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Favorable Outcome of Budd-Chiari Syndrome in Acute Promyelocytic Leukemia

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Acute promyelocytic leukemia (APL) is characterized by severe haemorrhagic diathesis as the major cause of treatment failure and fatal outcome. Less frequently the patient may either present with thrombosis or it may complicate remission induction therapy. We present a 49-year-old female with a low-risk APL, with translocation t(15;17), bcr3 isoform transcript, and an aberrant immunophenotype expression of CD2 and CD56 antigens. She developed thrombosis of the left hepatic vein during remission induction with idarubicin and all-trans-retinoic acid(ATRA). She received prophylaxis with low molecular weight heparin (LMWH). After four months of anticoagulant therapy, Doppler ultrasonography showed a complete recanalisation of the left hepatic vein. Besides APL, she had a thrombophylia, methylentetrahydrofolate reductase (C677T) gene mutation which contributed as an extra risk factor towards thrombosis. The patient achieved complete cytologic, cytogenetic and molecular remission after completing antileukemic treatment combined with a LMWH.
In patients diagnosed with APL and concomitant thrombotic events, the screening test for inherited and/or acquired thrombophilia are highly recommended.

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Keywords: Budd-chiari syndrome; acute promyelocytic leukemia; all-trans-retinoic acid; thrombophilia.

1. INTRODUCTION

The risk of thrombotic events persists in patients with acute leukemias with the highest incidence in APL [1,2]. Thrombosis may be a presenting manifestation at diagnosis in up to 9.6% of patients having a similar rate during treatment of APL [2]. We present a patient with APL and extremely rarely reversible Budd-Chiari syndrome in whom heterozygosity for methylentetrahydrofolate reductase (C677T) gene mutation, probably contributory factor to thrombosis was also diagnosed.

2. CASE REPORT

A 49-year-old female patient presented in June 2012 with a headache of three months duration. On admission, the physical examination was normal. Laboratory analyses showed white blood cell count (WBC) $1.3x10^9$/l, hemoglobin 135 g/l, and platelets $165x10^9$/l with the presence of 52% of blasts and 8% of promyelocytes in the peripheral blood. Tests of hemostasis: d-dimer 15 µg/l (normal<0.5µg/l), activated partial thromboplastin time was 25.5sec (control 27-35sec), prothrombin time 66% (control 75-120%), fibrinogen 4.34g/l (normal 2-4 g/l). The liver and kidney function tests were within normal limits. Bone marrow aspirate showed hypercellularity with 73% myeloblasts and promyelocytes with prominent Auer rods in the cytoplasm of some cells. The myeloperoxidase was strongly positive in blast cells and promyelocytes. Immunophenotype of the bone marrow cells disclosed a population of blasts which were positive for CD34, CD38, cMPO, cCD68, CD117, CD13, CD33, CD11a, CD11b, CD4, CD64, CD56, CD2. Conventional cytogenetic analysis showed t(15;17)(q21:q11-22). The polymerase chain reaction (PCR) analysis detected the *PML-RAR* alfa rearrangement, type bcr3 isoform transcript. The diagnosis of APL with aberrant expression of CD2 and CD56 molecules and bcr3 isoform transcript was made.

The therapy according to PETHEMA protocol was given [Idarubicin 20 mg on day(D) 2, and 30mg on D4, D6, D8 and ATRA orally in two divided doses 50+40mg until 90 day, dexason 15.2x4mg intravenously during 15 days]. After this therapy she developed deep pancytopenia and fever, lasting 12 days. After 12 days of fever and pancytopenia she started to experience an epigastric pain. On physical examination hepatomegaly, right and middle abdominal tenderness were found. Liver function tests were within normal limits. Electrocardiogram and myocardial destruction tests troponin (<0.01) (normal value 0.00-0.013 ug/l) creatine kinase 34U/l (normal 0.150 U/l), creatin kinase-mioglobin, cK-MG 8.0U/l (normal 0-24 U/l) were normal. Fibrinogen 3.24g/l, PT 83%, PTT 27.5 sec, d-dimer 1.29 µg/l. Serum Aspergillus antigen was negative. A thoracoabdominal computerized tomography showed an enlarged liver with heterogenous parenchyma and left hepatic vein occlusion which was confirmed by abdominal multisliced computed tomography.

Ultrasonography revealed enlarged congested liver 190 mm in diameter and occluded left hepatic vein. The thrombotic mass was passing into the inferior vena cava. The main trunk of right hepatic vein was patent while the distal branches except for VIII segment area were occluded with thrombotic mass (Figs. 1 and 2).

Hemostatic data: kaolin clotting time 71.7sec (70-90sec), Antithrombin III 97%(80-120%), protein C 92% (70-140%), Protein S 106% (63-135%). The patient was heterozygous carrier for the methylentetrahydrofolate reductase (MTHFR) mutation. Anticardiolipin and antiphospholipid antibodies were negative. Factor V Leiden and prothrombin gene mutations were not detected. LMWH was administered in prophylactic doses because of a recent neurosurgical operation (fragmin 2 x 2500 international units). The general condition of the patient improved and control bone marrow aspirate showed a complete cytologic remission. After one month a follow-up Doppler ultrasonography still showed the persistence of the thrombotic mass in the left hepatic vein but after 4 months a complete recanalisation was seen. The patient achieved complete cytologic, cytogenetic and molecular remission in which she remains ever since.

3. DISCUSSION

The bleeding problem is well known in all types of acute leukemias, while thrombotic complications were underestimated although they may be even more frequent than previously recorded [1,2]. According to published small series and case reports in APL patients thrombosis develops during remission induction therapy with ATRA, emphasizing a contributing

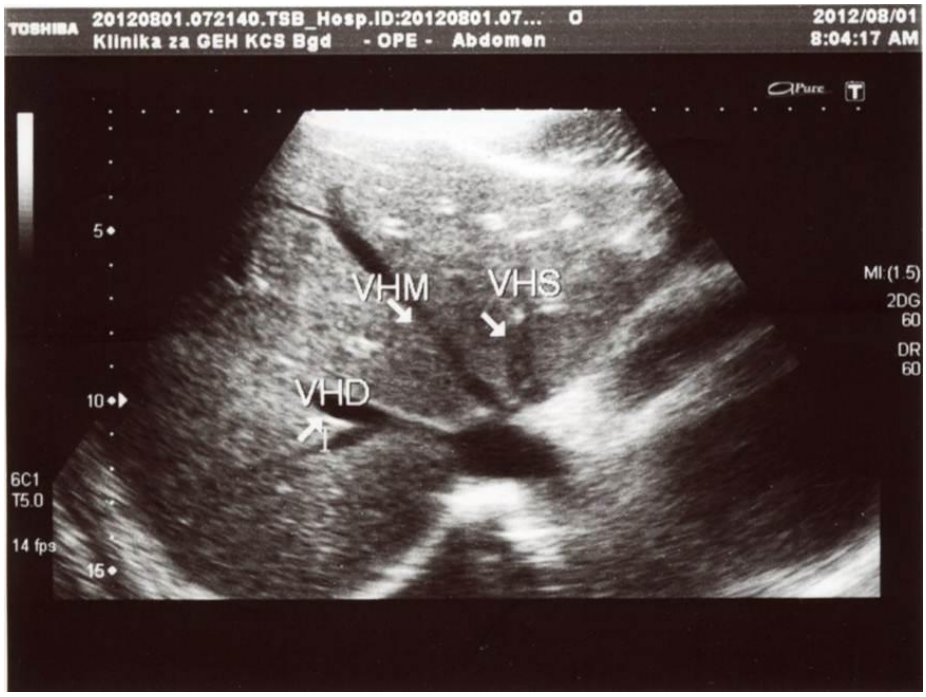

Fig. 1. Ultrasonographic presentation of a thrombotic mass within the left hepatic vein

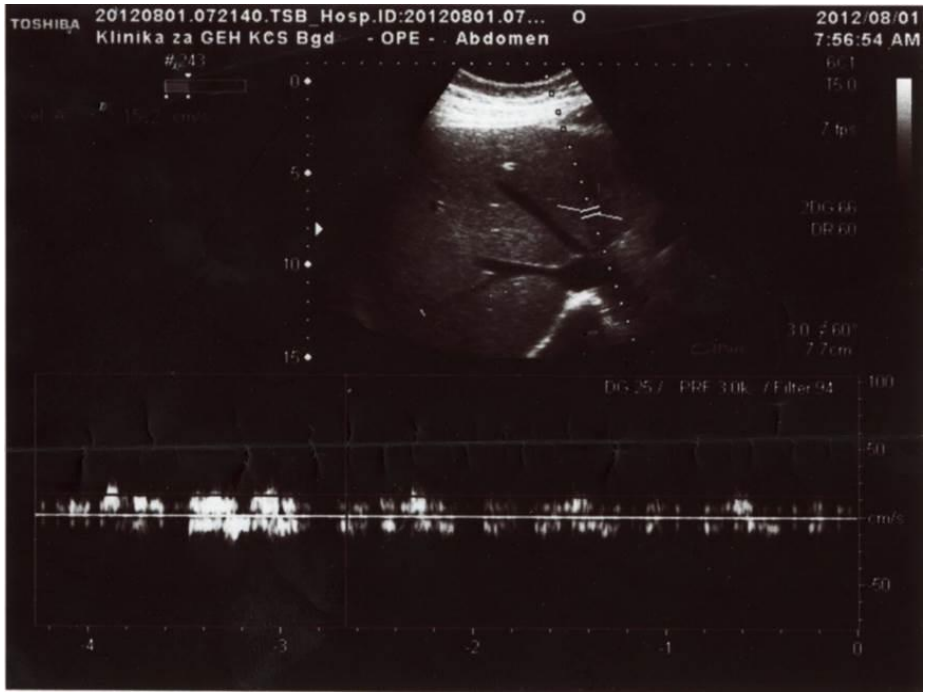

Fig. 2. Doppler ultrasonography showing an absent blood flow through the left hepatic vein

significance to thrombosis of ATRA [1-4]. But this untoward effect of ATRA was not confirmed in large cohorts of patient. Treatment with ATRA resolves coagulopathy in APL during several days but may produce imbalance between procoagulant and fibrinolytic factors leading to a

prothrombotic state [1-4]. The occurrence of arterial and venous thromboses in APL patients should be also analyzed in view of other usually nonleukemic prothrombotic contributory factors, such as hypertension, inflammation, malignancy, arteriosclerosis, diabetes, high level of low density lipoproteins, hyperhomocysteineamia, and advanced age. Furthermore, the infections which are common during remission induction chemotherapy in all subtypes of acute myeloid leukemia (AML) may produce endothelial cell damage followed by cytokine activation and consequent venous or arterial thrombosis [2].

The Budd-Chiari syndrome may be associated with various hematologic malignancies, mostly myeloproliferative neoplasms. Rarely, AML with leukocytosis followed by increased expression of the adhesion molecule CD56 may lead to accumulation and aggregation of blasts in microcirculation eventuating of blood vessel occlusions. If high WBC count is accompanied with disseminated intravascular coagulation (DIC), which may develop in all types of acute leukemia, hepatic vein thrombosis may occur but seldom. Usually the number of leukocyte in APL is low so that the risk of hepatic vein occlusion in this cohort of patients are extremely rare [2-7].

A Pub Med literature search yields only five case reports of hepatic vein occlusion reported so far [5-9]. Three patients had a fulminant course of the disease and diagnosis was established post mortem. Only one of these patients was treated with ATRA and, after establishing the diagnosis of Budd-Chiari syndrome, with thrombolytic therapy [8] which resulted in vein recanalisation. The course of the disease in the last case was not given [9]. The diagnosis of Budd-Chiari syndrome in our patient was suspected on the clinical ground and confirmed by imaging techniques, computed tomography, multisliced computed tomography, ultrasonography and Doppler ultrasonography. Our patient achieved a favorable outcome with conventional treatment, LMWH.

The opinion on the effect of WBC count on the incidence of thrombosis is not consistent. According to some new studies on patients with APL the WBC count does not influence the incidence of thrombosis [2]. Similar experience relates to the influence of platelet count [2]. The other studies provided an opposite evidence that risk factors for thrombosis in APL patients are high leukocyte count, prevalence of the bcr3 transcript type and expression of FLT3-ITD, CD2 and CD15 molecules [3]. In our case two of this predisposing factors were present in addition to inherited thrombophilia.

Hereditary thrombophilia may be a major contributory prothrombotic factor, the most frequent being factor V Leiden mutation (G1691A) [2,10]. In addition, *MTHFR* gene mutation, a C677T single nucleotide polymorphism leading to moderate hyperhomocysteineamia, has been reported as a factor with a significant risk of thrombosis [2].

4. CONCLUSION

In patients with APL and normal or low leukocyte count demonstrating an unusual thrombotic event, screening test for inherited and acquired thrombophilia are highly suggested.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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