Coagulopathy Case-2

Andy Nguyen, M.D.
2009
A 42 year-old man brought to the emergency room with severe burn. Patient was rescued by firemen in a serious fire. He had been found unconscious in his house. No other family members were present at the scene.

No other clinical information was available at the time of evaluation.
PHYSICAL EXAMINATION

• Physical examination showed 70% of the body surface area with second- and third-degree burns.
SCREENING COAGULATION LABORATORY RESULTS

- PT = 17 sec (Normal 8-14.6)
- aPTT = 49 sec (Normal 24-34.5)
- Plt = 20,000 /μL (Normal 150,000-350,000)
Differential diagnosis

- DIC -> mixing study, TT, Fibrinogen, FSP, D-dimer, blood smear review for schistocytes, clinical correlation
- Liver disease -> mixing study, clinical correlation
- SLE with lupus anticoagulant -> mixing study, dRVVT
- Other causes of factor deficiency and thrombocytopenia
DIAGNOSIS

• Disseminated Intravascular Coagulopathy
DIC

- Concurrent activation of the coagulation (thrombin) and secondary fibrinolysis (plasmin) with consumption of factors, inhibitors, platelets, and RBCs (microangiopathic hemolysis)
- The major triggering mechanism: exposure of the blood to tissue factor that initiates intense coagulation, overwhelming antithrombin and activated protein C
- Secondary to sepsis, malignancy (pancreatic cancer, APL), obstetrical complications (placental abruption, fetal demise, amniotic fluid embolism), tissue injury (esp. brain in head injury), etc.
Clinical presentation

- Most frequent: bleeding due to low levels of clotting factors and platelets
- Less often: vascular thrombosis (if fibrinolytic system or protein C is impaired)
Typical laboratory results in DIC

• ↑ PT & PTT, thrombocytopenia, ↓ fibrinogen, ↑ Thrombin Time, ↑ FSP/D-dimer
• Schistocytes in peripheral blood smear, ↑ LDH, ↓ haptoglobin
• Laboratory results in DIC vary greatly depending on the severity
FORMATION OF FIBRIN

A) Fibrinogen

B) Fibrin monomer

C) Cross-link

D) Cross-linked Fibrin
- Activators:
  - Tissue plasminogen activator (tPA)
  - Urokinase plasminogen activator (uPA)
- Inhibitors:
  - Plasminogen activator inhibitor-1 (PAI-1)
  - $\alpha_2$-antiplamin
FDP vs. D-DIMER

- Fibrin is formed as the end result of coagulation cascade activation.
- Fibrinolysis causes cleavage of fibrinogen, fibrin, and fibrin clot, yielding FSP (FDP).
- Only cleavage of fibrin clot (crosslinked fibrin) yields D-dimer -> D-dimer is more specific for DIC.
Testing: FSP and D-dimer

• Semi-quantitative FSP
• Qualitative D-dimer
• Semi-quantitative D-dimer
• Quantitative D-dimer
SEMİ-QUANTİTATİVE FSP

• The first test developed (in the early 70’s)
• Latex agglutination, FSP antibodies are bound on latex beads, if sample contains FSP, agglutination can be detected
SEMI-QUANTITATIVE FSP

• Semi-quantitation:
  – Serial dilution of sample (1: 20 through 1:640)
  – A positive result at 1:20 corresponds to 20 \( \mu \text{g/mL} \) of fibrinogen equivalent units (FEU)
SEMI-QUANTITATIVE FSP

• Early generation FSP polyclonal antibodies cross-react with fibrinogen
  – Must use serum or plasma in tubes with bovine thrombin (consumes fibrinogen)

• Current FSP monoclonal antibodies do not cross react with fibrinogen
  – Can use plasma or serum
  – False-positive result with rheumatoid factor

• Clinical application: DIC, hyperfibrinolysis
QUALITATIVE D-DIMER

• Monoclonal antibodies directed against D-dimer domain
  – More specific for in-vivo fibrin clot formation
• Manual latex agglutination technique (as for FSP), plasma or serum sample:
  – Cut-off value: 0.5 μg/mL FEU
  – Semi-quantitative format: dilutions 1:2 through 1:16
• Abnormal result in DIC
• Normal result in primary fibrinolysis
• False-positive result by rheumatoid factor
QUANTITATIVE D-DIMER

• Automated ELISA, immuno-turbidimetry
• Increased in DIC (>0.66 μg/mL)

• Quantitative D-dimer also has high negative predictive value for venous thromboembolism (VTE including DVT, PE):
  – <0.4 μg/mL, VTE can be ruled out
  – Very sensitive but not specific: high Negative Predictive Value / low Positive Predictive Value
DIC: Treatment:

- Treat underlying conditions
- Blood components (RBC, platelet concentrate, cryo, FFP)