DOI: https://doi.org/10.4038/tsljh.v16i2.46

SLJH. 2024; **16**(2): 28-31

Case report 1

Unexplained acute bleeding in chronic phase of chronic myeloid leukaemia due to acquired factor XIII deficiency induced hyperfibrinolysis – Experience at National Hospital of Sri Lanka, Colombo

AK Weerathunga[1], **MP Munasinghe**[1], **B Jayarathne**[1]

Key words: chronic myeloid leukaemia, factor XIII deficiency

Abstract

Chronic Myeloid Leukaemia (CML) is a significant myeloproliferative neoplasm, making up about 15% of all leukaemias, with an incidence rate of 1-2 cases per 100,000 adults. It is marked by the presence of the BCR-ABL1 fusion gene, which leads to the overproduction of a constantly active tyrosine kinase, driving the development of leukaemia. CML progresses through three phases, with bleeding complications more frequent in the accelerated and blast phases due to bone marrow infiltration and thrombocytopenia. The report highlights three cases of CML in the chronic phase, each presenting with unexplained acute bleeding due to isolated factor XIII deficiency-induced hyperfibrinolysis, a rare occurrence in this phase: A 49-year-old man with spontaneous intramuscular haematoma and severe leukocytosis, diagnosed with acquired factor XIII deficiency, managed with cryoprecipitate transfusion and imatinib mesylate, achieving complete remission before progressing to the blast phase. A 39-year-old man who developed multiple haematomas post-bone marrow biopsy, diagnosed with factor XIII deficiency, with bleeding resolving upon imatinib therapy, though he later progressed to the blast phase. A 53-year-old woman who presented with haematomas following a bone marrow biopsy, with diagnosis and management similar to the previous cases, achieving successful control of bleeding and remission. These cases emphasize the importance of recognizing and diagnosing acquired coagulopathy in CML patients with unexplained bleeding. Proper management involves specific factor replacement along with targeted CML therapy, as failure to diagnose can lead to significant morbidity and mortality.

Introduction

CML is a common myeloproliferative neoplasm, comprises approximately 15% of all leukaemia with an incidence of 1-2 cases per 100,000 adults[1,2]. It is characterized by fusion of the Abelson murine (ABL1) gene on chromosome 9 at break point cluster region (BCR) gene on chromosome 22. This results in expression of BCR-ABL1 oncoprotein which constitutively activate tyrosine kinase that promotes growth and replication of leucocytes causing leukaemogenesis. The natural course of CML defines three phases, the accelerated and blast phases that contain higher blast count and bleeding in these phases could occur due to bone marrow infiltration and thrombocytopenia. Bleeding in chronic phase with <05 % blast count is rare, and if occurs, it is described as a part of disseminated intravascular coagulation or platelet function defects[5,8,9]. We report three cases of CML in chronic phase presented with unexplained acute bleeding due to isolated factor XIII deficiency induced hyperfibrinolysis. Bleeding due to acquired deficiency of isolated coagulation factor has been reported rarely in chronic phase of CML. The management of these acute bleeding episodes depends on specific coagulation factor replacement and targeted therapy for CML with tyrosine kinase inhibitors.

[1]*Department of Haematology, National Hospital of Sri Lanka, Colombo.*

Correspondence: Dr. B Jayarathne

E-mail: bhaddikaj@gmail.com

Case 1

A 49-year-old man presented with a spontaneous intramuscular haematoma of right forearm for 04 days duration with pallor, massive splenomegaly (18 cm) and mild hepatomegaly on examination. He neither had bleeding manifestations in the past nor family history of bleeding disorders. He had undergone uneventful dental extractions twice during last 10 years and was not on any medications.

Haematological investigations revealed severe leukocytosis of 116 x 10^3/ µL (4 - 10 x 10^3/ µL) and a complete left shift of granulocytes with 01% blast count in the peripheral blood. BCR-ABL1 p210 translocation was positive and of low-risk category according to Sokal score. Haemoglobin level was 6.9 g/ dL and the platelet count was 106 x 10^3/ µL (150 - 400 x 10^3 µL).

The primary coagulation tests were normal. Prothrombin time (PT) was 13.6 seconds (9-13 seconds). Activated partial thromboplastin time (APTT) was 30.9 seconds (23-37 seconds) and thrombin time was 17 seconds (15-19 seconds). Rotational thromboelastometry (ROTEM) revealed higher maximum lysis (ML) at both EXTEM (48%) and INTEM (34%) and normal APTEM indicating hyperfibrinolysis. The clot solubility test was negative but the specific factor XIII assay was 13% (50-150%). Von Willebrand factor antigen and ristocetin cofactor activity (vW profile), clauss fibrinogen activity and D dimer levels were normal. Liver and renal functions were also normal.

The clinical history and the results of investigations together, confirmed the diagnosis of acquired factor XIII deficiency, hyperfibrinolysis and CML in chronic phase.

The acute bleeding was immediately managed by 02 pools of cryoprecipitate transfusion and subsequent ROTEM test showed a normal coagulation status. A definitive therapy of 400 mg daily dose of imatinib mesylate was started for CML with regular monitoring of blood counts. He achieved a complete haematological and cytogenetic remissions in 3 months and 6 months respectively and did not manifest bleeding during treatment. He had transformed in to blast phase at 10 months of his follow up.

Case 2

A 39-year-old previously healthy man had undergone a bone marrow biopsy for investigations for high white cell count of 453 x 10^3/ µL and a massive splenomegaly (20 cm). He developed multiple buttock haematomas at the site of the biopsy 02 hours after procedure followed by another 02 large haematomas on the other buttock next day. He had no past or family history of bleeding and was not on any medications. Blood picture, bone marrow findings and positive BCR-ABL1 translocation confirmed CML in chronic phase (blast count was 03%) with a low risk Sokal score. Platelet count was 218 x 10^3/ µL and haemoglobin was 8.3 g/ dL.

Primary coagulation investigations were normal. PT was 16 seconds; APTT 36.9 seconds and TT was 19 seconds. ROTEM test revealed a prolonged ML, 30% in EXTEM, 26% in INTEM and normal APTEM indicating hyperfibrinolysis. Factor XIII deficiency was confirmed by 34% plasma factor XIII level. The clot solubility test was negative. D dimer, plasma fibrinogen level, and vW profile were normal. Liver and renal function tests were normal. Factor XIII deficiency induced hyperfibrinolysis in chronic phase of CML was diagnosed.

The bleeding settled without any need of component transfusions after starting 400 mg daily dose of imatinib mesylate therapy and subsequent ROTEM studies revealed normal coagulation. He achieved a haematological remission after 3 months of therapy but gradually deteriorated with cytopenia and transformed in to blast phase in about another 3 months.

Case 3

A 53-year-old previously healthy woman had undergone bone marrow biopsy to investigate fever with high white cell count of 214 x 10^3/µL and moderate hepatosplenomegaly. She developed a buttock haematoma at the site of biopsy about 02 hours after the procedure followed by formation of a psoas haematoma at the same side. She had no past or family history of bleeding and not on any medications. The blood picture, bone marrow findings and positive BCR-ABL1 p210 confirmed CML in chronic phase.

Coagulation investigations revealed normal PT 10.6 seconds, APTT 31.4 seconds and TT 12.8 seconds. Prolonged ML in both EXTEM (31%) and INTEM (28%) with normal APTEM and plasma factor XIII level of 42% confirmed factor XIII deficiency with hyperfibrinolysis. Clot solubility test was negative. Plasma fibrinogen, D dimer levels and vW profile were normal. Liver and renal function tests were also normal. Acute bleeding had settled after starting 400 mg daily dose of imatinib mesylate without any need of component transfusion and subsequent ROTEM tests indicated normal coagulation status. She achieved complete haematolgical response in 3 months and major molecular response in 1 year.

Discussion

Incidence of bleeding in CML is reported to be the lowest among myeloproliferative disorders (29%)[5]. Bleeding diathesis in accelerated and blast phases of CML is mainly due to bone marrow infiltration, severe thrombocytopenia or global consumptive coagulopathy driven by cytokine secreting blasts. Platelet dysfunction or disseminated intravascular coagulation is described as possible causes of rare occurrence of bleeding in the chronic phase[5]. However acute incidence of bleeding in the chronic phase of CML due to acquired, isolated coagulation factor XIII deficiency is extremely rare[16].

The pathophysiological mechanism behind isolated factor XIII deficiency could be multifactorial but exactly unknown. Hypothetically it might be due to consumption or high turnover of coagulation factors by large masses of circulating leukocytes and quantitative or qualitative defects of coagulation factor XIII in plasma due to development of inhibitory antibodies.

In most of the cases acquired factor XIII deficiency is partial and does not lead to significant bleeding as 2-3% plasma factor XIII level is adequate to maintain haemostasis. On the other hand, diagnosis of factor XIII deficiency is a challenging task as the screening test for factor XIII deficiency is less sensitive (<5%)14 while the routine coagulation test results remain within normal limits. A high index of clinical suspicion and specialized laboratory tests such as ROTEM test and plasma factor XIII assay are important in the diagnosis.

Unexplainable episodes of acute bleeding manifestations in patients with haematological malignancies, with high cell turnover should be evaluated beyond first level haemostatic investigations for exact diagnosis of the coagulation defect to prevent its impact on morbidity and mortality. The management of such acquired coagulopathy depends on specific treatment of the coagulopathy and concurrent targeted therapy for the malignancy.

As a note of observation two out of these three patients with CML in chronic phase who developed bleeding due to acquired factor XIII deficiency had transformed in to more aggressive phase of the disease while on therapy.

Conclusion

Acute bleeding is rare in chronic phase of CML. Acquired deficiency of isolated plasma factor XIII induced hyperfibrinolysis was diagnosed in unexplained episodes of acute bleeding occurred in the three patients we evaluated during the chronic phase of the disease. Such bleeding manifestations are linked to high impact of morbidity and mortality unless the diagnosis of specific acquired coagulopathy was assessed beyond first level coagulation investigations. The management of acquired coagulopathy depends on specific plasma factor replacement and concurrent targeted therapy for CML.

Acknowledgement

Medical laboratory technicians at haematology laboratory, National Hospital of Sri Lanka, Colombo.

References

1. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. *Am J Hematol.* 2018; **93**(3): 442-59. doi:10.1002/ajh.25011. PMID: 29411417.
2. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of

chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer. 2012; **118**(12): 3123-7. doi: 10.1002/cncr.26679. Epub 2012 Jan 31. PMID: 22294282; PMCID: PMC3342429.

3. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html
4. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. *Br J Cancer.* 2010; 102 Suppl 1(Suppl 1): S2-9. doi: 10.1038/sj.bjc.6605599. PMID: 20386546; PMCID: PMC3315367.
5. Shatzel JJ, Scherber R, DeLoughery TG. (2018). Bleeding and Thrombosis in Hematologic Neoplasia. In: Wiernik P, Dutcher J, Gertz M. (eds) Neoplastic Diseases of the Blood. Springer, Cham. https://doi.org/10.1007/978-3-319-64263-5_59.
6. https:/www.thieme-connect.com/DOI/D0I,10.1055/s-0032-1331154
7. Wehmeier A, Scharf RE, Fricke S, Schneider W. Bleeding and thrombosis in chronic myelo-proliferative disorders: relation of platelet disorders to clinical aspects of the disease. *Haemostasis.* 1989; **19**(5): 251-9. doi: 10.1159/000215980. PMID: 2777137.
8. Olfa CW. Imen R. Leila K. Hichem K. Adnane A. Mourad C. Adel C. Choumous K. Noureddine R. Diagnosis of chronic myeloid leukemia from acute intracerebral hemorrhage. A case report. *Journal of Acute Disease.* 2015; **4**(3):252-4. https://doi.org/10.1016/j.joad.2015.03.004
9. Sachidananda R. Bhat VK. SaNtosh MC. Pai RV. Unusual presentation or chronic myeloid leukemia an emphasis on adequate preanesthesia work-up. *Anaesth Pain and Intensive Care.* 2014; **18**(3): 289-90. https://doi.org/10.1016/j.joad.2015.03.004
10. Wiegering V, Andres O, Schlegel PG, Deinlein F, Eyrich M, Sturm A. Hyperfibrinolysis and acquired factor XIII deficiency in newly diagnosed pediatric malignancies. *Haematologica*. 2013; **98**(8): e90-1. doi: 10.3324/haematol.2013.089045. Epub 2013 Jun 10. PMID: 23753026; PMCID: PMC3729890.
11. Abdulhamid MM, Li YM, Hall WA. Spontaneous acute subdural hematoma as the initial manifestation of chronic myeloid leukemia. *J Neurooncol.* 2011; **101**(3): 513-6. doi: 10.1007/s11060-010-0278-6. Epub 2010 Jun 27. PMID: 20582615.
12. Nijenhuis AV, van Bergeijk L, Huijgens PC, Zweegman S. Acquired factor XIII deficiency due to an inhibitor: a case report and review of the literature. *Haematologica.* 2004; **89**(5): ECR14. PMID: 15136243.
13. Gregory TF, Cooper B. Case report of an acquired factor XIII inhibitor: diagnosis and management. Proc (Bayl Univ Med Cent). 2006; **19**(3): 221-3. doi: 10.1080/08998280.2006.11928166. PMID: 17252037; PMCID: PMC1484527.
14. W Collins P, Chalmers E, Hart D, Jennings I, Liesner R, Rangarajan S, Talks K, Williams M, R M Hay C; United Kingdom Haemophilia Centre Doctors' Organization. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO. *Br J Haematol.* 2013; **162**(6): 758-73. doi: 10.1111/bjh.12463. Epub 2013 Jul 25. PMID: 23889317.
15. Theusinger OM, Baulig W, Asmis LM, Seifert B, Spahn DR. In vitro factor XIII supplementation increases clot firmness in Rotation Thromboelastometry (ROTEM). *Thromb Haemost.* 2010; **104**(2): 385-91. doi: 10.1160/TH09-12-0858. Epub 2010 Apr 29. PMID: 20431856.