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Case Report

CD5 negative CLL/SLL with Richter Transformation (RT) to CNS Lymphoma vs Disseminated Primary CNS Lymphoma (PCNSL) with Bone Marrow Infiltration

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Background

Systemic B-cell non-Hodgkin lymphomas (B-NHL) often present with constitutional symptoms, cytopenias, and organ infiltration, but central nervous system (CNS) involvement at diagnosis remains uncommon and is associated with a poor prognosis. Primary CNS lymphoma (PCNSL) is typically confined to the brain, eyes, or cerebrospinal fluid at diagnosis, while secondary CNS lymphoma (SCNSL) refers to spread from a systemic site. However, a subset of aggressive B-NHL may present with simultaneous CNS and systemic involvement, blurring the classical distinction between primary and secondary disease and complicating both diagnosis and management.

Patients with aggressive B-NHL with CNS involvement frequently present with non-specific symptoms such as fever, fatigue, and cytopenias, which can mimic infectious, autoimmune, or inflammatory disorders. This diagnostic overlap is compounded by laboratory findings common to both lymphoma and severe inflammation, including markedly elevated lactate dehydrogenase (LDH), hyperferritinemia, and polyclonal hypergammaglobulinemia. Such presentations often lead to delays in diagnosis and inappropriate initial management, adversely affecting outcomes.

Immunophenotyping by flow cytometry is critical in the diagnostic workup of B-cell lymphoproliferative disorders. Phenotypic markers such as CD5, CD10, CD20, CD23, and surface immunoglobulin light chain restriction are essential for subclassification and for excluding mimics such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), which typically expresses CD5 and CD23. The absence of these markers, along with expression of CD20, FMC7, and monotypic light chain, is more consistent with diffuse large B-cell lymphoma (DLBCL) or other aggressive B-NHL subtypes.

Here, we present a diagnostically challenging case of a middle-aged woman who presented with fever, hepatosplenomegaly, and progressive pancytopenia, initially suggestive of an infectious or inflammatory process. Subsequent evaluation revealed synchronous CNS lesions and bone marrow infiltration by a clonal CD5-/CD10- B-cell population, consistent with an aggressive B-NHL with a CNS-primary clinical picture and systemic dissemination. The case highlights the diagnostic pitfalls, the critical role of immunophenotyping, and the rapidly progressive nature of such lymphomas, particularly when complicated by infectious sequelae in the setting of therapy-induced immunosuppression.

Case Presentation

A 45-year-old female with no history of chronic illness presented in late December 2024 with symptoms diagnosed as a respiratory infection (COVID-19). She received supportive treatment, and a follow-up CT chest after two weeks was normal. However, she experienced intermittent attacks of fever, hepatomegaly, and

splenomegaly with no lymphadenopathy or identifiable source of infection. After consulting a tropical specialist, the following findings were noted:

CBCs consistently showed moderate normocytic/hypochromic anemia, mild thrombocytopenia, and mild to moderate leukopenia/pancytopenia. Notable findings included elevated RDW (anisocytosis), lymphopenia, and a left shift in neutrophils (presence of immature forms like promyelocytes).

- ESR was markedly elevated (135 mm/hr).
- LDH was elevated (329 U/L).
- Reticulocyte count was elevated at 3.8% (corrected to 2.5% noted later), indicating a bone marrow response.
- Serology (Toxo IgG/IgM): Negative.
- HIV: Negative.
- HCV Ab: Negative.
- HBV Ag: Negative.
- CMV: 100 by PCR.
- ANA: Negative.
- Anti-ds DNA: 88.9 (negative, less than 90).
- C3: 80.
- C4: 4.89.
- IgG: 1612.
- IgM: 74.
- IgA: 299.

The patient received supportive treatment with levofloxacin and paracetamol, but the fever did not subside. She began to develop attacks of tachycardia, dyspnea on exertion, and fatigue associated with weight loss. Symptoms were not associated with expectoration, cough, PND, dark urine, pruritus, or skin discoloration. Further investigation revealed:

- CBC: Anemia (Hb: 7.7 g/dL, MCV: 84 fL, RDW: 18%), thrombocytopenia (PLT: $107\times10^3/\mu L$), total leukocyte count $8.5\times10^3/\mu L$, reticulocytes 2.5%.
- Hb electrophoresis: Normal.
- Na, K, Ca: Normal.
- Renal function tests: Normal.
- Liver function tests: Normal.
- LDH: 400 U/L.
- Coomb's (direct & indirect): Negative.
- Iron studies: Ferritin highly elevated (1236 ng/mL), with low-normal iron (37 µg/dL) and saturation (14%); TIBC: 264 µg/dL—suggesting anemia of chronic disease/inflammation.
- Immunoglobulins: Polyclonal hypergammaglobulinemia with elevated IgG (1612 mg/dL) and Beta-2 Microglobulin (6.3 µg/mL).
- Serum protein electrophoresis (SPEP): Showed hypoalbuminemia and polyclonal hypergammaglobulinemia.
- Immunofixation: No monoclonal band detected (polyclonal pattern).

13 January – Bone Marrow Aspirate & Biopsy:

- Aspirate: Hypercellular marrow showing reactive/dysplastic changes in all cell lines (granulocytic, erythroid, megakaryocytic). Increased myeloid:erythroid ratio. No evidence of leukemia, lymphoma, or metastatic infiltration.

- Core Biopsy: Confirmed hypercellular marrow (~100%) with features of an intense inflammatory reaction, prominent plasma cells, and marked secondary fibrosis (myelofibrosis). Immunohistochemistry showed no increase in blasts (CD34 negative) and no atypical B-cell population (CD20 showed only few scattered B-cells).

The patient received supportive treatment with Eprex 4000 (epoetin alfa) and eltrombopag. Symptoms soon worsened, and she developed a headache.

17 January – MRI Brain (with Contrast): Multiple enhancing lesions in the left cerebral hemisphere (frontotemporal, caudate head, temporal lobe) and brainstem. Findings were highly suspicious for metastatic disease.

For further investigation, an F18-FDG PET/CT was performed:

- Brain: Two highly hypermetabolic (FDG-avid) space-occupying lesions—one in the left frontal lobe (SUVmax 13.68) and a larger one in the right caudate nucleus (SUVmax 19.9).
- Breast: Few small mildly avid nodules in the right breast.
- Lymph Nodes: Mildly avid small nodes in the neck and chest (reactionary appearance).
- Abdomen: Moderate splenomegaly and mild hepatomegaly.
- Skeleton: Diffusely increased FDG uptake throughout the bone marrow, indicating reactive hyperplasia.

Brain lesions were identified as described, and diffuse bone marrow uptake was noted. An excisional biopsy was recommended, but the patient refused and was lost to follow-up for two months.

In March, she presented with progressive anemia and thrombocytopenia. CBC showed:

- Hemoglobin (Hb): 10.0 g/dL.
- Mean Corpuscular Volume (MCV): 84.2 fL (NR: 78–97).
- Red Cell Distribution Width (RDW): 18.3% (NR: 11.5–14.5).
- Platelets Count: 39,000/mm³ (NR: 150,000–400,000).
- Total Leucocytes Count: 13.2 × 10^3/µL.

- White Blood Cell Differential: Staff neutrophils 2%, segmented neutrophils 45%, lymphocytes 15%.

Bone Marrow Aspiration revealed:

- Overall Cellularity: Diluted yet infiltrated.
- Infiltration: Abnormal cells from the lymphocytic series.
- Percentage of Nucleated Marrow Elements: 60%.
- Cell Characteristics: Small-to-medium sized lymphocytes with heterogeneous morphology. No large lymphoid cells infiltrate.
- Marrow Hematopoiesis: Reduced.

Flow Cytometry:

- Immunophenotype of Lymphocyte Population:
    - Positive Markers: CD19, HLA-DR, CD79b, CD20, CD22, CD38, FMC7, CD52.
    - Light Chain Restriction: Kappa.
    - Negative Markers: CD5, CD10, CD25, CD23, CD11c, CD103.
- Interpretation: Monoclonal B-cell population consistent with B-non-Hodgkin lymphoma.

Molecular Studies:

- BCL6 Rearrangement: Negative.
- MYC Rearrangement: Negative.
- t(14;18) BCL2/IGH Translocation: Negative.

The patient refused chemotherapy but continued follow-up. She progressed to pancytopenia, febrile neutropenia, and severe sepsis with a fungal infection. Culture showed Klebsiella MDR.

CT Scan (Brain, Chest, Abdomen, Pelvis – Non-Contrast):

- Brain: A large (~3.3 cm) hyperdense space-occupying lesion in the left basal ganglia/caudate nucleus with significant vasogenic edema and mass effect, correlating perfectly with prior PET/MRI findings.
- Sinus: Left maxillary sinusitis with bony erosion, suggestive of invasive fungal infection (e.g., mucormycosis).
- Chest: New minimal left pleural effusion.
- Abdomen/Pelvis: Moderate splenomegaly (21 cm) with a peripheral wedge-shaped defect suggestive of splenic infarction; moderate hepatomegaly.

Bone Marrow Aspiration:

- Differential Count: Normoblasts: 2, Blasts: 0, Promyelocytes: 0, Myelocytes: 0, Juvenile: 0, Staff: 0, Segmented: 6, Lymphocytes: 93 (10% immature cells), Monocytes: 0, Eosinophils: 0, Basophils: 0, Plasma Cells: 0.
- Comments: Hypocellular marrow, depressed all marrow elements, increased BM lymphocytes with some immature forms.
- Conclusion: Referred patient as NHL with BM infiltration; hypocellular marrow; picture suggestive of disseminated lymphocytic lymphoma for IPT.

Immunophenotyping on Peripheral Blood:

- Preliminary Interpretation: CD5-ve / CD10-ve Lymphoproliferative Neoplasm.
- Immunophenotype Results (% positive in gated population):
    - Positive Markers: CD19: 100%, CD20: 100% (positive intermediate), CD38: 95%, CD79b: 73%, Kappa (κ) Light Chain: 93%, FMC7: 95%, CD200: 100%.
    - Negative Markers: Lambda (λ) Light Chain: 1%, CD23: 2%, CD4: 3%, CD10: 1%, CD123: 2%, CD103: 1%, CD5: 3%.

- **Interpretive Comments:** Clonal B-lymphoid cells constitute about 82% of the gated population with kappa light chain restriction. Immunophenotype is consistent with a diagnosis of mature B-cell lymphoproliferative neoplasm (B-LPN), most likely B-cell non-Hodgkin lymphoma (B-NHL).

Differential Diagnosis

1. CLL/SLL with Richter Transformation to DLBCL
    - Why considered: Initial presentation included leukopenia, anemia, splenomegaly, and later bone marrow lymphocytosis (93% lymphocytes). Richter transformation can present with CNS lesions, aggressive course, and worsening cytopenias.
    - Why less likely: Flow cytometry shows CD5-, CD23-, which is unusual for CLL/SLL. CLL is typically CD5+, CD23+, CD20 dim. This immunophenotype argues against pre-existing CLL.
2. Lymphomatoid Granulomatosis or EBV+ DLBCL
    - Why considered: Can present with CNS and multi-organ involvement, but usually lung lesions are prominent (not seen here). EBV status not provided.
3. Intravascular Large B-cell Lymphoma (IVLBCL)
    - Why considered: Can present with fever, cytopenias, hepatosplenomegaly, CNS lesions, and bone marrow involvement. Diagnosis often missed on initial biopsies.
    - Why less likely: No skin rash or adrenal involvement noted; requires tissue biopsy for confirmation.
4. Secondary CNS Lymphoma from Systemic NHL
    - Why considered: PET/CT showed bone marrow and spleen involvement before clear CNS symptoms. This fits systemic DLBCL with CNS spread.
5. Mantle Cell Lymphoma (Blastoid Variant)
    - Why considered: Can be CD5- in some cases, aggressive, with CNS and marrow involvement.

- Why less likely: Usually CD5+, cyclin D1+; not tested here. t(11;14) not reported.

6. Burkitt-like Lymphoma
    - Why considered: High LDH, CNS involvement, aggressive course.
    - Why less likely: Usually CD10+, and MYC rearrangement negative here.

Key Supporting Evidence

- Brain imaging: Multiple enhancing lesions with high SUV.
- Bone marrow: Lymphocytic infiltration (93%), kappa restriction.
- Immunophenotype: CD19+, CD20+, CD38+, CD79b+, FMC7+, CD200+, CD5-, CD10-, CD23-.
- Clinical course: Rapid progression from fever/hepatosplenomegaly to CNS lesions and pancytopenia.
- Lab markers: Very high ferritin, elevated LDH, polyclonal hypergammaglobulinemia—consistent with lymphoma-associated inflammation.

Treatment: The patient was treated with systemic and intrathecal methotrexate but unfortunately rapidly developed septic shock and died due to suspected clinical mycosis and Klebsiella bacteremia. No autopsy was performed.

Discussion

This case presents a formidable diagnostic challenge, epitomizing the clinical and pathological overlap between aggressive lymphoma, indolent lymphoproliferative disorders with transformation, and severe systemic inflammation. The central question—whether this represents a Richter transformation (RT) of a cryptic indolent B-cell clone or a de novo aggressive B-cell non-Hodgkin lymphoma (B-NHL) with synchronous central nervous system (CNS) and systemic presentation—hinges on the nuanced interpretation of immunophenotypic data within the clinical context.

The Possibility of Richter Transformation from a CD5-Negative B-Cell Clone

Richter transformation, most commonly described in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), denotes the progression to an aggressive lymphoma, typically diffuse large B-cell

lymphoma (DLBCL), and carries a dismal prognosis [1]. While classic CLL/SLL is characterized by a CD5+, CD23+, CD20(dim) phenotype, approximately 5–10% of cases are CD5-negative and may exhibit atypical features such as brighter CD20 expression and FMC7 positivity, blurring the distinction from other B-cell neoplasms [2,3]. Our patient's immunophenotype—CD5-, CD23-, CD20(bright), FMC7+, CD79b+—theoretically fits within this rare variant. The clinical progression from constitutional symptoms and splenomegaly to aggressive CNS lesions and pancytopenia mirrors the tempo of RT. Furthermore, the terminal bone marrow showing 93% lymphocytes could be interpreted as the underlying leukemic component, with the CNS lesions representing the transformed clone.

Evidence Favoring a De Novo Aggressive B-NHL

Despite the above consideration, several lines of evidence argue more strongly for a diagnosis of de novo aggressive B-NHL, likely DLBCL or a related entity, rather than RT. First, there was no documented antecedent history of lymphocytosis, cytopenias, or lymphadenopathy to suggest a pre-existing indolent lymphoproliferative disorder. The patient presented acutely with a systemic inflammatory syndrome and rapid multi-organ failure, a pattern more consistent with an aggressive lymphoma from onset. Second, the immunophenotype, while compatible with atypical CLL, is more characteristic of other mature B-cell neoplasms. The bright CD20, strong CD79b, and FMC7 positivity are unusual for CLL (even CD5-negative variants, which often retain other typical features like CD200 positivity and CD79b weakness) but are hallmark features of DLBCL, mantle cell lymphoma (blastoid variant), or splenic marginal zone lymphoma (SMZL) [4]. The positive CD200 in our flow cytometry report, while seen in CLL, is also expressed in other lymphomas and is not discriminatory [5]. Third, the pattern of involvement was synchronous: highly FDG-avid CNS lesions, bone marrow infiltration, and hepatosplenomegaly were identified concurrently, suggesting a widely disseminated aggressive process rather than a focal transformation event.

The Pivotal Role of Immunophenotyping and Differential Diagnosis

The diagnostic odyssey underscores the critical role of comprehensive immunophenotyping in classifying B-cell lymphomas. The CD5-/CD10- phenotype efficiently narrows the differential. Alongside DLBCL, other considered entities included blastoid variant mantle cell lymphoma (typically CD5+, cyclin D1+), Burkitt-like lymphoma (typically CD10+), and intravascular large B-cell lymphoma. The reported immunophenotype, combined with the absence of cyclin D1 or MYC rearrangements, makes DLBCL or an aggressive variant of SMZL the most probable diagnoses. The early bone marrow biopsy (January 13) revealing hypercellularity with reactive changes and fibrosis, but no overt lymphoma, is particularly instructive. This likely represented a profound paraneoplastic or inflammatory state secondary to the occult lymphoma, a phenomenon well-

documented in aggressive lymphomas that can initially mimic myeloproliferative or autoimmune disorders [6]. The subsequent marrow (March) showed overt lymphomatous replacement, demonstrating the evolution from an inflammatory microenvironment to direct tumor infiltration.

Clinical Course and Management Implications

The rapid clinical deterioration, culminating in fatal septic shock from a multidrug-resistant Klebsiella and suspected invasive fungal infection, highlights the extreme vulnerability of patients with aggressive lymphoma involving the bone marrow and CNS. The profound immunosuppression from both the disease (marrow failure) and its treatment (intrathecal methotrexate) creates a perfect storm for opportunistic infections. This outcome reinforces the need for aggressive diagnostic pursuit in febrile pancytopenic patients with unexplained inflammatory markers (e.g., extreme ferritin elevation) and for robust antimicrobial prophylaxis during treatment of such high-risk cases [7].

Conclusion

In summary, this case illustrates a tragically rapid progression of a CD5-/CD10- B-cell lymphoproliferative neoplasm with dominant CNS and bone marrow involvement. While the rare possibility of Richter transformation from a CD5-negative indolent clone cannot be entirely excluded in the absence of molecular clonal tracking, the weight of evidence—the lack of an indolent phase, the immunophenotype more typical of DLBCL/SMZL, and the synchronous multi-organ presentation—favors a diagnosis of de novo aggressive B-NHL, most consistent with DLBCL. The case powerfully reiterates that lymphomas can masquerade as systemic inflammatory syndromes and that flow cytometry is indispensable in cutting through the diagnostic mimicry. Future management of similar cases may benefit from early integration of liquid biopsy and advanced molecular profiling to detect clonal evolution and guide targeted therapies, especially in the setting of CNS disease.

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