Mediterranean Journal of Hematology and Infectious Diseases

Scientific Letters

A Case of Pseudo-Richter Transformation Following Zanubrutinib Discontinuation in CLL

Keywords: Chronic lymphocytic leukaemia; Pseudo-richter; BTK inhibitors; Zanubrutinib.

Published: September 01, 2026 **Received: July 22, 2026** **Accepted: August 04, 2026**

Citation: Laurenti L., Quaranta T., Tomasso A., Stirparo L., Abbate P.L., Bakacs A., Cappoli N., Di Napoli A., Efremov D., Bellisario F., Gattei V., Caldarella C., Calcagni M.L., Autore F., Innocenti I. A case of Pseudo-Richter Transformation following zanubrutinib discontinuation in CLL. Mediterr J Hematol Infect Dis 2026, 18(1): e2026070, DOI: http://dx.doi.org/10.4084/MJHID.2026.070

Introduction. Covalent Bruton tyrosine kinase inhibitors (cBTKi), including ibrutinib, acalabrutinib, and zanubrutinib, are highly effective in both treatment-naïve and relapsed/refractory Chronic Lymphocytic Leukemia (CLL), producing durable disease control and significant improvements in progression-free and overall survival compared with conventional chemoimmunotherapy regimens.[1-4] Consequently, they have become a cornerstone of CLL management and are generally administered continuously until disease progression or unacceptable toxicity. The efficacy of cBTKi relies on sustained target inhibition, making long-term continuous therapy an essential of treatment.[5] However, temporary treatment interruptions are common in clinical practice, occurring in up to 40% of patients (pts)[6], the most frequent indication being the need for invasive or surgical procedures. Hemorrhage emerged as a notable adverse event during early clinical trials of ibrutinib, leading to recommendations that the drug be withheld for 3–7 days before and after surgery, depending on the anticipated bleeding risk.[7] Additional causes of treatment interruption include infections, hematologic and nonhematologic toxicities, and clinically significant drug–drug interactions requiring temporary discontinuation or dose modification. Emerging evidence suggests that temporary cessation of cBTKi therapy may trigger rapid disease reactivation, often referred to as "disease flare," characterized by worsening constitutional symptoms, enlarging lymphadenopathy, and laboratory evidence of increased disease activity.[6] A particularly challenging manifestation of this phenomenon is pseudo-Richter transformation (pseudo-RT), an uncommon but clinically important syndrome characterized by a transient proliferation of large, atypical B cells that closely mimics Richter transformation (RT) both clinically and histopathologically.[8] Most reported cases occur in patients with previously stable CLL/SLL, who develop symptoms within 1–2 weeks of cBTKi interruption; however, presentations as early as 48 hours after treatment cessation have been described. Clinical manifestations commonly include rapidly enlarging lymphadenopathy, constitutional ("B") symptoms, lymphocytosis, and elevated serum lactate dehydrogenase (LDH) levels;[9] some patients do not show any constitutional symptoms, others exhibit painful lymphadenopathy, akin to inflammatory/infectious diseases. Unlike true RT, however, pseudo-RT follows a reversible course and typically resolves after reinitiation of cBTKi therapy, without the need for chemotherapy. Despite increasing recognition of pseudo-RT, its incidence, pathobiology, and clinical characteristics remain poorly defined.

Case Presentation. We introduce a 75-year-old man with CLL carrying unmutated IGHV 1-69 and a NOTCH1 mutation, without TP53 aberrations or del(17p), who was initially treated in first line with the ibrutinib-venetoclax combination, achieving a complete remission. Approximately 15 months after completing treatment, he experienced disease progression characterized by recurrent lymphocytosis, lymphadenopathy, and splenomegaly. Molecular reassessment confirmed absence of TP53 abnormalities and did not detect resistance mutations involving BTK or PLCG2. He was started on zanubrutinib in December 2024. The patient achieved a deep clinical and hematologic response, with normalization of blood counts and marked reduction of disease burden. In April 2026, zanubrutinib was temporarily discontinued because of grade 3 hepatotoxicity, with alanine aminotransferase (ALT) over 5 times above the upper normal value and mild hyperbilirubinemia. At the same time, a mesenteric lesion adjacent to a jejunal loop was identified on surveillance imaging and was considered suspicious for a gastrointestinal stromal tumor (GIST). A ^18F-FDG PET/CT scan was performed 9 days after zanubrutinib suspension, as part of the diagnostic work-

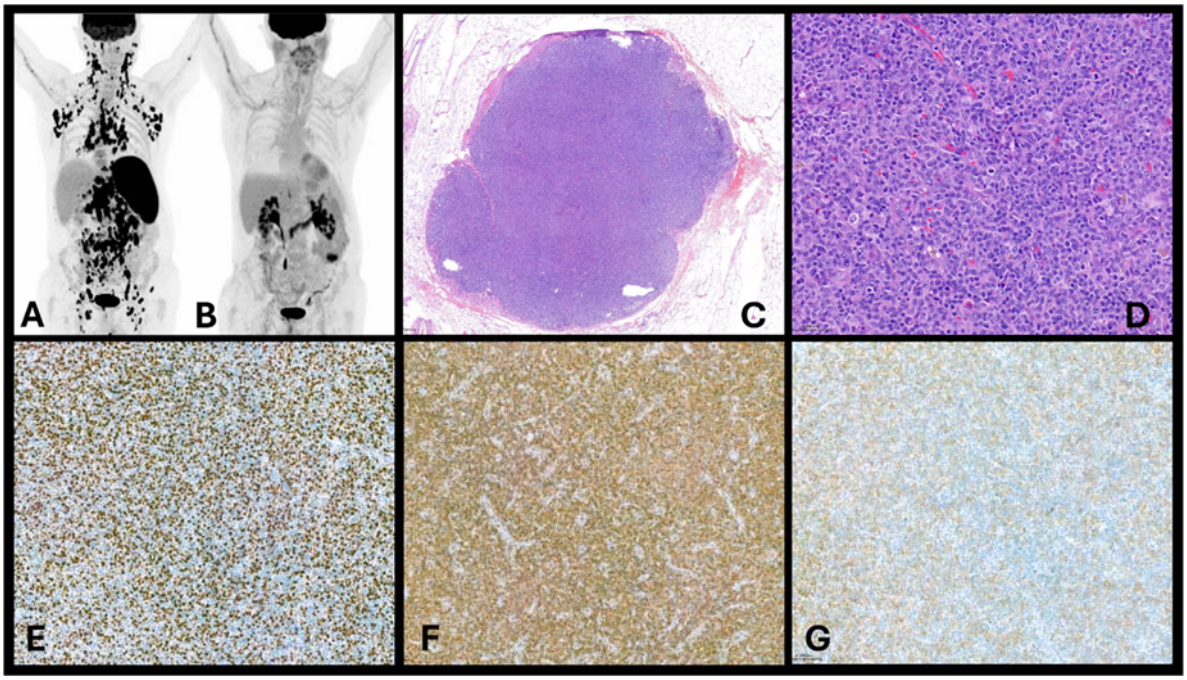

Figure 1. Panel A-B: comparison between FDG PET/CT on April 2026, at zanubrutinib discontinuation (**A**) and four weeks after restarting therapy (**B**). **Panel C-D**: excisional inguinal lymph node biopsy, stained with hematoxylin and eosin, original magnification 2.9X (**C**) and 28.2X (**D**). **Panel E**: Immunohistochemical staining for Ki-67, 11.8X. **Panel F**: Immunohistochemical staining for CD5, 9.4X. **Panel G**: Immunohistochemical staining for CD23, 12.1X.

up of the suspected GIST; it demonstrated widespread, intensely hypermetabolic lymphadenopathy involving cervical, supraclavicular, axillary, mediastinal, abdominal, pelvic, and inguinal nodal stations (**Figure 1, panel A)**. The highest metabolic activity was observed in the right internal iliac lymph node (SUVmax 48.1), left obturator lymph node (SUVmax 46.6), bilateral cervical level IIa lymph nodes (SUVmax 41.2 and 40.2), and the interportocaval region (SUVmax 41.1). Additional highly avid mediastinal nodes showed SUVmax values up to 40.0.[10] The scan also revealed diffuse splenic involvement with splenomegaly (18 cm, SUVmax 21.6). Blood cell count showed a WBC count of 25 x 10^3/mm3, with 41% atypical, medium/large-sized lymphocytes with occasional nucleoli. No cytopenia was reported. Serum LDH was moderately elevated (twice the upper normal value). Serum calcium levels were within the normal range. The patient had experienced no systemic symptoms or signs of clinical deterioration. An excisional inguinal lymph node biopsy was performed, which showed diffuse proliferation of large B cells with a high proliferative index (Ki-67 approximately 80%), consistent with RT (**Figure 1, panels C-E**). The following immunophenotype was demonstrated: CD3-, CD20+, CD79a+, CD5+, CD23+/-, bcl2+, MUM1+/-, CD10-, bcl6+/-, CyclinD1-, CD30+/-, CD38-, PD1+/-, ALK-, p53+ (5%), c-myc+ (15%) (**Figure 1, panels F-G**). Molecular analysis of the lymph node biopsy using Multiplex Ligation-dependent Probe Amplification (MLPA) to assess common CLL mutations and copy number alterations did not identify any additional genetic lesions beyond the NOTCH1 mutation. NGS sequencing of the variable region of the IGHV through PCR confirmed that the large-cell proliferation was clonally related to the underlying CLL clone. Because of the clinical suspicion of pseudo-RT, 18 days after discontinuation, zanubrutinib was reintroduced at a reduced dose of 80 mg twice daily, due to a grade 2 transaminase elevation still being present. It resulted in a striking clinical and metabolic response: a PET/CT performed four weeks later demonstrated near-complete resolution of the previously extensive hypermetabolic lymphadenopathy above and below the diaphragm, disappearance of extranodal lesions, and marked reduction of splenomegaly, consistent with a complete metabolic response (Deauville score 2) (**Figure 1, panel B**). In June, the patient underwent mid-distal jejunal resection to remove the suspected GIST. Histopathology confirmed a spindle-cell jejunal GIST (CD117+, DOG1+, S100-), with a mitotic rate of 2 per 5 mm^2 and small B-cell lymphocytic aggregates (CD20+, CD5+, CD23+). Both proximal and distal resection margins were clear of disease. At the time of writing, at 2-month follow-up, the patient is in full nodal/organ response, with complete resolution of hypertransminasemia and an absolute lymphocyte count of 8,000/µL.

Discussion. Disease flares after cBTKi discontinuation have been described in patients with CLL as well as in other B-cell malignancies, including Waldenström macroglobulinemia, and have been reported to resolve upon resumption of cBTKi therapy.[6,11] These observations underscore the dependence of disease

control on continuous BTK pathway inhibition. The term "pseudo-RT" was coined in 2020, when Barnea Slonim et al.[8] first reported 5 cases of biopsy-proven RT developing immediately after ibrutinib discontinuation; notably, 4/5 pts had trisomy 12, and the remaining one had del17p; the patients retained a CLL-like immunophenotype, with preserved CD5 and CD23 expression; they achieved response after restarting ibrutinib. Hampel et al.[12] reported 3 cases of pseudo-RT after ibrutinib interruption, in patients undergoing lymph node examination for second malignancies; they all expressed unmutated IGHV and were positive for TP53 mutation; they were successfully restarted on ibrutinib. In 2024, the Mayo Clinic group first reported a case ofpseudo-RT after acalabrutinib discontinuation.[13] A recent systematic review of 2026 by the University of Murcia[9] reported 15 pts with pseudo-RT after ibrutinib or acalabrutinib discontinuation: most patients showed a high proliferation index (Ki-67 50-90%), non-germinal center phenotype, retained CD5/CD23 expression, high risk characteristics (unmutated IGHV in 100% cases, TP53 mutation in 4/6 and NOTCH1 in 1/6 analyzed pts). To our knowledge, this is the first reported case of pseudo-RT following zanubrutinib discontinuation. Notably, several molecular features described in patients with pseudo-RT, such as NOTCH1 alterations and TP53 abnormalities, have also been associated with an increased risk of RT.[14-17] Although the limited number of reported cases precludes definitive conclusions, these observations raise the possibility that pseudo-RT may preferentially occur in biologically high-risk CLL subsets. Our case further expands the biological spectrum of pseudo-RT by documenting its occurrence in a pt with NOTCH1-mutated, TP53-wild-type CLL. At the time of biopsy, the histopathological features fulfilled diagnostic criteria for true RT. However, several clinical nuances, such as the strict temporal association with zanubrutinib withdrawal and the relative lack of systemic symptoms, raised clinical suspicion of a disease flare. A rapid, complete metabolic response was observed, despite the aggressive morphological features and the identical clonal origin, a feature historically associated with treatment resistance and dismal outcomes in the setting of true RT.[18] It must be acknowledged that the distinction between true RT and pseudo-RT in this setting relies retrospectively on clinical reversibility as the principal diagnostic criterion. The striking response observed merely four weeks after zanubrutinib reintroduction strongly supported the diagnosis of pseudo-RT *ex juvantibus*.

Conclusions. The rapid onset of clinically, radiologically, and histologically aggressive disease following zanubrutinib discontinuation, together with its prompt and complete metabolic remission after cBTKi reintroduction, supports the existence of a reversible pseudo-RT phenomenon that can closely mimic true RT. Clinicians should consider it as a key differential diagnosis whenever a patient presents with a Richter-like flare shortly after the interruption or discontinuation of a BTKi[19]. Awareness of this entity is crucial to avoid escalation to intensive chemotherapy and to consider prompt cBTKi resumption whenever clinically feasible. Further studies are needed to identify objective markers to distinguish pseudo-RT from true RT. Additional long-term follow-up of reported cases is warranted to determine whether pseudo-RT might represent an early stage in the evolution toward overt RT and, finally, whether pts experiencing this syndrome are at increased risk of subsequent CLL/SLL progression.

Data sharing. The datasets analyzed during the current study are not publicly available due to patient confidentiality considerations but are available from the corresponding author on reasonable request and subject to applicable ethical and institutional requirements.

Luca Laurenti[1,2], Tommaso Quaranta[2], Annamaria Tomasso[1], Luca Stirparo[1], Pier Luigi Abbate[2], Arianna Bakacs[3], Natalia Cappoli[3], Arianna Di Napoli[4], Dimitar Efremov[5], Flaminia Bellisario[6], Valter Gattei[7], Carmelo Caldarella[8], Maria Lucia Calcagni[8], Francesco Autore[1] and Idanna Innocenti[1].

[1] UOSD Leucemia Linfatica Cronica, Dipartimento di scienze di laboratorio ed ematologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy.
[2] Università Cattolica del Sacro Cuore, Istituto di Ematologia, Roma, Italy.
[3] Università Cattolica del Sacro Cuore, Fondazione Policlinico Gemelli Roma, Istituto di Patologia, Roma, Italy.
[4] Pathology Unit, Department of Clinical and Molecular Medicine, Sant'Andrea University Hospital, Sapienza University of Rome, Roma, Italy.
[5] Department of Medical Sciences, Macedonian Academy of Sciences and Arts, Skopje, North Macedonia.
[6] Fondazione Policlinico Universitario A. Gemelli IRCCS, UOSD Malattie Linfoproliferative Extramidollari, Dipartimento di scienze di laboratorio ed ematologiche, Roma, Italy.
[7] Clinical and Experimental Onco-Hematology Unit, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy.
[8] Unit of Nuclear Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, 00168 Rome, Italy.

Competing interests: The authors declare no competing interest.

Correspondence to: Tommaso Quaranta. Università Cattolica del Sacro Cuore, Istituto di Ematologia, Roma, Italy. E-mail: tommasoquarantamd@gmail.com

References:

1. Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: First-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Blood Advances. 2022;6(11):3440. https://doi.org/10.1182/bloodadvances.2021006434 PMid:35377947 PMCid:PMC9198904
2. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukemia (ELEVATE-TN): A randomized, controlled, phase 3 trial. The Lancet. 2021;395(10232):1278. https://doi.org/10.1016/S0140-6736(20)30262-2 PMid:32305093 PMCid:PMC8151619
3. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): A randomised, controlled, phase 3 trial. The Lancet Oncology. 2023;23(8):1031. https://doi.org/10.1016/S1470-2045(22)00293-5 PMid:35810754
4. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2023;388(4):319. https://doi.org/10.1056/NEJMoa2211582 PMid:36511784
5. Tam C, Thompson PA. BTK inhibitors in CLL: Second-generation drugs and beyond. Blood Advances. 2024;8(9):2300. https://doi.org/10.1182/bloodadvances.2023012221 PMid:38478390 PMCid:PMC11117011
6. Hampel PJ, Call TG, Rabe KG, et al. Disease flare during temporary interruption of ibrutinib therapy in patients with chronic lymphocytic leukemia. The Oncologist. 2020;25(11):974. https://doi.org/10.1634/theoncologist.2020-0388 PMid:32886416 PMCid:PMC7648348
7. Shatzel JJ, Olson SR, Tao DL, Mccarty OJT, Danilov AV, Deloughery TG. Ibrutinib-associated bleeding: Pathogenesis, management and risk reduction strategies. Journal of Thrombosis and Haemostasis. 2018;15(5):835. https://doi.org/10.1111/jth.13651 PMid:28182323 PMCid:PMC6152914
8. Barnea Slonim L, Ma S, Behdad A, Chen Q. Pseudo-richter transformation of chronic lymphocytic leukaemia/small lymphocytic lymphoma following ibrutinib interruption: A diagnostic pitfall. Br J Haematol. 2020;191(1):e22-e25. https://doi.org/10.1111/bjh.16948 PMid:32677079
9. Marco-Ayala J, García Malo MD, Ortuño FJ, Lozano ML. Pseudo-richter transformation following BTKi interruption in CLL: A systematic review of clinical, biological, and pathologic features. Clinical Lymphoma Myeloma and Leukemia. 2026;26(5):e596. https://doi.org/10.1016/j.clml.2026.01.010 PMid:41720666
10. Wang Y, Bold MS, Shi M, et al. The role of 18F-FDG-PET in detecting richter's transformation of chronic lymphocytic leukemia in patients receiving therapy with a B-cell receptor inhibitor. Haematologica. 2020;105(11):2675-2678. https://doi.org/10.3324/haematol.2019.240564 PMid:33131260 PMCid:PMC7604634
11. Castillo JJ, Gustine JN, Meid K, Dubeau T, Severns P, Treon SP. Ibrutinib withdrawal symptoms in patients with waldenstrom macroglobulinemia. Haematologica. 2018;103(7):e307-e310. https://doi.org/10.3324/haematol.2017.186908 PMid:29472352 PMCid:PMC6029546
12. Hampel PJ, Cherng HJ, Call TG, et al. Incidental richter transformation in chronic lymphocytic leukemia patients during temporary interruption of ibrutinib. Blood Advances. 2020;4(18):4508. https://doi.org/10.1182/bloodadvances.2020002454 PMid:32946567 PMCid:PMC7509865
13. Shi M, Yuan J. Pseudo-richter transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma after temporary acalabrutinib interruption. Mayo Clinic Proceedings. 2024;99(6):867. https://doi.org/10.1016/j.mayocp.2024.01.015 PMid:38691072
14. Rossi D, Gaidano G. Richter syndrome: Molecular insights and clinical perspectives. Hematol Oncol. 2009;27(1):1-10. https://doi.org/10.1002/hon.880 PMid:19206112
15. Rossi D, Cerri M, Capello D, et al. Biological and clinical risk factors of chronic lymphocytic leukemia transformation to Richter syndrome. Br J Haematol. 2008;142(2):202-215. https://doi.org/10.1111/j.1365-2141.2008.07166.x PMid:18492108
16. Tsimberidou A, Keating MJ. Richter syndrome: Biology, incidence, and therapeutic strategies. Cancer. 2005;103(2):216-228. https://doi.org/10.1002/cncr.20773 PMid:15578683
17. Rossi D, Rasi S, Fabbri G, et al. Mutations of NOTCH1 are an independent predictor of survival in chronic lymphocytic leukemia. Blood. 2012;119(2):521-529. https://doi.org/10.1182/blood-2011-09-379966 PMid:22077063 PMCid:PMC3257017
18. Barrett A, Harris C, Eyre TA. Clonal relatedness as a prognostic marker in richter transformation of chronic lymphocytic leukemia: A systematic review. Blood Adv. 2025;9(11):2773-2780. https://doi.org/10.1182/bloodadvances.2024015594 PMid:40127387 PMCid:PMC12166378
19. Eichhorst B, Ghia P, Bosch F, et al. EHA guidelines on management of chronic lymphocytic leukemia and richter transformation. Hemasphere. 2026;10(6):e70403. https://doi.org/10.1002/hem3.70403 PMid:42293463 PMCid:PMC13254007