

The Secret Behind Profuse Bleeding Following a Routine Skin Biopsy

Sreelatha Chalasani, MD, MPH; Satya SV. Bhupathi MD, MPH; Roxann Rokey, MD, FACC, FASE

ABSTRACT

A 73-year-old man underwent a facial skin biopsy, after which he experienced persistent, severe bleeding over a 4-day period that could not be staunched by suturing or cauterization. Patient history suggested a bleeding diathesis. A condition of chronic disseminated intravascular coagulation (DIC) that decompensated into an acute state of DIC subsequent to the biopsy was diagnosed based on laboratory findings. Physical examination followed by imaging revealed a large abdominal aortic aneurysm as the likely underlying etiology. The patient achieved stability with blood component replacement therapy and an initial round of heparin that was substituted with enoxaparin. Following cardiac catheterization, where triple vessel coronary artery disease was diagnosed, surgical correction of the abdominal aortic aneurysm and coronary artery bypass grafting were deemed to be too high risk. The patient was treated medically for his abdominal aortic aneurysm, coronary artery disease, and acute and chronic DIC. Within a year, the patient succumbed to a brainstem stroke. In patients with acute or chronic DIC, a thorough examination is recommended to exclude rare causes and to improve overall general management.

INTRODUCTION

Chronic non-overt disseminated intravascular coagulation (DIC) caused by an undiagnosed underlying pathology may easily be missed until a triggering event tips the coagulation balance in favor of a full-blown, acute DIC crisis. We present the case of a man whose wound bleeding could not be stopped after a routine skin biopsy until DIC was recognized. A previously undetected abdominal aortic aneurysm was assessed

to be the likely underlying etiologic pathology. After thorough evaluation, he was determined to be a poor candidate for surgical repair of the abdominal aortic aneurysm. The patient was managed medically and his acute and chronic DIC was treated with blood component replacement and low molecular weight heparin.

CASE REPORT

Subsequent to the biopsy of a suspicious lesion on the right temple, a 73-year-old man experienced persistent bleeding at the biopsy site. Over a 4-day period, he went to his primary care physician or emergency department (ED) 7 times, where the wound was both sutured and cauterized. While awaiting the results of an ongoing evaluation, he presented to the ED with severe bleeding and was admitted to the hospital.

His past medical history was significant for alcoholic cirrhosis, hypertension, and several bleeding events: a hemorrhagic cerebrovascular accident with residual right-sided hemiparesis 19 years previously, significant bleeding following a dental extraction 3 months previously, gastrointestinal bleeding attributed to a rectal polyp that required hospitalization 6 months previously, and approximately 2 months previously his right arm and right leg had turned black from ecchymosis following a fall. He is a former alcoholic who quit drinking 25 years ago.

His hematological workup in the ED revealed normal white blood cells (WBC) of 8300 cells/cu mm, low normal hemoglobin (Hgb) of 12.9 g/dL (normal range: 12.9-17.3 g/dL), low platelets (Plt) of 86,000/ μ L (normal: 175,000-450,000/ μ L), prolonged prothrombin time (PT) of 13.9 seconds (normal: 9.0-11.4 seconds), increased International Normalized Ratio (INR) of 1.4 (normal: 0.8-1.2), slightly prolonged activated partial thromboplastin time (aPTT) of 32.6 seconds (normal: 23.6-31.6 seconds), low plasma fibrinogen of 76 mg/dL (normal: 174-442 mg/dL), highly elevated fibrin degradation products >40 μ g fibrinogen equivalent units (FEU)/mL (normal: <5 μ g FEU/mL), and positive D-dimers.

Author Affiliation: Marshfield Clinic, Marshfield, Wis (Chalasani, Bhupathi, Rokey).

Corresponding Author: Roxann Rokey, MD, Department of Cardiology, Marshfield Clinic, 1000 N Oak Ave, Marshfield, WI 54449; phone 715.387.5080; fax 715.389.3808; e-mail rokey.roxann@marshfieldclinic.org.

A diagnosis of DIC was established and the patient was admitted to the hospital and treated with fresh frozen plasma and platelet transfusion. Bleeding stopped temporarily, but later resumed. Due to persistent bleeding he was transferred to our hospital the next day for further management. He was given vitamin K and fractionated heparin before he was transferred.

Upon arrival, his blood pressure was 151/80 mmHg, heart rate 70 bpm, respiratory rate 20/min, and temperature 98.2°F. The biopsy site was bleeding profusely, and multiple areas of ecchymosis were present around his right eye and over his chest. No other bleeding sites, including the sites of venipuncture were present. Abdominal examination revealed a large pulsating abdominal aortic aneurysm measuring about 6 cm wide and 12 cm in length, but no hepatosplenomegaly. Initial laboratory tests revealed a normal WBC of 6600 cells/cu mm, low Hgb of 8.3 g/dL (12.9 g/dL 2 days ago), low Plt 122,000/ μ L (an increase from 86,000/ μ L after 8 units of platelet transfusion), increased INR of 1.5, normal PT of 11.1 seconds, prolonged aPTT of 45.5 seconds, strongly positive D-dimers, and persistently positive fibrin monomers. His liver function test showed alanine aminotransferase of 29 IU/L, aspartate aminotransferase of 21 IU/L, albumin of 3.5 g/dL, and total bilirubin of 0.9 mg/dL. Troponins were elevated with a maximum of 2.3 ng/mL (normal: \leq 0.1 ng/mL) and EKG revealed first degree A-V block with inferior infarct pattern unchanged from a previous EKG 8 months ago.

The patient was further investigated to establish a cause for DIC. A sepsis screen was negative, prostrate specific antigen was normal, and his chest X-ray was clear. The coagulation factors, factors V, VIII, IX, XI, XII that were tested after multiple transfusions, were within the normal range. Mixing study was normal. Computed tomography (CT) of the abdomen showed a very large infrarenal abdominal aortic aneurysm (6.6 cm x 6.9 cm x 13 cm) with extensive mural thrombus, a cirrhotic liver, and portal hypertension.

Initial management at our institution consisted of fluids, switching to low molecular weight heparin, and pressure dressing over the biopsy. Hemostasis was achieved following infusion of cryoprecipitate. Two-dimensional echocardiogram showed posterobasal infarction. On the day of admission, he was switched to low dose unfractionated heparin in order to have cardiac catheterization. Following this, he was subsequently restarted on low molecular weight heparin.

During his 15-day stay in the hospital, he received a total of 5 units of cryoprecipitate, 8 units of fresh frozen plasma, 8 units of Plt, and 2 units of packed red

blood cells. His symptoms improved and coagulopathy was stabilized. He was found to have triple vessel coronary disease, and was felt to be at high surgical risk. He was managed conservatively and discharged to a nursing home on low molecular weight heparin with a plan of elective repair of the abdominal aortic aneurysm and coronary artery bypass graft surgery. During his follow-up as an outpatient, he reported no bleeding from the biopsy site or elsewhere (bruising, epistaxis, etc.). His DIC panel showed a normal PT and INR, normal fibrinogen, elevated PTT (between 33 and 37), elevated fibrin split products, low platelets (between 100-150), and persistently positive fibrin monomer, which is suggestive of continued chronic DIC. Two months after his last outpatient visit, the patient died suddenly, apparently as a result of a brain-stem stroke.

DISCUSSION

Stable non-dissecting abdominal aortic aneurysm is a rare but well-recognized cause of chronic DIC and, in cases of dissection with varying acuity, both chronic and acute DIC. In stable abdominal aortic aneurysm with other precipitating causes, acute DIC can become manifest, such as was seen in our patient. The first case of dissecting aortic aneurysm with DIC was described in 1967 by Fine.¹ Since then, many cases of DIC associated with arterial aneurysm have been reported.²⁻⁸ Clinically overt DIC has been reported to occur in about 1%-4% with aortic aneurysm,^{4-6,8,9} but chronic DIC may be under-diagnosed. Seibert and Natelson¹⁰ proposed 4 criteria for accepting stable aortic aneurysm as the primary etiological factor for chronic consumption coagulopathy. These are (1) chronic acquired bleeding disorder, (2) laboratory evidence of consumption coagulopathy, (3) disappearance of the haemostatic defect after successful aneurysm repair, and (4) maintenance of normal coagulation for at least 3 months thereafter.¹⁰ Our patient had fulfilled the first 2 criteria. In patients not deemed suitable for surgery, or in those patients who decline surgery, it is not possible to fulfill the last 2 criteria. Although our patient had not been diagnosed with chronic DIC in the past, for 6 months prior to admission he had new symptoms of ecchymosis, easy bruisability, and significant bleeding following tooth extraction consistent with chronic DIC. If further investigations had been done during his previous bleeding episodes, he could have been diagnosed with DIC early.

Liver cirrhosis can have an impact on the hemostasis system, the extent of which correlates with the degree of liver disease. Because liver parenchymal cells

synthesize most factors of the clotting and fibrinolytic systems, levels of these procoagulant and anticoagulant, as well as profibrinolytic and antifibrinolytic factors will decrease in plasma. These changes may be minor in patients with mild liver disease but are severe in patients with cirrhosis. Chronic DIC, fibrinolysis, or dysfibrinogenemia can present in cirrhosis, but are generally associated with advanced liver disease. The patient certainly had no evidence of worsening hepatic disease, which is suggestive from his unchanged Child Pugh score.^{11,12} Therefore, chronic stable liver disease is less likely to be the cause of his DIC, especially since he had a huge abdominal aortic aneurysm with extensive mural thrombus. We postulate that his large abdominal aortic aneurysm was the underlying etiology for the chronic DIC, and the skin biopsy with subsequent continued bleeding was the trigger that pushed him to a decompensated state.

The mechanism for DIC has been extensively discussed in the literature. Before Fine reported his first case of DIC, Prentice and his associates showed that the adhesion of platelets was greater in atheromatous areas of the aorta than normal.¹³ Studies with indium-111-labeled platelets, I-131-labeled fibrinogen have shown increased uptake in the aneurysm.^{14,15} It is thought that exposure of the subendothelial layer of the aortic wall and the relative stasis of the blood within the aneurysm stimulate both extrinsic and intrinsic coagulation.¹⁶

DIC is a complex syndrome that involves both the coagulation system and inflammatory mediators.^{17,18} It is characterized by thrombohemorrhagic symptoms: activation of procoagulants, activation of fibrinolytic system, inhibitor consumption, and end organ damage.¹⁹ It is not a primary disease but a disorder secondary to underlying disease that manifests itself in a broad spectrum of often confusing clinical and laboratory signs and symptoms that may change over time.²⁰ It is most frequently first clinically suspected when a patient presents with signs of extraordinary bleeding diathesis.

There is no single clinical symptom or test pathognomonic for the diagnosis of DIC. D-dimer appears to be the most sensitive and specific test in DIC, but it must be combined with other test results and clinical symptoms to derive a diagnosis.^{19,21}

DIC ranges in severity over a continuum from a subclinical compensated activation of haemostatic factors (non-overt, chronic, low-grade DIC) through decompensated coagulopathy (overt, acute, fulminant DIC).^{22,23}

In chronic non-overt DIC, blood is continuously or intermittently exposed to small amounts of tissue fac-

tor and the compensatory mechanisms in the liver and bone marrow are able to replenish the depleted factors and platelets.^{19,20} Chronic DIC is seen with malignancy, abdominal aortic aneurysm, vascular, inflammatory disorders, obstetric causes, etc. Clinically, patients may be asymptomatic, present with minor symptoms like skin or mucosal bleeding, or present with only laboratory evidence of DIC. But in a few cases, an additional condition may be present, such as new or worsening hepatic disease (of which our patient had no evidence), tooth extraction, dissecting or rapidly expanding aneurysm, or as postulated in our patient, skin biopsy with recurrent bleeding that may cause decompensation of this balance leading to manifestation of acute or chronic DIC.^{2,3}

Acute DIC is a serious complication associated with high mortality. Some have equated the DIC acronym with "death is coming."²⁴ Most commonly, mortality results from multiple organ failure secondary to tissue ischemia caused by widespread microvascular thrombotic obstruction. In acute overt DIC, blood is exposed to large amounts of tissue factor over a brief period with massive generation of thrombi. This overwhelms control mechanisms and there is no time for the compensatory mechanisms to recover. The clinical consequence is consumption of coagulation factors that leads to systemic bleeding diathesis or microvascular thrombosis.

Regardless of the etiology, the definitive treatment of DIC is usually considered to be removal of the cause. In our patient, repair of the abdominal aortic aneurysm would be a first choice of treatment.

Our patient was deemed a poor surgical candidate and anticoagulants and blood components were administered to correct the abnormal haemostatic parameters. Some caution should be utilized in using blood component replacement therapy (packed red blood cells, platelet transfusions, and fresh frozen plasma), since it could theoretically "add fuel to the fire."¹⁹ However, there is no clinical evidence on which to base such precautions and it is a widely ordered component of overall therapy.^{23,25}

Component replacement therapy is combined with carefully monitored low dose fractionated or unfractionated heparin administration to inhibit further coagulation. Low dose heparin acts principally by inhibiting the generation of Xa and thrombin.^{6,26,27} Our patient received fresh frozen plasma, cryoprecipitate, platelets, and packed red blood cells as replacement therapy and was anticoagulated with low dose heparin. This resulted in significant and stable improvement in symptomatology and hemostatic abnormalities.

CONCLUSION

Small triggering events, such as skin biopsy, can result in acute or chronic DIC. In the presence of continued bleeding and suspected acute or chronic DIC, a thorough physical examination and evaluation is warranted to evaluate for unsuspected causes of chronic DIC, such as abdominal aortic aneurysm.

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