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Central nervous system haemorrhage causing early death in acute promyelocytic leukaemia

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Abstract

Acute promyelocytic leukaemia (APL) is a rare type of paediatric leukaemia characterised by a specific genetic mutation and life-threatening coagulopathy. The discovery of all-trans retinoic acid (ATRA), which acts directly on promyelocytic locus-retinoic acid receptor α (PML-RARα) gene product, brought a revolution to the therapy of this disorder. Unfortunately, despite an improvement in the complete remission rate, the early death (ED) rate has not changed significantly, and the haemorrhages remain a major problem. The most common bleeding site, which accounts for about 65-80% of haemorrhages, is the central nervous system. Second in line are pulmonary haemorrhages (32%), while gastrointestinal bleedings are relatively rare. Haemorrhages result from thrombocytopaenia, disseminated intravascular coagulopathy (DIC), and systemic fibrinolysis. Herein we present a boy aged one year and nine months with APL. The patient was not eligible for ATRA administration due to poor clinical condition. He developed bleeding diathesis that presented as disseminated intravascular coagulation (DIC) and led to intracranial haemorrhage, which resulted in the patient's death.

Key words: *acute promyelocytic leukaemia, coagulopathy, early death.*

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Introduction

Acute promyelocytic leukaemia (APL), type M3 according to FAB classification, is a rare type of paediatric leukaemia, which is often associated with profound coagulopathy [1]. Peak incidence of APL in children is observed at 9-12 years of age, while in younger children the disease is observed sporadically. It accounts for 5-10% of acute myeloid leukaemia cases, with higher frequency in specific regions (e.g. Nicaragua or northern Italy) or populations (Latino/Hispanic) [1-3]. Acute promyelocytic leukaemia exhibits a characteristic clinical, morphological, immunophenotypical, and genetic features. Nearly all APL cases are due to the reciprocal translocation between chromosomes 15 and 17 that results in the formation of a fusion gene. This gene, promyelocytic locus-retinoic acid receptor α (PML-RARα) gene, is a nuclear receptor for retinoic acid. After ligand-receptor interaction, RARα forms a complex with its cofactor retinoid X receptor (RXR) and activates gene transcription. Fusion protein PML-RARα blocks transcription and restrains granulocytes maturation [4]. The description of PML-RARα oncogene led to the introduction of all-trans retinoic acid (ATRA) to the therapy. All-trans retinoic acid in therapeutic doses induces degradation of PML-RARα and enables promyelocytic differentiation [4]. Acute promyelocytic leukaemia cells are hypergranular with heavy azurophilic granules, Auer rods, and a bi-lobed or reniform nucleus [5]. Leukemic promyelocytes show expression of CD33, CD13, and CD117 and sporadically HLA-DR and CD34 [4].

Patients present with signs and symptoms of pancytopaenia, such as fatigue, pallor, purpura, and infections. Coagulopathy is a unique feature of APL and a major cause of early death [5-7]. Abnormalities in the coagulation cascade include low fibrinogen level, low platelet count, elevated prothrombin time (PT-INR), thrombin time (TT), partial thromboplastin time (aPTT), D-dimer level, and fibrin degradation products (FDP) [8, 9]. The pathogenesis of coagulopathy is complex. Proteolysis of clotting factors and fibrinogen is augmented by activation of fibrinolysis mediated by annexin-II, which enhances plasmin production together with tissue-type plasminogen activator (t-PA) and plasminogen [6, 8, 9]. High expression of annexin-II is probably linked to increased incidence of intracranial haemorrhages [8]. The most common bleeding site, which accounts for about 65-80% of haemorrhages, is the central nervous system. Second in line are pulmonary haemorrhages (32%), while gastrointestinal bleedings are relatively rare [6, 9]. Haemorrhages result from thrombocytopaenia, disseminated intravascular coagulopathy (DIC), and

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systemic fibrinolysis [7]. The diagnosis of APL is based on the identification of promyelocytes with specific morphology, flow cytometry, classical cytogenetics, and molecular testing by fluorescent *in situ* hybridisation (FISH) [10].

Case report

A boy, one year and nine months old, was admitted to the Department of Paediatric Haematology and Oncology because of suspicion of leukaemia. The patient had one-day history of fever up to 38.4°C, epistaxis, and a single episode of haematemesis. His parents noticed a loss of appetite for one week before admission. Laboratory investigations revealed severe anaemia, thrombocytopenia, and leucocytosis (Hb 3.5 g/dl; Ht 10.4%; RBC 1.3 × 10^6/µl; WBC 21.5 × 10^3/µl; PLT 28 × 10^3/µl). Physical examination revealed pallor, ecchymosis, subcutaneous bleeds, enlarged cervical lymph nodes, and hepatosplenomegaly. There was some fresh blood on the nose and lips; however, a laryngologist excluded active bleeding. On auscultation crackles and a systolic murmur (2/6 in Levine's scale) were observed. Peripheral blood smear revealed 50% lymphocytes, 1% monocytes, 49% blasts, hypergranular with bundles of Auer rods, some with bi-lobed nuclei. Bone marrow biopsy showed 36% blasts with Auer rods, bi-lobed nuclei, and granules in cytoplasm. Both the clinical presentation and the laboratory findings implicated a diagnosis of acute promyelocytic leukaemia. The diagnosis was confirmed by flow cytometry and cytogenetic test. Flow cytometry examination of the peripheral blood showed a population of abnormal cells from the granulocytic line with low SSC, comprising 35% of all peripheral blood leukocytes. Cells were positive for MPO, CD13, CD33, and CD64. CD34 expression was observed in 12.0% of cells, and CD15 in 10.8%. Expressions of HLA-DR and CD117 were dim and seen only in 4.9% and 3.2% cells, respectively. Cytogenetics revealed classical t(15;17) translocation (46, XY, t(15,1709q22;q21)/46, sl, del(1)(p13p36), add(13)(q34)/46, XY). Computed tomography of the central nervous system demonstrated meningeal involvement. Lumbar puncture was not performed because of coagulopathy (APTT 57-100 s, INR 2.7, fibrinogen 0.5 g/l). The patient received platelet transfusion, fresh frozen plasma, and vitamin K due to systemic bleeding diathesis. His haemoglobin concentration constantly decreased (Hb 3.5 g/dl; Ht 10.4%; RBC 1.3 × 10^6/µl) although he required RBC transfusions. Piperacillin with tazobactam were administered due to deep neutropaenia and neutropaenic fever.

ATRA was ordered; however, due to the patient's poor condition (tachycardia, tachypnoea, decreasing saturation, decreased diuresis, features of pulmonary congestion, seizures) it could not be administered. We observed high levels of urine acid and creatinine, and abnormal diuresis. After fluid supplementation and doses of diuretics, forced diuresis was used. He required rectal diazepam administration as he developed right-sided local seizures. Subsequently, generalised seizures occurred, which did not respond to medications even though continuous intravenous infusion of phenobarbital was started. Computed tomography (CT) scan was repeated and demonstrated massive intracerebral haemorrhage with brain oedema and uncal herniation. Due to increasing signs of circulatory and respiratory failure, the patient was transferred to the Intensive Care Unit, where he died.

Discussion

Discovery of the fusion gene PML-RARα enables the introduction of targeted treatment in APL patients. Besides the characteristic genetic pattern, the clinical diagnosis of APL is based on the presence of life-threatening bleedings. Introduction of ATRA into the clinical practice had a profound effect on disease-free survival; however, the early death rate (defined as death within 30 days of diagnosis) has not changed significantly and still accounts for 17-30% of deaths [5, 7]. Treatment of APL in Polish children is based on the AML-BFM2004 INTERIM protocol [10]. The induction phase consists of a combination of ATRA, cytarabine (intravenous and intrathecal), idarubicin, and etoposide. ATRA should be applied during the whole treatment period [10]. Combination of chemotherapy and ATRA induces complete remission in 80-95% of patients and improves treatment efficiency [8, 10–12].

Coagulopathy, frequently manifesting as intracranial and pulmonary haemorrhage, is the most common cause of early death. The majority of ED is caused by haemorrhage, particularly in the first week (44%) or within two weeks (65%) of presentation [10]. Other signs of bleeding diathesis include excessive blood loss from a trauma site, bruising, petechiae, mucus membrane bleeding, and gastrointestinal haemorrhages [8]. A severe haemorrhagic syndrome is present in 80-90% of patients at the diagnosis and around 5% patients are excluded from induction therapy due to poor clinical condition [7, 11]. However, if the patient survives induction therapy, the cure rate is about 80-90% [8]. The risk factors of lethal bleedings are: increased peripheral blast count > 30 × 10^3/µl, abnormal creatinine concentration, and symptoms of coagulopathy at presentation [6]. Our patient presented the fulminant course of APL with coagulopathy and fatal intracranial bleeding. Progression in this case was so rapid that proper treatment with ATRA could not be introduced. The ED rate is higher for patients who do not receive ATRA compared to patients who receive the drug; in this series, five high-risk patients died of bleeding before starting ATRA therapy [10]. The results of this analysis indicate that the percentage of ED increased with the delay in ATRA administration: from 33% of ED for bleeding if ATRA was administered on the first day that APL was suspected, to

70% when ATRA was administered one or more days after the leukaemia was suspected [10]. Retinoid acid derivate supports coagulopathy resolution and decreases relapses rate [7, 10, 13].

Conclusions

Acute promyelocytic leukaemia remains associated with a significant incidence of early death related to the characteristic bleeding diathesis. Very early ATRA administration significantly affects the patient survival with APL.

The authors declare no conflict of interest.

References

1. Testi AM, D'Angiň M, Locatelli F, et al. (2014): Acute promyelocytic leukemia (APL): Comparison between children and adults. Mediterr J Hematol Infect Dis 6: e2014032.
2. Kutny MA, Gregory J Jr, Feusner JH (2014): Treatment of paediatric APL: How does the therapeutic approach differ from adults? Best Pract Res Clin Haematol 27: 69-78.
3. Douer D, Preston-Martin S, Chang E, et al. (1996): High frequency of acute promyelocytic leukemia among Latinos with acute myeloid leukemia. Blood 87: 308-813.
4. Lo-Coco F, Hasan SK (2014): Understanding the molecular pathogenesis of acute promyelocytic leukemia. Best Pract Res Clin Haematol 27: 3-9.
5. Cassinat B, Chomienne C (2001): Biological features of primary APL blasts: their relevance to the understanding of granulopoiesis, leukemogenesis and patient management. Oncogene 20: 7154-7156.
6. Sanz MA, Montesinos P (2010): Open issue on bleeding and thrombosis in acute promyelocytic leukemia. Thromb Res 125 Suppl 2: S51-54.
7. Breccia M, Lo Coco F (2014): Thrombo-hemmorhagic deaths in acute promyelocytic leukemia. Thromb Res 133 Suppl 2: S112-116.
8. Choudhry A, DeLoughery TG (2012): Bleeding and thrombosis in acute promyelocytic leukemia. Am J Hematol 87: 596-603.
9. Stein E, McMahon B, Kwaan H, et al. (2009): The coagulopathy of acute promyelocytic leukemia revisited. Best Pract Res Clin Haematol 22: 153-163.
10. Balwierz W, Pawinska-Wasikowska K, Klekawka T, et al. (2013). Development of treatment and clinical results in childhood acute myeloid leukemia in Poland. Memo 6: 54-62.
11. Avvisati G, Lo Coco F, Mandelli F (2001): Acute promyelocytic leukemia: clinical and morphologic features and prognostic factors. Semin Hematol 38: 4-12.
12. Sanz MA, Grimwade D, Tallman MS, et al. (2009): Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LekemiaNet. Blood 113: 1875-1891.
13. Abrahão R, Ribeiro RC, Medeiros BC, et al. (2015): Disparities in early death and survival in children, adolescents and young adults with acute promyelocytic leukemia in California. Cancer 2015; 121: 3990-3997.