Biomedical Research and Therapy 2024, 11(3):6276-6281

Open Access Full Text Article

Case Report

An Uncommon Presentation of Chronic Myeloid Leukemia: Osteolytic Bone Lesion as the Initial Manifestation

Razan Hayati Zulkeflee[1,2], Mohd Nazri Hassan[1,2,*], Zefarina Zulkafli[1,2], Noor Haslina Mohd Noor[1,2], Azlan Husin[2,3], Abu Dzarr Abdullah[2,3], Shafini Mohamed Yusoff[1,2], Marini Ramli[1,2], Rosnah Bahar[1,2], Wan Suriana Wan Abd Rahman[3,4], Norzaliana Zawawi[2,4,5]

ABSTRACT

Background: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that typically occurs in the fifth and sixth decades of life with presentations usually confined to hematopoietic tissues—primarily blood, bone marrow, and spleen. However, primary presentation of CML as extramedullary involvement (osteolytic lesion) is extremely rare, occurring in less than 1% of cases. **Case Presentation**: Here, we present a case of a 25-year-old male with chronic myeloid leukemia (CML), characterized by an atypical presentation of a femur fracture accompanied by an osteolytic lesion. The peripheral blood findings displayed typical features of CML, including leukocytosis with a full spectrum of myeloid maturation stages, basophilia, and occasional blasts. The diagnosis of CML in the blastic phase was confirmed by the presence of the Philadelphia chromosome and the BCR-ABL1 fusion gene (b2a2), as well as features of myeloid sarcoma in the tissue biopsy. **Conclusion**: Given the aggressive nature of granulocytic sarcoma and its impact on prognosis, early recognition and intervention are essential to mitigate complications and improve patient outcomes.

Key words: Chronic myeloid leukaemia, Myeloid sarcoma, Osteolytic lesion

INTRODUCTION

Chronic myeloid leukemia (CML) is a Philadelphia-positive myeloproliferative neoplasm that typically presents at a median age of 50 to 60 years, with the majority presenting in the chronic phase, characterized by blasts less than 5% and the absence of extramedullary involvement[1]. According to Q Lin *et al.*, the incidence of CML varies considerably worldwide, with rates ranging from 0.4 to 1.75 cases per 100,000 people in different regions. A study conducted in East Malaysia pinpointed a particularly high estimated prevalence and incidence of CML in southern Sarawak, standing at 69.2 cases per 1,000,000 population[2,3]. Furthermore, extramedullary manifestations of the disease are noted to be extremely rare in this context.

Its presentation primarily involves hematopoietic tissues, including blood, bone marrow, liver, and spleen. Based on the most recent research conducted by Terjanian et al., extramedullary manifestations of chronic myeloid leukemia are exceptionally uncommon. The primary sites frequently involved include lymph nodes, bones, and skin. Bone lesions are characterized by some as osteoblastic, others as osteolytic, and in rare instances, they may present with both features simultaneously. Extramedullary disease indicates a blast crisis and is associated with a poor prognosis. According to the findings from Terjanian's study, out of the 24 patients analyzed, a staggering 96% progressed and eventually succumbed to the disease[4].

This report underscores an unusual instance of CML in a young adult who suffered a rare femur fracture accompanied by an osteolytic lesion. Such an event has been documented in only a handful of cases before, making it an exceedingly rare occurrence. The objective of this case study is to raise awareness among orthopedic surgeons to consider granulocytic sarcoma as a potential diagnosis for hip pain. Prompt diagnosis and early intervention are essential in instances of this atypical CML presentation because the prognosis is expected to be unfavorable due to the development of complications, as illustrated in the case we have presented.

CASE PRESENTATION

Patient History

A 25-year-old Malay man with no known medical history presented with right hip pain and difficulty walking following a fall one day prior to his presentation. There was no history of bone pain, swelling,

[1]*Department of Haematology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian Kelantan, Malaysia*

[2]*Hospital USM, Universiti Sains Malaysia, 16150 Kubang Kerian Kelantan, Malaysia*

[3]*Department of Internal Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian Kelantan, Malaysia*

[4]*School of Dental Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian Kelantan, Malaysia*

[5]*Department of Pathology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian Kelantan, Malaysia*

Correspondence

Mohd Nazri Hassan, Department of Haematology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian Kelantan, Malaysia

Hospital USM, Universiti Sains Malaysia, 16150 Kubang Kerian Kelantan, Malaysia

Email: nazrihas@usm.my

Cite this article : Zulkeflee R H, Hassan M N, Zulkafli Z, Noor N H M, Husin A, Abdullah A D, Yusoff S M, Ramli M, Bahar R, Rahman W S W A, Zawawi N. **An Uncommon Presentation of Chronic Myeloid Leukemia: Osteolytic Bone Lesion as the Initial Manifestation**. *Biomed. Res. Ther.* 2024; 11(3):6276-6281.

History
- Received: Nov 26, 2023
- Accepted: Mar 14, 2024
- Published Online: Mar 31, 2024

DOI : 10.15419/bmrat.v11i3.873

Table 1: Peripheral blood count, bone marrow aspirate and biopsy, cytogenetic analysis and molecular result

Parameter	Result	Normal reference range
White blood cell count (x10^9/L)	64	4-11
Haemoglobin (g/dL)	12.4	13.5-17.6
Platelet (x10^9/L)	646	150-450
Peripheral blood film report	Hyperleucocytosis with presence of all the stages of myeloid maturation, basophilia, occasional blasts and thrombocytosis with platelet anisocytosis	
Bone marrow aspirate and biopsy	Increased cellularity due to granulocytic proliferation and supported the diagnosis of myeloproliferative neoplasm	
Cytogenetic study	46, XX, t(9;22) (q34;q11)	
Molecular analysis	Major BCR-ABL1 fusion gene (b2a2)	

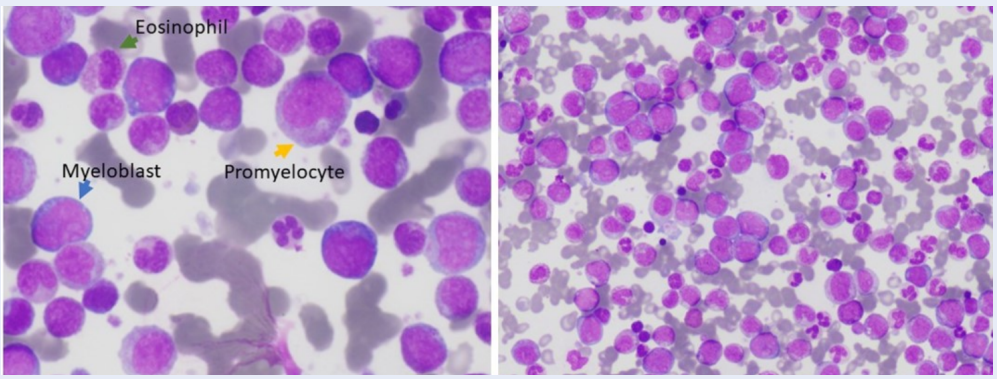

Figure 1: Hyperleucocytosis is observed with a bimodal peak and the presence of all stages of myeloid maturation. There are also occasional blasts, and thrombocytosis with platelet anisocytosis.

or any constitutional symptoms. Physical examination revealed tenderness in the upper region of the right thigh and restricted range of motion in the right hip joint. There were no bruises, swelling, or skin changes, and no remarkable findings in the other systems. There was neither lymphadenopathy nor hepatomegaly, but mild splenomegaly was noted (dull Traube's space).

Diagnostic Findings

The initial X-ray of the pelvis showed a fracture accompanied by a lytic lesion extending from the greater to the lesser trochanter of the right femur. Subsequent magnetic resonance imaging (MRI) of the entire body revealed multiple lytic lesions at the greater trochanter of the right femur, skull, and lumbar vertebra (L5), with no indications of bone metastasis. Given the presence of multiple bony lesions, several potential diagnoses were considered, including Ewing sarcoma, osteosarcoma, and underlying metastasis. Due to observed leukocytosis, an urgent blood film was requested. The results of both the peripheral blood and bone marrow examination at the time of diagnosis are outlined in **Table 1** and indicate chronic myeloid leukemia in the chronic phase, with blasts constituting less than 5% (refer to **Figure 1**).

The results of the bone and tissue biopsy from the right femur confirmed the presence of myeloid sarcoma (see **Figure 2**). Consequently, the diagnosis was revised to CML in the blast phase. The patient underwent a marginal resection and the placement of a proximal femur endoprosthesis for the fracture.

Treatment

Initially, the patient was administered the tyrosine kinase inhibitor (TKI) Imatinib (Glivec) at a daily dosage of 400mg, achieving a good hematological response within one month of initiating the TKI treatment. Additionally, the patient underwent chemotherapy using the AML 3+7 protocol, which involves administering daunorubicin for three consecutive days followed by cytarabine for seven days. No remission was documented during the treatment due to

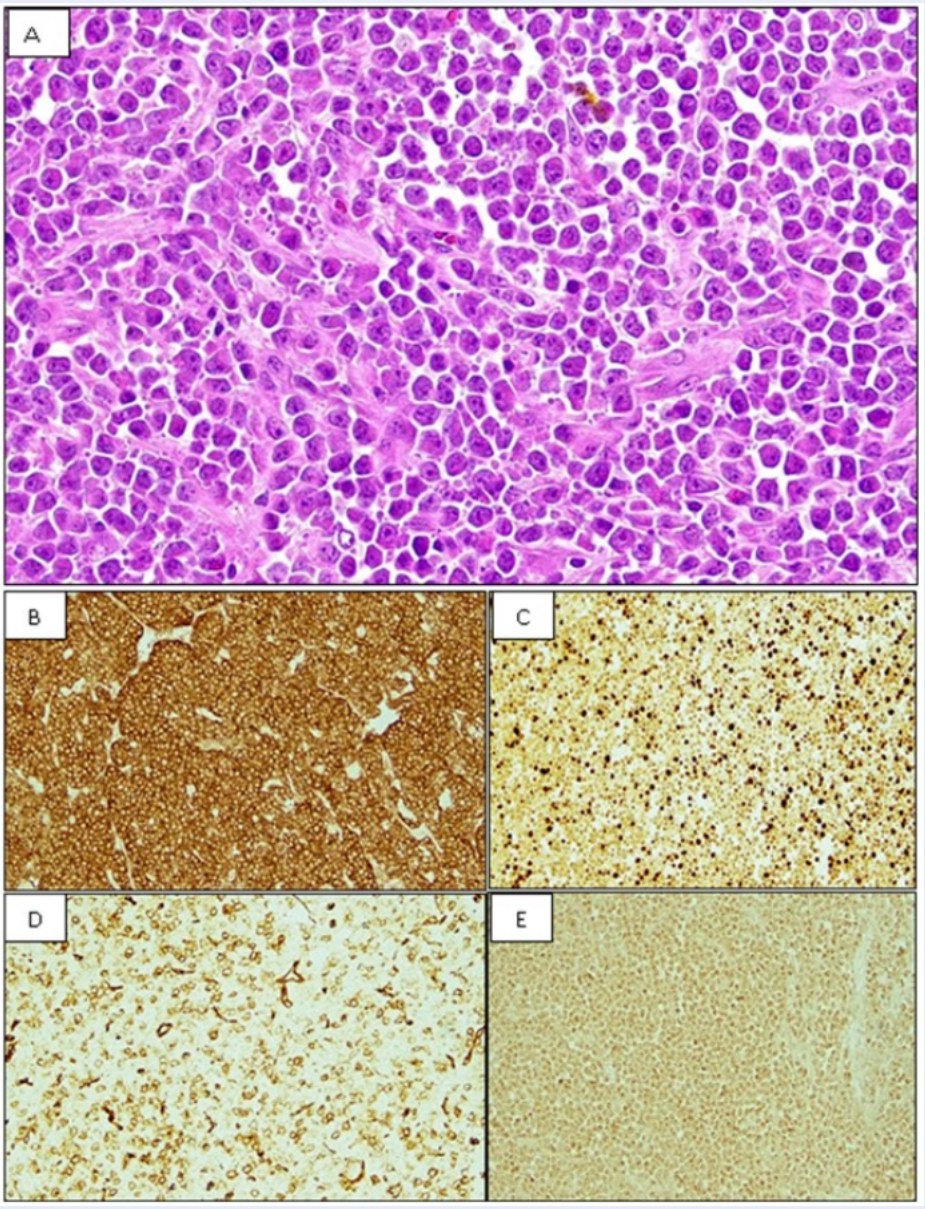

Figure 2: **Malignant cells are homogenous intermediate-size cells, displaying round to polygonal nuclei, prominent single to multiple nucleoli, and moderate amount of eosinophilic cytoplasm (A). The cells are diffusely positive for CD45 (B), MPO (C), CD34 (D), and CD99 (E).** H&E, 400X.

the suboptimal quality of the marrow obtained. This treatment approach was selected due to the presence of extramedullary disease indicating a blast crisis, and the patient was managed accordingly.

Outcome

However, after five months of treatment, a dislocation of the endoprosthesis occurred, resulting in the formation of a mass at the fracture site that subsequently became infected. Unfortunately, the patient's condition deteriorated, leading to his death due to septic shock resulting from neutropenic sepsis and disseminated intravascular coagulopathy.

DISCUSSION

Skeletal symptoms as an initial presentation of extramedullary involvement in CML are infrequent and are generally associated with acute blastic transformation. Radiographic evidence has revealed skeletal lesions in 16% of CML patients, encompassing diffuse

osteoporosis, focal osteoblastic/osteolytic lesions, granulocytic sarcoma (also known as chloroma), and arthritis[5]. Radiologically, the differential diagnosis in adults includes non-hematological diseases such as metastasis, chondrosarcoma, or malignant fibrous histiocytoma[6].

The osteolytic bony lesions observed in CML patients are postulated to arise from various mechanisms. One explanation suggests the direct invasion of leukemic cells into the bone, resulting in bone destruction. Another possibility is that leukemic cells trigger bone resorption, leading to localized bone destruction. Additionally, it is hypothesized that parathyroid hormone-related protein, produced by leukemic cells, acts on the PTH receptor, thereby stimulating bone resorption. These proposed mechanisms highlight the multifaceted nature of osteolytic lesions in CML and underscore the complexity of their pathogenesis[7].

To date, over the past five years, we have identified several cases of CML with osteolytic lesions (**Table 2**). Among these cases, two initially presented with osteolytic lesions. Two cases progressed to death, while one achieved treatment-free remission following a stem cell transplant. Based on the reviewed cases, it is noteworthy that patients with myeloid sarcoma who undergo allogeneic stem cell transplantation may benefit.

In scenarios akin to this, the disease is often not expected based on clinical observations, underscoring the need for a heightened level of suspicion. The blood and bone marrow characteristics conformed to the criteria for chronic phase chronic myeloid leukemia (CML). However, a tissue biopsy uncovered features suggestive of an unifocal extramedullary granulocytic sarcoma. The presence of extramedullary myeloblast proliferation classifies the CML as being in the blastic phase, necessitating swift diagnosis and aggressive treatment.

An accumulation of leukemic granulocytic precursors extramedullary, known as granulocytic sarcoma or chloroma, represents an infrequent and aggressive type of malignancy. Diagnosis can be challenging since it is not typically suspected during the initial presentation. Radiological assessments play a crucial role, and confirmation is achieved through histological examination. In terms of radiological presentations, skeletal lesions often manifest as lytic lesions, similar to the case at hand, necessitating differentiation from metastasis, malignant fibrous histiocytoma, or lytic chondrosarcoma[6]. Histologically, the diagnosis relies on the observation of sheets of leukemic granulocytic precursors or myeloblasts, confirmed by CD177 and MPO positivity.

According to the literature review by Soni et al. and the CML 2022 update by Jabbour *et al.*, extramedullary manifestations pose ongoing challenges in the management of CML. The blast crisis represents a significant hurdle in CML management, emphasizing the need for early consideration of allogeneic stem cell transplantation following initial therapy with tyrosine kinase inhibitors (TKIs). Newer-generation TKIs such as dasatinib or ponatinib are preferred over imatinib to effectively reduce the CML burden. In cases where TKIs alone are insufficient, initiating acute leukemia-type induction therapy, such as FLAG-IDA or a combination of chemotherapy tailored to the immunophenotype, following the MD Anderson approach, may be warranted[13,14]. This comprehensive approach highlights the importance of personalized treatment strategies to address the complexities of CML management.

CONCLUSION

The initial presentation of extramedullary involvement in CML patients is acknowledged to be exceedingly rare. The current case report seeks to raise awareness among general orthopedic surgeons regarding the possibility of granulocytic sarcoma in their differential diagnoses for hip pain. Reinforcing the importance of considering CML in the differential diagnosis of unexplained osteolytic lesions, especially in atypical patient populations, underscores the necessity for heightened awareness among clinicians beyond hematologists and oncologists. This includes orthopedic surgeons and emphasizes the need for future research in this area.

ABBREVIATIONS

AML: Acute Myeloid Leukemia, **BCR-ABL1:** Breakpoint Cluster Region-Abelson Murine Leukemia Viral Oncogene Homolog 1, **CML:** Chronic Myeloid Leukemia, **MRI:** Magnetic Resonance Imaging, **PTH:** Parathyroid Hormone, **TKI:** Tyrosine Kinase Inhibitor

ACKNOWLEDGMENTS

None.

AUTHOR'S CONTRIBUTIONS

The initial concept is by Mohd Nazri Hassan and Zefarina Zulkafli. The first draft is written by Razan Hayati Zulkeflee, Mohd Nazri Hassan and Marini Ramli. Shafini Mohamed Yusoff and Norzaliana Zawawi contributed to the full blood investigation and biopsy results. Azlan Husin and Abu Dzarr Abdullah contributed to the management of this case.

Table 2: Clinicopathology, Treatment, and Outcome of CML Cases with Osteolytic Presentation

Age and gender	35-year-old male	18-year-old male	58-year-old male	38-years-old male	17-year-old female	48-year old , gender not available
Chief complained	Fever and intense pain in both knees and ankles persisting for 5 days	Pain over the left shoulder over the past 4days	acute confusion, polyuria, and polydipsia for 7 days	Left buttock pain	Left hip joint pain	Right knee pain with reduced range of motion
Initial diagnosis	CML in CP on Imatinib	CML in CP on Imatinib	CML in CP	CML in CP on Imatinib	Myeloid sarcoma	Myeloid Sarcoma
Time elapsed from the initial diagnosis and extramedullary involvement (in months).	12 months	60 months	72 months	96 months	At presentation	At presentation
Treatment received	AML Induction therapy 7 + 3 and Dasatinib 140mg OD	Nilotinib 200mg BD	Received ponatinib and radiotherapy.	Received salvage combined chemotherapy	Dasatinib 70 mg BD and allo-HSCT after 4 months of the diagnosis	Imatinib.
Outcome	Discharged well till reported date.	Discharged well till reported date.	Expired 18 months after presentation	Expired	complete remission and achieved treatment free remission 30 months post-transplantation	Discharged well till reported date.
References	8	9	7	10	11	12

Rosnah Bahar and Wan Suriana Wan Abd Rahman are thoroughly reviewing it for essential intellectual substance. All authors read and approved the final manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Vol. 36, Leukemia. Springer Nature; 2022. p. 1703–19. . 2022;.

2. Lin Q, Mao L, Shao L, Zhu L, Han Q, Zhu H. Global, Regional, and National Burden of Chronic Myeloid Leukemia, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. Frontiers in Oncology. 2020;10. PMID: 33384954. Available from: https://doi.org/10.3389/fonc.2020.580759.
3. Kuan JW, Michael MS. The epidemiology of chronic myeloid leukaemia in southern Sarawak, Borneo Island. .
4. Terjanian T, Kantarjian H, Keating M, Talpaz M, McCredie K, Freireich EJ. Clinical and prognostic features of patients with Philadelphia chromosome-positive chronic myelogenous leukemia and extramedullary disease. Cancer. 1987;59(2):297–300. PMID: 3467820. Available from: https://doi.org/10.1002/1097-0142(19870115)59:2<297::AID-CNCR2820590221>3.0.CO;2-B.
5. Palejwala AH, O'Connor KP, Shi H, Villeneuve L, Scordino T, Glenn CA. Chronic myeloid leukemia manifested as myeloid sarcoma: review of literature and case report. Journal of Clinical Neuroscience. 2019;64:269–76. PMID: 31029526. Available from: https://doi.org/10.1016/j.jocn.2019.04.011.
6. Maloisel F, Favre G, Mahmal L, Zamfir A, Andrès E. Isolated lytic bone lesion as extramedullary disease in chronic myelogenous leukemia: a report of three new cases. European Journal of Internal Medicine. 2005;16(4):288–90. PMID: 16084356. Available from: https://doi.org/10.1016/j.ejim.2004.11.011.
7. Toro-Tobón D, Agosto S, Ahmadi S, Koops M, Bruder JM. Chronic myeloid leukemia associated hypercalcemia: A case report and literature review. The American Journal of Case Reports. 2017;18:203–7. PMID: 28239141. Available from: https://doi.org/10.12659/AJCR.902467.
8. Rujirachun P, Junyavoraluk A, Owattanapanich W, Suvannarerg V, Sirinvaravong S, Journal of Medical Case Reports. Leukemic arthritis and severe hypercalcemia in a man with chronic myeloid leukemia: A case report and review of the literature. Journal of Medical Case Reports. 2018;12:1–7. Available from: https://doi.org/10.1186/s13256-018-1798-5.
9. Aisyi M, Syarif AH, Meisita A, Kosasih A, Basuki A, Sari RM. Pathological Fracture: An Unusual Presentation in Childhood Chronic Myeloid Leukemia. Indonesian Journal of Cancer. 2019;13(4):140. Available from: https://doi.org/10.33371/ijoc.v13i4.675.
10. Wang Y, Hospital R, Tong SJ, Sun H, Zhang S. Myeloid Sarcoma Transformed From CML Presenting Ectopic Expression of AFP: A Case Report. researchsquare. 2022;2022. Available from: https://doi.org/10.21203/rs.3.rs-1374914/v1.
11. Tsukamoto S, Ota S, Ohwada C, Takeda Y, Takeuchi M, Sakaida E. Extramedullary blast crisis of chronic myelogenous leukemia as an initial presentation. Leukemia Research Reports. 2013;2(2):67–9. PMID: 24371785. Available from: https://doi.org/10.1016/j.lrr.2013.07.002.
12. Gauthier M, Mouchel PL, Syrykh C, Couture G. Chronic myeloid leukemia revealed through focal bone lesions responding to imatinib: the bee's knees. Joint, Bone, Spine. 2021;88(2). PMID: 33346104. Available from: https://doi.org/10.1016/j.jbspin.2020.105118.
13. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2022 update on diagnosis, therapy, and monitoring. American Journal of Hematology. 2022;97(9):1236–56. PMID: 35751859. Available from: https://doi.org/10.1002/ajh.26642.
14. Soni A, Paluri R, Deal T, Peker D. Extramedullary Involvement by Chronic Myelogeneous Leukemia in Five Patients With Unusual Clinicopathologic Features: A Review of the Effectiveness of Tyrosine Kinase Inhibitors. Journal of Clinical Medicine Research. 2016;8(6):480–5. PMID: 27222678. Available from: https://doi.org/10.14740/jocmr2566w.