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Fatal Outcome in Chronic Lymphocytic Leukemia with Extreme Leukocytosis: Nemtabrutinib-İnduced Rash, Acute Myocardial İnfarction, and Unsuccessful Leukapheresis

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ABSTRACT

Background: Chronic lymphocytic leukemia [CLL] is usually indolent, but patients with extreme leukocytosis and delayed therapy may develop catastrophic complications. Novel non-covalent Bruton tyrosine kinase [BTK] inhibitors, such as nemtabrutinib, show promise, but their real-world toxicity profile is not fully defined.

Case Presentation: We report a 62-year-old female diagnosed with CLL in May 2025 [TP53 wild-type, normal 17p]. Due to social factors, she delayed therapy until July 2025, presenting with WBC 449 × 10^9/L, anemia, thrombocytopenia, hepatosplenomegaly, and disseminated lymphadenopathy. Nemtabrutinib [65 mg/day] was started on August 12, 2025, within a clinical trial. On day 12, she developed a diffuse erythematous rash, which resolved rapidly with systemic corticosteroids [prednisolone 60 mg/day, tapered weekly]. Therapy was withheld. On day 23, she presented with acute myocardial infarction [99% LAD stenosis], and concurrent WBC had increased to 894 × 10^9/L. Leukapheresis was attempted for hyperviscosity risk but could not be completed due to refractory hypotension in the context of recent angioplasty. Despite intensive care, the patient died 21 hours later from cardiac arrest.

Conclusion: This case highlights the lethal interaction of extreme leukocytosis, cardiovascular complications, and novel BTK inhibitor toxicity. To our knowledge, this is the first report of nemtabrutinib-associated rash followed by fatal cardiovascular deterioration in CLL. Early intervention, vigilant toxicity monitoring, and individualized supportive care are crucial in high-risk patients.

Introduction

Chronic lymphocytic leukemia [CLL] is the most common adult leukemia in Western countries, typically following an indolent clinical course [1]. While many patients may be observed without treatment for years, symptomatic disease or those with high tumor burden require therapy. Bruton tyrosine kinase [BTK] inhibitors have transformed CLL management by improving progression-free and overall survival across different risk groups [2, 3]. However, cardiovascular and dermatologic toxicities, particularly with covalent BTK inhibitors such as ibrutinib, are well documented [4].

Nemtabrutinib, a novel non-covalent BTK inhibitor, has shown promising efficacy in early clinical trials of relapsed/refractory CLL [5]. Nevertheless, real-world data on toxicity remain scarce, and severe complications are rarely described. Hyperleukocytosis in CLL is also an uncommon but potentially fatal event, often complicating the clinical course when therapy is delayed [6]. Herein, we present a fatal case of untreated CLL with extreme leukocytosis, complicated by nemtabrutinib-induced rash, acute myocardial infarction, and unsuccessful leukapheresis.

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Case Presentation:

A 62-year-old female was diagnosed with chronic lymphocytic leukemia [CLL] on May 26, 2025. Cytogenetic analysis revealed TP53 negativity and normal 17p status; IGHV mutational status was not available.

Due to social reasons, the patient did not seek hematologic treatment until July 2025. At presentation, laboratory results showed:

- WBC: 449 × 10^9/L [lymphocytes 429 × 10^9/L, monocytes 10.5 × 10^9/L]
- Hemoglobin: 9 g/dL
- Platelets: 134 × 10^9/L

Radiologic evaluation with contrast-enhanced CT demonstrated disseminated lymphadenopathy involving cervical, mediastinal, abdominal, and inguinal regions, with the largest nodes measuring up to 30 mm. In addition, hepatomegaly [192 mm] and splenomegaly [178 mm] were noted, along with a small hypodense hepatic lesion.

The patient was enrolled in a clinical trial and initiated nemtabrutinib 65 mg/day orally on August 12, 2025.

On day 12 of therapy, she developed a diffuse erythematous rash involving the trunk and extremities. Dermatology consultation suggested drug eruption. Nemtabrutinib was withheld, and the patient was treated

with prednisolone 60 mg/day, tapered weekly by 4 mg. Rash resolved within 24 hours and did not recur.

On day 22, she presented to our clinic with worsening fatigue. On day 23, she developed acute left arm pain. Cardiology evaluation revealed 99% LAD occlusion, and urgent percutaneous coronary intervention was performed. At that time, hematologic values were as follows:

- WBC: 894 × 10^9/L [neutrophils 35 × 10^9/L, lymphocytes 850 × 10^9/L]
- Hemoglobin: 9 g/dL
- Platelets: 236 × 10^9/L

Table 1: Laboratory Trends During Clinical Course.

Date / Day	WBC [×10^9/L]	Hb [g/dL]	Platelets [×10^9/L]	Key Events
26 May 2025 [Diagnosis]	449	9	134	CLL diagnosis
12 Aug 2025 [Day 1]	480	9	130	Nemtabrutinib initiation
24 Aug 2025 [Day 12]	512	9	140	Rash, steroids started
03 Sep 2025 [Day 23]	894	9	236	Acute MI, LAD 99% stenosis, leukapheresis

Given the risk of hyperviscosity associated with extreme leukocytosis, leukapheresis was initiated on the same day, supported by plasma infusion. However, during the session, the patient—already post-coronary angioplasty—developed refractory hypotension. The last hour of leukapheresis could not be completed. Despite intensive care support, she became progressively hypotensive, required mechanical ventilation, and died 21 hours after ICU admission due to cardiac arrest.

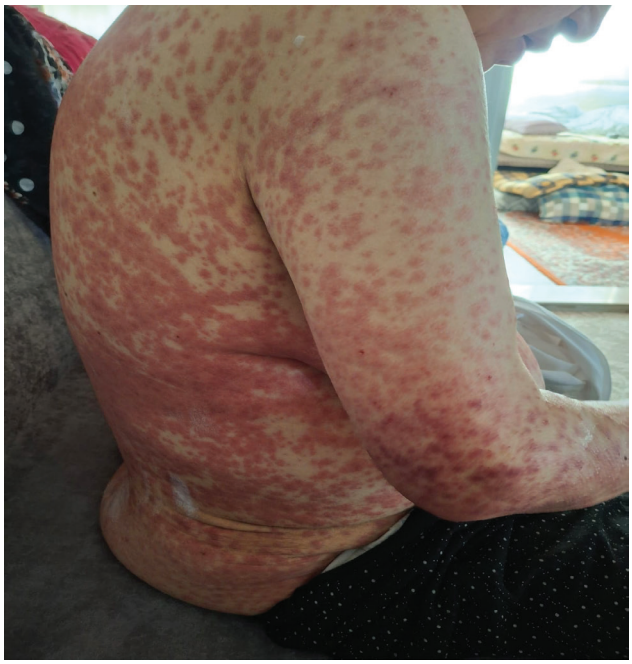

Figure 1: Diffuse erythematous maculopapular rash on the trunk and upper limbs [day 12 of nemtabrutinib therapy].

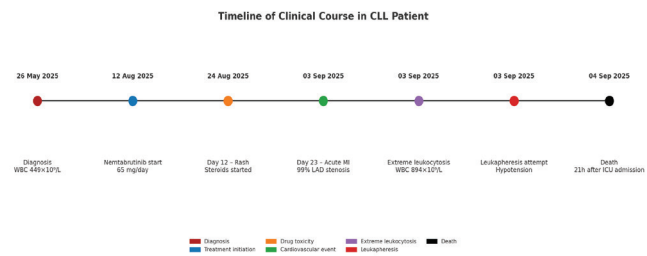

Figure 2: Timeline of clinical events [diagnosis → nemtabrutinib start → rash → myocardial infarction → leukapheresis → death].

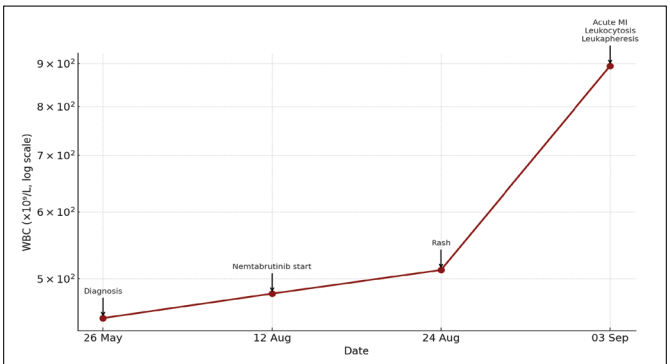

Figure 3: WBC trend during clinical course.

Discussion:

This case highlights the potentially fatal interaction between extreme leukocytosis, cardiovascular complications, and novel BTK inhibitor toxicity in CLL. While CLL typically follows an indolent course, untreated high-burden disease may predispose patients to rare but catastrophic events [7].

1. Delayed therapy and disease burden

Prolonged absence of therapy in symptomatic or high-risk CLL may result in excessive leukocytosis and hyperviscosity-like syndromes, conditions more commonly described in acute leukemias. Although rare in CLL, WBC counts approaching 900 × 10^9/L, as in this case, significantly increase the risk of end-organ ischemia [8]. Reports suggest that hyperleukocytosis in CLL is exceptional, but when present, it is associated with increased morbidity and mortality.

2. BTK inhibitor-associated toxicities

BTK inhibitors have dramatically changed CLL management. Ibrutinib, the first-in-class covalent inhibitor, is associated with cardiovascular complications, including atrial fibrillation, hypertension, and bleeding. Acalabrutinib and zanubrutinib demonstrate lower cardiovascular risk, but dermatologic adverse events are still reported [9, 10].

Nemtabrutinib, a non-covalent BTK inhibitor, remains under clinical investigation. The Phase 1/2 study demonstrated overall manageable toxicity, though dermatologic reactions and rare severe events were observed [5]. Our case represents, to our knowledge, the first report of nemtabrutinib-associated rash followed by fatal cardiovascular deterioration.

3. Cardiovascular complications in CLL under BTK therapy

Cardiovascular disease is an important comorbidity in CLL, particularly in older patients. Novel BTK inhibitors are not yet widely linked with acute myocardial infarction, but the 99% LAD stenosis in this case suggests an interplay between pre-existing atherosclerosis, extreme leukocytosis, and possible drug-related endothelial effects. Similar cardiovascular toxicities have been described with ibrutinib, where endothelial dysfunction and platelet inhibition contribute to vascular events [4, 11].

4. Challenges of leukapheresis in unstable patients

Leukapheresis is recommended for hyperleukocytosis-related hyperviscosity, mainly in AML. In CLL, evidence is limited, and benefit remains uncertain [7, 12]. In our patient, leukapheresis was indicated due to extreme leukocytosis in the setting of acute myocardial infarction, where hyperviscosity risk was considered additive. However, the procedure was complicated by refractory hypotension following recent coronary intervention. This underscores the difficulty of performing leukapheresis in hemodynamically unstable patients.

5. Literature gap and clinical implications

The novelty of this case lies in the fatal cascade triggered by nemtabrutinib toxicity, extreme leukocytosis, and cardiovascular instability. Unlike AML and ALL, where hyperleukocytosis management is well-defined, there is little guidance for CLL. Furthermore, severe complications with nemtabrutinib remain scarcely reported, highlighting the need for vigilance and close monitoring in clinical practice and trials.

Key Message

To our knowledge, this is the first documented case of fatal outcome in CLL with extreme leukocytosis, complicated by nemtabrutinib-induced rash, acute myocardial infarction, and unsuccessful leukapheresis. This report emphasizes the importance of:

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- Early initiation of therapy in high-burden CLL,
- Close toxicity surveillance during novel BTK inhibitor treatment,
- Careful risk–benefit assessment before leukapheresis in unstable cardiovascular settings.

Conclusion

This case demonstrates the catastrophic potential of extreme leukocytosis in untreated CLL and the challenges encountered during therapy with novel BTK inhibitors. Nemtabrutinib-induced rash, acute myocardial infarction, and unsuccessful leukapheresis combined to a fatal course.

Key Clinical Message: Early intervention, vigilant monitoring for toxicities, and individualized supportive strategies are essential when managing high-risk CLL patients treated with novel agents.

Ethics and Consent: Written informed consent was obtained from the patient's family for publication of this case report and accompanying clinical data.

Conflict of Interest: The authors declare no competing interests.

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Author Contributions: Fikriye Esra Gürses Ulubay [FEGU]: Collected clinical data, conducted the literature review, and drafted the manuscript.

Engin Kelkitli [EK]: Contributed to case management, critically reviewed the manuscript, and supervised the preparation.

Mehmet Turgut [MT]: Provided academic supervision, contributed to manuscript revision, and approved the final version.

References

1. Hallek M. Chronic Lymphocytic Leukemia: 2025 Update on the Epidemiology, Pathogenesis, Diagnosis, and Therapy. Am J Hematol. 2025;100[3]:450-80.
2. Burger JA. Bruton Tyrosine Kinase Inhibitors: Present and Future. Cancer J. 2019;25[6]:386-93.
3. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. Mol Cancer. 2018;17[1]:57.
4. Quartermaine C, Ghazi SM, Yasin A, Awan FT, Fradley M, Wiczer T, et al. Cardiovascular Toxicities of BTK Inhibitors in Chronic Lymphocytic Leukemia: JACC: CardioOncology State-of-the-Art Review. JACC Cardio Oncol. 2023;5[5]:570-90.
5. Woyach JA, Stephens DM, Flinn IW, Bhat SA, Savage RE, Chai F, et al. First-in-Human Study of the Reversible BTK Inhibitor Nemtabrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia and B-Cell Non-Hodgkin Lymphoma. Cancer Discov. 2024;14[1]:66-75.
6. Ganzel C, Becker J, Mintz PD, Lazarus HM, Rowe JM. Hyperleukocytosis, leukostasis and leukapheresis: practice management. Blood Rev. 2012;26[3]:117-22.
7. Singh N, Singh Lubana S, Dabrowski L, Sidhu G. Leukostasis in Chronic Lymphocytic Leukemia. Am J Case Rep. 2020;21:e924798.
8. Lichtman MA, Rowe JM. Hyperleukocytic leukemias: rheological, clinical, and therapeutic considerations. Blood. 1982;60[2]:279-83.
9. Tam C, Thompson PA. BTK inhibitors in CLL: second-generation drugs and beyond. Blood Advances. 2024;8[9]:2300-9.
10. Vallabhaneni S, Adusumalli S, Wu J, Groeneveld PW, Gerson J, O'Quinn RP. Cardiotoxicity from bruton tyrosine kinase inhibitors [BTKi]-an analysis of an administrative health claims database. Cardiooncology. 2024;10[1]:33.
11. Boriani G, Menna P, Morgagni R, Minotti G, Vitolo M. Ibrutinib and Bruton's Tyrosine Kinase Inhibitors in Chronic Lymphocytic Leukemia: Focus on Atrial Fibrillation and Ventricular Tachyarrhythmias/Sudden Cardiac Death. Chemotherapy. 2023;68[2]:61-72.
12. Cukierman T, Gatt ME, Libster D, Goldschmidt N, Matzner Y. Chronic lymphocytic leukemia presenting with extreme hyperleukocytosis and thrombosis of the common femoral vein. Leuk Lymphoma. 2002;43[9]:1865-8.