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# Management of Asymptomatic Hyperleukocytosis Induced by Ibrutinib in a Patient with Chronic Lymphocytic Leukemia: A Case Study and Structured Follow-Up

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Case Report

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# Abstract

### Background

The use of irreversible bruton tyrosine kinase inhibitors (iBTK) represented a change in the history of cancer management, thanks to higher response and maintenance rates. However, these new medications bring with them adverse effects, even putting patients' lives at risk.

**Case presentation**: This report describes a patient with chronic lymphocytic leukemia (CLL) treated with ibrutinib who developed persistent, asymptomatic hyperleukocytosis with a maximum leukocyte count of 593.66×10/L, over a two-month period. The leukocyte count gradually normalized without intervention.

### Conclusions

The absence of established guidelines for managing such cases poses diagnostic and monitoring challenges. This case underscores the utility of expectant management and emphasizes the need for stricter leukocyte monitoring to better characterize the duration and evolution of this phenomenon. Given the limited data on hyperleukocytosis in iBTK-treated patients, further case reports are essential, not only in CLL but also in other malignancies treated with iBTKs.


# Introduction

Irreversible Bruton tyrosine kinase inhibitors (BTKi), such as ibrutinib, acalabrutinib, zanubrutinib, and others, have become increasingly central to the treatment of various hematologic malignancies, including lymphomas and leukemias [1–4] These inhibitors have also shown promise in treating solid tumors like breast, ovarian, colorectal, and prostate cancers. Among leukemias, chronic lymphocytic leukemia (CLL) is particularly prevalent in Western populations, accounting for approximately 11% of all hematologic malignancies. CLL exhibits a highly variable clinical course, ranging from indolent to aggressive forms, often requiring novel therapeutic approaches [5].

Ibrutinib, the first BTKi approved by the US Food and Drug Administration (FDA) in 2013 and by the European Medicines Agency (EMA), has revolutionized CLL treatment. Clinical trials have demonstrated significant improvements in overall survival and progression-free survival for CLL patients treated with ibrutinib [6]. As a first generation BTKi, ibrutinib differs from newer agents in this class, particularly in its adverse effect profile, which has become more apparent with widespread use [7].

Ibrutinib's side effects include cardiovascular complications such as atrial fibrillation, ventricular arrhythmias, conduction disorders, heart failure, hypertension, and bleeding

[8]. Other systemic adverse effects encompass arthralgia, dermatologic reactions (e.g., rashes, petechiae, hematomas), and increased susceptibility to infections, including *Pneumocystis jiroveci* pneumonia, fungal infections, and reactivation of hepatitis B. Gastrointestinal issues such as diarrhea and pneumonitis have also been reported [9–11].

A less frequently discussed but clinically significant phenomenon associated with BTKi therapy is hyperleukocytosis. This hematologic effect occurs when ibrutinib promotes the rapid migration of lymphocytes from lymphoid tissues into the bloodstream, leading to a transient increase in white blood cell counts. While often asymptomatic, extreme hyperleukocytosis can pose serious risks, necessitating careful monitoring and management [12].

We present a case of a patient with CLL who developed marked hyperleukocytosis following the initiation of ibrutinib with asymptomatic course.

## Case presentation

A 65-year-old male with a 10-year history of well-controlled hypertension (managed with Valsartan 80 mg orally every 12 hours) was diagnosed with CLL in 2019. His CLL was classified as Binet stage A and Rai stage 1, with normal TP53 and unmutated IgHV. After four years of stable disease, the patient presented with new constitutional symptoms over three months, including a 5% unintentional weight loss, night sweats, and progressive lymphadenopathy, primarily in the axillary region, along with an increase in total leukocyte count (WBC).

Given the clinical progression and laboratory findings, including a total leukocyte count of 320.30 x 10□/L with lymphocytosis of 297.22 x 10□/L, hemoglobin (Hb) of 8.3 g/dL, and platelets at 100.0 x 10□/L, the patient met the criteria for initiating treatment with a Bruton tyrosine kinase inhibitor (BTKi). Ibrutinib was started at a dose of 420 mg per day (Fig. 1).

# **INSERT FIGURE 1**

**Figure 1.** Timeline of Evolution and Follow-Up of Cell Count in Patients with CLL Before and After Ibrutinib Administration.

Within 24 hours of starting ibrutinib, the patient's leukocyte count increased significantly to 496.07 x 10□/L, with lymphocytes rising to 487.8 x 10□/L. Concurrently, hemoglobin levels decreased to 7.4 g/dL, and platelets dropped to 69.0 x 10□/L. During the first week of treatment, the patient developed purpuric-type lesions in the right popliteal area, characterized by a palpable, stony, non-mobile mass measuring approximately 5x5 cm in the right calf region and another mass measuring 2x1 cm in the lower back (Fig. 2).

# **INSERT FIGURE 2**

**Figure 2.** Patient’s Purpuric Lesions. A) Two erythematous-purpuric macules are visible in the popliteal fossa, with diffuse borders and a smooth surface. The lower macule measures approximately 2x2 cm and coalesces with the upper macule, which measures 1x1 cm in diameter. B) Multiple coalescent purpuric macules with some petechiae on the surface are present in the right calf region, varying in size.

Ultrasound confirmed the presence of oval, heterogeneous focal areas, predominantly echogenic with hypoechoic regions, consistent with hematomas associated with diffuse edema of the subcutaneous cellular tissue in the posteromedial region of the thigh. These were treated with a topical anti-inflammatory agent.

Complete resolution of these manifestations was achieved four weeks after initiating treatment, although hemoglobin levels remained persistently low, without any associated bleeding. A ferrokinetic profile revealed low serum iron levels of 20.2 mg/dL and ferritin of 110 ng/mL. Consequently, the patient was treated with a single dose of intravenous iron carboxymaltose (1000 mg) while continuing the ibrutinib regimen.

The patient's hematological profile was monitored weekly for six weeks, then biweekly, followed by a three-week interval, and finally monthly check-ups. During weeks 2 and 3, a gradual decrease in leukocyte levels was observed, accompanied by a corresponding increase in hemoglobin, reflecting the correction of iron deficiency, as well as an improvement in platelet levels (Fig. 1). A peripheral blood smear performed during week 2 revealed a predominance of mature lymphocytes, Gumprecht shadows, macrocytosis, and anisocytosis, ruling out other causes of leukocytosis.

Despite the progressive decrease in leukocyte and lymphocyte levels, the patient’s leukocyte count peaked at 593.66 x 10□/L, with lymphocytes reaching 582.49 x 10□/L after five weeks of treatment. These elevated levels persisted for two weeks without any associated symptoms or clinical manifestations. From week 7 onward, the leukocyte count began to gradually decrease during subsequent periodic controls (Fig. 1). Notably, the patient remained asymptomatic throughout the entire process, requiring no additional management. The BTKi therapy was never suspended, and as the patient’s cell lines stabilized, he remained clinically stable. Monthly follow-up visits have been planned to continue monitoring his condition.

## Discussion

The introduction of tyrosine kinase inhibitors has revolutionized the management of oncological pathologies that previously had limited treatment options, often confined to observational approaches by physicians. With this advancement, our understanding of the

real-life safety profiles and potential adverse effects of these drugs has expanded, including the phenomenon of hyperleukocytosis. Hyperleukocytosis is defined as a leukocyte count exceeding 100.00 x 10⁹/L in patients diagnosed with hematological neoplasms, identified through blood counts in the absence of clinical symptoms [13]. This condition differs from leukostasis, a clinical diagnosis where hyperleukocytosis is accompanied by symptoms such as headache, blurred vision, confusion, dyspnea, hypoxemia, and tachypnea—symptoms indicative of multiorgan involvement due to leukocyte aggregation [14].

In our patient, we encountered an atypical scenario. Despite exceeding a leukocyte count of 590.0 x 10⁹/L, the patient remained asymptomatic, aside from a self-limiting local hematoma that resolved after one month. This case generated significant interest within the medical team, especially considering the scarcity of literature on similar cases. Previous reports have documented fatal outcomes in patients with leukocytosis of similar magnitude and the same disease, as noted by Ibrahim et al. described an 81-year-old woman with a leukocyte count of 500.8 x 10⁹/L three weeks after initiating ibrutinib, who developed lumbar pain followed by right pleural effusion consistent with chylothorax, ultimately resulting in multisystem organ failure and death shortly after leukapheresis [15].

Similar symptomatic effects have been reported in CLL cases without ibrutinib. For instance, Cukierman et al. described a 73-year-old woman with newly diagnosed CLL who experienced extreme hyperleukocytosis of 2000 x 10⁹/L, leading to thrombosis of the common femoral vein, which resolved following leukapheresis [16].

In our patient, the leukocyte elevation induced by ibrutinib occurred almost immediately, as observed in a correlative analysis of a phase II study conducted in 2014. Significant increases in leukocyte count were noted within four hours of treatment initiation, mirroring the pattern seen in our patient, who showed a substantial increase in leukocytes within 24 hours of starting ibrutinib [13], The study further reported that 46% of patients exhibited significant leukocyte elevations by day two, and 78% by the fourth week. Our patient reached peak leukocyte levels in the fifth week. Interestingly, the greatest increases were typically associated with patients having an IGHV mutation, which our patient did not possess. Nonetheless, our patient's absolute lymphocyte count (ALC) reached 582.49 x 10⁹/L, far surpassing the highest ALC recorded in the study, which was 475.00 x 10⁹/L.

In phase III studies, hyperleukocytosis was reported as a rare event, occurring in only 1% of BTKi users. However, these studies were limited in their ability to provide detailed observations and personalized follow-up, as was done in our case. We implemented a tailored weekly monitoring scheme using blood counts, gradually extending the intervals

to two, three, and four weeks as the patient's condition stabilized, a novel approach that proved successful.

Management of hyperleukocytosis in patients on BTKi therapy depends on whether the patient is symptomatic or asymptomatic. Options range from temporarily suspending ibrutinib and adopting a watchful waiting approach, to using concomitant therapy with rituximab to mitigate lymphocytosis, or in extreme cases, employing leukapheresis. The success rates of these interventions vary and are often based on isolated case reports [16, 17].

In our patient, the high leukocyte counts initially caused concern, but the absence of symptoms justified a conservative management approach. We achieved a successful outcome through vigilant monitoring under a structured weekly scheme, with stabilization of leukocyte levels by 18 weeks, without the need to discontinue ibrutinib. This case expands the therapeutic understanding of ibrutinib, demonstrating its effects with prolonged follow-up and underscoring the importance of individualized patient management. Furthermore, it highlights the significance of documenting such cases in regions like South America, where data on these phenomena are scarce, thus contributing valuable insights to the global medical community.

## Conclusions

This case underscores the critical importance of vigilant follow-up and individualized management for patients with CLL, particularly when dealing with BTKi (ibrutinib)-associated hyperleukocytosis. The structured follow-up strategy employed in this case, characterized by regular blood count monitoring, proved effective in managing this rare but potentially concerning side effect. The findings suggest that with careful observation and a personalized approach, ibrutinib can be safely continued in patients who develop hyperleukocytosis, without compromising treatment efficacy or patient safety.

## Declarations

# Informed consent:

Written informed consent was obtained from the patient for publication of the details of his medical case. The participant has consented to the submission of the case report to the journal.

**Conflicts of Interest:**

The authors declare no conflicts of interest.

# Funding:

This research received no external funding.


# Author Contribution

HANC, ILP, MAO, and RGG contributed to the conceptualization of the study. Methodology was developed by HANC, MAI, and JSIC. Resources were provided by HANC, ILP, MAO, and RGG. Software was managed by HANC, ILP, MAO, and JSST. Validation was carried out by JSIC. Formal analysis was performed by HANC, ILP, ADSM, MAO, RGG, JSST, and JSIC. Visualization was conducted by HANC, MAI, and JSIC. The original draft of the manuscript was written by HANC, ILP, ADSM, MAO, RGG, and JSIC. Review and editing of the manuscript were performed by JSST, MAI, and JSIC. All authors have read and agreed to the published version of the manuscript.


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None.


# Data availability:

Data are available on reasonable request from the authors.

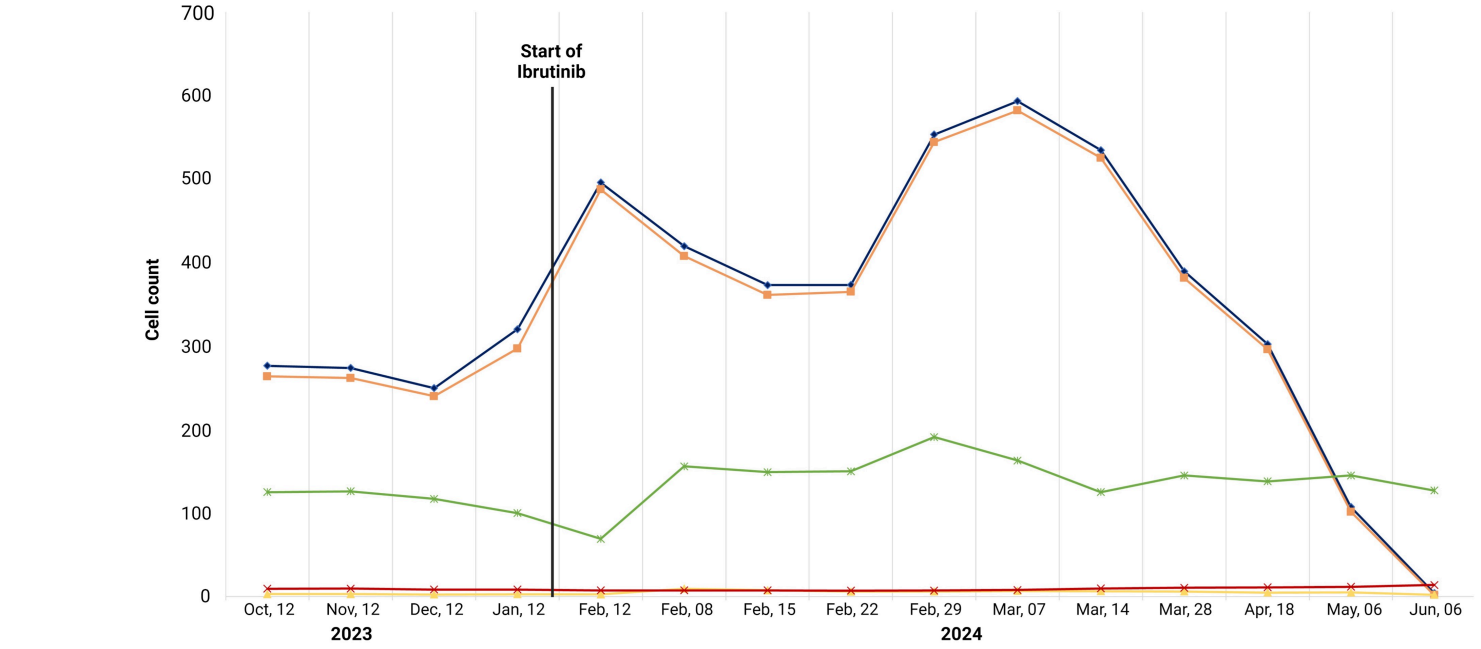
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# Figures




| | Oct, 12 | Nov, 12 | Dec, 12 | Jan, 12 | Feb, 12 | Feb, 08 | Feb, 15 | Feb, 22 | Feb, 29 | Mar, 07 | Mar, 14 | Mar, 28 | Apr, 18 | May, 06 | Jun, 06 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Leukocytes (10^9/L) | 276.5 | 273.8 | 249.7 | 320.3 | 496.1 | 419.8 | 373.2 | 373.4 | 553.6 | 593.6 | 534.9 | 389.8 | 302.5 | 107.2 | 3.98 |
| Lymphocytes (10^9/L) | 263.8 | 261.7 | 239.9 | 297.2 | 487.8 | 408.1 | 361.3 | 365.1 | 544.5 | 582.4 | 525.6 | 381.7 | 296.2 | 101.4 | 1.67 |
| Neutrophils (10^9/L) | 2.92 | 2.93 | 2.38 | 2.71 | 2.64 | 9.41 | 7.59 | 5.81 | 6.04 | 6.68 | 6.35 | 6.05 | 4.7 | 4.8 | 2.05 |
| Hemoglobin (g/dL) | 9.4 | 9.5 | 8.3 | 8.3 | 7.4 | 7.4 | 7.3 | 7.1 | 7.2 | 7.8 | 9.7 | 10.5 | 11 | 11.6 | 13.8 |
| Platelets (10^9/L) | 125 | 126 | 117 | 100 | 69 | 156 | 149 | 150 | 191 | 163 | 125 | 145 | 138 | 145 | 127 |

Figure 1

Timeline of Evolution and Follow-Up of Cell Count in Patients with CLL Before and After Ibrutinib Administration.

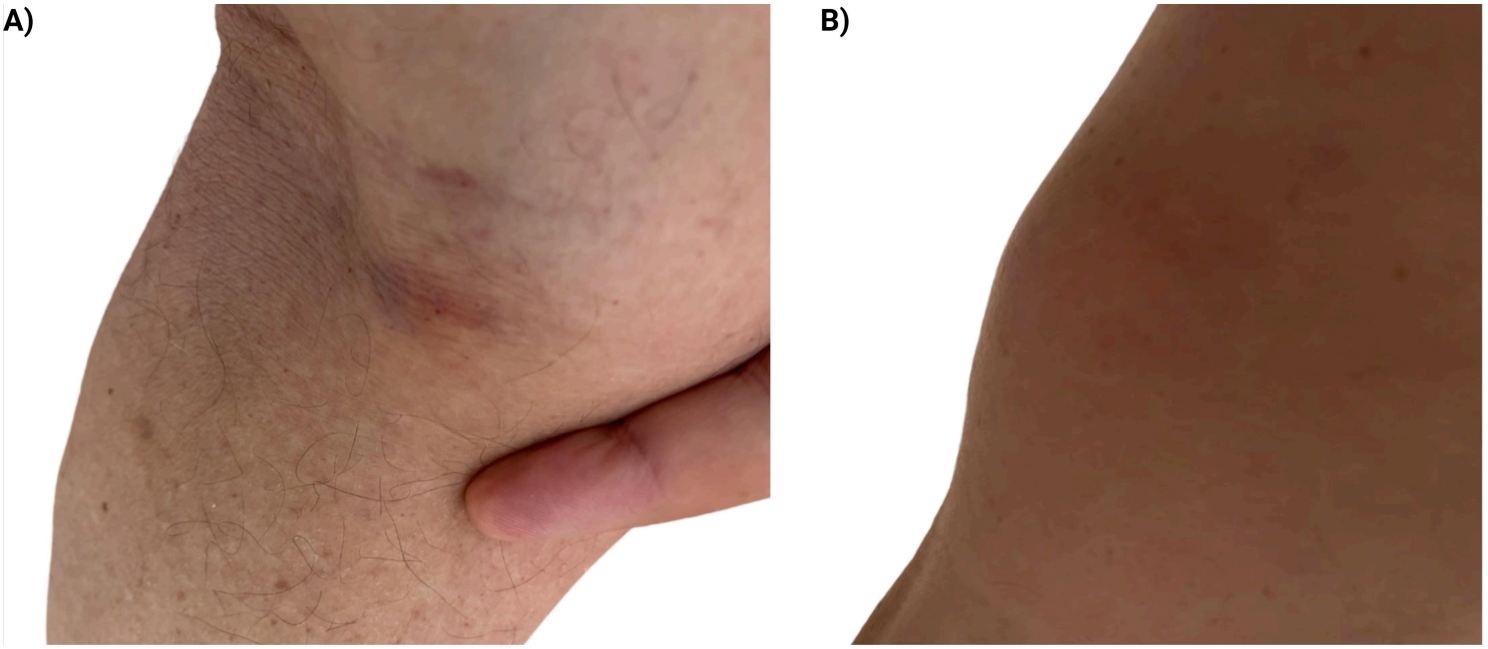



Figure 2

Patient’s Purpuric Lesions. A) Two erythematous-purpuric macules are visible in the popliteal fossa, with diffuse borders and a smooth surface. The lower macule measures approximately 2x2 cm and coalesces with the upper macule, which measures 1x1 cm in diameter. B) Multiple coalescent purpuric macules with some petechiae on the surface are present in the right calf region, varying in size.