Neuro-Oncology

23(12), 2076–2084, 2021 | doi:10.1093/neuonc/noab109 | Advance Access date 13 May 2021

The value of bone marrow biopsy for staging of patients with primary CNS lymphoma

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Abstract

Background. In patients with presumed primary CNS lymphoma (PCNSL), a systemic manifestation is found only in a small minority. Although bone marrow biopsy (BMB) is recommended for staging, its diagnostic value is unclear.

Methods. A retrospective analysis of 392 patients with presumed PCNSL from 3 university hospitals and 33 patients with secondary CNS lymphoma (SCNSL) and initial CNS involvement from a multicenter Germany-wide prospective registry was performed.

Results. A BMB was performed and documented in 320/392 patients with presumed PCNSL; 23 had pathologic results. One harbored the same lymphoma in the brain and bone marrow (BM), 22 showed findings in BM discordant to the histology of brain lymphoma; n = 12 harbored a low-grade lymphoma in the BM, the other showed B-cell proliferation but no proof of lymphoma (n = 5), monoclonal B cells (n = 3), or abnormalities not B-cell-associated (n = 2). In the group of SCNSL with initial CNS manifestation, 32/33 patients underwent BMB; 7 were documented with bone marrow involvement (BMI); 1 had concordant results in the brain and BM with no other systemic manifestation. Six had additional systemic lymphoma manifestations apart from the brain and BM.

Conclusions. In only 2 out of 352 (0.6%) patients with CNS lymphoma (320 presumed PCNSL and 32 SCNSL), BMB had an impact on diagnosis and treatment. While collected in a selected cohort, these findings challenge the value of BMB as part of routine staging in presumed PCNSL.

Key Points

- Bone marrow biopsy (BMB) in staging of presumed PCNSL seems dispensable.
- Only in 2 out of 352 patients with CNS lymphoma BMB influenced diagnosis and treatment.

Primary CNS lymphoma (PCNSL) is a rare, aggressive disease which by definition affects the brain, leptomeninges, spinal cord, and/or the vitreo retina of the eyes; it accounts for about 2% of all primary brain cancers and 7% of malignant primary brain tumors.[1] Histopathologically, most PCNSL are diffuse large B-cell lymphomas (DLBCL). PCNSL

Importance of the Study

We report the results of a retrospective analysis on bone marrow biopsy (BMB) as part of staging in CNS lymphoma. For correct diagnosis and appropriate treatment planning, most centers perform BMB for histology, cytology, and molecular genetics, although only few case reports on bone marrow involvement in presumed primary CNS lymphoma exist. Our data in a large cohort suggest that this invasive procedure may be dispensable.

has to be distinguished from secondary CNS lymphoma (SCNSL)—defined as CNS lymphoma occurring concomitantly with or as relapse of systemic lymphoma—since prognosis and treatment may significantly differ. In 4%-12% of presumed PCNSL patients, a systemic manifestation was reported at first diagnosis, when a systematic thorough staging was performed.[2,3]

To exclude systemic tumor manifestation in presumed PCNSL, the guidelines of the International PCNSL Collaborative Group (IPCG) and of the European Association of Neuro-Oncology (EANO) recommend a PET-CT (positron emission tomography and computed tomography or chest and abdominal CT scan with contrast medium) and a bone marrow biopsy (BMB).[4,5] The analysis of bone marrow (BM) in PCNSL and SCNSL as in all other lymphomas comprises histopathology, cytology, flow cytometry, and sometimes PCR-based immunoglobulin heavy chain (IgH) analysis to prove B-cell clonality. The histopathology has the main impact on the interpretation of these findings.

While most of (neuro-)oncological centers, especially within clinical trials,[4] perform BMB at diagnosis of presumed PCNSL, its necessity is questioned by some investigators.[6–10] To our knowledge, there are no data on the frequency of simultaneous lymphoma manifestation in CNS and BM. Two single cases of concordant findings, with BM as the only systemic manifestation of the lymphoma, had been reported.[2,3] Some retrospective studies showed small numbers of discordant findings which did not influence treatment: one found 2 out of 86 patients from a clinical trial with low-grade B-cell lymphoma in the BM[11] and another detected monoclonal B cells in the BMB flow cytometry in 8 of the 51 patients; 4 of those showed histological confirmation of a low-grade B-cell lymphoma in BM.[12]

For patients with systemic DLBCL, concordant BMI was reported in 5%-10% of patients[13–17] and discordant findings in 5%-12%.[13–17] In systemic DLBCL, concordant BMI is an independent negative prognostic factor for progression-free survival (PFS) and overall survival (OS),[13–16,18,19] while no prognostic impact of discordant BMI on OS has been found in most studies as compared to patients without BMI.[13–15,18,19] However, some series showed a lower PFS[14] or even a negative impact on OS in discordant BMI.[16]

The possibility of valuable diagnostic information has to be balanced against the invasiveness of a procedure. BMB may cause discomfort and pain. However, the risk for relevant complications like arterial bleeding during BMB is extremely low.[20] The objective of the present analysis was to evaluate if BMB adds relevant information to staging of patients with CNS lymphoma.

Patients and Methods

Data of 425 patients from 2 groups were retrieved: the PCNSL group (n = 392) consisted of patients from the Department of Hemato-Oncology, Charité University of Berlin (n = 138, between 2009 and 2018), from the Department of Neurology, Knappschaftskrankenhaus, University Hospital, Ruhr-University Bochum (n = 167, between 2004 and 2018) and from the Departments of Hemato-Oncology and Neurology at the University Hospital Bonn (n = 87, between 1995 and 2004). All those 392 patients had presented with initial CNS lymphoma and no history nor clinical signs or symptoms of systemic lymphoma.

The SCNSL group comprised 33 patients with initial CNS involvement from a prospective registry with 200 patients from the Department of Haemato-Oncology, Charité University of Berlin, documented between 2011 and 2018.

We analyzed the records of all 425 patients if a BMB was performed, its results and for demographic information (sex, age at diagnosis). Detailed original reports for histologic, cytologic, and flow cytometry BM examination were evaluated. In case of insufficient data, we contacted the Department of Pathology, to which the biopsy had been sent. If written pathologic reports were not accessible, we used comments in the medical records as eg "no pathological findings in BM." Only patients with information about the histology of BMB were included in the final analysis.

All pathology reports were anonymized and reviewed by a board-certified neurologist (U.S.) and by a board-certified haemato-oncologist (A.K.).

This analysis had been approved by the ethics committee of the University of Bochum. Data were analyzed using Excel and SPSS software. None of the authors had/report conflicting interests on this topic.

Results

Patients' Characteristics

In the group of 392 patients with presumed PCNSL, 192 (49%) were male, the median age was 67 years (range: 26-87 years); 96% of the patients harbored a DLBCL in the CNS (see Table 1 for more details).

Table 1 Characteristics of CNS Lymphoma Patients With No Signs of Systemic Lymphoma, But Findings in the Bone Marrow

No.	Sex	Age	Bone Marrow Biopsy					Biopsy of CNS Lymphoma
			Histology	Cytology	Flow Cytometry	PCR	Diagnosed as	Histology
1	F	72	Normal	CLL	CLL	Not performed	Low-grade NHL	B-cell lymphoma[a]
2	F	72	Hypercellular BM, 3 paratrabecular B-cell infiltrates	Normal	Normal	Normal	Low-grade NHL	DLBCL
3	F	70	Paratrabecular B-cell infiltrates	Normal	Normal	Normal	Low-grade NHL	DLBCL
4	F	76	Normal	Proliferation of lymphocytes	Light chain restriction Possible B-cell NHL	Not performed	B-cell proliferation, no proof of lymphoma	DLBCL
5	M	65	Normal	Normal	Normal	Monoclonal B cells	Monoclonal B cells in PCR	DLBCL
6	M	68	Normal	Normal	Normal	Monoclonal B cells	Monoclonal B cells in PCR	DLBCL
7	F	71	Paratrabecular B-cell infiltrates	Highly elevated number of adult lymphocytes, possible infiltration	Normal	Not performed	Low-grade NHL	Not performed[b]
8	F	71	Normal	Proliferation of adult lymphocytes	B-cell proliferation dominate lambda light chain expression	Normal	B-cell proliferation, no proof of lymphoma	DLBCL
9	M	54	Normal	Proliferation of adult lymphocytes	B-cell proliferation	Not performed	B-cell proliferation, no proof of lymphoma	High malignant lymphoma
10	M	68	Hypercellular BM, B- and T-cell proliferation	No result available	No result available	Not performed	B-cell proliferation, no proof of lymphoma	B-cell lymphoma
11	F	52	Normal	Normal	Immunocytoma	Not performed	Low-grade NHL	DLBCL
12	F	78	Infiltration by B-cell lymphoma possible mantle cell lymphoma	Normal	Normal	Monoclonal B cells	Low-grade NHL	DLBCL
13	M	47	MDS	Normal	Normal	Not performed	MDS	DLBCL
14	M	75	Medium-sized peritrabecular lymphoid infiltrates: possible NHL or reactive changes	Normal	Normal	Monoclonal B cells	Monoclonal B cells in PCR	DLBCL
15	M	83	CMN	Normal	Not available	Not performed	Other	DLBCL
16	M	70	Pathological immunohistology, possible low grad NHL	Normal	Normal	Normal	B-cell proliferation, no proof of lymphoma	DLBCL
17	F	76	Normal	Normal	Pathological light chain restriction	Not performed	Low-grade NHL	DLBCL
18	F	61	Normal	Normal	CLL	Not performed	Low-grade NHL	Diagnosis by CSF[c]
19	F	58	CLL	Normal	Normal	Not performed	Low-grade NHL	DLBCL
20	M	68	Normal	Normal	B-CLL	Not performed	Low-grade NHL	DLBCL

Table 1 Continued

No.	Sex	Age	Bone Marrow Biopsy			PCR	Diagnosed as	Biopsy of CNS Lymphoma
			Histology	Cytology	Flow Cytometry			Histology
21	F	70	Normal	Pathological plasma cell infiltration (40%)	Normal	Not performed	Low-grade NHL	DLBCL
22	F	61	Hypercellular BM, small-/medium-sized B-cell infiltrates	Normal	Normal	Not performed	Low-grade NHL	DLBCL
23	M	74	Infiltration by DLBCL	Infiltration by lymphoma	Normal	Not performed	Concordant findings	DLBCL
24	M	72	Infiltration by adult cell NHL lymphoma	Proliferation of adult B cells	Infiltration by B-NHL	Not performed	Concordant findings	DLBCL

Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; B-NHL, B-cell non-hodgkin lymphoma; CLL, Chronic lymphocytic leukemia; CMN, chronic myeloproliferative neoplasm; DLBCL, diffuse large B-cell lymphoma; F, female; M, male; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma.
[a]Unspecific result, because of, biopsy under steroid therapy.
[b]Typical brain lesions, malignant large B cells in vitreous aspiration.
[c]Typical brain lesions, B-cell lymphoma in CSF.

A BMB was performed in 330 cases (84%). The most important reason for not carrying out BMB was a low clinical performance status and the consecutive decision of starting immediate treatment (n = 12) or symptomatic therapy only (n = 2), in 30 patients, there was no information why BMB was not done (n = 30). For 18 patients, it remained unclear, if BMB was performed.

Results of the BMB were available in 320/330 patients (97%), mostly as written original reports (see Table 2). Additional PCR analyses were performed in 26 cases (8%) when the report of histopathology and cytopathology stated "unclear findings/significance." In synopsis of histology, cytology, and flow cytometry, 23/320 cases were classified as abnormal (see Figures 1 and 2); 1 represented concordant lymphoma in BM with regard to the brain lymphoma, and 22 were discordant (see Figure 3 and Table 1 for details). Out of the 320 patients evaluated, brain lymphoma had been diagnosed by biopsy of the brain lesion in 313, in the cerebrospinal fluid (CSF) in 2, and in the vitreous fluid in 5.

The median age of the cohort of 33 SCNSL patients with CNS involvement at initial diagnosis was 64 years (range: 35-86 years), 20 (61%) were male. A BMB was performed in 32 cases with all results available. Seven patients showed pathologic results with 2 concordant and 3 discordant results in histology, for 2 patients, there was no further specification of "BMI." Six of these 7 patients with pathologic findings in BM had other systemic lymphoma manifestations in addition to BMI. In only 11 of the 32 SCNSL patients with BMB, a biopsy of the brain lymphoma was performed: 10 had a DLBCL, 1 had a low-grade malignant B-cell non-Hodgkin lymphoma. The others were diagnosed by biopsy of the systemic lymphoma and typical lesions in the brain, CSF, or both (see Supplementary Table S1 for details).

Concordant Findings

Two patients with concordant findings in CNS and BM with BM representing the only systemic/extra-CNS manifestation of a DLBCL were identified—one in the "presumed PCNSL" group and the other in the SCNSL group. Both were diagnosed and treated as SCNSL with R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone) according to the results of BMB. These 2 patients were 72 and 74 years old and had a grievous course of disease with an early progression and an OS of only 7 months each.

Discordant Findings in Patients With Presumed PCNSL

Discordant pathological findings in BM were reported in 7% (22 of 320 BMBs). In 12 of these, a low-grade lymphoma was found in BM, 5 showed B-cell proliferations without proof of lymphoma, and 3 monoclonal B cells. Only 2 patients had BM findings not related to lymphoma or B cells (1 myelodysplastic syndrome, 1 chronic myeloproliferative neoplasm; see Figure 3 and Table 1).

Patients with discordant findings in BM were slightly older than those with normal results with a median of 70 vs 66 years (range: 47–83 years vs 26-84 years).

Table 2 Availability of Bone Marrow Biopsy Results

	Patients With Presumed PCNSL (n = 320)				Patients With SCNSL (n = 32)			
	His-tology	Cy-tology	Flow Cytometry	PCR Analysis	His-tology	Cy-tology	Flow Cytometry	PCR Analysis
Available results	320	297	216	26	32	30	27	Not assessed
Available as original reports	277	265	214	26	20	18	15	Not assessed
Available as cited in medical reports	43	32	2	0	12	12	12	Not assessed

Abbreviations: PCNSL, primary CNS lymphoma; PCR, polymerase chain reaction; SCNSL, secondary CNS lymphoma.

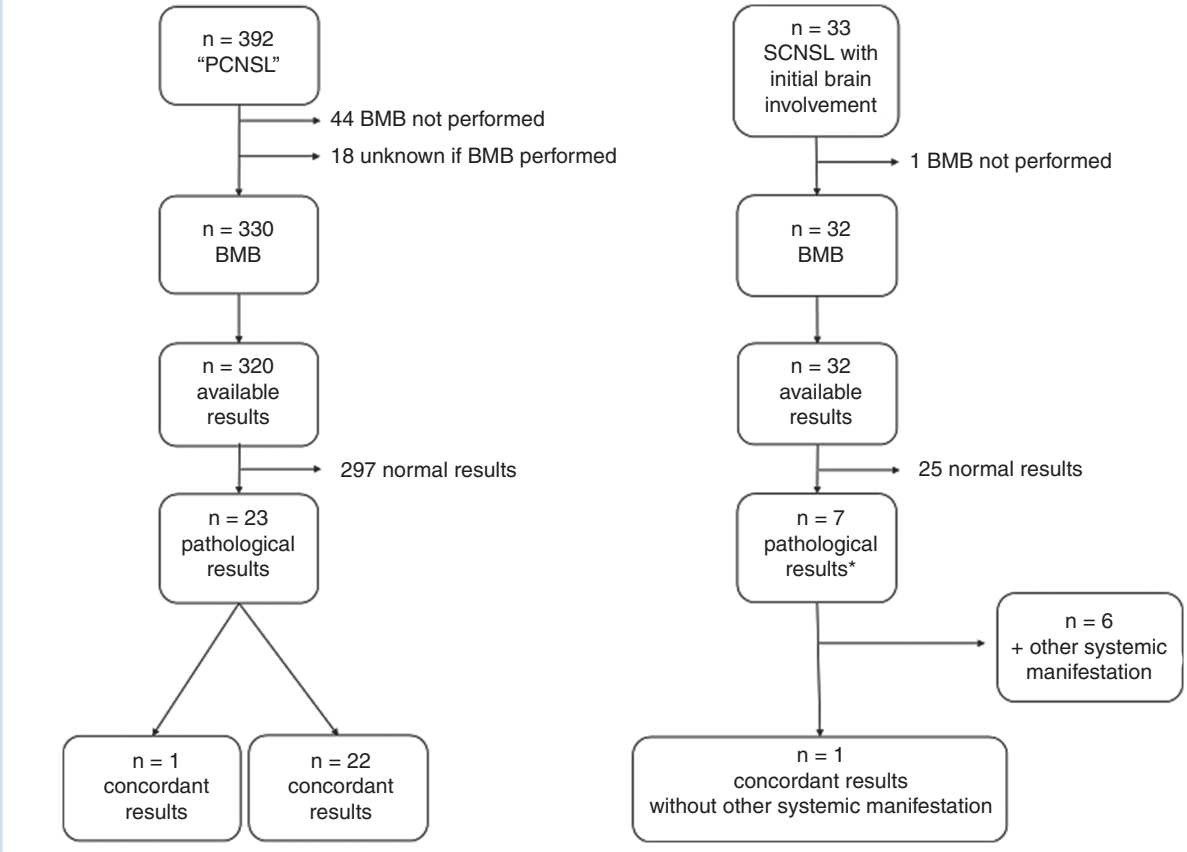

Fig. 1 Results of bone marrow biopsy in patients with CNS lymphoma. Abbreviations: BMB, bone marrow biopsy; PCNSL, primary central nerve system lymphoma; SCNSL, secondary central nerve system lymphoma. *n = 2 concordant, n = 3 discordant, n = 2 "BMI" not further specified.

Data on OS were available for 192 patients with PCNSL who had undergone BMB, 10 of those had discordant findings in BM. There was no significant difference in OS for patients with discordant and normal findings in BM (26 months [95% CI: 3-49 months] and 35 months [95% CI: 20-50 months]; $P = 0.55$; Figure 4).

Discussion

BMB is a recommended part of systemic staging in presumed PCNSL.[4,5] The aim of this study was to investigate the diagnostic value of BMB in patients with

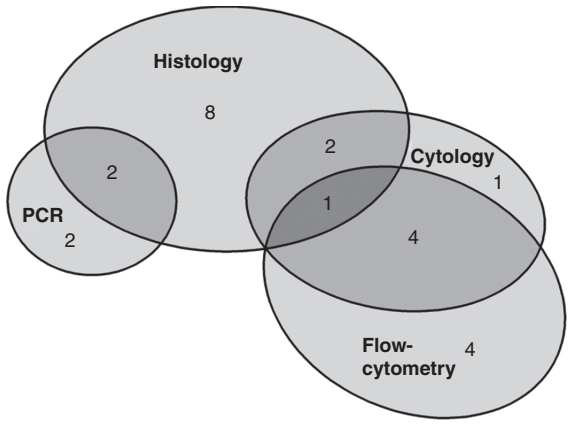

Fig. 2 Distribution of pathological findings in bone marrow of patients with CNS lymphoma and no signs of systemic lymphoma (n = 24).

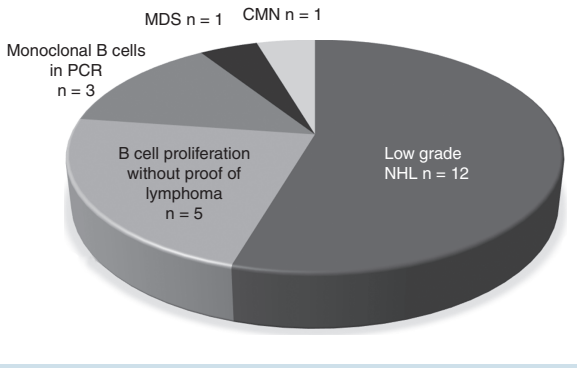

Fig. 3 Twenty-two patients with presumed PCNSL and discordant results in bone marrow biopsy. Abbreviations: CMN, chronic myeloproliferative neoplasm; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; PCNSL, primary central nerve system lymphoma.

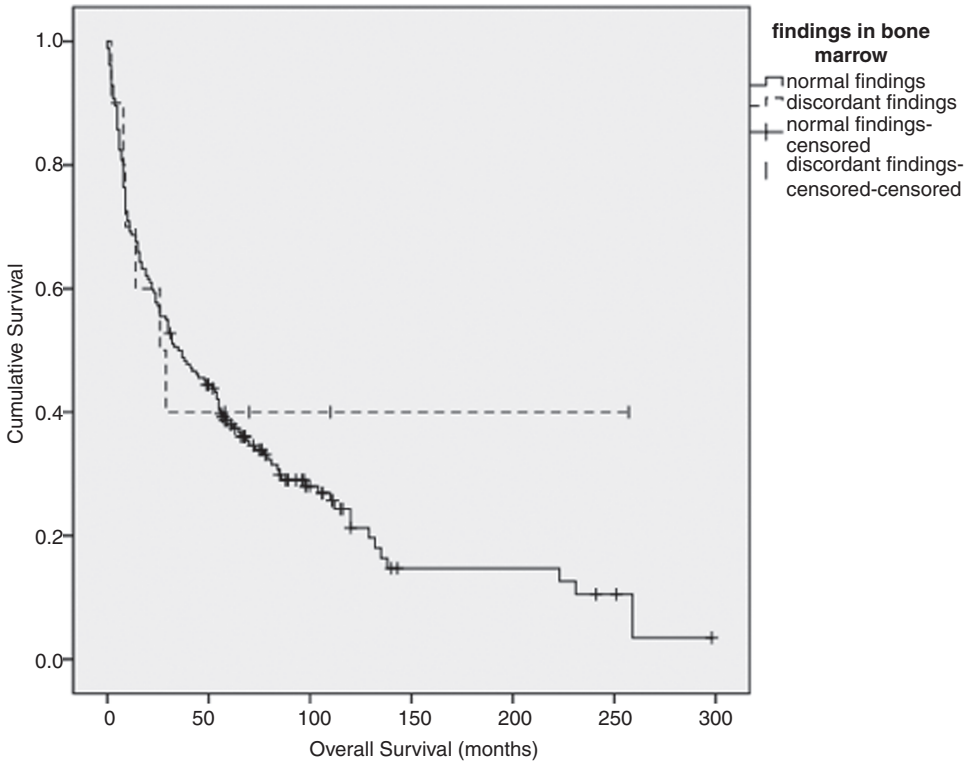

Fig. 4 Kaplan-Meier curve of patients with PCNSL and discordant (n = 10) and normal findings (n = 182) in bone marrow biopsy. Abbreviation: PCNSL, primary central nerve system lymphoma.

CNS-lymphoma and no sign of systemic lymphoma manifestation in other examinations. In other words, how often has the diagnosis of presumed PCNSL to be changed by BMB alone to SCNSL due to detection of concordant lymphoma in BM and brain with no other sign of systemic lymphoma? In the literature, only rare reports[2,3] document bone marrow involvement (BMI) as the only systemic manifestation in brain lymphoma. Is it such a rare event, that we can therefore spare patients this invasive procedure?

While the present study could address this question only in pre-selected cohorts, all those patients with presumed PCNSL, ie, patients presenting with initial CNS lymphoma and no history of preexisting systemic lymphoma were systematically analyzed: the reports on BM histology, cytology, flow cytometry, and optional PCR analysis in 320 "PCNSL" patients from different institutions and in 32 SCNSL patients with initial brain involvement from a registry were evaluated. Our data show that in only 2 of the 352 patients with evaluable reports on BMB results, concordant findings of a diffuse large B-cell non-Hodgkin lymphoma in the brain and in the BM as the only systemic manifestation were documented. In these 2 cases (one retrieved from a SCNSL registry, one from a cohort of presumed PCNSL patients), the diagnosis was changed from presumed PCNSL to SCNSL by BMB alone. We conclude from these numbers—in line with sparse reports in the literature—that the frequency of concordant CNS and BM lymphoma with no other systemic manifestation is exceedingly low.

Concordant BM infiltration is associated with poor prognosis in systemic DLBCL.[13–16,18,19] We encountered only 2 such patients in this series, but both suffered from an early progression and showed an OS of only 7 months each.

In addition to these 2 patients with concordant findings, we found 22 others with suspected PCNSL and abnormal, but discordant findings in BM; 12 of them harbored a low-grade lymphoma, 8 another B-cell-associated pathology (B-cell proliferation without proof of lymphoma, n = 5; monoclonal B cells, n = 3) and only 2 had a not B-cell-related pathology (myelodysplastic syndrome, n = 1, chronic myeloproliferative neoplasm, n = 1). In accordance with these findings, Wong and colleagues reported 2/86 patients with PCNSL and a low-grade B-cell lymphoma in BM,[11] whereas Brandt and colleagues reported on 8/51 PCNSL patients with monoclonal B cells in BM and evidence of low-grade lymphoma in 4 of these.[12] Compared to systemic DLBCL, the rates of discordant findings in BM (5%-12% in the literature[13–17]) are similar to those in PCNSL including the present series with 7%.

Interestingly, the findings of monoclonal B cells in BM disappeared in 3/3 PCNSL patients from the cohort investigated by Brandt and colleagues who underwent a second BMB after treatment.[12] The same group proved clonal relation between DLBCL in the brain and monoclonal B cells in BM via immunoglobulin heavy chain variable (IGHV) sequencing in 1 of the 2 cases, both of them showed histopathological signs of a low-grade lymphoma in BM.[12] With the same method, Malecka and colleagues reported clonal relation between CNS lymphoma and monoclonal B cells in BM for 3 of the 6 PCNSL patients.[21] In relation to that, Kremer and colleagues report a common clonal origin (detection of clonal IgH or BCL-2 rearrangement) in distinct patients with systemic DLBCL and discordant BMI (8/12), while the other 4 of those seemed to harbor 2 clonally unrelated neoplasms, leading to the hypothesis that patients with discordant findings in BM may not be a homogeneous group.[22]

Also using IGHV-gene and immunoglobulin variable analysis, respectively, 2 groups reported tumor-related B-cell clones in BM in 4/7 and 2/3 PCNSL patients,[23,24] which they considered as subclinical systemic disease. McCann and colleagues proved unique extracerebral variants "as a sign of separate development without a re-entry in the brain."[24] In contrast, other IGHV gene analyses and gene expression profiling pointed to the possibility, that lymphoma precursor cells might develop outside the CNS and give rise to PCNSL by malignant transformation in the microenvironment of the brain.

Most authors did not observe systemic relapse of PCNSL in patients with discordant findings in BM or tumor-related B cells outside the CNS.[12,23,24] This is in contrast to our observation in 1 patient of this series with a low-grade lymphoma in BM at initial staging and relapse of a DLBCL in a cervical lymph node. Provencher and colleagues described 2 PCNSL patients among 209 with a systemic relapse of a DLBCL in BM/soft tissue, who had lymphoid small cells in BM at initial staging.[25] However, it cannot be concluded from these rare observations that patients with PCNSL and discordant findings in BM have a higher risk for systemic relapse.

The question if there is a specific subgroup among patients with presumed PCNSL for which BMB should be considered cannot be answered based on our findings, because of the small number of only 2 patients with concordant findings in BM. Unfortunately, there are no comprehensive molecular data on these specimens.

For systemic DLBCL, ^{18}FDG-PET/CT has a high negative predictive value for detection of BMI,[26,27] and there is also one study that suggests that this might also be true for PCNSL.[28] The question if ^{18}FDG-PET/CT can be used to identify a subgroup of patients which should receive a BMB performed might be the subject of future investigations.

A limitation of our study is that in 104/320 of patients flow cytometry had not been performed or its results were not longer available. This was the case for many patients who were diagnosed with PCNSL prior to 2004. Further, emerging technologies like circulating tumor DNA (ctDNA) in blood or flow cytometry in blood have not been performed in this patient cohort. For systemic DLBCL, the concentration of circulating tumor DNA in blood correlates with tumor burden and shows a significant correlation to the international prognostic index (IPI) and with lactate dehydrogenase (LDH) levels.[29,30] Corresponding data concerning ctDNA in blood of PCNSL patients have not yet been published. As peripheral blood involvement in DLBCL is very rare and infrequent in PCNSL, flow cytometry in blood is not part of diagnostic work up in PCNSL yet.

Conclusion

According to the results of the present series, BMB is not essential for staging of patients with presumed PCNSL.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

Keywords

bone marrow involvement | diffuse large B-cell lymphoma | PCNSL | primary CNS lymphoma | staging

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement. M.M. received sponsoring as a participant of Scholarship of Interdisciplinary Oncology (SIO) from Medac. U.H. reports advisory board and/or speaker's honoraria from Bayer, Daiichi Sankyo, Janssen, Karyopharm, Medac, Navitas, and Noxxon. A.K. is an employee of Lilly Pharma Germany and affiliated to Department of Hemato-Oncology, Charité University of Berlin. U.S. has received honoraria as a speaker from Novartis, GSK, and Medac. All other authors declare no conflict of interest.

Authorship statement. M.M. and U.S. conceived of the presented idea. M.M. collected data with the help of S.S., T.K., U.H., I. G.H.S.-W. A.V.F., and A.K. M.M. wrote the manuscript with support from S.S., S.L.-B., and U.S. U.S., A.K., and R.S. supervised the project. A.B. provided critical feedback. All authors discussed the results and commented on the manuscript and approved the final version.

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