Deep Vein Thrombosis in Acute Myelogenous Leukemia

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ABSTRACT

Thrombotic complications in acute leukemia are often underestimated because bleeding complications generally dominate the clinical picture. While there are many thrombogenic factors shared by both solid tumors and leukemia, many additional prothrombotic features are present in leukemia. The prothrombotic factors include hyperleukocytosis, increased expression of tissue factor and its activation in leukemic cells, and the prothrombotic adverse effects of therapeutic agents and vascular access cathethers.

A 18-year old woman came with swelling on her right leg 10 days before hospital admission. Since 2 months before she had had weakness, pallor and fever without bleeding manifestation. Hematologic examinations showed anemia, leukocytosis with monoblast and thrombocytopenia. Deep vein thrombosis in right femoral and right popliteal vein was confirmed using compression ultrasonography.

The treatment of such complications is challenging because of the high risk of hemorrhage in this group of patients, especially due to their severe thrombocytopenia.

Key words: *deep vein thrombosis, leukemia, hemorrhage.*

INTRODUCTION

The association between thrombosis and cancer has been extensively studied since first pointed out by Trousseau in 1895. It is, however, not commonly appreciated that the incidence of thrombosis in malignant hematologic disorders is as high as or even highers than in solid tumor.[1]

Among the malignant hematologic disorders, the incidence of thrombosis is higher in patients with lymphoma or acute leukemia. Significant morbidity and high mortality in acute leukemia due to complications of bleeding and infection frequently overshadows thromboembolic events. Case-controlled studies in patients with cancer revealed a fourfold increase in thromboembolic occurrence in acute leukemia, with about the same rate in acute myelogenous leukemia (AML) and in acute lymphoblastic leukemia (ALL). Among patients with acute leukemia, thrombosis has the highest incidence in acute preomyelocytic leukemia (APL). Of interest, increased thromboembolic events take place even prior to the diagnosis of acute leukemia, similar to the situation seen in solid tumors, indicating that a prothrombotic state is present even at the earliest phase of leukemia.[1]

In 455 leukemia patients, Mohren reported the venous thromboembolism in 10.8% of AML patients (without APL), 42.8% of APL patients and 13.0 of ALL patients.[2]

Virchow's classical triad of abnormalities in blood flow, vessel integrity and blood components have now evolved into a complex picture with multiple prothrombotic factors. These various factors interact with each others, thereby enhancing their combined effects.[1]

Here we report a case of AML patient with deep vein thrombosis on her right femoral and popliteal vein. This case is very interesting and important to be reported due to it being rarely found and the treatment of such

complications is challenging because of the high risk of hemorrhage.

CASE ILLUSTRATION

An 18-year old woman was admitted to Hasan Sadikin hospital because of swelling and pain on her right leg 10 days prior to admission. Since 2 months before, she had fatique , pallor and low grade fever. She had had no bleeding manifestation.

On physical examination, she was alert, her blood pressure and temperature were within normal limit. She had tachycardia (pulse 104 beat/minute). Her conjunctivas were anemic. There were no abnormalities on heart and lung examination. There was no lymphadenopathy or hepatosplenomegaly. There was swelling on her right leg without any sign of inflammation. The size of her right vs left thigh was 41 cm vs 38 cm and her right vs left calf was 33 cm vs 28 cm, respectively.

The laboratory examinations showed anemia (hemoglobin 7.5 g/dL, leukocytosis (white blood count 68.200/mm3), thrombocytopenia (platelet 51.000/mm 3), prothrombin time (PT) 13.0 seconds, INR 1.15, activated partial thromboplastin time (aPTT) 30.3 seconds and d-dimer 5.8 mg/L (normal < 0.3 mg/L). The renal function and electrolytes were within normal limits. On peripheral blood smear we found anisocytosis, polychromation on red blood cells, leukocytosis with monoblast and low platelet, which was diagnosed as acute monoblastic leukemia (AML M5) (Figure 1).

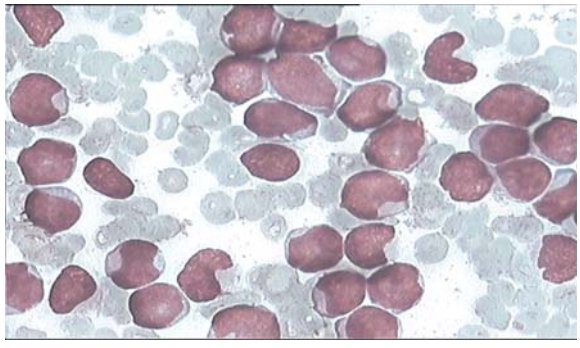

Figure 1. Peripheral blood smear: monoblast

The Doppler and compression ultrasonography showed non compressible right femoral and tibialis posterior vein (Figure 2).

We treated her with unfractionated heparin 60 U/kg body weight IV bolus, followed by 12 U/kg body weight continuous IV drip with target aPTT 2 times baseline. She was also treated with warfarin 2 mg. On the second day of heparinization, the platelet count decreased to

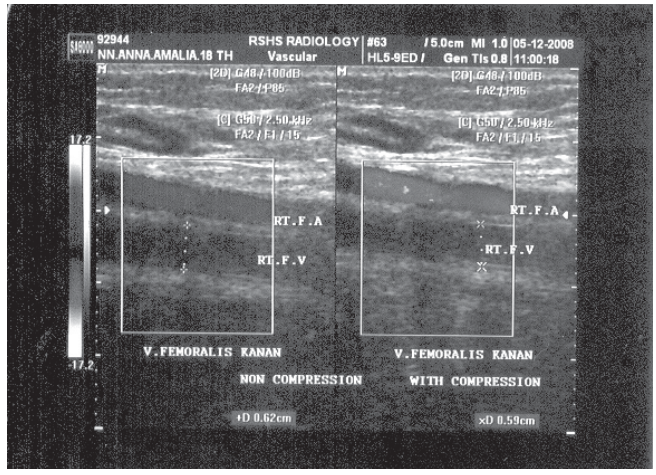

Figure 2. Compression ultrasonography: non compressible right femoral vein

47.000/mm3 with vaginal bleeding. At that time, the aPTT was 35.6 seconds, INR 1.38 and hemoglobin decreased to 6.6 g/dL. We stopped the heparin and warfarin. We gave her 16 mg protamin IV, 2 units of packed red cells and 4 units of random platelet transfusion. The vaginal bleeding was stopped on 5th day of treatment. The chemotherapy was not given due to financial problems. On the 7th day of hospitalization, the result of laboratory examinations were hemoglobin 8.8 g/dL, white blood count 54.300/mm3, platelet 74.000/mm3. She still had swelling on her right leg and was discharged without further anticoagulant.

DISCUSSION

The rate of venous thromboembolism (VTE) in patients with acute leukemia or lymphomas is comparable with that other "high risk" cancer types. The rate of thrombosis in 1752 children with acute lymphoblastic leukemia was 5.2%, most of the events occurred during the induction phase of therapy.[3] Thrombosis can be a presenting symptom at diagnosis in a significant portion (9,6%) of cases with acute promyelocytic leukemia (APL / AML-M3) and 3.2% in non-M3 AML.[4]

Patients with hematologic malignancies often present with a hypercoagulable state or chronic disseminated intravascular coagulation (DIC) in the absence of active thrombosis and/or bleeding.[5] Major determinants of the pathogenesis of clotting activity in hematologic malignancies include : tumor-cell derived procoagulant, fibrinolytic and proteolytic factors and inflammatory cytokines, cytotoxic therapies and infectious complication.[4]

The patophysiology of thrombosis in patients with leukemia, lymphoma or multiple myeloma is complex,

but is simplified and illustrated in figure 3, corresponding to abnormalities of one or more of the three classical categories of host defense mechanism as described by Virchow : blood flow (stasis) ; blood vessel wall function (injury) ;and dysfunction of the blood elements (both soluble and cellular). This process, in which tumor cell products interact with host cells (monocytes/ macrophages, endothelial cells, platelets, fibroblasts, parenchymal cell, etc) to produce the hypercoagulable state, is futher complicated by the prolonged periods of therapy-induced cytopenias and the rapid induction by chemotherapy of malignant cell destruction (with elaboration of tumor products).[5]

Blast cells isolated from patients with acute leukemia express procoagulant, fibrinolytic and protetolytic mediators as well as inflammatory cytokines, including tissue factor and cancer procoagulant. All subtypes of acute myelogenous leukemia express some procoagulant activity.[5]

Anticoagulant therapy is a particular challenge in patients with hematologic malignancies, since these patients are at very high risk for hemorrhage. No guidelines are available for the prophylaxis or treatment of VTE. Prolonged periods of treatment-induced thrombocytopenia in patients with hematologic malignancies require a more judicious application of standard anticoagulant approaches.[5]

No published results of randomized controlled trial studies have specifically addressed the issue of VTE treatment in acute leukemia. As previously noted for patients with solid tumors, a therapeutic strategy based on low molecular weight heparin (LMWH) administered for 6 months after VTE episode has proved safe and superior to warfarin in preventing VTE recurrence.[6,7] A similar approach was tested in a small group of patients with hematologic malignancies and VTE.[8] The use of LMWH in these patients is an attractive choice due to the safety profile, lack of requirement for laboratory monitoring , and reduced risk (compared with warfarin) for drug and food interactions.[8]

From 25 adult leukemia patients between December 2000 and December 2002, Imberti reported

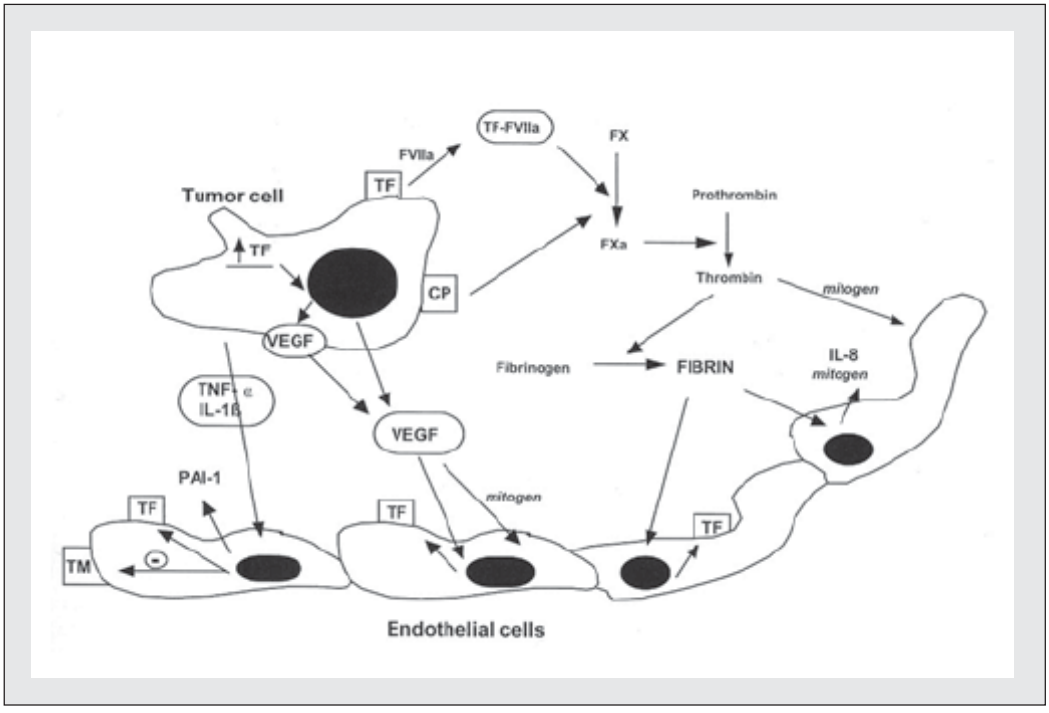

Figure 2. Host-tumor cell interaction and the hypercoagulable state of cancer.[5]

Tissue factor (TF) and cancer procoagulant (CP) are synthesized and expressed on the surface of tumor cells. The effects of these tumor cell procoagulants (made by both solid tumor and leukemic cells) are enhanced by the production of proangiogenic cytokines such as interleukin-8 (IL-8) and vascular endothelial growth factor (VEGF), both by the tumor cells and local endothelial cells. Release of proinflammatory cytokines, such as tumor necrosis factor (TNF-a) and interleukin-1 (IL-1b), by the tumor cells and host inflammatory cells further stimulates the hypercoagulable stase, as follows. These cytokines are indirect procoagulants by virtue of their ability to convert the anticoagulant endothelium to a procoagulant endothelium by (1) down-regulation of thrombomodulin (TM) expression and (2) increased endothelial cell synthesis of TF and plasminogen activator type 1 (PAI-1). Generation of fibrin at the endothelium enhances thrombogenesis by inducing additional TF and IL-8 production by the injured endothelial cells.[5]

4 leukemia patient with VTE (VTE incidence 11.4%); consisting of 2 ALL and 2 AML patients (AML M2 and AML M4). The two ALL patients developed DVT during the administration of chemotherapy. The AML M2 patient had pulmonary thromboembolism at diagnosis, while another AML M4 patient showed DVT as the first symptom of leukemia. All patients were treated with enoxaparin 100 IU/kg subcutaneously twice daily for one month, followed by 150 IU/kg once daily for at least 5 months. When the platelet count was below 20.000/mm3, the dose was reduced by 50%. During antithrombotic treatment neither VTE recurrence nor hemorrhagic complication or heparin-induced thrombocytopenia occurred.[8] In view of the high risk for bleeding in patients with hematologic malignancies, however, greater effort should be made to standardize dose-reduction regimens and provide guidelines for temporary suspension of LMWH administration according to the degree of thrombocytopenia.[5]

Falanga recommends the initial use of standard doses of LMWH preparations, but with frequent monitoring of peak anti-Xa levels, as in other high-risk groups for whom good pharmacokinetic parameters are not yet available (e.g., renal failure, obesity, pregnancy, children). Tight maintenance of peak levels between 0.5 and 1.0 IU/mL may improve the risk –benefit ratio for patients with hematologic malignancies and VTE. When the platelet count is reduced below 50.000/uL, the LMWH dose is reduced to 50% of the therapeutic dose; below 20.000/ uL, the LMWH is temporarily discontinued.[5]

Use of newer antithrombotic agents (e.g., the factor Xa inhibitor fondaparinux or the direct thrombin inhibitos hirudin, bivalrudin or argatroban) has not been reported in this group of patients.[5]

Our patient's symptoms and clinical presentations, along with laboratory and radiographic findings suggested with DVT in AML M5 patient. Our patient showed DVT as the first symptom of leukemia. DVT as the first symptom of AML also reported by Imberti.[8] In this past 5 years, in Hasan Sadikin Hospital Bandung, there was no report of DVT in leukemia patient. In this case, the patient did not get optimal treatment for leukemia and DVT because of financial problem. The UFH and warfarin treatment caused bleeding complication. This is keeping with recently reported findings showing that vitamin K antagonists are associated with a higher incidence of major hemorrhages in cancer patients than in non-cancer patients. With vitamin K antagonist, the overall incidence of recurrent venous thromboembolism and major bleeding in the patients with malignancy was significantly higher than in those without malignancy. (27.1% vs 13.3% and 9.0% vs 2.1% per patient-year, respectively).[9,10]

In this study Hutten observed that during treatment with vitamin K antagonists of documented venous thromboembolism, patients who were also known to have malignant disease had a three-to-six-fold higher risk for both recurrence and major bleeding compared with patients without malignancy.[10] Another study by Prandoni reported that 12-month cumulative incidence of major bleeding in DVT patients with vitamin K antagonist was 12.4% in patients with cancer and 4.9% in patients without cancer, for a hazard ratio of 2.2.[11] Inspite of there is no guidelines for DVT treatment in hematologic malignancies, based on the previous case report, we should use LMWH with close monitoring of hemorrhagic symptoms and platelet count.

CONCLUSION

Patients with acute leukemia are prone to develop venous thromboembolic complications, although the real incidence of this complication is unclear. The treatment of such complications is challenging because of the high risk of hemorrhage in this group of patients, especially due to their severe thrombocytopenia. The treatment choice is LMWH. When the platelet count is reduced below 50.000/uL, the LMWH dose is reduced to 50% of the therapeutic dose; below 20.000/uL, the LMWH is temporarily discontinued.

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