Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: April 30, 2024

Citation: Roberts N, Obiorah I, et al., 2024. Follicular Lymphoma with Cranial Nerve and Central Nervous System Involvement Successfully Treated with Bendamustine and Rituximab: A Case Report and Literature Review, Medical Research Archives, [online] 12(4). https://doi.org/10.18103/mra.v12i4.5379

DOI
https://doi.org/10.18103/mra.v12i4.5379

ISSN: 2375-1924

REVIEW ARTICLE

Follicular Lymphoma with Cranial Nerve and Central Nervous System Involvement Successfully Treated with Bendamustine and Rituximab: A Case Report and Literature Review

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ABSTRACT
Follicular lymphoma is the most common indolent non-Hodgkin lymphoma (NHL) and accounts for approximately 20-30% of all NHL cases in Western countries. In general, systemic therapies are not considered to be curative. Despite this, prognosis is excellent with a 5-year relative survival rate of 90% and median overall survival rates ranging from 10-20 years across numerous studies. The exact incidence of central nervous system (CNS) involvement in cases of follicular lymphoma is unknown, however retrospective data suggest an incidence of 0.2% though this likely represents an underestimation of the true incidence. The optimum treatment approach for CNS disease in follicular lymphoma is poorly defined and no randomized studies exist which prove the superiority of one approach over another. Retrospective data suggest that resection, with or without adjuvant radiation, is an effective strategy for patients with local disease limited to the CNS. In cases where synchronous systemic disease is present, treatment regimens incorporating high-dose methotrexate and bendamustine or anthracycline-based chemotherapy have demonstrated efficacy. We report a case of a 59-year-old female with stage IV follicular lymphoma with synchronous systemic and leptomeningeal involvement who achieved complete remission following treatment with bendamustine, rituximab, and intra-thecal methotrexate. More long-term follow up data are needed to better characterize the prognosis for patients with CNS involvement who obtain complete remission following initial therapies. Treatment selection for patients with CNS involvement should take into account the presence or absence of systemic disease, patient comorbidities and performance status, and the likelihood of transformation to a high-grade process.

Keywords: Bendamustine, Chemoimmunotherapy, Follicular Lymphoma, Lymphoproliferative Disorders, Neurolymphomatosis, Non-Hodgkin Lymphoma, Rituximab, Secondary CNS Lymphoma

Introduction

Follicular lymphoma is a mature B-cell malignancy that arises from transformed germinal center B lymphocytes residing in secondary lymph node follicles.[1] It is the most common indolent NHL diagnosed in the United States with approximately 14,000 new cases per year or 2.5 cases per 100,000 persons, equating to ~20-30% of all NHL cases.[2] Although the causative etiology is the subject of ongoing investigation, lymphomagenesis is hypothesized to occur as a result of repeated germinal-center (GC) passages by IgM or IgG+ memory B-cells harboring the characteristic t(14;18)(q32;q21) translocation which is present in 85-90% of cases.[1] Repetitive GC interactions promote the accumulation of mutations and genomic instability, thereby driving cancer precursor cells towards transformation to overt FL. Table 1 summarizes several prognostic models that have been developed to risk-stratify patients, including the FLIPI, FLIPI2, m7-FLIPI, and PRIMA-PI.[3-6] As illustrated in Figure 1, the performance of these prognostic models was recently evaluated in a retrospective study that compared 6-year outcomes in symptomatic patients treated with chemoimmunotherapy in the front-line setting.[7]

Table 1. Prognostic Models and Risk Factors in Follicular Lymphoma

FLIPI	FLIPI2	m7-FLIPI	PRIMA-PI	GELF Criteria
• Age > 60 • Stage ≥ III • Hemoglobin < 12 g/dL • >4 nodal areas involved • LDH > ULN	• Age > 60 • Lymph node >6 cm • Hemoglobin <12 g/dL • Bone marrow involvement • β2-microglobulin > ULN	• FLIPI score • ECOG performance status • Presence of mutation in genes *EZH2, ARID1A, MEF2B, EP300, FOX01, CREBBP, CARD11*	• Bone marrow involvement • β2-microglobulin > 3 mg/L	• Any node or extra-nodal mass > 7 cm • 3 or more nodes >3 cm each • B symptoms • Splenomegaly • Visceral compression or obstruction • Presence of serous effusion • Leukemic phase • Presence of cytopenias (ANC < 1,000/uL or PLT < 100k/uL)
Risk Groups • Low: 0-1 points • Intermediate: 2 points • High: ≥3 points	**Risk Groups** • Low: 0 points • Intermediate: 1-2 points • High: 3-5 points	**Risk Groups** • Low: Score < 0.8 • High: Score ≥0.8	**Risk Groups** • Low: β2-microglobulin ≤3 mg/L and no BMI • Intermediate: β2-microglobulin ≤3 mg/L with BMI • high: β2-microglobulin > 3 mg/L	

Figure 1.

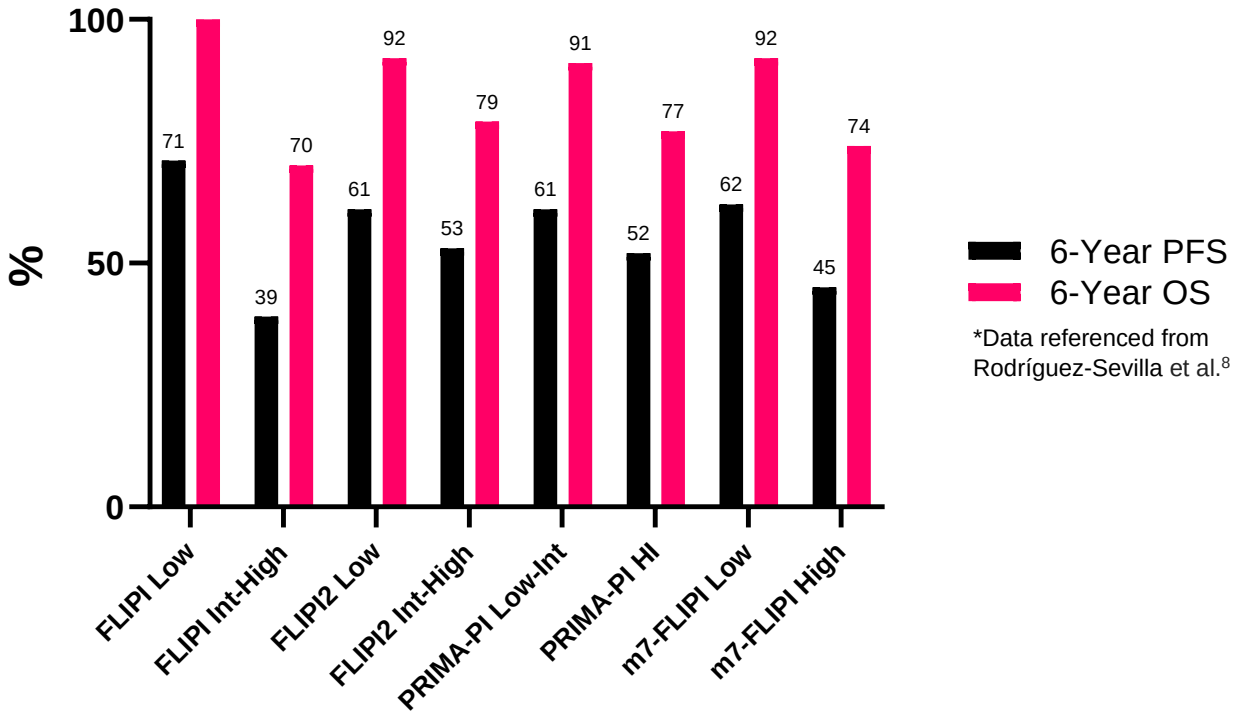

Figure 1. Comparison of Prognostic Models and Risk Groups among Follicular Lymphoma Patients Treated with Chemoimmunotherapy in the Front-Line Setting

A minority (<10%) of patients will be found to have early stage (I/II) disease at diagnosis.[8] Initial treatment options for patients with early-stage disease include radiation alone, immunotherapy (I.e., anti-CD20 antibodies), or chemoimmunotherapy regimens such as BR, R-CVP, or R-CHOP. However, given the excellent prognosis of patients with early-stage disease and potential toxicity associated with chemotherapy, many experts recommend radiotherapy or immunotherapy alone over combination chemoimmunotherapy. It is also important to note that not all patients with newly diagnosed disease require immediate treatment. A retrospective study of patients (n=43) with stage I/II disease whose therapy was deferred for at least 3 months after diagnosis showed 5, 10, and 20-year overall survival (OS) rates of 97%, 85%, and 22%, respectively.[9] Additionally, after median follow-up time of 86 months, 63% of patients had received no treatment at all. Randomized studies have also confirmed that a "watch and wait" approach is safe and effective in asymptomatic patients with advanced-stage disease. In a randomized trial comparing oral chlorambucil versus observation among 309 patients with low-grade NHL (among whom ~66% had FL), median OS was not significantly different between the two groups (median OS 5.9 years with chlorambucil versus 6.7 years with observation, p=0.84).[10] Among patients with advanced-stage disease, a risk-adapted approach is preferred to identify patients who warrant prompt initiation of treatment. The GELF (Groupe d'Etude des Lymphomes Folliculaires) Criteria (Table 1) represents one risk-assessment model that can identify patients with increased tumor burden who are at risk for adverse outcomes and who may be inappropriate for a "watch and wait" approach.[11] Patients with at least 1 positive GELF criterion should be offered prompt treatment. Preferred induction regimens for treatment-naïve patients with systemic disease include bendamustine plus obinutuzumab or rituximab (BO/BR), rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP), rituximab plus cyclophosphamide, vincristine, prednisone (R-CVP), rituximab plus lenalidomide (R^2), or rituximab monotherapy. Following induction, select patients may be considered for continued treatment with single-agent rituximab as maintenance therapy, however a full discussion of this strategy is beyond the scope of this paper.

Central nervous system (CNS) involvement represents a rare but dreaded complication of non-Hodgkin lymphoma. De novo CNS involvement in the absence of systemic disease is referred to as primary CNS lymphoma (PCNSL), whereas CNS

involvement with concurrent or prior systemic disease is referred to as secondary CNS lymphoma (SCNSL). The incidence of CNS involvement by diffuse large B-cell lymphoma (DLBCL) is well described, and reported in approximately 5 to 15% of patients.[12] Long-term outcomes in SCNSL patients with DLBCL treated with intensive, multi-agent chemotherapy followed by autologous stem cell transplantation remain poor, with several prospective studies showing 2-year overall survival (OS) rates ranging from 41-63%.[13-15] The CNS International Prognostic Index has been previously validated as a robust and reproducible tool to identify DLBCL patients at increased risk for CNS relapse.[12] In contrast, less is known regarding the epidemiology, risk factors, and optimal treatment of secondary CNS involvement by indolent non-Hodgkin lymphomas, including follicular lymphoma. In a retrospective review of 9,435 cases of CNS lymphoma reported in the National Cancer Database (NCDB) between 2004-2013, 475 cases (~5%) had low-grade histology.[16] Among these 475 cases, follicular lymphoma was the most common histology with 228 cases (48%), equating to ~25 cases/year or ~0.2% of all follicular lymphoma cases diagnosed annually in the United States. The median age at time of diagnosis of CNS disease is in the 6th decade of life (~61 years), similar to the median age of diagnosis of 64 for systemic follicular lymphoma. Males and females appear to be equally affected with no clear sex predilection. The most common site of CNS involvement is leptomeningeal, with extra-axial, dural-based masses the most commonly described presentation. Cases of parenchymal involvement, including cerebral and cerebellar locations, and cranial nerve involvement have also been described although less commonly. Here we report a case of a patient with follicular lymphoma who presented with concurrent systemic and CNS involvement, and provide a narrative review of previously reported cases and recommendations on the management of this rare entity.

Case Report

A 59-year-old Caucasian female presented with a chief complaint of stabbing substernal chest pain radiating to the back, shoulders, and neck. CT angiography of the chest revealed diffuse enlargement of the mediastinal, chest wall, axillary, cardio-phrenic, and supraclavicular lymph nodes, with largest left supraclavicular lymph node measuring 2.1 cm. A core-needle biopsy of a left axillary lymph node was obtained which revealed an abnormal lymphoid proliferation with a nodular growth pattern (Figure 2). Immunohistochemical analysis detected a kappa restricted CD10 positive B-cell population with BCL2 expression and a Ki-67 score of 20% (Figure 3). The overall features were consistent with classical follicular lymphoma, grade 1-2. The patient was referred to medical oncology for evaluation. Initial staging ^{18}F-fluorodeoxyglucose (FDG) PET/CT demonstrated widespread hypermetabolic lymphadenopathy, enlarged and hypermetabolic spleen, and extensive hypermetabolic osseous disease involving axial and proximal appendicular skeleton which included the central skull base (clivus, dorsum sella and left petrous apex), consistent with stage IV disease (Figures 4-5A).

At her initial visit, the patient also reported new onset left facial numbness. Magnetic resonance imaging (MRI) of the brain confirmed involvement of the central skull base with altered marrow signal and enhancement (Figure 5B-D). A contiguous mass like enhancement was noted in the left Meckel's cave with extension along the cisternal segment of left trigeminal nerve, mandibular and maxillary divisions of left trigeminal nerve through foramen ovale and rotundum, respectively, compatible with perineural spread. Lumbar puncture with cerebrospinal fluid (CSF) sampling was performed, and this demonstrated the presence of a kappa restricted CD10+ B-cell population within the CSF, suggesting secondary CNS involvement. The patient was treated with bendamustine 90 mg/m^2 on days 1 and 2 with rituximab 375 mg/m^2 on day 1 given every 28 days. The patient received intra-thecal methotrexate and hydrocortisone with cycles 1 and 3 of treatment. PET/CT following 3 cycles of treatment showed complete remission (Figure 6). Brain MRI following 3 cycles of treatment showed near resolution of previously demonstrated enhancing soft tissue lesion of the left trigeminal nerve and clivus. CSF analysis following cycle 3 showed no evidence of lymphomatous involvement. The patient tolerated treatment well with no serious treatment-related adverse events, treatment interruptions, or dose reductions. As of this writing, she remains on active treatment with the goal of completing 6 cycles of induction therapy.

Figure 2

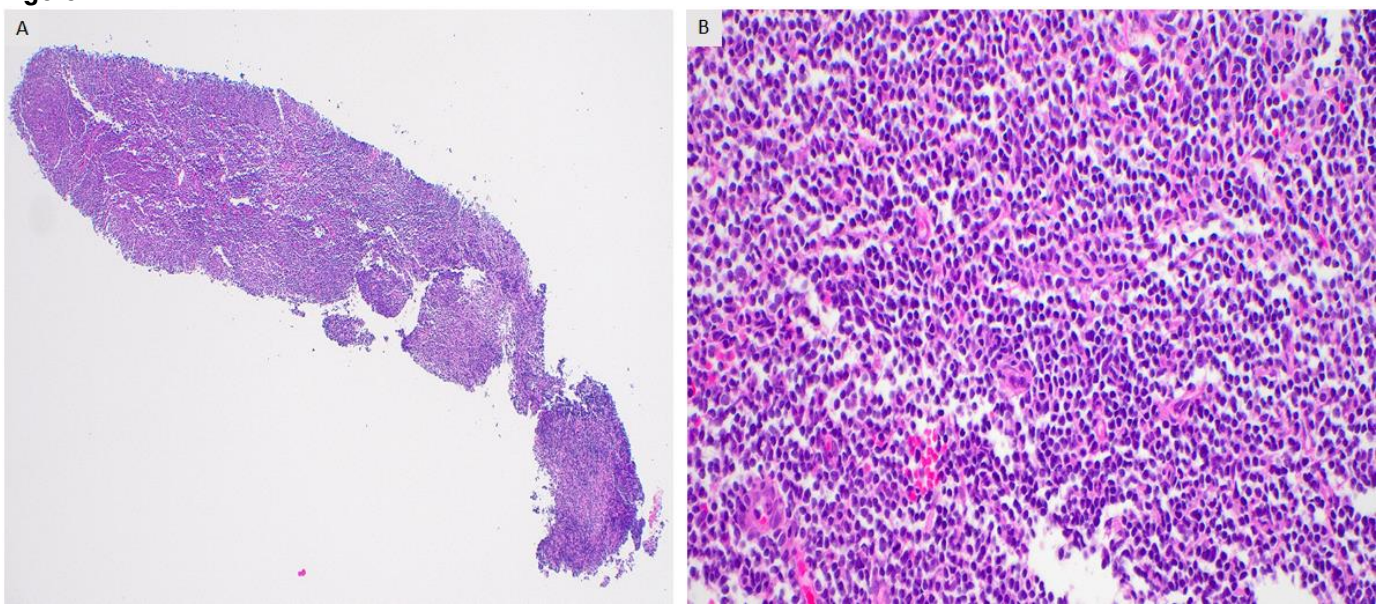

Figure 2 - Histologic examination of the lymph node. A) Sections of the biopsy show thin cores of lymphoid tissue with involvement by an atypical lymphoid infiltrate with a vaguely nodular growth pattern (Hematoxylin and eosin (H&E) stain×50). B) The majority of the atypical lymphoid cells appear small and centrocyte-like (H&E x4000).

Figure 3

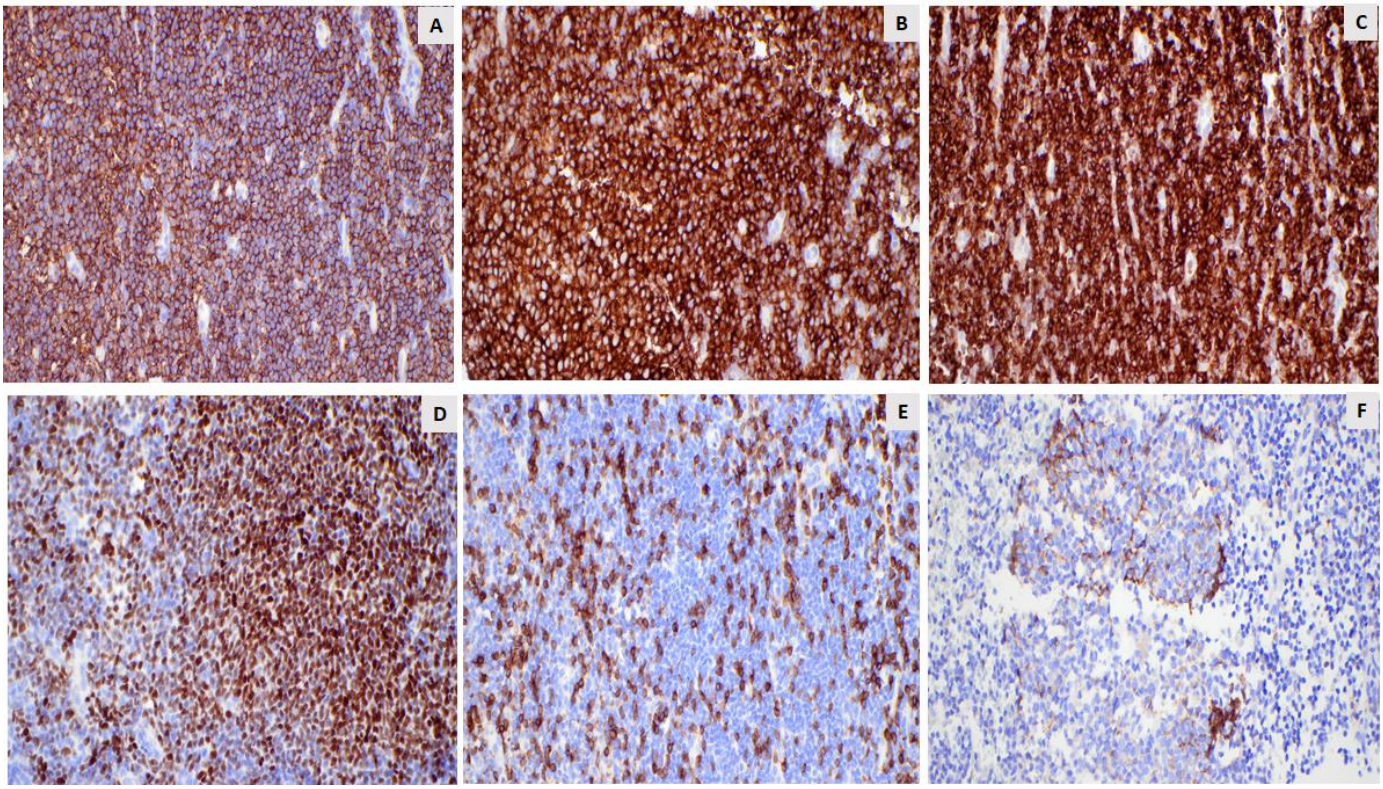

Figure 3 - Immunohistochemical staining of the lymph node. Immunohistochemistry revealed neoplastic cells positive for (A) CD20, (B) CD10, (C) BCL2 and (D) BCL6. (x 4000 each). (E) CD3 stains background T cells (x 4000). (F) CD21 stains residual follicular dendritic meshwork (x 4000).

Figure 4

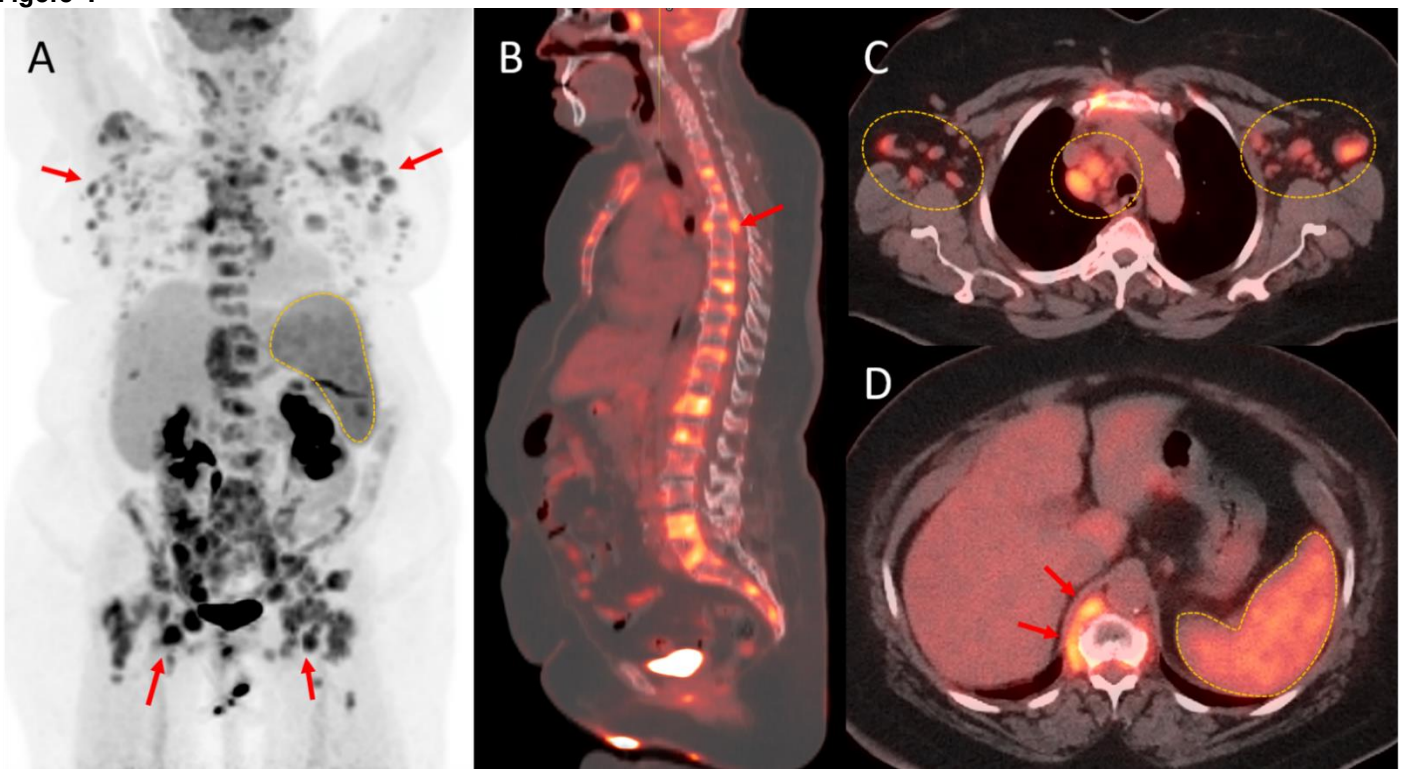

Figure 4 – A) Maximum intensity projection of the whole body ^{18}F-FDG PET shows multi-station hypermetabolic lymphadenopathy including the axillary and inguinofemoral region (arrows), and hypermetabolic spleen (dotted line), with uptake level well above the reference liver, consistent with lymphoma. B) Sagittal PET/CT shows multiple hypermetabolic lesions in the spine and skull base consistent with osseous and marrow involvement. Focal activity apparently within the spinal canal (arrow) was concerning for epidural disease and was confirmed as subtle enhancement on subsequent MRI (not shown). C-D) Axial PET/CT demonstrates the axillary and mediastinal hypermetabolic lymphadenopathy (dotted ellipse), paravertebral disease adjacent to lower thoracic vertebrae (arrows) and hypermetabolic spleen (dotted ROI).

Figure 5

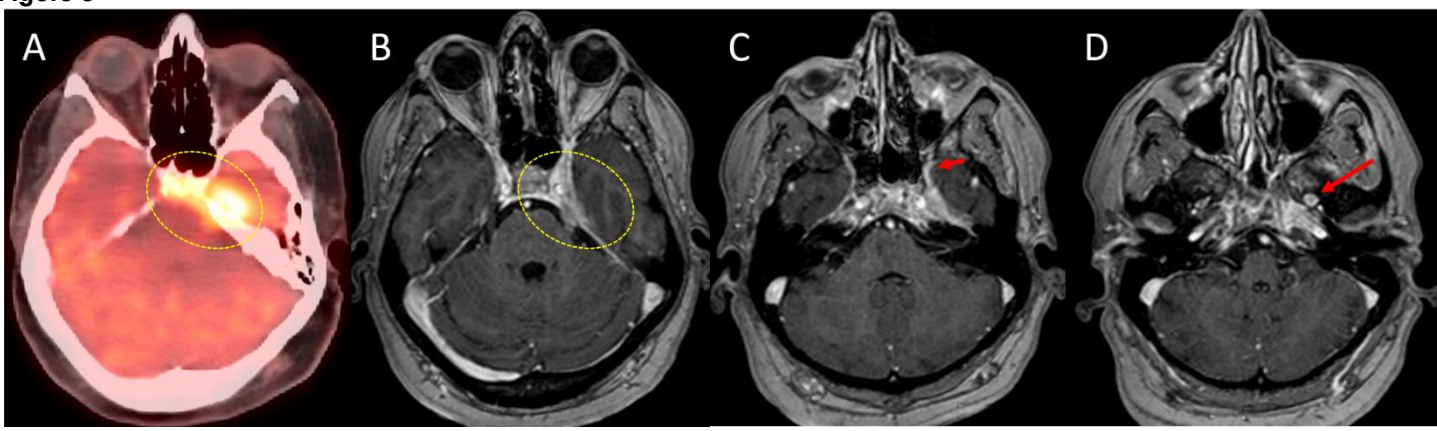

Figure 5 – A) Axial PET/CT at the level of skull base shows hypermetabolic lesion involving left petrous apex, dorsum sella, left cavernous sinus region (dotted ellipse) from lymphoma. B-D) Axial post contrast MRI shows a corresponding mass like enhancement in left Meckel's cave region and cisternal segment of left trigeminal nerve (dotted ellipse) also extending along the maxillary division (short arrow) and along mandibular division (long arrow) of left trigeminal nerve consistent with perineural spread.

Figure 6

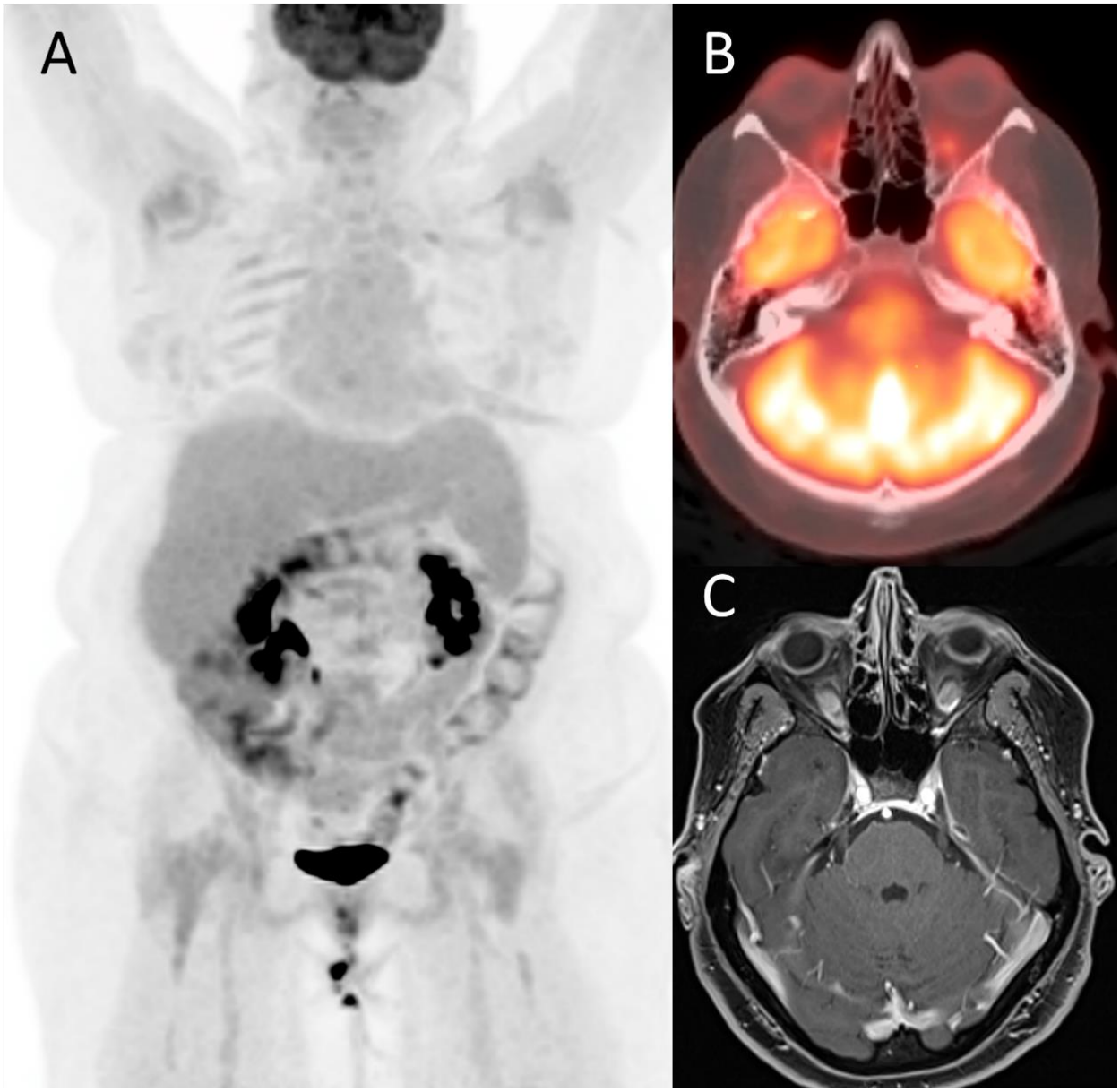

Figure 6 – A) Maximum intensity projection of the whole body ^{18}F-FDG PET demonstrates complete resolution of hypermetabolic adenopathy and splenomegaly, with markedly decreased extent and intensity of osseous uptake (Deauville 3). B) Axial PET/CT at the level of skull base shows resolution of previously demonstrated hypermetabolic lesion at the left petrous apex, dorsum sella, left cavernous sinus. C) Axial post contrast MRI of the brain shows resolution of the abnormal enhancing tissue along the left trigeminal nerve, left Meckel's cave, cavernous sinus, and foramen rotundum.

Discussion

Neurolymphomatosis (NL) is a rare neurological manifestation of lymphoma caused by the direct invasion of cranial or spinal peripheral nerves, plexus or nerve roots by neurotropic lymphoma cells. An extremely limited number of cases of cranial nerve involvement by follicular lymphoma have been formally described. In our case, the patient presented with facial numbness which prompted a work-up for CNS disease. Our patient demonstrated radiographic evidence of lymphomatous involvement of the left trigeminal nerve on ^{18}F-FDG PET which also correlated with findings on gadolinium-enhanced MRI. Although the trigeminal nerve is considered to be a peripheral nerve arising from the brainstem and is thus a structure of the peripheral nervous system (PNS), the presence of a kappa restricted CD10 population within our patient's CSF otherwise supported CNS involvement. In a prior case report published by Ando et al., a 49-year-old female endorsed numbness of the chin at initial diagnosis.[17] However, initial ^{18}F-FDG PET did not demonstrate evidence of

CNS involvement and no further work-up was undertaken prior to initiation of R-CHOP for systemic disease. Unfortunately, the patient experienced overt CNS relapse (despite improvement in her systemic disease) following 5 cycles of R-CHOP and later succumbed to complications related to secondary CNS involvement by follicular lymphoma, which was only pathologically confirmed at the time of autopsy. In a separate case published by Costa et al., a 52-year-old male presented with neurologic symptoms including ptosis, headache, and phobophobia.[18] Initial brain MRI in this case was negative for evidence of lymphomatous involvement, but a subsequent MRI following an unspecified time period revealed enhancement of the third and fifth cranial nerves, and later CSF sampling confirmed involvement by follicular lymphoma. The patient's CSF cleared following 1 cycle of treatment with R-MTX/Ara-C and the patient achieved complete remission following 6 cycles of therapy with R-MTX/Ara-C alternating with Hyper-CVAD and remained in remission at 1 year following original diagnosis. These cases illustrate the importance of obtaining advanced imaging with MRI and/or FDG-PET as well as CSF sampling in cases where there is strong clinical suspicion for NL or CNS involvement. Table 2 summarizes available case series which have described the accuracy of MRI and FDG-PET to identify NL in cases of NHL. The main limitation of these studies is that most were enriched for patients with DLBCL and thus may or may not reflect the true sensitivity of FDG-PET and MRI in identifying follicular lymphoma patients with NL. Regardless, patients with follicular lymphoma who do have imaging findings suggestive of NL or CNS involvement should undergo CSF sampling in cases where surgical biopsy has not already been performed or is not feasible. The sensitivity of CSF cytology and flow cytometric analysis in patients with NL due to NHL has previously been reported to be ~24% and 44%.[19] The exact sensitivity of CSF cytology and flow cytometry in patients with CNS involvement due to follicular lymphoma exclusively remains unknown.

Table 2 – Positivity rates of FDG-PET and MRI for detecting neurolymphomatosis in cases of non-Hodgkin lymphoma

Patients (n)	FDG-PET/CT	MRI	Reference
40	100%	74%	Khurana et al.[19]
25	88%	95%	DeVries et al.[20]
5	100%	78%	Kinoshita et al.[21]

The timing of CNS involvement is highly variable and patients have been reported to present with de novo CNS involvement as well as CNS relapse following a prior diagnosis of systemic disease. Among reported cases, a majority of patients presenting with dural lesions also had concurrent systemic disease, highlighting the importance of obtaining systemic imaging in cases where CNS pathology is available and confirms a diagnosis of lymphoma. In cases of CNS relapse following a prior diagnosis of systemic disease, the timing of CNS relapse can range from a few months to years after initial diagnosis and treatment of systemic disease. Patients with advanced-stage disease with extra-nodal involvement, including bone and bone marrow, are over-represented in the number of reported cases with CNS involvement, suggesting that this could be a strong risk factor.

Table 3. Reported cases of follicular lymphoma with subsequent CNS relapse following prior diagnosis of systemic disease

Age	Sex	Site of CNS Involvement	Systemic Disease Status (Location)	CNS Disease Histology (Grade)	Treatment	Best Response to Therapy	Survival from Time of CNS Recurrence	Reference
67	F	Leptomeningeal (dural mass) with parenchymal extension	No	FL (G1)	Resection followed by RT	CR	In CR at 18 months	Beriwal, 2003[22]
41	M	Parenchymal (frontal lobe)	Yes - lymph node, bone	FL (G1)	Resection followed by RT	NR	PD at 8 months	Hamilton, 2005[23]
72	F	Leptomeningeal (dural mass)	No	FL (G1)	Resection followed by craniospinal RT	CR	In CR at 1 year	Low, 2006[24]
70	M	Leptomeningeal (dural mass)	Yes - lymph node* *-systemic disease onset 2 months after CNS disease	FL (G3b)	Resection followed by R-CHOP, IT-MTX	CR	In CR at 1 year	Riccioni, 2007[25]
48	M	Leptomeningeal (dural mass)	Yes – lymph node, bone	FL (G4)	Subtotal resection followed by R-mini-CHOP with IT-MTX/cytarabine/depomedrol, radiation for systemic disease	PR (refractory systemic disease)	In CR at 3 years	Peltier, 2009[26]
65	F	Leptomeningeal (dural mass)	No	FL (low-grade)	Cranial RT	CR	In CR at 6 months	Tandon, 2012[27]
52	M	Leptomeningeal (cranial nerve, CSF)	Yes – lymph node, bone	FL	R-MTX/Ara-C/Hyper-CVAD	CR	In CR at 2 years	Costa, 2014[18]
31	M	Leptomeningeal (dural mass)	Yes – lymph node	Pediatric type FL	Subtotal resection followed by R-CHOP	CR	In CR at 1 year	Yamaguchi, 2018[28]
41	F	Leptomeningeal (dural mass)	Yes – lymph node, bone marrow	FL (G1-2)	Resection followed by cranial RT; R-CHOP with HD-MTX and maintenance rituximab	CR	In CR at 2 years	MacCann, 2018[29]
62	F	Leptomeningeal (dural mass) with parenchymal extension	Yes – lymph node	FL (G3)	Methotrexate plus R-CHOP, radiation	CR of CNS disease, PR of systemic disease	NR	Altshuler, 2021[30]
59	F	Leptomeningeal (cranial nerve, cerebrospinal fluid)	Yes – lymph node, bone, bone marrow, lung,	FL (G1-2)	Bendamustine with rituximab, IT MTX/hydrocortisone	CR	In CR following cycle 3 of treatment	This case

Abbreviations – CNS, central nervous system; CR, complete remission; FL, follicular lymphoma; HD-MTX, high-dose methotrexate; IT, intra-thecal; MTX, methotrexate; NR, not reported; OS, overall survival; PR, partial remission; PD, progression of disease; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RT, radiotherapy; WBRT, whole brain radiotherapy

Table 4. Reported cases of follicular lymphoma with subsequent CNS relapse following prior diagnosis of systemic disease

Age	Sex	Site of CNS Involvement	Time from Diagnosis of Systemic Disease to CNS Relapse	Systemic Disease Status (Location)	CNS Disease Histology	Treatment for Systemic Disease	Treatment for CNS Disease	Best Response to CNS-Directed Therapy	Survival from Time of CNS Recurrence	Reference
43	F	Parenchymal and leptomeningeal	7 years	Yes – bone marrow	FL	CC	HD-MTX, IT-MTX, RT	PD	OS = 1 year	Spectre, 2005[31]
60	F	Parenchymal	6 months	Yes – bone marrow	Large cell transformation	Observation	HD-MTX, IT-MTX	CR	OS = 2.5 years	Spectre, 2005[31]
73	F	Parenchymal	4 years	Yes – bone marrow	Large cell transformation	CC, RT	HD-MTX, IT-MTX	PR	OS = 2+ years	Spectre, 2005[31]
78	F	Leptomeningeal	4 years	NR	Large cell transformation	CCIT, RT	Dexamethasone	PD	OS = 3 months	Spectre, 2005[31]
53	M	Parenchymal	8 years	Yes - bone	Large cell transformation	CVP	WBRT followed by resection	PD	NR	Grupka, 2005[31]
57	M	Leptomeningeal (dural surface of cerebellum)	1 year	Yes – lymph node, bone, muscle, bone marrow	FL	R-CHOP x6 cycles	Fludarabine, cyclophosphamide, rituximab with WBRT	CR	In CR at <1 year	Karadurmus, 2013[33]
49	F	Leptomeningeal (cranial nerve, cervical nerve roots)	5 months	Yes – lymph node, bone	FL (G2)	R-CHOP x5 cycles	HD-MTX with leucovorin and Ara-C alternating with Hyper-CVAD, total craniospinal RT	PD	OS = 1 year	Ando, 2022[17]
62	F	Parenchymal	1 month (while receiving chemotherapy)	Yes – lymph node, bone, kidney, pancreas, lung	FL	R-CHOP x1 cycle followed by BR x3 cycles	HD-MTX with rituximab, ranimustine, methylprednisolone, and IT-MTX; WBRT (at time of CNS progression)	PR	OS = 5 months	Tsuboi, 2023[34]

Abbreviations – CC, combination chemotherapy; CCIT, combination chemotherapy/immunotherapy; CNS, central nervous system; CR, complete remission; CVP, cyclophosphamide/vincristine/prednisone; FL, follicular lymphoma; HD-MTX, high-dose methotrexate; IT, intra-thecal; MTX, methotrexate; NR, not reported; OS, overall survival; PR, partial remission; PD, progression of disease; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RT, radiotherapy; WBRT, whole brain radiotherapy

Data describing treatment outcomes are limited to case reports or small case series, and no prospective or randomized studies exist to show the superiority of one approach over another. A paucity of long-term follow up among reported cases poses another challenge when assessing the long-term efficacy of previously described treatment approaches. Systemic therapy options that have been described include high-dose methotrexate (HD-MTX), cytarabine, and rituximab in combination with chemotherapy (CHOP, FCR, HD-MTX). Many cases have also incorporated intra-thecal therapy, typically methotrexate, into systemic therapy regimens. Limited reports have shown surgical resection followed by radiation to be effective for patients with limited dural or parenchymal involvement in the absence of other systemic involvement. In cases where patients present with symptomatic CNS disease in addition to systemic disease, locally-directed therapies such as surgical resection or radiation are reasonable for more rapid symptom control. To our knowledge, our case represents the only case describing the usage of a bendamustine-based chemoimmunotherapy regimen in the treatment of follicular lymphoma with secondary CNS involvement. Prior studies have shown that bendamustine is detected in CSF at low levels, indicating it can cross the blood-brain barrier.[35] Regardless of treatment approach, available case reports suggest a good prognosis for most patients with indolent or low-grade histology in the CNS. Five-year survival for patients with follicular histology was reported to be 75% in the NCDB.[16] Within the limitations of reported follow-up time, available case reports suggest that most patients will be alive and in complete remission at 1 year following treatment of their disease. These data stand in contrast to data describing outcomes in patients with aggressive NHL involving the CNS where prognosis is generally worse. For example, in the Phase 2 MARIETTA trial, DLBCL patients with secondary CNS involvement achieved 2-year overall survival of only 46% following treatment with MATRix/RICE followed by autologous stem cell transplantation.[13]

Several novel therapies have recently been approved for the treatment of relapsed/refractory (R/R) follicular lymphoma. In 2020, tazemetostat was granted accelerated approval for the treatment of R/R follicular lymphoma failing 2 prior lines of systemic therapy.[36] Similarly, mosunetuzumab-axgb, a bispecific CD20-CD3 T-cell engaging antibody, was granted accelerated approval for R/R follicular lymphoma failing 2 prior lines of systemic therapy in 2022.[37] Both approvals were granted on the basis of positive results from single-arm, phase 2 studies. Patients with confirmed CNS involvement were excluded from both trials and at this time there are no published reports of patients with CNS disease who were treated with either agent. Two chimeric antigen receptor T-cell therapies (CAR-T), axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are approved for R/R follicular lymphoma, however patients with active CNS disease were similarly excluded from both phase 2 trials leading to their approval.[38-39] As of this writing there do not appear to be any formal reports describing patients with CNS involvement who were treated with CAR-T therapy. However, as there is now growing data that CAR T-cell therapy is safe and effective for R/R large B-cell lymphomas involving the CNS, these therapies could potentially be considered for follicular lymphoma involving the CNS as well.[40]

Conclusion

We report a case of a 59-year-old female with stage IV follicular lymphoma who presented de novo with concurrent systemic and CNS involvement. To our knowledge this represents only the second case in the published literature (excluding 1 other case where cranial nerve involvement was identified at autopsy) describing cranial nerve involvement and the *only* case describing successful treatment of CNS disease with a bendamustine-based chemoimmunotherapy regimen in conjunction with intrathecal therapy. Follicular lymphoma with CNS involvement represents an extremely rare event with no well-established treatment guidelines. Based on very limited data, patients with limited CNS involvement may be reasonably offered locally-directed therapy such as resection and/or radiation. In cases of concurrent CNS and systemic involvement, systemic therapy regimens should be selected with activity against both systemic and CNS disease. While traditional CNS-directed regimens including high-dose methotrexate are appropriate for some patients, our approach with bendamustine and intra-thecal therapy provides an alternative approach for patients not fit to receive high-dose methotrexate or whole-brain radiation.

Declaration of Conflict of Interest: The individual authors report the following disclosures - Nathan Roberts: none; Emily Ayers: Honoraria- ADC Therapeutics, Genentech; Prem Batchala: none; Ifeyinwa Obiorah: none

Ethical approval: Consent for the publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal, stating that all patients

gave written consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

Author contributions: Nathan Roberts and Emily Ayers contributed equally to the literature review for this manuscript. All authors contributed equally to the drafting and editing of this manuscript. Ifeyinwa Obiorah provided interpretation of all biopsy specimens included in this manuscript. Prem Batchala provided interpretation of all radiographic studies included in this manuscript.

Acknowledgements: The authors would like to thank the patients and their families for participating in this review, and the University of Virginia Department of Hematology and Oncology for supporting this review.

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