Special article

# Marrow T cell response after B cell-targeted immunotherapy mimicking lymphoma

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## Introduction

B cell-targeted immunotherapy, particularly anti-CD20 monoclonal antibodies (e.g. rituximab) in combination with CHOP, has been shown to be more effective and to significantly improve survival in patients with diffuse B cell lymphoma (DLBCL) compared with the conventional CHOP regimen alone.[1] At present, additional B cell-targeted immunotherapeutic options are available.[2-4]

An understanding of normal B cell development helps explain why B cell-targeted immunotherapy does not completely eliminate B cells after treatment. Normal bone marrow B cell precursors (so-called "hematogones") do not express CD20 and therefore survive anti-CD20 immunotherapy.[5] It is also important to recognize that bone marrow evaluation for residual lymphoma following B cell-targeted immunotherapy cannot rely solely on morphology or immunohistochemistry (IHC) for CD20 in conventional bone marrow biopsies. Residual lymphoma cells may downregulate CD20 expression and thus escape detection by CD20 IHC. Accordingly, additional B cell markers such as PAX5, CD19, CD22 and CD79a are required for accurate B-cell indentification.[6]

Conventionally, bone marrow evaluation for lymphoma staging relies on morphologic assessment of marrow aspirate smears and histologic sections, together with flow cytometric analysis of marrow aspirates and, when available, molecular genetic studies.[7] Morphologic evaluation is particular effective in identifying lymphoma cells, especially those of large size. IHC performed on bone marrow biopsy specimens can provide immunophenotypic evidence to determine marrow involvement by lymphoma.[8,9] Naemi et al. described the distribution patterns of B and T cells in benign lymphoid aggregates (BLAs) in the bone marrow, suggesting a benign process when T cells predominate, when a central core of T cells is surrounded by a rim of B cells, or when B and T cells show a mixed distribution. In contrast, B cell lymphoma should be suspected when there is a predominance of B cells or a central core of B cells (excluding reactive germinal center) surrounded by a rim of T cells, particular when additional features of lymphoma are present, including large aggregate size, infiltrative boarders, cytologic atypia and paratrabecular localization.[10] Flow cytometry is especially useful for identifying lymphoma populations in cases with small-cell morphology.[11] In some cases, molecular genetic studies provide definitive evidence for minimal residual disease.[12]

Anti-CD20 immunotherapy in B cell lymphoma has altered the approach to bone marrow evaluation following treatment. A boarder panel of markers is now required to detect CD20-negative lymphoma cells. In addition, increased awareness is needed regarding abnormal T cell responses that may mimic lymphoma (Table 1).[10,13-16]

## Marrow T Cell Response after B Cell-Targeted Immunotherapy Mimicking Lymphoma

When evaluated by morphology alone, the bone marrow may contain a large number of lymphoid cells, most of which are small, making it challenging to distinguish

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**Table 1** Marrow T cell response after B Cell-Targeted Immunotherapy Mimicking Lymphoma[10,13-16]

| Authors | No. of BM tested | Morphology+ | IHC (no. of positive cases) |
|---|---|---|---|
| Douglas et al. (1999)[13] | 16 | 11 (P, 5; S, 6) | CD3+ (6) CD20- CD79a- |
| Foran et al. (2001)[14] | 35 | 25 | CD3+ (3; CD8+, 2; CD4/CD8, 1) CD20- CD79a+ (1) |
| Goteri et al. (2006)[15] | 26 | 10 | CD3+ (10) CD20- |
| Raynaud et al. (2008)[16] | 39 | 13 | CD3+ (13; mixed CD4/CD8) CD20- |
| Naemi et al. (2013)[10] | NA | NA | CD3+ (NA) |

BM, bone marrow; IHC, Immunohistochemistry; morphologic +, positive for lymphoma by histologic evaluation; NA, not available; P, positive for lymphoma; S, suggestive of lymphoma

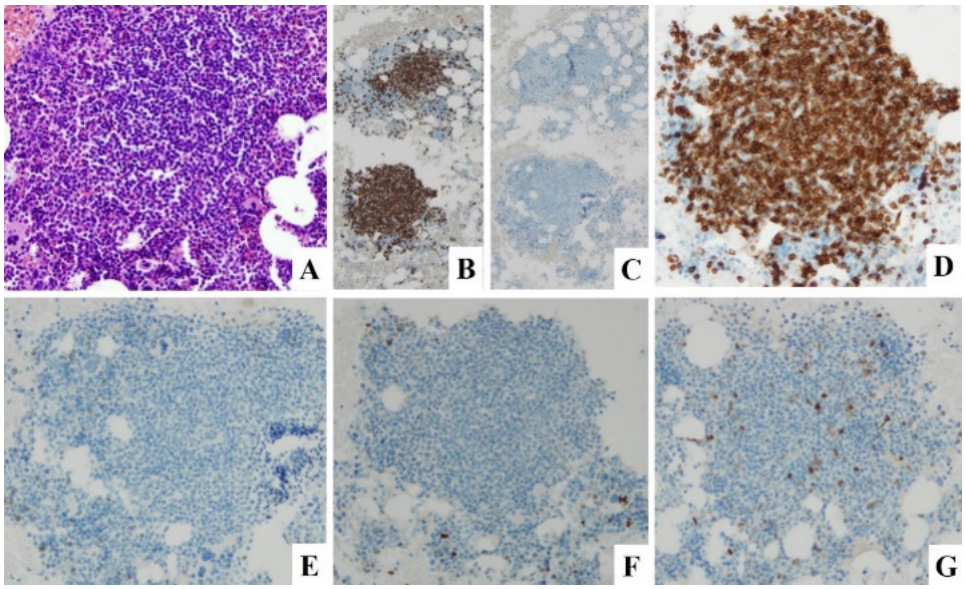


**Figure 1 A**) Lymphoid aggregate in the marrow taken from a known case of mantle cell lymphoma following treatment with rituximab-based regimen. The small lymphoid cells exhibit nuclear irregularities leading to interpretation as residual lymphoma cells as frequent lymphoid clusters and aggregates in the marrow. **B**) CD3+ T cells in two lymphoid aggregates. **C**) Absence of CD20+ B cells. **D**) Higher magnification of CD3+ T cells in the same lymphoid aggregate shown in #A but without CD20+ B cell (**E**) or PAX5+ B cell in the aggregate (**F**), containing a few scattered PAX5+ normal marrow precursor B cells outside the aggregate. **G**) Cyclin D1+ internal positive control cells without corresponding B cells.

residual or relapsed lymphoma in patients with a known history of B cell lymphoma with small-cell morphology. The diagnostic challenge becomes evident when IHC reveals only small T cells, with no detectable B cells (Figure 1).

The exact frequency of this abnormal T cell response in bone marrow samples from patients with B cell lymphoma following B cell-targeted immunotherapy is not well-established. In a series of 67 patients with B cell lymphoma treated with single-agent rituximab reported by Foran, et al. (2001), 39 patients had marrow involvement before treatment. One month after therapy, three patients showed persistent marrow infiltration by lymphoid cells; however, immunophenotyping demonstrated only CD3+ T cells-two cases with predominantly CD8+ T cells and one case with mixed CD4+/CD8+ T cell population. Therefore, approximately 3 of 67 patients (4.5%) overall, or 3 of 39 patients (7.7%) patients with pre-treatment marrow involvement, may exhibit an abnormal T cell response in the marrow following B cell-targeted immunotherapy. Interestingly, one case showed scattered CD79a+/CD20- lymphoma B cells within

a dense CD3+ T cell infiltrate.[14] This finding underscores the importance of careful evaluation before diagnosing an abnormal T cell response.

The etiology of abnormal T cell response in the bone marrow of patients with B cell lymphoma following B cell-targeted immunotherapy remains unknown. However, T cell responses in patients with lymphoma are known to differ from those in healthy individuals. Recently, God, et al. (2025) demonstrated that lymphoma-secreted factors broadly disrupt HLA class II-mediated antigen presentation in both malignant B cells and dendritic cells, resulting in suppression of T cell responses. This inhibition is allele-independent (affecting DR1, DR4 and DR7) while sparing HLA class I-mediated CD8+ T cell recognition. These findings suggest that lymphoma cells may employ immune evasion strategies by secreting such factors.[17] We further speculate that the underlying immune repertoire in patients with B cell lymphoma may also contribute to the development of abnormal marrow T cell responses.

Positron emission tomography/computed tomography (PET/CT) has been shown to detect bone marrow involvement more sensitively than conventional bone marrow biopsy.[18] It would be of interest to determine whether PET/CT can distinguish abnormal T cell proliferation from residual or relapsed lymphoma in the bone marrow. However, based on case reports, PET/CT is unable to differentiate acute adult infectious mononucleosis from malignant lymphoma.[19] Because exuberant T cell responses can also be observed in infectious mononucleosis,[20] PET/CT appears to lack sufficient discriminatory power in this setting.

A final but critical issue is the effective use of IHC when encountering lymphoid aggregates in bone marrow histologic sections. This situation should be approached in a manner analogous to the evaluation of focal lesions in core needle biopsies. Only a carefully planned IHC panel can accurately determine the nature of a lymphoid aggregate. A skilled histotechnologist can provide an adequate number of tissue sections from the lymphoid aggregate to perform IHC staining for CD20, CD19, CD79a, PAX5, CD3, CD4 and CD8, as well as and two to three unstained sections for additional markers if required.[21]

## Conclusion

B-cell lymphoma represents a major category of malignant lymphoma worldwide. B cell-targeted immunotherapy has significantly improved patient survival compared with combination chemotherapy (CMT) alone. Nevertheless, refractory or relapsed B cell lymphoma following B cell-targeted immunotherapy remains a clinical challenge, particular during bone marrow evaluation. Morphologic assessment of marrow aspirate smears and hematoxylin-and-eosin-stained histologic sections was once a practical approach for evaluating response after CMT; however, in the era of B-cell-targeted immunotherapy, this approach may be misleading. Exaggerated marrow T cell response can occur and may closely mimic residual lymphoma or relapsed disease. This brief review highlights this important diagnostic pitfall and emphasizes a comprehensive multimodal approach to bone marrow evaluation following B cell-targeted immunotherapy.

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The authors declare they have no conflict of interest.

## Ethics approval

This article does not contain any studies with human participants performed by any of the authors.

## Informed consent

For this literature review, informed consent is not required.

### Consent for publication

For this literature review, consent for publication is not required.

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