Disseminated Intravascular Coagulation: Laboratory Support for Management and Treatment

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ABSTRACT

Disseminated intravascular coagulation (DIC) is a condition in which hemostasis is altered, resulting in unregulated activation of the coagulation cascade. The hallmarks of DIC are thrombosis (from excess clotting), bleeding (from consumption of the coagulation proteins), and thrombocytopenia and anemia (from mechanical destruction of red cells and platelets by coagulation in the microvasculature). DIC is not an isolated disease, it is a symptom of another illness such as endothelial trauma, sepsis, malignancy, or a complication of pregnancy. Therefore, treatment of the underlying medical condition and supportive care with blood products is the mainstay of therapy for DIC. Measurement of platelet count, prothrombin time/activated partial thromboplastin time (PT/aPTT), fibrinogen, and D-dimer, can help diagnose DIC, but treating with blood components only to correct abnormal laboratory tests may not be efficacious. Replenishing coagulation factors, platelets, and red cells should be attempted cautiously as dictated by the clinical scenario. In this report, we discuss the role of the blood bank in helping to manage DIC in hematologic malignancy.

Keywords: disseminated intravascular coagulation, hemostasis, thrombocytopenia, coagulation, fresh frozen plasma

To illustrate key points, we describe a fictitious 18-year-old Hispanic male presenting to the emergency department of his local community hospital after a 3-week history of nose bleeds and increasingly severe fatigue. His past medical history is unremarkable. He was born at term by Cesarean section and achieved all of his developmental milestones at their appropriate times. He has no siblings. There is no family history of abnormal bleeding or clotting. He is not taking any prescribed medications and denies the use of recreational drugs and alcohol. Physical examination reveals blood clots in both nostrils and petechial hemorrhages in his mouth and lower extremities. A laboratory evaluation included a complete blood count (CBC), a basic metabolic profile, and prothrombin time/activated partial thromboplastin time (PT/aPTT). Upon review of his laboratory results and clinical picture, he was admitted for inpatient evaluation and treatment.

Although the patient's bleeding subsided, his laboratory results were monitored closely and blood products were administered throughout his hospital stay.

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Abbreviations

RBC, red blood cells; PT, prothrombin time; aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; TRALI, transfusion-related acute lung injury; AHF, antihemophilic factor; UK, United Kingdom; APL, acute promyelocytic leukemia ; MCV, mean corpuscular volume; AML, acute myelogenous leukemia; PML, promyelocytic leukemia; RARA, retinoic acid receptor-alpha; FP24,plasma frozen within 24 hours after phlebotomy; TP, thawed plasma

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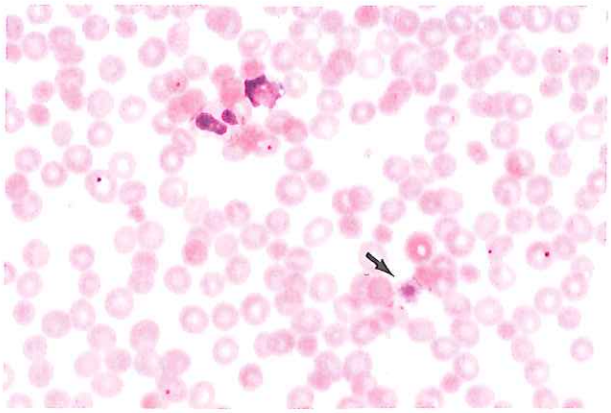
Patient Test Results

The laboratory data (**Table 1**) revealed profound anemia (hemoglobin 6.7 g/dL) with significant reticulocytosis (8%) and an increased mean corpuscular volume (MCV) of 95 fL, suggesting hemolytic anemia with appropriate bone marrow response. Platelets were decreased (9000/μL) with numerous giant forms seen on a peripheral smear and an increased mean platelet volume (MPV) of 12 fL (**Image 1**). The coagulation profile included a PT of 47 seconds and an aPTT of 75 seconds that corrected to near normal with mixing studies, suggesting multiple factor deficiencies. The

Image 1

This peripheral smear is an example to illustrate a giant platelet (arrow). Giant platelets are younger platelets produced by the bone marrow in response to platelet destruction as seen in DIC.



treating physician requested a fibrinogen level (which was <76 mg/dL), degradation-dimer (D-dimer) (9.0 µg/mL), and a direct antiglobulin test, which was negative. The patient's white count was normal (7.7 K/uL), but a marked left shift with numerous promyelocytes (47%) was observed in the peripheral smear (**Image 2**).

Table 1. Patient's Test Results from Emergency Department Admission

Laboratory Test	Laboratory Results	Reference Range*
WBC count	7.7 K/µL	4.23-9.07 K/µL
RBC count	1.7 M/µL	4.63-6.08 M/µL
Hemoglobin	6.7 g/dL	13.7-17.5 g/dL
Hematocrit	19.5%	40.1-51.0%
MCV	95 fL	79.0-92.2 fL
MCH	30.5 pg	25.7-32.2 pg
MCHC	34.9 g/dL	32.3-36.5 g/dL
RDW	14.3%	11.6-14.4%
Reticulocyte	8%	0.51-1.81%
Platelet count	9 K/µL	161-347 K/µL
MPV	12 fL	9.4-12.4 fL
Polys	29.0%	34-67.9%
Bands	**With Polys**	**%**
Metamyelocytes	7%	0
Promyelocytes	47%	0
Myelocytes	5%	0%
Myeloblasts	6%	0%
Lymphocytes	5%	21.8-53.1%
Monocytes	1%	5.3-12.2%
Eosinophils	0	0.8-7.0%
Basophils	0	0.2-1.2%
PT	47 sec	11.6-15.2 sec
aPTT	75 sec	25.3-37.3 sec
Fibrinogen	<76 mg/dL	177-466 mg/dL
D-dimer	9.00 µg/mL FEU	0.00-0.50 µg/mL FEU

WBC, white blood cells; RBC, red blood cells; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; MPV, mean platelet volume; polys, polymorphonuclear cells; PT, prothrombin time; aPTT, activated partial thromboplastin time; D-dimer, fibrin degradation fragment.
**Reference ranges are those established and used at the Department of Laboratory Medicine, National Institutes of Health.*

The clinical and laboratory findings suggested DIC secondary to acute myelogenous leukemia (AML), and the likely diagnosis was acute promyelocytic leukemia (APL). Molecular studies for the PML-*retinoic acid receptor-alpha (RARA)* gene fusion were positive. This molecular alteration occurs in more than 95% of cases of APL and is a fusion of the promyelocytic leukemia (PML) gene on chromosome 15q22 and the *RARA* gene on chromosome 17q21.[1]

Review of Hemostasis

Hemostasis relies on a precarious equilibrium between bleeding and clotting. Four components act together to maintain hemostatic balance: the vascular system, platelets, coagulation factors, and fibrinolytic tissue repair.[2] Coagulation factors are activated by various stimuli, including tissue injury and inflammation. There are 2 coagulation pathways, the intrinsic and extrinsic, which converge into the common pathway (**Figure 1**).

Coagulation can be initiated in vitro by either the extrinsic or intrinsic pathways, depending on the stimulus, although in vivo the extrinsic pathway is the dominant mechanism of coagulation.[3] In the extrinsic pathway, platelet tissue factor is released by disrupted cells and enters the circulation. In the presence of tissue factor, factor VII is activated to factor VIIa. In the presence of ionized calcium, factor VIIa activates factor X to factor Xa. In the intrinsic pathway, contact activation factors prekallikrein, high molecular weight kininogen, factor XII, and factor XI interact to activate factor IX to IXa. Activated factor IXa converts factor X to factor Xa in the presence of calcium and factor VIII. The common pathway intersects these two cascades,

Image 2

This peripheral blood smear is an example showing promyelocytes with characteristic large nuclei, fine chromatin pattern, nucleoli, and the presence of multiple rod-shaped structures (Auer rods) in the cytoplasm.

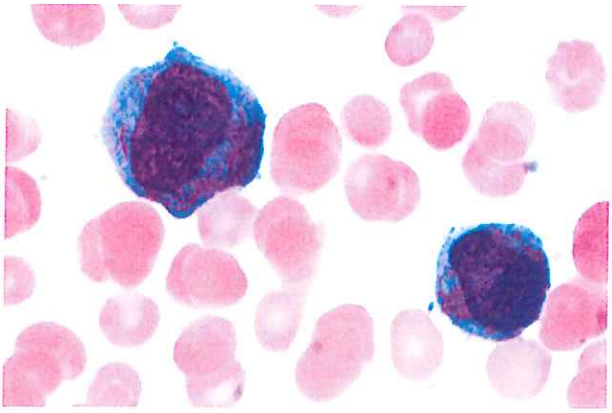
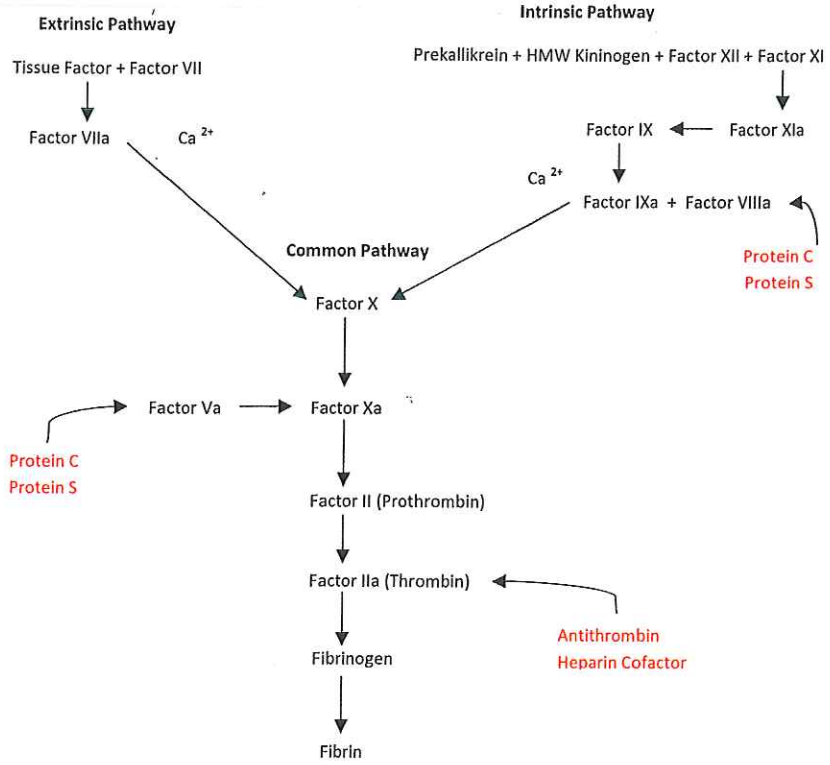


Figure 1

Basic coagulation pathways.



beginning with activated factor X, which converts factor II (prothrombin) to thrombin that in turn converts fibrinogen to fibrin, leading to clot formation.[2] Fibrinolysis releases the factors to be recycled. Other proteins, most prominently antithrombin and proteins C and S, work together to inhibit the coagulation cascade while fibrinolytic proteins, such as plasmin, work to degrade it.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) results from unregulated and excessive generation of fibrin leading to thrombosis and, paradoxically, bleeding due to consumption of coagulation proteins.[4] Laboratory studies show elevated coagulation times (PT, aPTT), decreased fibrinogen, increased fibrin degradation fragments, thrombocytopenia, and anemia. DIC is a secondary manifestation of several underlying diseases including hematologic malignancies. As many as 15% of patients with cancer and virtually all patients with APL develop DIC.[4] Untreated APL is fatal in 56% of cases in the first few days after diagnosis, due to uncontrolled hemorrhage from DIC.[5]

Table 2. Description of Plasma Alternatives for Coagulation Factor Replacement

Product	Source	Storage	Expiration	Thawing	Storage After Expiration	Factor Activity Within Normal Range of Human Plasma?
Fresh frozen plasma	Whole blood or plasmapheresis	≤-18°C or ≤-65°C	≤-18°C, 12 mo or ≤-65°C, 7 y	1-6°C	24 h post thaw	Yes
Plasma frozen within 24 hours after phlebotomy	Whole blood	≤-18°C	12 mo	1-6°C	24 h post thaw	Yes
Thawed plasma	Whole blood	1-6°C	5 days from date original product was thawed	Not applicable	Not applicable	No

FFP, fresh frozen plasma; PF24, plasma frozen within 24 hours after phlebotomy; TP, thawed plasma.

The diagnostic feature of most acute leukemias is the presence of circulating blasts (immature hematopoietic cells). APL blasts are particularly rich in tissue factor. The lysis of blast cells in APL, whether by natural cell turnover or induced by treatment, causes the release of tissue factor.[4] Tissue factor activates the extrinsic pathway and excess amounts lead to uncontrolled fibrin clot formation.

Component Support

DIC is a condition in which the normal balance of hemostasis is altered to favor fibrin formation. Factors that promote and inhibit coagulation are consumed faster than they are synthesized, disrupting hemostatic control. The natural sequence following fibrin formation is fibrinolysis, yet in DIC this process is disrupted, resulting in uncontrolled consumption of coagulation factors, platelets, and the formation of fibrin degradation products. The patient begins to bleed at the same time disseminated coagulation is occurring.

When a patient presents with clinical and laboratory evidence of DIC, the first-line therapy is to treat or remove the underlying cause and provide supportive care. Transfusion is an important component in the care of patients with DIC although consideration of transfusion with blood products should be not be based solely on laboratory results, but instead should take into account clinical evidence of active bleeding. Transfusion with plasma, platelets, cryoprecipitated antihemophilic factor (AHF), and red blood cells (RBCs) may be indicated.[6] Use of these components may fuel clot formation, yet be essential to maintain hemostasis.[7]

Transfusion with plasma to replace diminished coagulation factors is helpful when clotting times are prolonged and there is evidence of bleeding.[8] Plasma transfusions introduce a risk for transfusion-related acute lung injury (TRALI) that should be considered before indiscriminately including plasma products when RBCs are given. Clotting tests, such as PT and aPTT, should be used to monitor the impact of infusion of fresh frozen plasma (FFP). Several plasma alternatives that can be used for coagulation factor replacement include FFP, plasma frozen within 24 hours after phlebotomy (FP24), and thawed plasma (TP).[9] These plasma products differ in regard to traceability source, storage, expiration, and factor activity (**Table 2**).[10] The heat liable factors V and factor VIII in thawed plasma are not within the normal range for human plasma, but are above the hemostatic threshold of 35%. When plasma is given for coagulation factor replacement, the typical dose is 10 to 20 mL/Kg.[9]

Platelet transfusion should be considered in patients with severe thrombocytopenia. A reasonable target for platelet transfusion is 50,000/μL, depending on the risks for bleeding.[7] Platelets obtained through apheresis or in whole blood donations can be transfused. When transfusing apheresis platelets, it is important to take into account the number of equivalent units in the collection bag. The expected increase in the platelet count may be lower in patients with ongoing coagulopathy.[11]

Another component of plasma important in supporting a patient with DIC is fibrinogen. According to a study by Kitchens, fibrinogen levels should be kept between 50 and 100 mg/dL, and the best source of fibrinogen is cryoprecipitated AHF.[7] Although there is a fibrinogen concentrate, haemocomplettanP/RiaSTAP, it is only available in the United Kingdom (UK) and is used to treat congenital hypofibrinogenaemia.[8]

Red blood cells (RBCs) should be administered to maintain hemoglobin in the range of 6 to 10 g/dL.[7,11,12] One unit of RBCs should increase the hemoglobin level by about 1 g/dL in an adult with normal blood volume.[9] As with all blood

products, transfusion of RBC can cause untoward reactions and should be administered only when medically necessary.

Beyond standard blood component therapy, the use of antifibinolytic agents is controversial.[8] Other therapeutic options include heparin, antithrombin, and, at one time, recombinant human activated protein C (**Figure 1**). Heparin may be considered in DIC when thrombotic complications are predominant, or used prophylactically in nonbleeding patients at high risk of thromboembolism.[5,11] Heparin inhibits thrombin and may be indicated in DIC with predominantly thromboembolic manifestations. If heparin is used, close monitoring of aPTT and heparin levels is important. Because antithrombin is consumed in DIC, its replacement may increase clearance of thrombin. Recombinant human activated protein C was once used since it inhibits thrombin activation. Recently, however, the product has come under scrutiny and was withdrawn from the US and European markets in 2011 after numerous studies failed to show any benefit from its use in either DIC or sepsis, and some studies showed potential harm. Use of activated protein C in combination with medications such as corticosteroids is currently under review.[13]

The role of the blood bank in providing blood components to a patient with DIC is vital to the patient's successful outcome. There needs to be a coordinated effort in obtaining laboratory values, transfusing blood components, and monitoring the effects of transfusions to correct or stabilize coagulation status. Blood bank involvement is critical when managing a patient with DIC. If prolonged use of products is anticipated, the blood bank must be notified early to ensure the availability of products necessary for treatment of the patient. Hematology and coagulation laboratories also are valuable members of the team working with physicians to manage a patient with DIC.

Summary

DIC is associated with sepsis, obstetric disorders, and hematologic malignancies. We present a fictitious case report of a young male with bleeding and laboratory results consistent with APL and DIC. The patient received appropriate medical support, including blood product therapy, until resolution of his bleeding symptoms and remission of his leukemia. Platelet count, PT/aPTT, fibrinogen, and fibrin degradation fragments were key laboratory values. An understanding of the coagulation process and the role of coagulation factors in hemostasis is important for laboratory personnel. Patients with DIC need blood components to replenish and maintain levels of coagulation factors and platelets. The laboratory provides constant monitoring of coagulation parameters and therapeutic blood components in the supportive care of these patients. **LM**

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