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April 2024 Critical Care Case of the Month: A 53-year-old Man Presenting with Fatal Acute Intracranial Hemorrhage and Cryptogenic Disseminated Intravascular Coagulopathy

Robert A. Raschke MD MS [1,2]
Kim Josen MD [2]
Ethan Weisman BS [3]

[1]Department of Medicine and Biomedical Informatics, University of Arizona College of Medicine-Phoenix, Phoenix AZ USA
[2]Pulmonary and Critical Care Medicine, HonorHealth Osborne, Scottsdale, AZ USA
[3] The Honors College, Arizona State University, Tempe, Arizona, USA

History of Present Illness: A 53-year-old man was admitted for acute onset of left hemiparesis, left facial droop and dysarthria witnessed by his wife (a nurse) while they were watching TV that evening. She reported the patient had no previous history of coronary artery disease or cerebral vascular disease, prior to an admission occurring three weeks earlier. The patient presented at that time with acute, severe left-sided chest pain that began while he was doing some heavy yardwork. While being evaluated in the emergency department (ED), he developed left-sided facial numbness, hemiparesis and dysarthria. A CT scan of the brain was normal. Neurological symptoms resolved before lytic therapy could be administered. Troponins and EKG were normal. A D-dimer was >20 mg/L, but a CTA of the chest showed no pulmonary embolism and was otherwise unrevealing. The chest pain resolved without specific therapy. Subsequent CTA of the head and neck and a brain MRI were both normal. Other labs drawn during that two-day hospitalization, including a CBC, complete metabolic profile, INR and aPTT, were all essentially normal. The patient was diagnosed with transient ischemic attack, atypical chest pain and new onset hypertension, and discharged on 81 mg aspirin and 2.5 mg amlodipine daily.
The patient did well over the intervening three weeks except for poor control of his hypertension, with blood pressures measured at home as high as 178/105. On the morning before his current presentation, the patient coughed up blood. The patient's wife examined his mouth and noted several "blood blisters" of his buccal mucosa which she attributed to his poorly fitting dentures. The patient was otherwise well until the onset of stroke symptoms at 2200, after which he complained of diffuse headache.

Past Medical History: The patient had no known allergies. He had a history of emphysema, GERD and hypercholesterolemia and was taking rosuvastatin, esomeprazole and inhaled fluticasone/umeclidinium/vilanterol in addition to amlodipine and aspirin. He had a remote history of major trauma resulting in

asplenia. He didn't smoke, vape, drink alcohol excessively or use drugs. He worked as a truck driver.

Physical Examination: Initial physical examination was significant for HR 117 bpm, RR 18 bpm, temp. 36.5°C, BP 169/99 mmHg. His Glascow Coma Scale (GCS) was 14 and he was dysarthric, with a rightward gaze preference and a dense L hemiplegia. Ecchymoses of his left knee and right shoulder were noted. A stat CT brain showed a 6x4x4cm intraparenchymal hematoma centered on the right basal ganglia, effacing the right lateral ventricle and causing 6mm of midline shift. It was confirmed that the patient had not taken any antithrombotic medications or clopidogrel. Admission labs demonstrated a WBCC 22.8 $x10^3$/uL, Hb 12.8 g/dL and platelet count of 64 $x10^3$/uL. An automated five-part differential (neutrophils, lymphocytes, monocytes, basophils, and eosinophils) was normal. The INR was 2.2 and aPTT 38 secs. Fibrinogen was 62 mg/dL and a D-dimer >20 ml/L. A complete metabolic profile was unremarkable.

Routine management of acute hemorrhagic stroke includes which of the following ***except***?

1. Rapid control of systolic blood pressure to levels <140mmHg using intravenous antihypertensives if necessary.
2. Rapid reversal of antithrombotic effects of medications such as warfarin with four-factor prothrombin complex concentrate (4F PCC), and Xa inhibitors with andexanet alpha or 4FPCC.
3. Platelet transfusion to maintain platelet count >100 $x10^3$/uL in patients with thrombocytopenia.
4. Platelet transfusion to restore platelet function in patients with normal platelet counts, but platelet dysfunction due to aspirin or other antiplatelet drugs.
5. Neurosurgical consultation.

Correct!

4. Platelet transfusion to restore platelet function in patients with normal platelet counts, but platelet dysfunction due to aspirin or other antiplatelet drugs.

Hypertension control to a goal systolic blood pressure of 140 mmHg should ideally be achieved within the first hour of presentation with hemorrhagic stroke. The effects of antithrombotic therapies such as warfarin, heparin, and oral Xa inhibitors and dabigatran should be rapidly reversed and platelets transfused if needed to achieve >100 $x10^3$/uL. These therapies may limit hemorrhagic extension – an independent predictor of mortality and poor outcome. Clinical trial data suggests that platelet transfusions in patients receiving antiplatelet drugs, but without thrombocytopenia, may be hazardous and should be avoided. Neurosurgical consultation should be emergently pursued for management of intracranial hypertension.

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Emergent neurosurgical consultation was obtained and a nicardipine infusion was administered to maintain SBP $\leq$140 mmHg. Fresh frozen plasma (FFP), cryoprecipitate and platelets were administered with a goal of achieving a platelet count $\geq$100 $x10^3$/uL and fibrinogen $\geq$150 mg/dL. Four-factor prothrombin complex concentrate (50u/kg) was administered in a further attempt to reverse coagulopathy given the life-threatening nature of the hemorrhage. A ROS focused on symptoms of infection was negative. A chest radiograph was clear and a urinalysis showed no pyuria. The

procalcitonin was 0.12. Blood cultures were draw and cefepime and vancomycin started empirically for a presumptive diagnosis of sepsis-related DIC.

Which of the following is ***true*** of disseminated intravascular coagulation?

1. Pathogenesis involves abnormal simultaneous activation of coagulation and fibrinolysis, potentially leading to bleeding and clotting complications.
2. Causes include sepsis, solid tumors (typically associated with chronic DIC), obstetrical catastrophes such as placental abruption, and acute hemolytic transfusion reactions.
3. Differential diagnosis includes acute liver failure, heparin-induced thrombocytopenia, HELLP syndrome, TTP/HUS and COVID-19 coagulopathy.
4. The diagnosis is made based on clinical and laboratory data; there is not a single pathognomonic diagnostic laboratory test for DIC.
5. Many patients, such as those with sepsis-related DIC, do not require specific therapy of DIC except for aggressive treatment of the underlying cause.
6. All the above.

Correct!
6. All of the above

Six hours later, the patient's GCS decreased to eight. A repeat CT scan showed enlargement of the hematoma to 10x6x6cm with extension into the lateral and fourth ventricles (Figure 1).

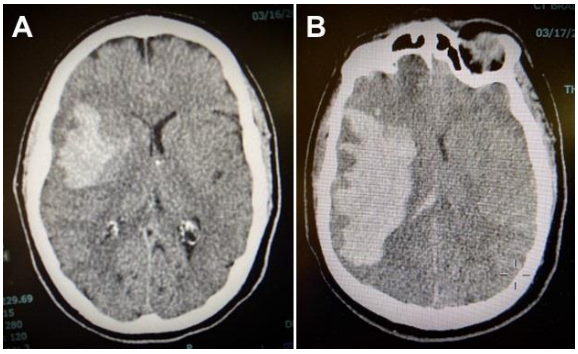

Figure 1. CT of the head at the time of admission and repeat CT six hours later. To view figure 1 in a separate, enlarged window click here.

The repeat platelet count was 118 x10^3/uL, INR 1.7, and fibrinogen 99 mg/dL. Platelets, FFP and cryoprecipitate were again transfused. An epsilon-aminocaproic acid bolus and infusion were started. The patient was intubated and taken to the operating room for decompression of the hematoma. Our laboratory's automated hematology analyzer triggered a reflex manual peripheral blood smear review of the admission CBC. An amended manual differential was reported on the morning of the second hospital day, noting 44% atypical mononuclear cells of unclear lineage, favored to be immature monocytes. No schistocytes were noted. A clinical diagnosis was made, diagnostic tests ordered and specific therapy emergently administered.

Which of following hematological emergencies is ***most likely*** in this patient?

1. CNS leukostasis due to acute myelogenous leukemia.
2. Hyperviscosity syndrome due to multiple myeloma.
3. Thrombotic thrombocytopenic purpura related to surreptitious use of clopidogrel.
4. Stroke due to delayed heparin-induced thrombocytopenia.
5. Fibrinolytic DIC secondary to acute promyelocytic leukemia (APL).

Correct!
5. Fibrinolytic DIC secondary to acute promyelocytic leukemia (APL).

Leukostasis presents with prominent neurological complications that can include intracranial hemorrhage, but it is usually seen in patients with acute myelogenous leukemia and hyperleukocytosis exceeding 100 $x10^3$/uL, and it is not typically associated with coagulopathy. Hyperviscosity syndrome due to multiple myeloma or Waldenstrom macroglobulinemia causes obstruction of CNS vasculature leading to a variety of neurological complications including coma and stroke, due to alteration of the physical properties of blood rather than through coagulopathy. Thrombotic thrombocytopenia purpura (TTP) is associated with thrombocytopenia and CNS hemorrhage, but is typically also associated with fever, acute kidney injury, and microangiopathic hemolytic anemia with prominently apparent schistocytes. TTP does not typically perturb the INR or aPTT. Delayed heparin induced thrombocytopenia (HIT) (occurring after the typical 10-day window) related to his previous hospitalization, during which he likely received heparin, could explain thrombocytopenia and thrombotic stroke, but would not explain DIC or a bleeding diathesis. Fibrinolytic DIC secondary to APL best explains the patient's clinical and laboratory presentation.

A presumptive diagnosis of acute promyelocytic leukemia (APL) with secondary fibrinolytic DIC was made. Flow cytometry and quantitative RAR*a*/PML by real-time PCR testing were performed. A repeat manual differential of peripheral blood showed 52% "blasts," some of which contained Auer rods.

Which of the following are ***true*** regarding APL with fibrinolytic DIC?

1. Transfusion of platelets and FFP is contra-indicated because they "fuel" worsening DIC.
2. Anti-neoplastic therapy with all-trans retinoic acid (ATRA) should be withheld until the diagnosis of APL is definitively confirmed.
3. Heparin is absolutely contraindicated in all patients with fibrinolytic DIC due to APL.
4. None of the above are true

Correct!
4. None of the above are true

Intensive transfusion support with platelets and fresh frozen plasma are an important adjunct in the treatment of hemorrhagic complications of DIC and should not be withheld for fear of "fueling the fire." All-trans retinoic acid (ATRA) induces rapid differentiation of neoplastic promyelocytes, ameliorating DIC, and should be emergently initiated in patients suspected of experiencing fibrinolytic DIC due to APL while awaiting confirmatory test results. The use of heparin in fibrinolytic DIC is controversial, but it may be used in patients with venous or arterial thrombotic complications. Antifibrinolytic therapy and PCC are generally contraindicated in DIC, but may be appropriate in patients with life-threatening bleeding complications.

All-trans retinoic acid (ATRA) 45mg/m^2 was emergently administered. The patient developed an upper gastrointestinal hemorrhage despite ongoing intensive transfusion support. Flow cytometry subsequently demonstrated a subpopulation of white cells consistent with acute promyelocytic leukemia (+CD13, +CD33, +CD117, +myeloperoxidase, weakCD34, -CD10 and -CD15), constituting 53% of peripheral WBCC. Additional treatment with arsenic trioxide (ATO) was discussed, but unfortunately the patient's neurological

condition further declined and his wife decided to transition to comfort care to honor the patient's previously expressed wishes. The duration of his hospitalization was 40 hours. Results of quantitative RAR*a*/PML t(15;17) by real-time PCR are pending.

Although APL accounts for only 10% of acute leukemia in adults, it is of special importance to critical care practitioners. Once regarded as the most malignant subtype of leukemia, discovery of its biological mechanism led to a novel form of differentiation therapy including ATRA, which achieved 90% 5-year survival. Nevertheless, many patients with APL experience fatal hemorrhage before treatment can be started, emphasizing the importance of rapid clinical recognition. APL was first reported in the late 1950's by LK Hillestad and J Bernard who observed patients with hyperacute promyelocytic leukemia often complicated by catastrophic intracranial and pulmonary hemorrhages within the first week of diagnosis (1,2). Elucidation of the unique molecular pathogenesis of APL began in the 1970s with the discovery of an associated translocation between chromosomes 15 and 17 (3). The involved segment on chromosome 15 was shown to be a tumor suppressor gene controlling cell proliferation, senescence and apoptosis, subsequently named the Promyelocytic Leukemia (PML) gene (4). The segment on chromosome 17 was within the locus of the Retinoic Acid Receptor alpha (RAR*a*) gene (5,6). In a healthy promyelocyte cell, transcription of RAR*a* protein promotes transcription of the retinoic acid response elements (RARE) which allow healthy myeloid differentiation. This translocation, uniquely found in over 95% of APL patients, came to be known as PML/RAR*a* (7,8).

The PML/RAR*a* translocation results in a fusion of the two gene products, impairing the function of both. PML/RAR*a* protein complex inhibits transcription of RARE, blocking myeloid precursors in the promyeloid stage (9). In addition, the fusion of PML proteins with RAR*a* inhibits apoptosis, allowing promyelocytes to proliferate without regulation (10). The combined effects of RARE inhibition and PML activation allows promyelocytic cells to progressively accumulate in the bone marrow impairing normal hematopoiesis. Fibrinolytic DIC is experienced by the majority of patients with APL and remains the major cause of death. This coagulopathy is caused by overexpression of annexin II (an endogenous tissue plasminogen activator) on the surface of promyelocytes, which triggers fibrinolysis (11). Excessive release of proinflammatory cytokines also likely play a role, as in sepsis-related DIC. APL patients are also less commonly at risk for life-threatening venous and arterial thrombotic complications, caused activation of tissue factor forming a complex with factor VIIa (12) and the increase in thrombin and fibrin by the release of chromatin and phosphatidylserine during APL cell death (13).

ATRA was first proven effective in inducing remission in APL in 1988 (14). The primary mechanism of ATRA is the conversion of the PML/RAR*a* complex into a RARE transcriptional activator that prompts differentiation of promyelocytes into neutrophils (15). ATRA also down-regulates the transcription of annexin II leading to rapid improvement of fibrinolytic DIC (16).

A patient being treated with ATRA for APL develops fever, peripheral edema, acute kidney injury and hypoxic respiratory failure with pleural effusions and diffuse infiltrates.

Which of the following that are ***true***?

1. The patient most likely has neutropenic fever and septic shock due to the myelosuppressive effects of ATRA chemotherapy.
2. Cultures should be obtained and empirical antibiotics started.
3. ATRA should be immediately discontinued.
4. Dexamethasone 10mg Q12hourly should be immediately started.
5. 2 and 4
6. All of the above

Correct!
5. 2 and 4

ATRA acts as a differentiation agent, distinct from chemotherapy, and not associated with myelosuppression or other toxicities typical of chemotherapy agents. However, up to 20% of patients receiving ATRA develop "differentiation syndrome" early in the course of treatment. This is caused by rapid synchronous maturation of promyelocytes into neutrophils, leading to hypercytokinemia and endothelial injury. Differentiation syndrome is characterized by fever, hypotension, anasarca, acute renal failure, and interstitial pulmonary infiltrates (17). The diagnosis is made clinically, and treated emergently with corticosteroids. ATRA and other differentiation agents such as ATO may be continued in patients with differentiation syndrome who rapidly improve with corticosteroids.

Some final thoughts about the diagnosis of APL in our patient. The WBCC in APL may be low, normal or high, and the peripheral smear is typically dominated by promyelocytes and myelocytes rather than blasts. These features may delay identification of APL by automated or manual examination of the peripheral blood smear. In our patient, the paucity of Auer rods (c/w hypo-granular variant APL) further obscured the lineage of the "unclassified white blood cells" identified on his admission CBC differential. When leukemia is suspected, flow cytometry will rapidly make the diagnosis. We hypothesize that our patient experienced early non-specific symptoms of DIC prompting his initial hospitalization three weeks prior to the onset of intracranial hemorrhage, at which time an elevated D-dimer was the only associated abnormal lab value.

APL is a rare but important cause of otherwise unexplained DIC. The inherent limitations of automated CBC differentials can delay diagnosis. When APL-associated DIC is reasonably suspected based on clinical and preliminary laboratory data, intensive transfusion therapy plus ATRA can be life-saving, if the patient has not already experienced a non-survivable complication.

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