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Letter to the Editor

CD20 Loss as a Mechanism of Resistance to Mosunetuzumab in Relapsed Follicular Lymphoma

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To the editor.

Mosunetuzumab (mosu), a CD20×CD3 bispecific antibody, has emerged as an effective therapeutic option for relapsed/refractory (R/R) follicular lymphoma (FL), yielding durable remissions even in heavily pretreated patients. In the pivotal phase II GO29781 study, mosu achieved substantial clinical activity and subsequently received accelerated approval in this setting. Updated analyses confirmed its long-term benefit, with complete remission (CR) rates approaching 60% and a 2-year progression-free survival of 77%.[1,2] Nonetheless, resistance is increasingly recognized, and loss of CD20 expression has gained attention as a clinically relevant immune-escape mechanism. Here, we describe a case of R/R FL in which CD20 loss emerged during mosu therapy, emphasizing the value of re-evaluating antigen expression at each relapse.[3,4]

A 49-year-old man was diagnosed in 2019 with FL involving the mediastinum, abdomen, and bone marrow (**Figure 1A-1B**). First-line R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) induced a Lugano-defined CR. He relapsed in 2021; biopsy confirmed FL, and treatment with obinutuzumab–bendamustine followed by autologous stem cell transplantation again achieved CR. His post-transplant course was complicated by SARS-CoV-2 pneumonia, invasive aspergillosis, and cytomegalovirus (CMV) reactivation — an infectious trifecta that would make even the hardiest immune system consider a career change.

In January 2023, PET-CT revealed mediastinal progression, managed with 40 Gy radiotherapy. In March 2024, new abdominal disease appeared (SUV 12.5). Biopsy showed relapse of FL (**Figure 1C**) At this time the patient initiated mosu (Nov 2024–Apr 2025). A CT scan in May 2025 -after 6 cycles- showed progression, and lymph node biopsy demonstrated FL with complete CD20 loss (**Figure 1D, 1E**). The patient was evaluated for CAR-T, received bridging R-GemOx (gemcitabine 1000 mg/m² and oxaliplatin 100 mg/m²), and underwent axicabtagene ciloleucel infusion in July 2025. Grade 2 cytokine release syndrome (CRS) resolved with tocilizumab and dexamethasone, while hemophagocytic lymphohistiocytosis (HLH) syndrome on day +23 from CAR-T infusion improved with anakinra. He currently remains clinically well, with a 3-month post-infusion PET-CT showing the reduction of the previous lymphoma mass.

Recent investigations have shed light on the biology of CD20 loss in the context of CD20-directed bispecific antibodies. Schuster et al.[3] reported that although CD20 loss is not common, it correlates with disease progression in a subset of GO29781 participants, with approximately one-third of evaluable biopsies demonstrating marked downregulation — particularly among patients with low baseline antigen density. However, most patients progressing on mosu retain CD20, suggesting additional resistance pathways, including MS4A1 transcriptional suppression, CD20 structural alterations, and microenvironment-driven immune dysfunction. Olszewski et al.[4] have proposed three temporal patterns of failure under bispecific therapy: (1) early progression, shaped by an immunosuppressive tumor microenvironment and insufficient T-cell infiltration; (2) intermediate progression, driven by MS4A1 mutations or silencing leading to reduced CD20 expression; and (3) late progression, associated with T-cell exhaustion. Our clinical case clearly fits the intermediate pattern, in which antigen loss results in complete abrogation of the therapeutic target. In our patient, CD20 expression — consistently assessed using the same immunohistochemical protocol and antibody clone — was 100% at diagnosis, while a complete loss of CD20 expression was documented during treatment. This finding plausibly places our case within the second hypothesis proposed by Olszewski et al.[4] This case

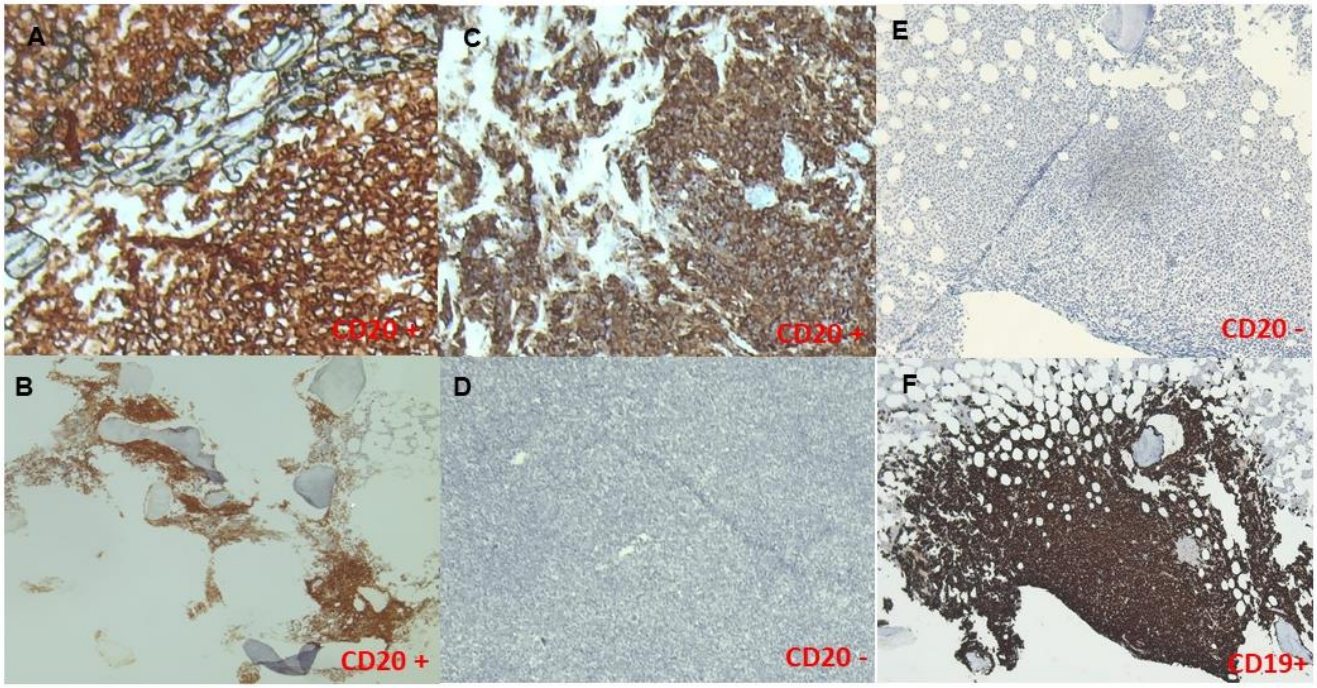

Figure 1. LN A) and BM B) at diagnosis showing diffuse expression of CD20 (100%) by IHC.LN (C) pre-mosu showing persistent CD20 expression (100%) by IHC; LN (D) and BM (E) post Mosu CD20 negative. F) BM post-mosu CD19 positive.
LN: Lymphonode, BM: bone marrow, IHC, immunohistochemistry; Mosu, mosunetuzumab

underscores the need for systematic reassessment of antigen expression at each relapse, especially when progression occurs on CD20-directed therapies. In patients with diminished or absent CD20 expression, alternative therapeutic routes — such as CD19-directed bispecific antibodies, CAR-T cell products,[5] or investigational strategies aimed at restoring antigen expression or augmenting T-cell function — may offer greater benefit. For this reason, assessing CD19 expression was decisive in determining eligibility for CAR-T therapy.[-8] In conclusion, while mosu has meaningfully expanded the treatment landscape for R/R FL, emerging resistance mechanisms — particularly CD20 loss — highlight the importance of dynamic antigen reassessment. Incorporating routine evaluation at diagnosis and at each relapse may facilitate more refined therapeutic sequencing and decision-making to improve patient outcomes.

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