdiagnosed due the location of metastases, the resulting neurologic deficit, response to cortisone therapy, and results of cerebrospinal fluid (CSF) examinations (6). Examination of oligoclonal bands (OCB) in CSF with outdated low-sensitivity modalities including electrophoresis might provide false negative or positive results. Additionally, it has been reported that OCB positivity might also be seen in several diseases other than MS (7). According to the McDonald 2010 diagnostic criteria, which are based on the evaluation of magnetic resonance imaging (MRI) in MS diagnosis, dissemination in space and time are important in defining the disease. Therefore, patience holds a significant place in establishing a correct MS diagnosis (8).

Case Report

The patient had presented to a neurology specialist 2 years ago with imbalance that had lasted a week. Cranial MRI had demonstrated a few periventricular lesions and in the centrum semiovale. A detailed examination was initiated with a pre-diagnosis of demyelinating disease (Figure 1). Lumbar puncture was performed and OCB type III was determined in the CSF.

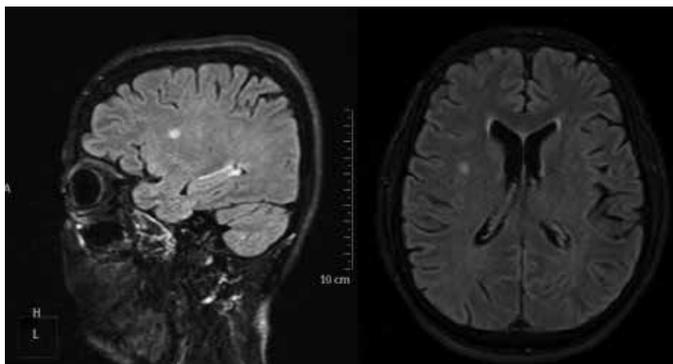


Figure 1. Two hyperintense lesions are seen in a periventricular location and in the centrum semiovale in FLAIR sequences of cranial magnetic resonance imaging obtained 2 years ago

Somatosensorial evoked potentials (SEP) were bilaterally prolonged, and the patient was diagnosed as having clinical isolated syndrome and followed up. Upon referral with symptoms of imbalance and vertigo, no new lesions were seen in cranial MRI obtained a year later. Laboratory examinations revealed ANA positivity. The patient was treated with pulse steroid 500 mg/day for 5 days and discharged with a prescription of azathioprine 2 mg/kg upon regression of symptoms.

The patient presented to our clinic with symptoms of vertigo, diplopia, and imbalance a year after the last presentation. The patient reported that her symptoms had started and gradually become worse for 2 weeks; her vertigo was accompanied by nausea and she could not walk unassisted, in addition to having a mild weakness in the left leg. In the meantime, she had been prescribed medication for hypertension and was being followed up by rheumatology. The patient also continued the azathioprine therapy. Neurologic examination revealed a left-beating horizontal nystagmus. Deep tendon reflexes (DTR) were bilaterally brisk, and the plantar reflex (PR) was extensor on the left. Dysdiadokinesia and dysmetria were determined bilaterally, though more prominent on the left. The Romberg test was also positive and the patient was ataxic to right and left in the tandem walk test.

Cranial MRI revealed infratentorial lesions with weak peripheral contrast enhancement, and without restricted diffusion in the medulla oblongata, pons, and both cerebellar hemispheres. No novel lesions were seen supratentorially, other than those already reported in the older cranial MRI (Figure 2). The results of

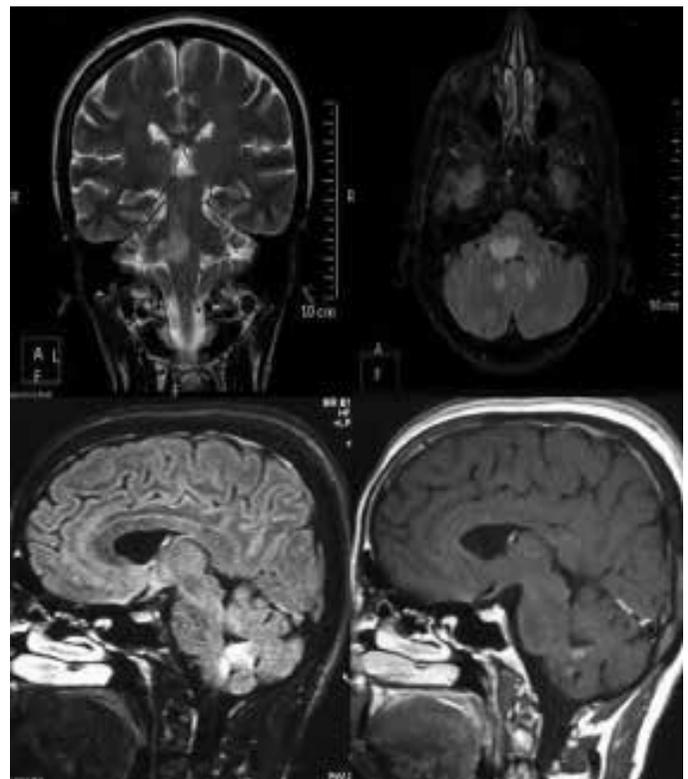


Figure 2. Multiple lesions in cranial magnetic resonance imaging that were hyperintense in FLAIR and T2 sequences, and contrast enhanced in T1 sequences

concurrent laboratory examinations performed showed that levels of urea and creatinine were elevated, albumin was decreased, which lead to a pre-diagnosis of nephrotic syndrome with the addition of hyperlipidemia and pitting edema. The level of protein was also elevated in the 24-hour urine sample. Renal ultrasonography revealed grade I parenchymal injury and a solid mass of 7x7x4 cm in the right adrenal lodge. A biopsy was performed to the right kidney to investigate both the nephrotic syndrome and solid mass and the results showed high grade B cell non-Hodgkin's lymphoma. A whole body positron emission tomography-computerized tomography (PET CT) scan revealed that the mass lesion in the right surrenal lodge had enhanced fluorodeoxyglucose (FDG) involvement, which was interpreted in favor of malignity, as well as signs of malignant lymphatic involvement, including enhanced aorto-caval FDG involvement. Abdominal MRI was performed to attain a complete anatomical localization of the lesion and lymph node involvement was identified neighboring the right adrenal. The patient tested negative for HIV.

Parenchymal cranial involvement was retrospectively interpreted as secondary brain lymphoma. The patient was treated with 6 courses of multiple chemotherapy involving R-HCVAD -rituximab (375 mg/m²), cyclophosphamide (800 mg/m²), vincristine (1.4 mg/m²) and doxorubicine (50 mg/m²)-, and almost complete regression was observed in cranial lesions and the mass lesion in adrenal lodge following the 6 courses (Figure 3). Neurological examination was normal except for the existing mild ataxia. The patient continues to be followed at our clinic without medications and has provided written informed consent for this case report.

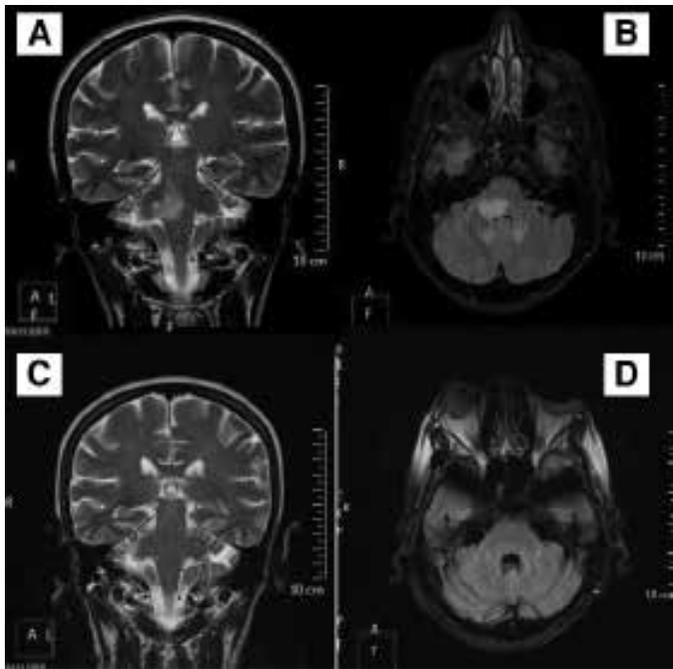


Figure 3. (A, B) Hyperintense lesions seen in FLAIR and T2 magnetic resonance imaging sequences prior to therapy, (C, D) disappeared following therapy

Discussion

CNS lymphomas are grouped into two as primary and secondary (1,2). Secondary brain lymphomas are less common compared with other types of metastatic tumors; therefore, the establishment of diagnosis might be delayed in some cases. Our patient had been put on azathioprine therapy at another center with a pre-diagnosis of demyelinating disease, and referred to our clinic with signs of cerebellar syndrome a year later. Initially, the simultaneous contrast enhancement of cranial lesions and their localization particularly in the infratentorial region had resulted in a pre-diagnosis of demyelinating disease; however, these lesions were finally described as secondary brain lymphoma after establishing a diagnosis of "high grade B cell NHL" resulting from renal biopsy that was performed to elucidate nephrotic syndrome. Almost complete regression of the lesions in response to chemotherapy finalized our diagnosis. Although azathioprine toxicity has been suggested to be a greater issue in cases with renal failure, associated results of controlled studies have been inconclusive. Studies have also reported that the risk of lymphoma is increased in transplantation patients who receive aggressive doses of azathioprine. The exact effect of azathioprine on the increase in cranial lesions cannot be determined in this case; however, the fact that lesions progressed during treatment creates enough basis for suspicion. Although the toxicity debate remains controversial in patients with renal failure, we believe our patient may have been subjected to higher than needed dosages (3,9,10,11,12,13).

The diagnosis of MS might be confused with granulomatous diseases, vasculitic syndromes, infection and metastases involving the brain (13). Additionally, steroid responsiveness of both lymphomas and MS attacks create added difficulty in diagnosis (14,15). MS is diagnosed by excluding other diagnoses using imaging features, CSF examinations, and demonstration of clinical attacks. In other words, the diagnosis of MS is a diagnosis of exclusion. Physicians may have concluded that the correct diagnosis for our patient was MS because of the type III OCB positivity in the CSF; however, the supratentorial lesions seen in MRI obtained a year ago did not meet the Barkoff criteria. It should be noted that OCB positivity can be seen in several diseases other than MS, and that the currently accepted method of OCB examination is isoelectric focusing rather than electrophoresis. High rates of false positivity have been reported with electrophoresis (16).

Hodgkin's lymphoma has a well-known association with paraneoplastic cerebellar degeneration. Tr and mGluR1 antibodies are the suspected culprits of this association, although these are partly characterized paraneoplastic antibodies. In addition, paraneoplastic syndromes including peripheral neuropathy, Lambert-Eaton myastenic syndrome, and myositis are more common in Hodgkin's lymphoma compared with non-Hodgkin lymphomas (17,18,19).

The prognosis of high grade B cell NHL depends on international prognostic index, morphologic data, features of immune phenotyping, and molecular characteristics. Often an aggressive course is expected in CNS involvement (20). Treatment comprises either of the R-HCVAD or R-CHOP (rituximab, cyclophosphamide, vincristine, and prednisone) protocols. R-HCVAD is a novel protocol used in the treatment of high grade

B cell NHL (21). Our patient responded well to chemotherapy and has been followed up relapse-free for 1 year.

Informed Consent: Consent form was filled out by all participants. **Concept:** Serkan Demir, Erdem Toğrol, Tolga Tuncel, Ali Rıza Sonkaya, **Design:** Serkan Demir, Erdem Toğrol, Tolga Tuncel, Ali Rıza Sonkaya, **Data Collection and Processing:** Serkan Demir, Erdem Toğrol, Tolga Tuncel, Ali Rıza Sonkaya, **Analysis or Interpretation:** Serkan Demir, Erdem Toğrol, Tolga Tuncel, Ali Rıza Sonkaya, **Literature Search:** Serkan Demir, Erdem Toğrol, **Writer:** Serkan Demir, **Peer-review:** External and Internal peer-reviewed. **Conflict of Interest:** Authors declare no conflicts of interest regarding this manuscript. **Financial Support:** Our study has not received financial supports from any institution or person.

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