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Short Communication

The contribution of IL-10 and IL-6 as potential biomarkers for detecting central nervous system involvement in non-Hodgkin lymphomas

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ABSTRACT

Introduction: A significant clinical challenge in the management of hematologic malignancies is the occurrence of central nervous system (CNS) involvement. In non-Hodgkin lymphoma (NHL), it occurs in varying percentages depending on the subtype and identifying patients is crucial but challenging. Furthermore, a definitive gold standard for diagnosing leptomeningeal involvement is still lacking. Conventional cytology (CC) of cerebrospinal fluid (CSF) has high specificity but low sensitivity. Multiparametric flow cytometry offers superior sensitivity but is limited by CSF cellularity and the need for specialized expertise, a resource not available at every institution. CSF cytokine analysis is emerging as a promising diagnostic approach, with IL-6 and IL-10 showing potential as biomarkers.

Objective: This prospective study investigated the utility of dosing the aforementioned cytokine in serum and CSF samples for diagnosing CNS involvement in non-primary CNS lymphoma patients.

Methods: CSF samples were analyzed using CC and IL-6/IL-10 assays. IL-6 and IL-10 levels were then compared between CC-positive (CC +) and CC-negative (CC–) patients.

Results: The study cohort included 27 patients, with a median age of 71 years. Six patients (22.2 %) were CC + . In CSF, statistically significant differences were observed for both IL-6 ($p = 0.02$) and IL-10 ($p = 0.04$) levels between CC + and CC– patients, with higher levels in CC + patients. Elevated CSF IL-6 and IL-10 levels were also associated with elevated LDH, advanced disease stage, and elevated CSF protein.

Conclusions: This study suggests that CSF IL-6 and IL-10 are potential, widely available biomarkers for early detection of CNS involvement in NHL, offering a complement to traditional cytological analysis in clinical laboratories.

1. Introduction

1.1. Background

Central Nervous System (CNS) involvement remains a serious complication of several hematologic malignancies.

Among adult lymphoproliferative disorders, it occurs in 2 % to 6 % of patients with diffuse large B-cell lymphoma (DLBCL), and in up to 30 % of patients in certain high-risk subcategories [1].

To date, a significant effort has been devoted to identifying patients at risk for CNS involvement. Currently, the CNS-International Prognostic Index (CNS-IPI) is used to assess risk in non-Hodgkin lymphoma (NHL) patients. However, this scoring system does not account for the biological aggressiveness of certain lymphoma subtypes (e.g., double- and

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triple-hit lymphomas) and has shown limited sensitivity [2].

At present, a definitive gold standard for the diagnosis of leptomeningeal involvement has yet to be established, and its identification remains a topic of active investigation [3].

Historically, conventional cytology (CC) was associated with a good specificity but low sensitivity [4], since malignant cells in cerebrospinal fluid (CSF) are often outnumbered and with inconclusive morphologies.

In contrast to other methods, multiparametric flow cytometry (MFC) exhibits superior sensitivity; however, its practical application is constrained by two important considerations. First, the frequently limited cellularity of CSF samples can increase the risk of false negative results. Second, the successful implementation and interpretation of MFC require a high level of expertise, which is not available across all centers. Therefore, although MFC may provide valuable information, it is not considered the gold standard for diagnosing CNS involvement in NHL.

Given these considerations, the identification of a useful biomarker to complement CC is crucial.

In this setting, CSF cytokine analysis is gaining increasing attention emerging as a potential diagnostic approach.

While numerous cytokines have been evaluated as potential biomarkers in CSF/serum of patients with NHL, recent studies have identified IL-6 and IL-10 as particularly promising candidates.

IL-6, a pleiotropic cytokine with immunomodulatory properties, is produced by various cell types, including lymphocytes, and plays a crucial role in NHL, particularly DLBCL [5]. IL-10, secreted by diverse immune cells (e.g., monocytes, macrophages, T helper 2, T helper 17, B cells, and dendritic cells) [6], in lymphocyte development acts as a B-lymphocyte growth factor and influences lymphoma progress by activating the Bcl-2 antiapoptotic pathway. However, since IL-10 is involved in various conditions, including autoimmune diseases, inflammation, and other tumors, its levels require careful interpretation.

Of the numerous cytokines investigated, evidence suggests a role specifically for IL-10 and IL-6 for the diagnosis of primary CNS lymphoma (PCNSL) [7–9]. Moreover an IL-10/IL-6 ratio exceeding 1 is a well-established diagnostic criterion for vitreoretinal lymphoma, a subtype of PCNSL [10], as it effectively differentiates lymphoma from benign inflammatory conditions that can present with similar symptoms.

However, given the limited literature on the utility of cytokines as an adjunct to CC in diagnosing CNS involvement in non-PCNSL lymphomas, this prospective study investigated whether serum and CSF IL-6 and IL-10 levels differ between NHL patients with positive or negative CC. The aim was to identify a valuable, accessible, and easily interpretable tool to complement traditional cytological analysis across all facilities.

2. Materials and methods

From 2022 to 2023, 30 consecutive adult patients were enrolled in the study, 21 were diagnosed and treated at Policlinico Tor Vergata in Rome, and 9 at Campus Biomedico University Hospital in Rome. Three (10 %) were excluded due to insufficient CSF collection, being 27 patients evaluable. According to current guidelines, in NHL diagnostic lumbar puncture (LP) was performed in specific categories of patients, therefore were included in the study patients whose CNS-IPI score was 4–5, mantle cell lymphoma (MCL) with high mantle cell IPI score and patients considered at high risk due to disease site (kidney, adrenal gland, testis, breast), presence of a serum paraprotein [11] or specific lymphoma subtype, for example high-grade B-cell lymphoma (HGBCL) or Burkytt lymphoma (BL). Individuals with any of the following conditions were excluded from the study: clinical or radiological evidence of increased intracranial pressure; uncorrectable coagulopathy; clinical instability or acute medical condition that could have made the procedure unsafe; known vertebral anomalies or spinal deformities. Samples were collected after obtaining written informed consent in accordance with the Declaration of Helsinki and local regulations. Inadequate CSF sampling led to exclusion from the study (e.g., an insufficient sample, contamination with blood from a traumatic tap, delayed processing or improper storage before analysis). The morphologic evidence of neoplastic cells and/or a white blood cell count $\geq 5/\mu l$ with less than 10 erythrocytes/μl was considered as a CC positive finding (CC +). IL-10 and IL-6 levels were quantified in both serum and CSF. Samples were centrifuged at 1,300 rpm for 10 min, then aliquoted into 100 μL portions and stored at −80 °C until analysis. IL-10 concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) with the Human IL-10 ELISA Kit (Invitrogen, Thermo Fisher Scientific, USA), (detection range 1–200 pg/mL). IL-6 levels were measured using a chemiluminescent automated immunoassay (CLIA) with the SNIBE MAGLUMI-ITA IL-6 kit, (reference range of 0.5–5000 pg/mL). Categorical data were described as numbers (percentages), while continuous variables as medians (range). Associations between variables were analyzed by Fisher's exact test and by Mann-Whitney *U* test. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using NCSS 10 Statistical Software. NCSS, LLC. Kaysville, UT, USA.

3. Results

Among the 27 patients, 9 (33.3 %) were female and 18 (66.7 %) were male. The median age at diagnosis was 71 years (range 41–80). None exhibited clinical and/or radiological signs or symptoms of CNS involvement. Regarding concomitant conditions, no patients exhibited inflammatory autoimmune disorders or active infections at the time of sample collection. The cohort comprised 3 (11,1%) non-Hodgkin T-cell lymphomas (T-NHL) and 24 (88,9%) non-Hodgkin B-cell lymphomas (B-NHL). Among the B-NHL cases, 4 (16,6%) were MCL, 1 (4,2%) was HGBCL, 1 (4,2%) was BL, and the remaining 18 patients (75 %) had a diagnosis of DLBCL. Regarding CSF cytological analysis, 6 (22.2 %) were CC^{+}, with a median cell count of 11.5 cells/μl (range 5–419 cells/μl). The median cell count in the 21 negative patients (CC^{-}) was 1 cell/μl (range 0–4 cells/μl).

In serum, median concentration of IL-6 and IL-10 were 4.04 pg/ml (range 0.84–52.1) and 4.88 pg/ml (range 1.52–336.45), respectively, with a median IL-10/IL-6 ratio of 1.67 (range 0.1–50).

In CSF, median IL-6 and IL-10 levels were 3.74 pg/ml (range 1.78–921) and 2.47 pg/ml (range 0.75–200), respectively, with a median IL-10/IL-6 ratio of 0.56 (range 0.062–39.68).

IL-6 and IL-10 levels measured in both serum and CSF were compared between CC positive and negative (CC^{-}) patients. In the CC + group, the median serum IL-6 level was 12.5 pg/ml (range 1.73–52.1), while the median serum IL-10 level was 2.93 pg/ml (range 2.15–336.45). In CSF the median IL-6 level was 9.89 pg/ml (range 3.29–921), and the median IL-10 level was 4.01 pg/ml (range 2.49–200). The median serum IL-10/IL-6 ratio was 0.82 (range 0.1–6.46), and the median CSF IL-10/IL-6 ratio was 0.39 (range 0.33–1.37).

For the CC– group, the median serum IL-6 level was 3.61 pg/ml (range 0.84–33.4), and the median serum IL-10 level was 5.13 pg/ml (range 1.52–200). In the CSF, the median IL-6 level was 3.64 pg/ml (range 1.78–25.6), while the median IL-10 level was 2.09 pg/ml (range 0.75–87.7). The median serum IL-10/IL-6 ratio was 1.83 (range 0.18–50), and the median CSF IL-10/IL-6 ratio was 0.57 (range 0.06–39.68).

Overall, the CC + patients exhibited significantly higher median levels of both IL-6 ($p = 0.02$) and IL-10 ($p = 0.04$) in the CSF compared to the CC– patients, although their serum cytokine levels did not show a significant difference (Table 1).

We consequently evaluated CSF IL-10 and IL-6 levels in relation to patients' clinical characteristics. As detailed in Table 2-3, no significant correlation was found between cytokine levels and either age ($p = 0.3$) or gender ($p = 0.3$ for IL-6, $p = 0.4$ for IL-10). However, statistically significant associations were observed between cytokine levels and

Table 1
Measure of IL6 and IL10 in serum and CSF of CC^+ and CC^- patients.

	CC^+	CC^-	p value
Serum IL-6 median (range)	12.5 (1.73–52.1)	3.61 (0.84–33.4)	0.07[a]
Serum IL-10	2.93 (2.15–336.45)	5.13 (1.52–200)	0.8[a]
CSF IL-6	9.89 (3.29—921)	3.64 (1.78–25.6)	**0.02**[a]
CSF IL-10	4.01 (2.49–200)	2.09 (0.75–87.7)	**0.04**[a]
Serum IL-10/IL-6 ratio	0.82 (0.1–6.46)	1.83 (0.18–50)	0.2[a]
CSF IL-10/IL-6 ratio	0.39 (0.33–1.37)	0.57 (0.06–39.68)	0.3[a]

CC: conventional cytology; IL-6: interleukin-6; IL-10: interleukin-10; CSF: cerebrospinal fluid.
[a] *Mann-Whitney U test*.

Table 2
CSF IL-6 levels according to clinical characteristics.

Age	**<60**	**≥60**	**p**
	4.03 (2.19–25.6) [a]	3.25 (1.78–921) [a]	0.3[a]
Gender	**Male**	**Female**	**p**
	3.49 (1.78–606) [a]	4.03 (2.33–921) [a]	0.3[b]
Stage	**Ann Arbor II**	**Ann Arbor III-IV**	**p**
	3.13 (1.78–4.71) [a]	4.44 (2.09–921) [a]	**0.03**[b]
LDH (U/L)	**<250**	**≥250**	**p**
	2.99 (1.78–25.6) [a]	4.71 (3.2–921) [a]	**0.002**[b]
CSF protein (g/L)	**≤40**	**>40**	**p**
	3.64 (1.78–6.09) [a]	9.89 (2.21–921) [a]	**0.02**[b]

CSF: cerebro spinal fluid; LDH: lactate dehydrogenase.
[a] CSF IL-6 pg/ml, median (range).
[b] Mann-Whitney *U* test.

Table 3
CSF IL-10 levels according to clinical characteristics.

Age	**<60**	**≥60**	**p**
	2.09 (0.87–10.7)[a]	3.02 (0.75–200) [a]	0.3[b]
Gender	**Male**	**Female**	**p**
	2.58 (0.75–200) [a]	2.05 (0.87–10.32) [a]	0.4[b]
Stage	**Ann Arbor II**	**Ann Arbor III-IV**	**p**
	1.7 (0.75–3.06) [a]	2.8 (0.87–200) [a]	0.05[b]
LDH (U/L)	**<250**	**≥ 250**	**p**
	1.87 (0.75–87.7) [a]	3.26 (1.1–200) [a]	0.02[b]
CSF protein (g/L)	**≤40**	**>40**	**p**
	2.09 (0.75–10.7) [a]	4.01 (1.53–200) [a]	0.04[b]

CSF: cerebro spinal fluid; LDH: lactate dehydrogenase.
[a] CSF IL-10 pg/ml, median (range).
[b] Mann-Whitney *U* test.

three variables: disease stage, LDH, and CSF protein. Both CSF IL-6 and IL-10 levels were significantly higher in patients with advanced disease (Ann Arbor stage III-IV) compared to those with stage II disease ($p = 0.03$ and $p = 0.05$, respectively). Cytokine levels were also significantly elevated in patients with LDH levels >= 250 U/L, with the strongest association for CSF IL-6 ($p = 0.002$) and a significant association for CSF IL-10 ($p = 0.02$). Similarly, both cytokines showed significantly higher levels in patients with elevated CSF protein (>40 g/L) ($p = 0.02$ for IL-6 and $p = 0.04$ for IL-10).

4. Discussion

In this study we observed increased CSF cytokine levels in asymptomatic NHL patients exhibiting CC^+ assays.

Current literature has extensively investigated cytokines' role almost exclusively in PCNSL [7–9], suggesting a more prominent role for IL-10 than IL-6 in CSF analysis. These studies concluded that CSF IL-10 levels appear to be a sensitive biomarker with the potential to guide differential diagnosis, facilitate early recurrence detection, inform prognostic evaluation, and direct therapeutic strategy in this type of NHL.

Our study demonstrated that both IL-10 and IL-6 CSF levels were informative, aligning with findings from another study [12]. In fact, Gu's study indicates that IL-10 and IL-6 CSF measurements can enhance diagnostic accuracy and more accurately identify patients with secondary CNS lymphoma. Notably, both our study and Gu's found that elevated cytokine levels in CC + patients correlated with high tumor burden, as evidenced by elevated LDH levels and advanced disease stage.

We incorporated serum cytokine analysis based on previous findings of elevated inflammatory cytokine levels in various lymphoma subtypes compared with healthy controls [13]. Moreover, a recent study observed that elevated serum IL-6 and IL-10 levels in NHL correlated with poorer prognosis, elevated LDH and IPI levels [14].

However, in our analysis serum cytokine levels did not differ significantly between patients with positive or negative CC. Given the pleiotropic nature of these cytokines, their levels may be a result of other concurrent conditions, including infections, inflammatory processes, or autoimmune disorders, therefore, elevated serum levels may not correlate with CNS involvement.

Unlike IL-10, IL-6 can cross the blood–brain barrier. As a result, systemic inflammatory processes characterized by elevated serum IL-6 concentrations could potentially confound the interpretation of CSF IL-6 measurements. Nevertheless, the absence of statistically significant elevations of serum IL-6 levels among CC^+ patients in our study supports the hypothesis that the IL-6 detected in the CSF originates from disease cells within the CNS compartment.

It is unclear though, the precise origin of these cytokines and the underlying mechanisms responsible for their altered levels in CSF, which requires further investigation.

A significant challenge in establishing the clinical utility of cytokines is the variability in the CSF cutoff values reported across different studies. For instance, Calimeri et al. reported a lower CSF IL-10 cut-off value than Gu et al. (2 pg/ml and 7.82 pg/ml respectively) [8,12]. In our work, we chose not to implement a cut-off value for cytokine levels for two primary reasons: first, the limited sample size would have reduced the statistical power to reliably determine an appropriate and meaningful cut-off, and second, the considerable heterogeneity of the cut-off values for cytokines reported in the literature made it difficult to justify the selection of any threshold. This allowed us to analyze and compare the data continuously, avoiding potential bias introduced by an arbitrary categorization of cytokine levels.

Future studies should prioritize recruiting a sufficiently large and homogeneous patient cohort to establish a universally applicable cut-off value for CSF cytokine levels. This cut-off should then be rigorously validated in prospective, randomized, and ideally multi-center cohorts to ensure its robustness and generalizability. Such standardization would enable consistent interpretation of results across different laboratories, improving the reproducibility and comparability of research findings and ultimately facilitating clinical translation.

Emerging analyses gaining traction for identifying CNS involvement include molecular next-generation sequencing assays that explore the mutational profile of lymphomas in the CSF of patients with negative CC, aiming to enhance diagnostic capability [15]. However, this approach is limited to centers with the necessary methodology and is often not applicable in smaller facilities. Cytokine analysis, on the other hand, is simple to perform, more readily applicable across various centers, and can offer effective assistance at a minimal cost for clinical laboratories.

Our study provides preliminary insights about the contribution and the role of cytokines, but the small sample size limited the scope of our analysis. This weakness was primarily due to the challenges of obtaining CSF samples, as LP can be difficult to perform in patients with conditions such as profound asthenia, immobility, or muscular-skeletal issues. A

major limitation of this study is the presence of confounding factors that could affect the analysis. These include the heterogeneity of the patient cohort, which consists of multiple lymphoma subtypes with varying degrees of aggressiveness and tumor burden. In fact, despite the careful selection of patients with high-risk features, the underlying histologic diversity of the lymphoma subtypes may have influenced our analysis. This is because each subtype has a distinct genetic profile and a unique tumor microenvironment, both of which can impact cytokine secretion.

Although our study is a two-center experience, to the best of our knowledge, it is the first study in Italy addressing the role of IL-6 and IL-10 levels in the laboratory diagnosis of secondary CNS involvement in high-risk NHL.

5. Conclusion

In summary, while the role of cytokines in PCNSL has been extensively explored, research on secondary CNS spread in NHL remains limited and our study contributes to the growing evidence supporting the role of both IL-6 and IL-10 as potential biomarkers, widely available to laboratories, for early detection of CNS involvement.

To gain a deeper understanding of this issue and establish the clinical utility of cytokines as diagnostic and potentially prognostic markers, further research with larger cohorts is required.

Data Availability Statement

All relevant data are included in this article. For additional data inquiries, a request can be directed to the corresponding author.

CRediT authorship contribution statement

Elisa Buzzatti: Writing – original draft, Formal analysis, Conceptualization. **Fabiana Esposito:** Writing – original draft, Formal analysis, Conceptualization. **Maria Morello:** Writing – review & editing, Investigation. **Vanessa Rossi:** Investigation. **Maria Christina Cox:** Writing – review & editing. **Ombretta Annibali:** Writing – review & editing. **Enrico Santinelli:** Writing – review & editing, Investigation. **Maria Antonietta Irno-Consalvo:** Investigation. **Giovangiacinto Paterno:** Writing – review & editing. **Lucia Cardillo:** Writing – review & editing. **Massimiliano Postorino:** Writing – review & editing. **Adriano Venditti:** Supervision. **Maria Ilaria Del Principe:** Supervision, Conceptualization.

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Ethics approval statement

The study was approved by the local institutional review board and conducted in accordance with the ethical principles set forth by the Declaration of Helsinki. With respect to privacy, all personal information was treated in a confidential manner, and all clinical data were anonymized.

Informed consent statement

Written informed consent was obtained from all subjects involved in the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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