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Acute myeloid leukemia with severe coagulation disorder and concomitant central nervous system bleeding – a clinical diagnostic case report

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ABSTRACT

We report a case of severe central nervous system bleeding in a patient with acute monocytic leukemia. The patient was admitted to our emergency department because of massive back pain and positive meningeal signs. MR imaging yielded a spontaneous epidural hematoma of the thoracic vertebral column. Coagulation studies revealed fibrinogen levels below the linear measuring range and blood smears showed myeloid blast cells in the peripheral blood. The diagnosis of acute monocytic leukemia was confirmed by flow cytometric analysis. Despite of substitution with more than 12 g fibrinogen per day over 3 days plasma fibrinogen levels couldn't be stabilized. After starting the induction chemotherapy with cytarabine, laboratory coagulation test results were improved. Despite all intensive medical efforts, the patient died due to cerebral epidural hematoma.

INTRODUCTION

Acute myeloid leukemia (AML) is a result of malignant transformation of hematopoietic stem or progenitor cells and is the most frequent acute leukemia in adults. (1, 2) DIC is one of the most feared and fatal complication in acute promyelocytic leukemia (APL), however it is rare in all other subtypes of acute myelogenous leukemia (AML). (3) The incidence of disseminated intravascular coagulation (DIC) induced by hematologic malignancies was 12.7% in a large cohort of patients, studied by Okajima et al., with an overall mortality of more than 50% (4) *A typical feature of* DIC in acute leukemia is hyperfibrinolysis and reduction of natural anticoagulants like protein C and antithrombin III. (5, 6)

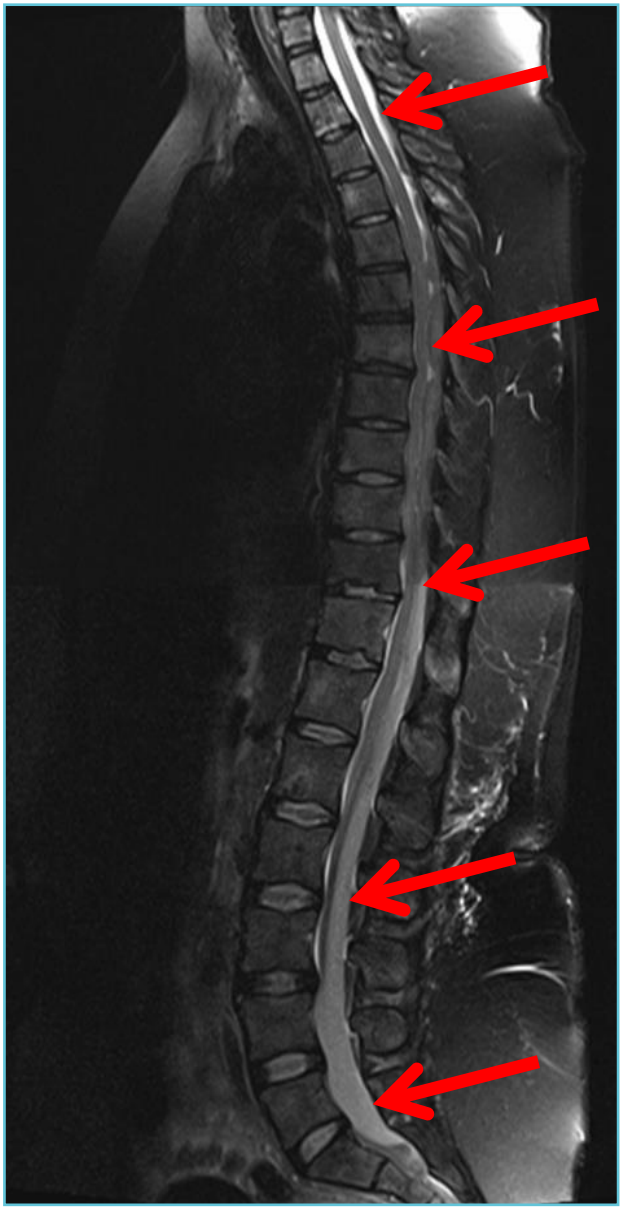
In our case report we show that early eradication of the leukemia by using high dose chemotherapy is the foremost option to control DIC and improve the coagulation test results as well as overall survival.

CLINICAL-DIAGNOSTIC CASE

A 36-year-old woman presented to the emergency department with acute back pain, fatigue and fever. Physical examination revealed positive meningeal signs (Lhermitte, Laseque). For further evaluation of the back pain, a magnetic resonance imaging was performed, which yielded massive epidural bleeding from the first thoracic vertebral body to the fourth lumbar vertebral body. (Figure 1 A)

Laboratory testing revealed leukocytosis [18,520 /µL] and mild thrombocytopenia [100.000 G/l], additionally a severely decreased fibrinogen level [< 80 mg/dL] using the Clauss method as well as a massively elevated D-Dimer value of >33 mg FEU/L could be detected. A hematological cause of hyperfibrinolysis was suspected and blood smear as well as flow-cytometric analysis (FACS) was performed. Because of the severe clinical and laboratory findings pointing towards disseminated intravascular coagulation, the most probable diagnosis was APL and a therapy with all-trans-retinoic acid 45mg/m^2/day was administered. The patient was transferred to the intensive care unit and substitution of fibrinogen was initiated.

Figure 1A Magnetic resonance imaging of the thoracic, lumbar and sacral spine*



**Revealing epidural hematoma reaching from thoracic vertebral level 1 to sacral vertebral level 1 and compressing thoracic spinal cord as well as conus medullaris (arrows)*

During the first day of hospitalization, a total amount of 16 g fibrinogen was given, despite substitution fibrinogen levels in plasma remained undetectable, no signs of bleeding could be detected. The patients' condition improved and was hemodynamically stable with pain controlled by continuous morphine infusion.

During the second day, results of the blood smears including cytochemistry revealed 10% myeloid blasts with Auer rods, 15% atypical monocytes, 40% lymphocytes as well as 35% band stage and mature neutrophil granulocytes. (Figure 1B) FACS confirmed these results resulting in the diagnosis of an acute monocytic leukemia (FAB M4 according to French American British classification of acute leukemia). On the second day, again 12 g fibrinogen and 1 g tranexamic acid were administered without any effect on plasma fibrinogen level (Figures 1C; 2A).

After confirmation of the diagnosis FAB M4, a bone marrow biopsy was performed and chemotherapy with cytarabine 200mg/m²/day was administered. Due to DIC and possible tumor lysis syndrome, daunorubicine 60mg/m² was postponed to day 5.

Directly after administration of cytarabine and fibrinogen, plasma fibrinogen levels increased into normal ranges for the first time after initial diagnosis (Figure 1C). Due to chemotherapy, platelet count started to decrease and one irradiated

Figure 1B Peripheral blood smear showing myeloid differentiated blast cells

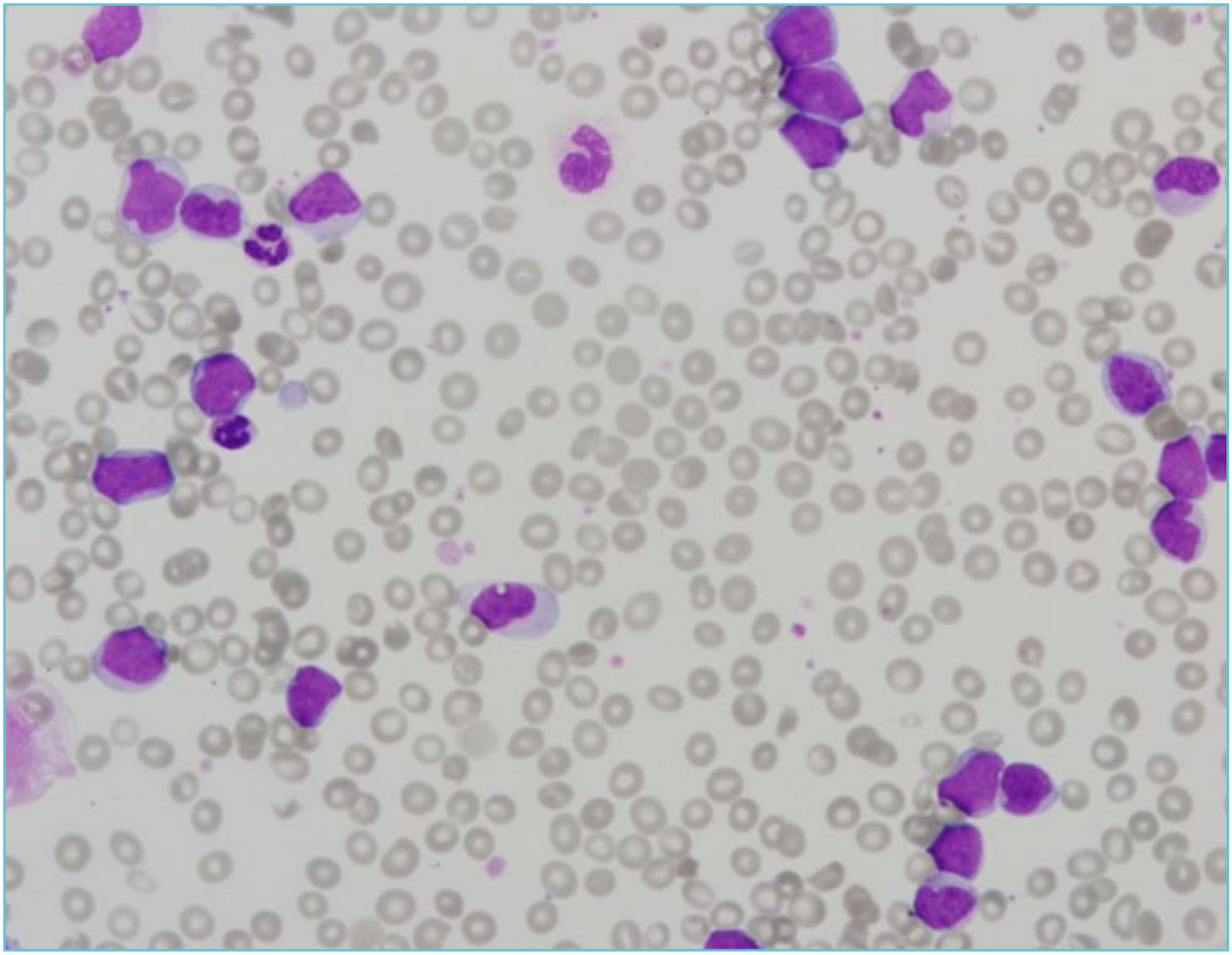
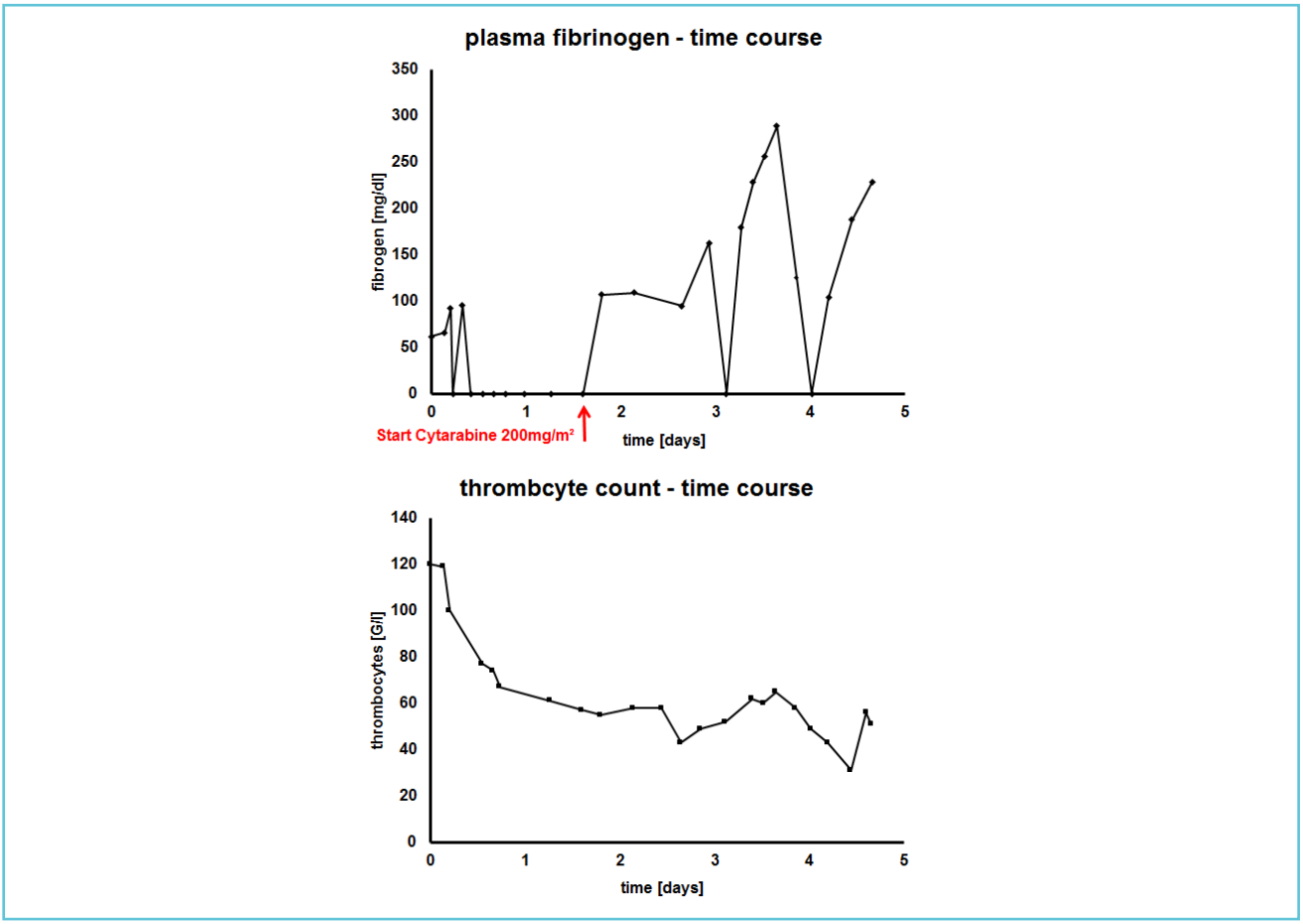


Figure 1C Time course of fibrinogen level and thrombocyte count during AML induction chemotherapy



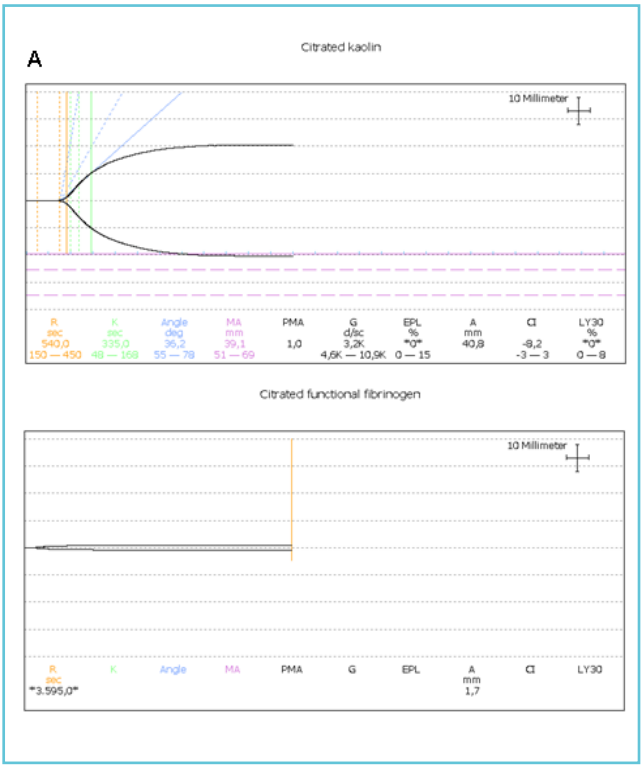
thrombocyte concentrate was administered to keep thrombocyte count above 50.000 G/L.

On the third day of hospitalization, the patient developed pronounced macrohematuria and multiple disseminated skin hematomas. Four irradiated erythrocyte concentrates were needed to maintain a hemoglobin level of 7.0 g/L. Subsequently, the patients' neurological deficits were relieved, reaching a Glasgow Coma Scale score of 15 points.

However, on the morning of the fourth day the patient was comatose and did not respond to any stimulation reaching a Glasgow coma scale of 3 points. Due to neurological impairment, immediate endotracheal intubation was performed and total intravenous anesthesia with propofol and remifentanil as continuous infusion was initiated.

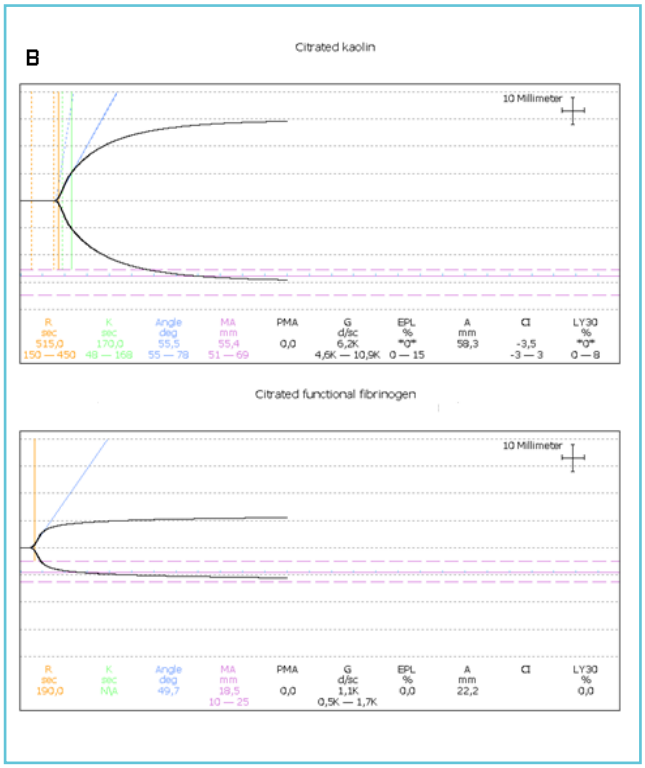
Cranial computer tomography (CCT) revealed a temporally right sided newly developed epidural bleeding causing a midline-shift of the brain towards left. Emergency craniotomy was successfully performed for intracranial decompression. A Thrombelastography (TEG) was performed to re-evaluate the coagulation status again revealing low fibrinogen levels and additionally a newly developed thrombocytopathia/thrombocytopenia was detected. This triggered a subsequent continuous infusion of fibrinogen (3 g/h) together with administration of tranexamic acid 3g daily plus Factor XIII concentrate with the aim

Figure 2A Initial TEG (citrated kaolin and citrated functional fibrinogen)*



*Before administration of fibrinogen and factor XIII concentrate

Figure 2B Follow Up TEG day 4 (citrated kaolin and citrated functional fibrinogen)*



*After administration of fibrinogen and factor XIII concentrate

to enhance the clot stability which was achieved as demonstrated in following TEGs. (Figure 2B)

On the fifth day after the diagnosis of AML, intravenous anesthesia was stopped and the patient was extubated. On this day, the patient reached again a Glasgow Coma Scale score of 15 points, the coagulation status remained stable and fibrinogen substitution was stopped. Seven hours later, however, the patient's neurological status deteriorated and mechanical ventilation was necessary again. CCT scan showed a massive haemorrhagic infarction of the occipital lobe with massive brain edema.

In the evening of the sixth day after the diagnosis, electroencephalography revealed zero-line consistent with the brain death of the patient.

DISCUSSION

The standard of care therapy for acute myeloid leukemia is a 7 + 3 days chemotherapy regimen including continuous infusion of cytarabine (200 mg/m²) for seven days combined with bolus infusion of an anthracycline for three days. (1)

All other forms of acute leukemia like acute lymphoblastic leukemia and acute promyelocytic leukemia also respond to administration of cytarabine. (7, 8)

The paradigm for treating acute promyelocytic leukemia with impaired coagulation test results is that even if acute promyelocytic leukemia is just suspected, treatment with all-trans retinoic acid should be immediately started.

However, the main issue in treatment of patients with acute leukemia associated DIC and without correct subtype diagnosis is that all-trans retinoic acid is only effective in acute promyelocytic leukemia.

In our case, the patient did not receive any effective treatment for more than one day with active central nervous bleeding. Additionally, plasma fibrinogen level did not respond to massive replacement. We could observe that coagulation parameters ameliorated and leukemic blast cells decreased after starting chemotherapy. In summary, the main goal to stop DIC and bleeding complications must be the early eradication of the leukemia. Coagulation management in these patients is very difficult to handle, thus by using frequent TEG testing a better control of bleeding complications could be achieved.

We conclude that immediate continuous infusion with cytarabine would have been adequate to start with because of expectable response in any form of acute leukemia. This might have allowed an early control of DIC even before receiving results of acute leukemia subtype diagnostics. An early detection of DIC and early improvement of the coagulation status can potentially improve the outcome of such patients.

TAKE HOME MESSAGES/ LEARNING POINTS

- In case of unknown differentiation of acute leukaemia, Cytarabine can be used as the cytoreductive agent of choice because of the high effectiveness in all forms of acute leukaemia whether lymphoblastic or myelogenous.
- TEG result-based consequent substitution of pro-coagulative agents like fibrinogen, factor XIII and tranexamic acid independently may help to improve coagulation in such patients with DIC and underlying haematological malignancy.

REFERENCES

1. Dohner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. N Engl J Med. 2015 Sep 17;373(12):1136-52.

2. Hatzl S, Geiger O, Kuepper MK, Caraffini V, Seime T, Furlan T, et al. Increased Expression of miR-23a Mediates a Loss of Expression in the RAF Kinase Inhibitor Protein RKIP. Cancer Res. 2016 Jun 15;76(12):3644-54.

3. Lo-Coco F, Ammatuna E, Montesinos P, Sanz MA. Acute promyelocytic leukemia: recent advances in diagnosis and management. Semin Oncol. 2008 Aug;35(4):401-9.

4. Okajima K, Sakamoto Y, Uchiba M. Heterogeneity in the incidence and clinical manifestations of disseminated intravascular coagulation: a study of 204 cases. Am J Hematol. 2000 Nov;65(3):215-22.

5. Franchini M, Di Minno MN, Coppola A. Disseminated intravascular coagulation in hematologic malignancies. Semin Thromb Hemost. 2010 Jun;36(4):388-403.

6. Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med. 2014 Feb 27;370(9):847-59.

7. Gokbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. Semin Hematol. 2009 Jan;46(1):64-75.

8. Lo-Coco F, Avvisati G, Vignetti M, Breccia M, Gallo E, Rambaldi A, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. Blood. 2010 Oct 28;116(17):3171-9.