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Clinicopathological Spectrum of Indolent Small B-Cell Lymphomas: Diagnostic Challenges from a Tertiary Care Center

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ABSTRACT

Introduction: Indolent small B-cell lymphomas represent a heterogeneous group of mature B-cell neoplasms characterized by overlapping clinical, morphological, and immunophenotypic features. These similarities often create diagnostic challenges, particularly in patients presenting with atypical clinical manifestations such as predominant bone marrow involvement, paraproteinemia, or unusual immunophenotypic profiles. Accurate classification is essential for appropriate prognostication and therapeutic decision-making. This study aims to evaluate the clinicopathological spectrum and diagnostic challenges associated with indolent small B-cell lymphomas in adult patients at a tertiary care center.

Methods: A retrospective observational study was conducted including adult patients diagnosed with indolent small B-cell lymphoma at a tertiary care center. Clinical presentation, hematological parameters, radiological findings, bone marrow examination, histopathological features, immunohistochemistry findings, cytogenetic analysis, and follow-up data were reviewed. Diagnoses were established according to the latest international classification systems for hematolymphoid neoplasms.

Results: Patients aged 43–70 years presented with varied clinical manifestations including anemia, peripheral neuropathy, and lymphadenopathy. Bone marrow involvement was observed in the evaluated cases. Immunophenotypic analysis demonstrated variable expression patterns among small B-cell populations, including both CD5-positive and CD5-negative profiles, with absence of Cyclin D1 and CD23 expression in selected cases. Monoclonal paraproteinemia was detected in some patients, including immunoglobulin A kappa and immunoglobulin M kappa proteins. Cytogenetic abnormalities such as deletion 13q14 and trisomy 12 were also identified. During follow-up, patients demonstrated an indolent clinical course with stable disease.

Conclusion: Indolent small B-cell lymphomas frequently demonstrate overlapping clinicopathological features that complicate definitive classification. Comprehensive integration of clinical findings, morphology, immunophenotyping, cytogenetic studies, and longitudinal follow-up is essential for accurate diagnosis and appropriate management.

Keywords: *Indolent lymphoma; Small B-cell lymphoma; Bone marrow involvement; Immunohistochemistry; Diagnostic challenges.*

INTRODUCTION

Non-Hodgkin lymphoma (NHL) represents a heterogeneous group of lymphoid malignancies arising from B cells, T cells, or natural killer cells and accounts for a significant proportion of hematological cancers worldwide. The global incidence of NHL has shown a gradual increase over recent decades, with considerable geographic variation influenced by

environmental, genetic, and demographic factors [1, 2]. In India, mature B-cell lymphomas constitute the majority of NHL cases, among which indolent small B-cell lymphomas form an important subgroup characterized by relatively slow disease progression and prolonged survival [3, 4].

Indolent small B-cell lymphomas include entities such as marginal zone lymphoma, lymphoplasmacytic lymphoma, and other low-grade B-cell neoplasms. These lymphomas frequently exhibit overlapping morphological and immunophenotypic features, which may create diagnostic challenges in routine hematopathology practice. Contemporary classification systems, including the recent World Health Organization classification of hematolymphoid tumors and the International Consensus Classification, recommend an integrated diagnostic approach combining histopathology, immunophenotyping, molecular findings, and clinical correlation to achieve accurate classification [5, 6].

Despite advances in diagnostic techniques, atypical clinical presentations—such as predominant bone marrow involvement, monoclonal gammopathy, or aberrant antigen expression—may complicate the distinction between various indolent small B-cell lymphoma subtypes. Such diagnostic uncertainty may influence prognostic assessment and therapeutic decision-making. Furthermore, limited data are available from regional tertiary care centers regarding the clinicopathological spectrum and diagnostic challenges of indolent small B-cell lymphomas in the Indian population.

Therefore, the present study was undertaken to evaluate the clinicopathological characteristics and diagnostic challenges associated with indolent small B-cell lymphomas in adult patients at a tertiary care center. By correlating clinical presentation, morphology, immunophenotypic findings, and cytogenetic features, this study aims to highlight potential diagnostic pitfalls and emphasize the importance of an integrated approach for accurate classification.

MATERIALS AND METHODS

Study Design and Setting

The present study was designed as a retrospective observational analysis conducted in the Department of Pathology at a tertiary care teaching hospital. The study period extended from January 2022 to November 2025. Clinical records, laboratory data, radiological findings, histopathology reports, immunohistochemistry results, cytogenetic information, and follow-up details were reviewed from institutional archives and electronic medical records.

Study Population

Adult patients diagnosed with indolent small B-cell non-Hodgkin lymphoma during the study period were included in the analysis. Particular attention was given to cases demonstrating atypical clinical presentations or overlapping morphological and immunophenotypic features that could pose diagnostic challenges.

Inclusion Criteria

Patients were included in the study if they fulfilled the following criteria:

1. Age 18 years or older.
2. Histopathologically confirmed diagnosis of indolent small B-cell lymphoma.
3. Availability of adequate tissue material and immunohistochemical evaluation for definitive diagnosis.

Exclusion Criteria

Cases were excluded if clinical records were incomplete, tissue samples were inadequate for proper histopathological assessment, or if patients had previously been diagnosed with aggressive lymphoma or had received prior lymphoma-specific therapy.

Histopathological Evaluation

All tissue specimens were fixed in formalin and processed using routine paraffin-embedding techniques. Sections were stained with hematoxylin and eosin and carefully examined by experienced pathologists. Morphological evaluation included assessment of lymphoid cell morphology, architectural patterns, and the presence of bone marrow infiltration when applicable.

Immunohistochemical Analysis

Immunohistochemical staining was performed using a panel of antibodies commonly used in the evaluation of B-cell lymphomas, including CD20, CD5, CD23, CD10, Cyclin D1, BCL2, and BCL6. Bone marrow biopsy specimens were also assessed to determine the pattern and extent of lymphomatous

Diagnostic Criteria

Final classification of lymphoma subtypes was established according to the latest international guidelines for hematolymphoid neoplasms, incorporating morphological findings, immunophenotypic features, cytogenetic results, and relevant clinical information.

Ethical Considerations

The study was conducted in accordance with institutional ethical standards. The study protocol was approved by the Institutional Ethics Committee of Bhagyoday Medical College, Kadi, Gujarat, India (Approval No: BMC/IEC/2025/Path/07).

RESULTS

A total of three adult male patients diagnosed with indolent small B-cell lymphoma were included in the study. The age of the patients ranged from 43 to 70 years, with a median age of 69 years. Clinical presentation varied among the patients and included unexplained anemia, peripheral neuropathy, and localized cervical lymphadenopathy. Constitutional (B) symptoms were absent in all cases. Bone marrow involvement was identified in all three patients at the time of diagnosis. The clinical and laboratory characteristics of the patients are summarized in **Table 1.**

Table 1: Clinical and Laboratory Profile of Patients

Case	Age	Sex	Presenting Symptom	B Symptoms	Lymphadenopathy	Bone Marrow Involvement	Serum Paraprotein	Neurological Features
1	70	Male	Anemia	Absent	Absent	Present	IgA-kappa	Absent
2	69	Male	Peripheral neuropathy	Absent	Absent	Present	IgM-kappa	Present
3	43	Male	Cervical swelling	Absent	Present	Present	Absent	Absent

The histopathological and immunophenotypic findings are presented in Table 2. Morphological patterns included interstitial marrow infiltration, paratrabecular infiltration, and nodal architectural effacement **(**Figure 1, 2**).** All cases demonstrated CD20 positivity, confirming B-cell lineage. CD5 expression was variable, while CD23, CD10, and Cyclin D1 were negative in most cases. Based on these findings, cases were interpreted as probable marginal zone lymphoma, lymphoplasmacytic overlap lymphoma, and low-grade B-cell lymphoma, unclassifiable.

Table 2: Histopathological and Immunophenotypic Comparison

Case	Morphological Pattern	CD20	CD5	CD23	CD10	Cyclin D1	Final Interpretation
1	Interstitial marrow infiltration	Positive	Negative	Negative	Negative	Negative	Probable marginal zone lymphoma
2	Paratrabecular marrow infiltration	Positive	Positive	Negative	Negative	Negative	Lymphoplasmacytic overlap lymphoma
3	Nodal architecture effacement	Positive	Variable	Negative	Negative	Negative	Low-grade B-cell lymphoma, unclassifiable

Cytogenetic and molecular findings are summarized in **Table 3.** Chromosomal abnormalities were identified in one case, including deletion of chromosome 13q14 and trisomy 12. Another case was negative for t (11; 14), helping to exclude mantle cell lymphoma. No cytogenetic abnormality was detected in the third case.

Table 3: Cytogenetic and Molecular Findings

Case	Cytogenetic Abnormality	Molecular Study	Diagnostic Significance
1	del(13q14), Trisomy 12	Not available	Overlap with CLL-like genetic changes
2	Negative for t(11;14)	Not available	Helps exclude mantle cell lymphoma
3	No abnormality detected	Not available	Supports unclassifiable low-grade lymphoma

The differential diagnostic considerations and distinguishing features are outlined in **Table 4**. Major differentials included chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma, and marginal zone lymphoma. Final diagnostic interpretation was supported by integration of morphological features, immunophenotypic profile, and clinical findings.

Table 4: Differential Diagnosis Considered

Case	Major Differentials	Features Supporting Final Diagnosis
1	CLL/SLL, Marginal zone lymphoma	CD5 negative profile with compatible morphology

2	Mantle cell lymphoma, Lymphoplasmacytic lymphoma	Cyclin D1 negative with IgM paraproteinemia
3	Follicular lymphoma, Marginal zone lymphoma	Lack of CD10 expression and clinical stability

A comprehensive clinicopathological summary of all cases is provided in **Table 5**, including clinical presentation, primary disease site, immunohistochemical profile, cytogenetic findings, and follow-up outcomes. During follow-up, all patients demonstrated an indolent clinical course with stable disease, with follow-up periods extending up to 48 months.

Table 5: Summary of Clinicopathological Findings

Case	Age	Clinical Presentation	Primary Site	Diagnosis	IHC Profile	Cytogenetics	Stage	Paraproteinemia	Follow-up Outcome
1	70	Anemia	Bone marrow & nasopharynx	CD5-negative small B-cell lymphoma	CD20+, CD5-, CD23-, CD10-, Cyclin D1-	del(13q14), Trisomy 12	Marrow predominant	IgA-kappa	Stable at 42 months
2	69	Peripheral neuropathy	Bone marrow	CD5-positive indolent lymphoma	CD20+, CD5+, CD23-, Cyclin D1-	Negative for t(11;14)	Marrow predominant	IgM-kappa	Stable at 48 months
3	43	Cervical lymphadenopathy	Lymph node & marrow	Low-grade B-cell lymphoma, unclassifiable	CD20+, CD5 variable, CD23-, CD10-, Cyclin D1-	None detected			

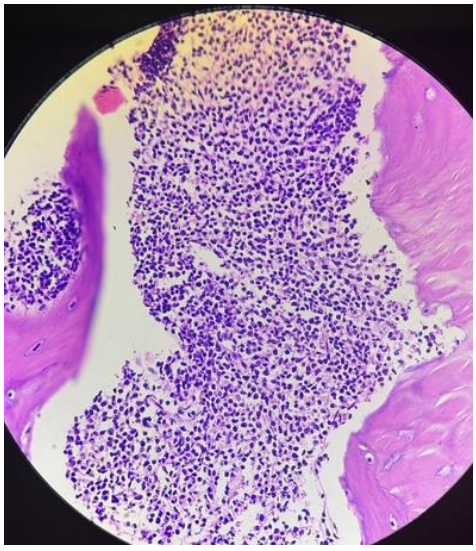

Figure 1: Case 1-Bone marrow biopsy showing interstitial infiltration by small mature lymphoid cells (Hematoxylin & Eosin stain, ×400)

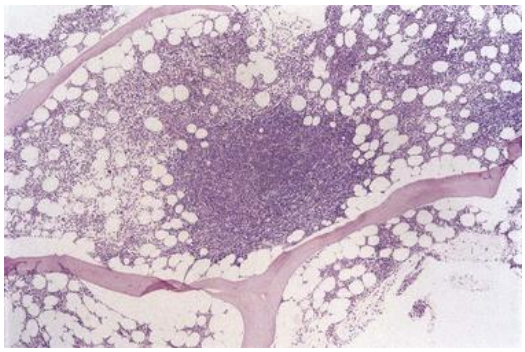

Figure 2: Case 2- the bone marrow biopsy showing a -paratrabecular infiltrate of small, mature B-cell lymphocytes (Hematoxylin & Eosin stain, ×100)

DISCUSSION

Indolent small B-cell lymphomas represent a heterogeneous group of mature B-cell neoplasms characterized by slow clinical progression but considerable diagnostic overlap in morphology and immunophenotype. Contemporary classification systems, including the World Health Organization (WHO) 5th edition and the International Consensus Classification (ICC), emphasize an integrated diagnostic approach combining morphology, immunophenotyping, cytogenetic findings, and clinical correlation for accurate disease classification [5, 6].

Bone marrow involvement is commonly observed in indolent lymphomas and may occasionally represent the primary site of disease presentation. Previous studies have reported significant marrow infiltration in entities such as marginal zone lymphoma and lymphoplasmacytic lymphoma [7, 8]. In addition, marrow involvement has been described in several indolent lymphoid neoplasms presenting with unexplained cytopenias or monoclonal gammopathy [9, 10]. In the present study, bone marrow involvement was observed in all cases, emphasizing its diagnostic relevance.

Immunophenotyping remains essential in differentiating indolent B-cell lymphomas. Expression of CD20 confirms B-cell lineage, while variable expression of markers such as CD5 may create diagnostic difficulties. Aberrant CD5 positivity has been reported in certain indolent lymphomas and may mimic chronic lymphocytic leukemia or mantle cell lymphoma [11, 12]. In such situations, the absence of Cyclin D1 expression is helpful in excluding mantle cell lymphoma [13].

Monoclonal paraproteinemia is another important finding in indolent lymphomas, particularly lymphoplasmacytic lymphoma, which is commonly associated with IgM monoclonal gammopathy [14]. Therefore, serum protein electrophoresis can serve as a useful adjunct in the diagnostic workup of suspected lymphoid neoplasms. Cytogenetic abnormalities such as deletion of chromosome 13q14 and trisomy 12 have also been reported in indolent lymphoid neoplasms and may overlap with genetic changes seen in chronic lymphocytic leukemia [15].

Clinically, indolent lymphomas generally demonstrate a stable course, and many patients may be managed with observation in the absence of symptomatic disease. This “watch-and-wait” approach has been supported by several clinical studies [16, 17]. However, long-term follow-up remains important because transformation into aggressive lymphoma, such as diffuse large B-cell lymphoma, may occur in a subset of patients [18].

The present study has limitations, including a small sample size and limited molecular testing. Nevertheless, careful clinicopathological correlation provides useful insight into the diagnostic spectrum of indolent small B-cell lymphomas. Overall, these findings highlight the importance of an integrated diagnostic approach combining clinical, morphological, immunophenotypic, and cytogenetic data for accurate classification and appropriate patient management.

CONCLUSION

Indolent small B-cell lymphomas represent a heterogeneous group of lymphoid neoplasms that often display overlapping clinical, morphological, and immunophenotypic features, posing significant diagnostic challenges in routine practice. The present study highlights the importance of a comprehensive diagnostic approach integrating histopathology, immunophenotyping, cytogenetic findings, and clinical correlation for accurate subclassification. Recognition of atypical presentations, including bone marrow–predominant disease and associated monoclonal paraproteinemia, is essential to avoid diagnostic misinterpretation and inappropriate management.

This study contributes to the existing literature by emphasizing real-world diagnostic complexities encountered in indolent lymphoma cases within a tertiary care setting. Improved awareness of these clinicopathological variations may facilitate more precise diagnosis, appropriate risk stratification, and optimized patient management. Continued research with larger cohorts and advanced molecular testing will further enhance understanding of the biological behavior and classification of indolent small B-cell lymphomas.

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