

ORIGINAL RESEARCH

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**Assessment of secondary central nervous system involvement in patients with lymphoma;
MR imaging findings****Hediye Pinar Gunbey***Ondokuz Mayıs University, Faculty of Medicine, Department of Radiology, Samsun, Turkey*

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Abstract

Secondary central nervous system (CNS) involvement of lymphoma is a rare but critical complication of aggressive systemic lymphomas. We aimed to evaluate the incidence of CNS involvement and the value of magnetic resonance imaging (MRI) of neuroaxis in patients with systemic lymphoma. A total of 205 (93 women, 112 men) patients who have biopsy proven systemic lymphoma and underwent MRI for brain and spinal screening have included into this retrospective study. Based on patient data age, gender, histologic type of lymphoma, duration from initial diagnosis, survey of patients, brain and spinal MRI findings were determined. Secondary CNS involvement observed on 37 patients (18%). There were two HL patient with nodular sclerosing subtype (5.4%) and 35 NHL patients (94.5) were with diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma, mantle cell lymphoma, T-cell lymphoma and B-cell lymphoma subtypes. Nodal disease was 59.4% and extranodal focus of NHL was 31.6%. MRI findings revealed 35 % brain parenchymal lesion, 35% dural enhancement, 29.7% leptomeningeal enhancement, 21.6% cranial nerve enhancement, 13.5% spinal pial-nerve root enhancement, 5.4% ependymal enhancement, 5.4 % hydrocephalus and 2.7% spinal cord lesion. Dural enhancement was significantly higher in nasopharynx ($p=0.034$) and nodal NHL ($p=0.021$). Brain leptomeningeal ($p=0.021$) and spinal pial ($p=0.009$) enhancement was significantly higher in DLBCL patients. MRI of whole neuroaxis with contrast media is a quite beneficial technique for detecting parenchymal, leptomeningeal, cranial and peripheral nerve involvement in both primary diagnosis and follow-up survival processes of lymphoma.

Keywords: Lymphoma, secondary, magnetic resonance imaging**Introduction**

Secondary central nervous system (CNS) involvement of lymphoma is the more common type rather than primary CNS lymphoma in the nervous system lymphomas. Metastatic or secondary CNS involvement of systemic lymphoma has an approximately 10-15% incidence with a high risk of progressive and relapsing disease [1]. While Non-Hodgkin lymphoma (NHL) has the prominent responsibility of these metastasis, the patients with Hodgkin lymphoma (HL) also have a 0.2-0.5% risk to progress in this situation [2]. The histologic subtype plays a major role on metastatic disease, that aggressive diffuse large B-cell lymphoma, mantle cell lymphoma, Burkitt's lymphoma and lymphoblastic lymphoma are seen more frequently. The primary site of lymphoma also effects the CNS involvement that extranodal origins like orbita, testis, nasopharynx and paranasal sinuses have a higher risk of CNS relaps [3]. Metastatic disease frequently tends to occur between 5 to 12 months after primary diagnosis and represents with different clinical symptoms that depend on the involvement site [4].

The CNS metastasis of systemic lymphoma indicates the progressive stage of disease and have to take diagnosis as soon as possible for effective treatment plans. The diagnostic role of imaging is remarkable on CNS lymphoma because of non-available lesions for biopsy. The positive imaging is actually valuable to confirm the clinical suspicions and to guide for cytological analysis of cerebrospinal fluid (CSF). In contrast to primary CNS lymphoma, secondary CNS lymphoma tends to present much more as leptomeningeal spread than parenchymal disease.

In the assessment of leptomeningeal involvement the computed tomography (CT) imaging often fails to demonstrate the pathologies. Magnetic resonance imaging (MRI) is the preferred imaging technique with high resolution and ability to show leptomeningeal contrast enhancement on leptomeninges, cranial nerves and spinal nerve roots. MRI is also essential to evaluate the parenchymal disease with contrast material and additional diffusion weighted imaging on both primary diagnosis and follow-up courses. In this study we aimed to evaluate the incidence of secondary CNS involvement of systemic lymphoma and clinical outcome in patients undergoing brain and spinal MR imaging at our institution. Furthermore we aimed to define the value of MRI in demonstrating different faces of CNS involvement of lymphoma like neurolymphomatosis.

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Material and methods

A total of 205 (93 women, 112 men) patients who have biopsy proven systemic lymphoma and underwent MRI for brain and spinal screening at our institution from January 2012 to January 2018 have included into this retrospective study. To avoid repetition of the same data for follow-up imaging, the data for one imaging included in the study. Based on patient data age, gender, histologic type of lymphoma, duration from initial diagnosis, survey of patients, brain and spinal MRI findings were determined. Post-operative processes, trauma, CNS infections, spondylodiscitis and additional inflammatory diseases were the exclusion criteria for this study.

MR imaging were performed with 1.5 Tesla and 3 Tesla MR devices (Philips Achieva and Philips Ingenia, Netherlands) at our radiology department. MRI included T1-weighted (W) axial conventional spin-echo sequence without gadolinium (repetition time [TR]/echo time [TE], 457/14 milliseconds; slice thickness, 5 mm; field of view [FOV], 230; matrix, 204 _ 256; number of excitations [NEX], 2); T2W axial turbo spin-echo sequence (TR/TE, 6160/ 100 milliseconds; section thickness, 5 mm; FOV, 230; matrix, 231 _ 384; NEX, 2); fluid attenuation inversion recovery (FLAIR) coronal (TR/TE/TI, 8000/82/2800 milliseconds; section thickness, 5 mm; FOV, 230; matrix, 224 _ 256; NEX, 2); T2W sagittal turbo spin-echo sequence (TR/TE, 4560/92 milliseconds; section thickness, 5 mm; FOV, 230; matrix, 261 _ 384; NEX, 3); post-contrast T1W 3D gradient-echo sequence (TR/TE, 7.2/33 ms; matrix, 256x256; slice thickness, 5 mm; NSA, 1; FOV, 256 mm; slice thickness, 1 mm; gap, 0 mm; flip angle, 8°) images. Diffusion weighted imaging were also included in our brain MRI protocol. The spinal imaging included pre-contrast T1W, T2W, short tau inversion recovery (STIR) sagittal, T2W axial images and post-contrast T1W sagittal and axial images. DICOM files were retrieved from archive system and transferred to Macintosh computer (Apple iMac ME087TU/A i5) for review.

Brain MRI findings were evaluated in terms of leptomeningeal, cranial nerve, dural, ependymal enhancement, presence of parenchymal lesion and hydrocephalus. Spinal MRI findings were evaluated in terms of spinal cord lesion, pial enhancement and spinal nerve root enhancements. The confirmation of leptomeningeal involvement was performed CSF cytological analysis results.

Statistical analyses was done with SPSS, 21.version (IBM Corporation, Armonk, NY, USA). Shapiro-Wilk test was used to determine the normality in the distribution of the quantitative data. To compare two independent groups Student's t-test were used. Correlation analyses performed with the Spearman's rho test. A p value less than 0.05 was considered statistically significant.

Results

205 patients, including 112 males (56%) and 93 females (44%), enrolled to the study. The mean age of the patients was 59.8 (range, 27-89) years. Secondary CNS involvement observed on 37 patients (18%) including 18 males (55%) and 19 females (45%). There were two HL patient with nodular sclerosing subtype (5.4%). The remaining 35 patients (94.5) were NHL with subtypes as follows: diffuse large B-cell lymphoma (DLBCL) in 30 patients (85%), Burkitt's lymphoma in two patients (5.7%), mantle cell lymphoma

in one patient (2.8%), T-cell lymphoma in one patient (2.8%), and B-cell lymphoma in one patient (2.8%).

Twenty-two patients had nodal disease (59.4%). The extranodal focus of NHL (31.6%) were as follows: gastric in four patients, breast in three patients, nasopharynx in three patients, palatine in two patients, orbita in one patient, liver in one patient and pancreas in one patient. The demographic data of patients is given in table 1. The mean duration time between primary lymphoma diagnosis and secondary CNS involvement was 15.6 month. This time varied in the extranodal sites with 15.5 months for gastric side, 13 months for breast and 9.3 months for nasopharynx. The distribution pattern of lymphoma in patients is given in Table 2.

According to data obtained from the hospital medical information system 16 patients (43%) had died among 37 patients with CNS involvement. There was no available data regarding the survival of remaining 21 patients. The mortality rate was 46.6% in DLBCL patients, 66% with nasopharynx NHL patients and 30 %with breast NHL patients.

MRI findings revealed 35 % brain parenchymal lesion, 35% dural enhancement, 29.7% leptomeningeal enhancement, 21.6% cranial nerve enhancement, 13.5% spinal pial-nerve root enhancement, 5.4% ependymal enhancement, 5.4 % hydrocephalus and 2.7% spinal cord lesion (fig 1). Total leptomeningeal enhancement with pial, dural, cranial-peripheral nerve root enhancement rate was 54%. 80% of spinal pial enhancements associated with cranial nerve involvement.

In correlation analyses there was no correlation between gender, lymphoma type, extranodal site and duration from initial diagnosis ($p>0.05$). Dural enhancement was significantly higher in nasopharynx ($p=0.034$) and nodal NHL ($p=0.021$). Brain leptomeningeal ($p=0.021$) and spinal pial ($p=0.009$) enhancement was significantly higher in DLBCL patients between histologic subtypes.

Table 1. The demographic data of patients

	Number of cases
Gender	
*Female	19
*Male	18
HL	2
NHL	
*Nodal	22
*Extranodal	15
Gastric	4
Breast	3
Nasopharynx	3
Palatine	2
Orbita	1
Liver	1
Pancreas	1

Table 2. The distribution patern of lymphoma

	NHL					HL	Nodal	extranodal
	DLBCL	BURKITT	MANTLE	T-CELL	B-CELL			
Number of cases	28	2	1	1	1	2	22	15

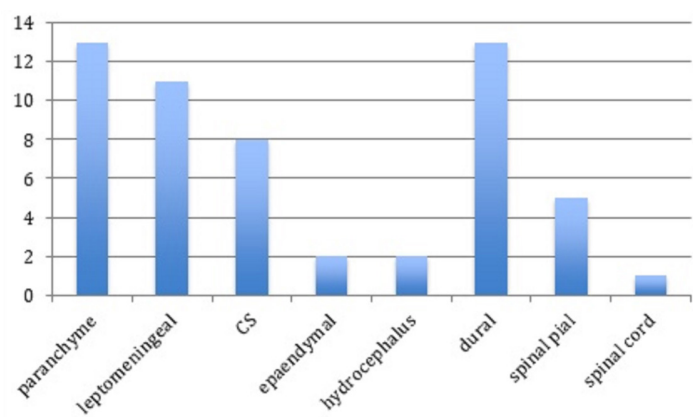


Figure 1. MRI findings of secondary CNS involvement

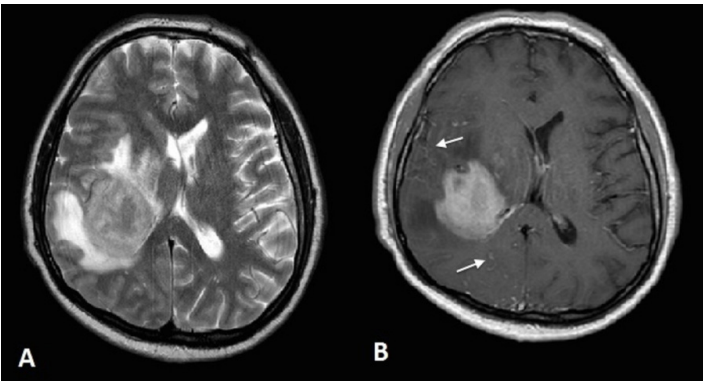


Figure 2. T2W (A) and post-contrast T1W (B) axial images demonstrates CNS involvement of gastric mantle cell lymphoma representing with a periventricular enhancing mass and pial enhancements (arrows) around the mass.

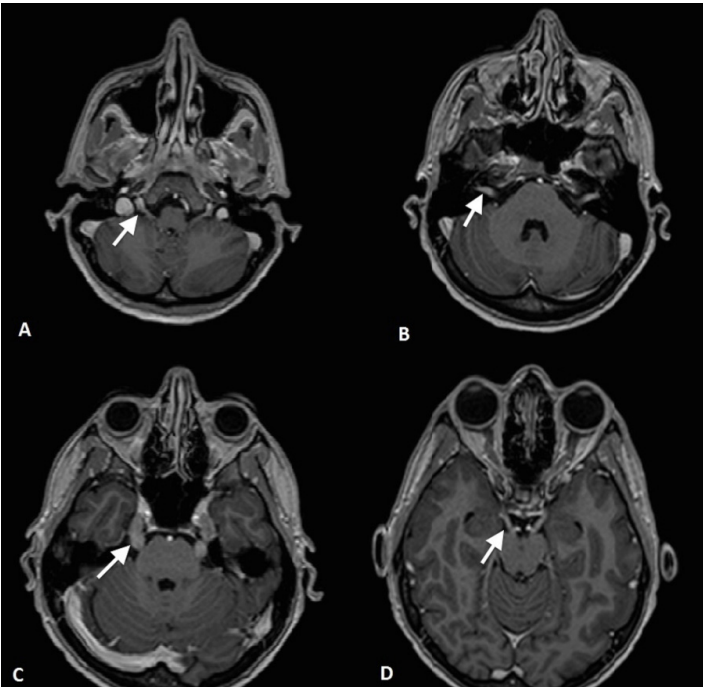


Figure 3. Neurolymphomatosis patient with multipl cranial nerve enhancements on post-contrast 3D T1W images. Bilateral 9-11 (A), 7-8 (B), 5 (C) and 3. (D) cranial nerve enhancements (arrows).

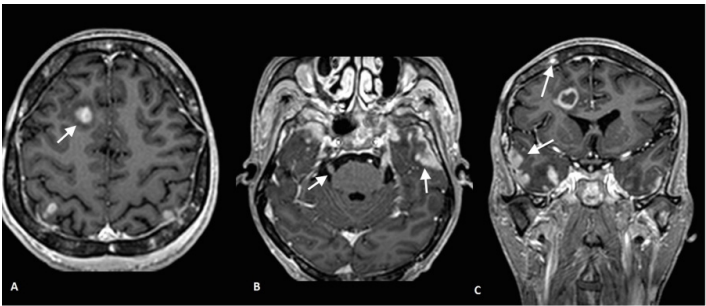


Figure 4. Superficial cortical, cranial nerve and calvarial metastasis (arrows) of systemic lymphoma on post-contrast 3D T1W axial (A,B) and coronal (C) images

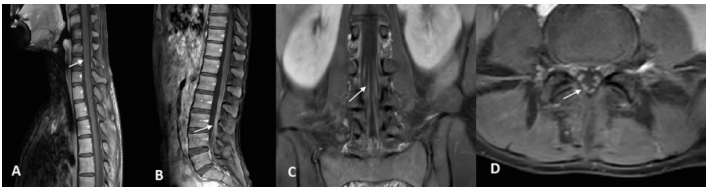


Figure 5. Spinal post-contrast T1W images demonstrates spinal pial and nerve root enhancements (arrows) on sagittal cervical (A), sagittal lumbar (B), coronal lumbar (C) and axial lumbar (D) images

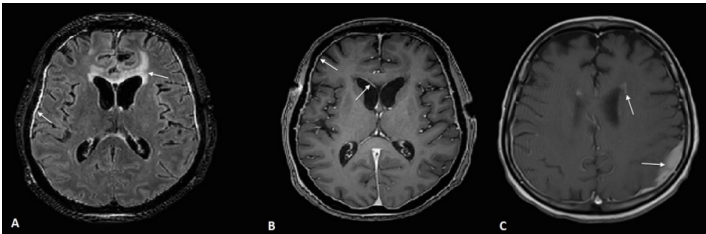


Figure 6. CNS metastasis of dural, supepandymal and periventricular region (arrows) in the same patient with lymphoma demonstrated on axial FLAIR (A) and post-contrast T1W (B) images. Coexistence of dural and periventricular enhancing metastatic lesions (arrows) in another lymphoma patient demonstrated on post-contrast T1W (C) images

Discussion

Secondary CNS involvement of systemic lymphoma is a crucial complication which influences the life span of patients. Frequently the patients with CNS involvement have a poor prognosis with worrying results than the other organ systems involvement [5]. The overall 18 % incidence of CNS involvement in our study seems higher than the incidence mentioned in literature. It may be due to high cancer population in the black sea region we live in. Otherwise with 83% percent of NHL in this study, this results may reflect the risk of CNS relapse in aggressive NHL with 2%–27% incidence [4-6]. 0.9% CNS involvement in HL patients in this study also correlated with the fairly low 0.5% incidence of historical data.

Aggressive histologic subtypes of NHL have been reported to be more prone to CNS involvement in the literature [7]. Regarding with this data our study showed metastatic CNS disease most commonly in DLBCL subtype and fewer in mantle cell lymphoma,

Burkitt's lymphoma, T-cell and B-cell lymphoma. The higher risk factor of CNS involvement with extranodal focus is proven in this study that 31.6% of patients with positive MRI findings had extranodal disease [8]. The mean duration time between primary lymphoma diagnosis and secondary CNS involvement was higher than the literature data in our study. This may be due heterogeneous patient populations, treatment and patient monitoring protocols in different centers. The earliest group representing CNS metastasis was nasopharyngeal lymphoma patients with DLBCL histology in the study. The adjacent neighborhood may have played a role in this rapid spread of aggressive lymphoma cells. The poor diagnosis of systemic lymphoma with CNS metastasis is also confirmed with this retrospective study that 43% of patients had died according to limited data. The mortality rate was highest in nasopharyngeal lymphoma.

In the management of patients early diagnosis of CNS involvement so that the role of imaging is crucial for hematologic malignancies[9,10]. Because of non-available lesions for biopsy imaging is essential to suspect CNS involvement and guide for histologic diagnosis based on cytology of the CSF. While CT has some limitations, MRI is the preferred imaging technique with high resolution contrast of soft tissues using gadolinium. Contrast enhanced images especially 3D T1W images with 1 mm slice thickness increases the detection of millimetric leptomeningeal and cranial nerve enhancing lesions which may poorly detected on non-contrast MRI and CT [11]. Despite imaging features may mimic infectious, inflammatory, or metastatic disease, a history of systemic lymphoma specifies the diagnosis.

CNS involvement of secondary lymphoma presents more frequently as leptomeningeal metastasis [12]. Regarding with literature on the fact that two-thirds of the CNS involvement is leptomeningeal and one-third of is parenchymal disease our study also demonstrated 65% leptomeningeal and 35% parenchymal spread of lymphoma [4]. As suggestive neuroimaging findings of leptomeningeal metastasis leptomeningeal superficial cerebral lesions, subependymal, dural, cranial and spinal nerve root enhancement defined which represented with headache, cranial or spinal neuropathies [13-15].

Leptomeningeal enhancement which is usually associated with meningitis with alterations in the permeability of the blood-brain-barrier, may also be produced by the spread of neoplastic cells on the brain surface and subarachnoid spaces. The peripheral and cranial nerves never show enhancement within the subarachnoid space that the opposite is always abnormal. Lumbar puncture is an iatrogenic cause of leptomeningeal enhancement therefore it should be avoided before neuroimaging [14]. The leptomeningeal and so cranial nerve involvement may be related hematogen spread of lymphoma cells through arachnoidal-pial vessels and vasa vasorum. The coexistence of cranial and spinal nerve root enhancement with a rate of 80% indicates the how fast the spread of neoplastic cells via vasa vasorum.

One of our patients of NHL represented with neurolymphomatosis (NL) diagnosis which is an uncommon syndrome and poorly recognized by clinicians.

It is characterized by the lymphomatous infiltration of a nerve root, cranial or peripheral nerves most commonly with B-cell lymphoma

[16-18]. Our patient had a T-cell lymphoma history which is mentioned with only a few cases in the literature [19-20]. She had a complaint of only diplopia but MRI has demonstrated nearly all 2-11. cranial and spinal nerves enhancement. She showed full response to chemotherapy and steroid treatment consistent with literature [21]. This situation expressed the benefits of screening patients with MRI both in primary diagnosis and follow-up processes.

The pathogenesis of dural enhancement is different from leptomeningeal enhancement that the dural capillaries are nonneural and have no blood-brain barrier. The reactive processes of neoplastic cells may produce vasocongestion and accumulation of interstitial edema which leads to enhancement of dura mater. Apart from hematologic spread dural invasion like to cavernous sinus may occur neighborliness of nasopharyngeal lymphoma as in our two patients.

Parenchymal invasion of metastatic lymphoma tends to occur at periventricular or superficial location as defined in our patients. Periventricular invasion is thought to be secondary involvement from the leptomeninges via perivascular Virchow-Robin spaces. The superficial cortical and subcortical gray matter-white matter pattern may projects intravascular neoplastic cells in the region, where vessels branch and taper at the transition from the abundant vessels in the cortical gray matter into the relatively sparse vasculature of the white matter. Diffusion weighted imaging is a valuable imaging tool for the diagnosis of lymphoma which is characterized with restricted diffusion with lower apparent diffusion coefficient (ADC) values than normal brain as in our patients. Coexistence of lower ADC values is also useful to differentiate lymphoma from high-grade gliomas and metastases [22].

Progressive hydrocephalus may be the only sign on imaging as a result of metastatic obstruction of CSF flow/absorption [13].

Conclusion

Secondary involvement of systemic aggressive lymphomas is rare and critical complication that diagnosis is essential to extend the survival period. Imaging of whole neuroaxis is necessary for detecting parenchymal, leptomeningeal, cranial and peripheral nerve involvement. MRI is the preferential imaging technique with the advantage of demonstrating millimetric contrast enhancement of nerves and pial surfaces with high soft tissue resolution. Further we believe that improved MR imaging with PET will probably increase the diagnostic incidence of CNS involvement and affect the therapeutic processes in the future.

Competing interests

The authors declare that they have no competing interest.

Financial Disclosure

There are no financial supports .

Ethical approval

This work has been approved by the Institutional Review Board.

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