Autopsy Findings and Venous Thromboembolism in Patients With COVID-19

A Prospective Cohort Study

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Learning Objectives

By the end of this journal club, participants will be able to:

1. Identify which imaging modality to use based on PE pretest probability
2. List genetic, provoking, and non-provoking risk factors for PE
3. Know both ‘classic’ and atypical presentations of acute PE
4. Understand why PE suspicion should be higher in COVID-19 patients
Module Outline

I. Case
II. Background
III. Article Overview
IV. Clinical Questions
V. Key Points
UNC Case: 69 yo female presents with *peristaltic left flank pain, ‘some’ SOB, and fever*. BP 127/55, Pulse 88, T 99.3, RR 18, *SpO2 87%*. Physical exam remarkable for borderline tachycardia, borderline tachypnea, respiratory sounds diminished bilaterally. She was discharged from the hospital 3 days ago after being treated for acute hypoxic respiratory failure (2/2 COVID-19).

1. Which imaging studies would you like to order?
2. Are the emboli bilateral or unilateral?
3. Why would you hesitate to order a V/Q scan in this case?
Case

• Underwent **CTA chest with IV contrast**
  • And CT abdomen/pelvis w/o contrast

• **Diagnosis:** **Pulmonary embolism**
  • Bilaterally within lobar arteries
  • Peripheral left lower lobe consolidation/atelectasis, likely atelectasis 2/2 infarction in setting of pulmonary emboli
  • Mild right heart strain (flattening of the intraventricular septum)

• **Treatment:**
  • Pulmonary Embolism
    • Started on heparin thrombosis nomogram
  • Right Renal Calculus
    • Urology consulted
    • Started on CTX for possible UTI
Case – Questions to Consider

• When should you suspect PE?
• What imaging modality should you use when PE is high on your differential?
• Should the patient’s positive COVID-19 status affect your suspicion of PE?
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Background on Pulmonary Embolism

Types:
- Acute (immediate), subacute (days-weeks), chronic (years)

Risk Factors:
- Genetic (Factor V leiden, prothrombin mutation, deficiencies in Protein C, S, or AT-III)
- Acquired:
  - Provoking (surgery, trauma, immobilization, hormone therapy, cancer, pregnancy, acute inflammation)
  - Non-provoking (obesity, heavy cigarette smoking, old age, hypertension, metabolic syndrome)

Epidemiology:
- Believed to have been underreported until 1990’s (with CTPA and D-dimer testing)
- Increased incidence in males and with increasing age
- Accounts for 100,000 deaths in US annually

Presentation:
- Variable (no symptoms to shock or sudden death)
- Most common presentation is dyspnea followed by pleuritic chest pain, cough, and symptoms of DVT
- Atypical presentations: seizures, syncope, abdominal pain, fever, productive cough, wheezing, decreased level of consciousness, new-onset atrial fibrillation, hemoptysis, flank pain, delirium (esp. in elderly patients)
Pathology

- **Pathogenesis**: Virchow’s triad
  - Stasis of blood flow, hypercoagulability, endothelial injury
- **Source**: Lower extremity proximal veins (iliac, femoral, popliteal)
- **Consequences**
  - Respiratory
    - Increased alveolar dead space
    - Hypoxemia
    - Hyperventilation
  - Hemodynamic
    - Reduced cross-sectional area of pulmonary vascular bed $\rightarrow$ increased pulmonary vascular resistance $\rightarrow$ increased RV afterload (possible RV failure)
Hypercoagulability in COVID-19

- Novel phenomenon referred to as thromboinflammation or COVID-19 associated coagulopathy (CAC)
- Incidence unknown
- DIC-like state
  - High D-dimer and fibrinogen
  - Normal/mildly prolonged PT and aPTT
  - Mild thrombocytopenia
- Positive correlation between elevated D-dimer on admission and in-patient mortality
- Anticoagulation with LMWH is associated with better prognosis in patients with markedly elevated D-dimer
Which study to order?

**Variant 1:** Suspected pulmonary embolism. Intermediate probability with a negative D-dimer or low pretest probability.

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRL *</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray chest</td>
<td>9</td>
<td></td>
<td>⚫</td>
</tr>
<tr>
<td>CTA chest with IV contrast</td>
<td>5</td>
<td>This procedure should be optimized for pulmonary arterial enhancement. This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.</td>
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<tr>
<td>CT chest with IV contrast</td>
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<td>This procedure should be optimized for pulmonary arterial enhancement.</td>
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</tr>
<tr>
<td>US duplex Doppler lower extremity</td>
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<td>This procedure has a low yield in the absence of symptoms of DVT.</td>
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<tr>
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<tr>
<td>Te-99m V/Q scan lung</td>
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<td>⚫⚫⚫</td>
</tr>
<tr>
<td>CTA chest with IV contrast with CT venography lower extremities</td>
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<td>⚫⚫⚫</td>
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<tr>
<td>MRA chest without and with IV contrast</td>
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<tr>
<td>US echocardiography transesophageal</td>
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<tr>
<td>Angiography pulmonary with right heart catheterization</td>
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<td>⚫⚫⚫⚫</td>
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<tr>
<td>MRA chest without IV contrast</td>
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<td>US echocardiography transesophageal</td>
<td>1</td>
<td></td>
<td>⚫</td>
</tr>
</tbody>
</table>

*Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

**Variant 2:** Suspected pulmonary embolism. Intermediate probability with a positive D-dimer or high pretest probability.

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<td></td>
<td>⚫</td>
</tr>
<tr>
<td>CTA chest with IV contrast</td>
<td>9</td>
<td>This procedure should be optimized for pulmonary circulation.</td>
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</tr>
<tr>
<td>CT chest with IV contrast</td>
<td>9</td>
<td>This procedure should be optimized for pulmonary circulation.</td>
<td>⚫⚫⚫⚫</td>
</tr>
<tr>
<td>Te-99m V/Q scan lung</td>
<td>7</td>
<td>This procedure may be an alternative to CTA, but both should not be performed.</td>
<td>⚫⚫⚫⚫</td>
</tr>
<tr>
<td>US duplex Doppler lower extremity</td>
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<td>This procedure may be an initial study prior to CTA.</td>
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</tr>
<tr>
<td>MRA chest without and with IV contrast</td>
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<td>⚫</td>
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<td>2</td>
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<td>⚫⚫⚫</td>
</tr>
<tr>
<td>MRA chest without IV contrast</td>
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<td>This procedure has limited sensitivity and may be indicated for rare situations or certain contraindications for a specific patient.</td>
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*Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

*Relative Radiation Level

[Logo: UNC School of Medicine Radiology]
CXR and PE

• Decreased pulmonary vascularity, aka ‘Westermark sign’ (sens 14%, spec 92%)
• Vascular redistribution (sens 10%, spec 87%)
• Dome-shaped opacification, aka ‘Hampton’s hump’ (sens 22%, spec 82%)
• Pleural effusion (sens 36%, spec 70%)
• Elevated diaphragm (sens 20%, spec 85%)
Clinical Treatment and Outcome

- **Pulmonary Embolism**
  - Apixaban (Eliquis) 10mg BID x 7 days, then 5mg BID x 3 months
  - Follow-up with Hematology in 3 months

- **UTI**
  - UA has large LE, increased WBC, and rare bacteria
  - Finishes 3-day course of CTX

- **COVID-19**
  - No longer needs to be on isolation since >14 days since initial symptom onset
  - IgG test negative 1.5 months after positive nasopharyngeal PCR
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Article Nuts and Bolts

**Purpose:** A study of deceased COVID-19 patients to validate and compare clinical findings with postmortem findings

**Journal:** Annals of Internal Medicine, May 2020

**Study Type:** Prospective cohort study of the first 12 consecutive COVID-19-positive deaths.

**Number of Cases:** 12 patients

**Data:** Medical autopsy, virtual autopsy, and virologic tests
Material and Methods Continued

• All deceased patients received:
  • Postmortem CT
  • Complete autopsy (w/ histopathologic and virologic evaluation)

• Clinical records checked for:
  • Preexisting medical conditions
  • Medications
  • Current medical course
  • Antemortem diagnostic findings
<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age</th>
<th>Sex</th>
<th>Preexisting Medical Conditions</th>
<th>Treatment</th>
<th>BMI, kg/m²</th>
<th>Clinical Cause of Death</th>
<th>PMI, h</th>
<th>Cause of Death</th>
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<td>Parkinson disease, CHD, PAD, COX</td>
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<td>PE, pneumonia</td>
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<tr>
<td>3</td>
<td>71</td>
<td>Male</td>
<td>AI, nicotine abuse, granulomatous pneumopathy</td>
<td>CA, MV</td>
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<td>PE, pneumonia</td>
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<tr>
<td>4</td>
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<td>Male</td>
<td>T2DM, obesity, bronchial asthma</td>
<td>CA, MV, lysis of right ventricular thrombus, CPR</td>
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<td>Cardiorespiratory failure</td>
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<td>11</td>
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<td>Male</td>
<td>CHD, AK, bronchial asthma, atopic fibrosis</td>
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<tr>
<td>12</td>
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<td>34.1</td>
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### Table 2

**Overview of Laboratory Results Taken at the Time of Hospitalization**

<table>
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<tr>
<th>Case Number</th>
<th>Hgb, g/dL</th>
<th>MCV, fl</th>
<th>Platelets, × 10^9/L</th>
<th>Leukocytes, × 10^9/L</th>
<th>INR</th>
<th>aPTT, s</th>
<th>D-dimer, μg/L</th>
<th>LDH, μkat/L</th>
<th>Creatinine, μmol/L</th>
<th>AST, UI/L</th>
<th>Sodium, mmol/L</th>
<th>Potassium, mmol/L</th>
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<td>348</td>
<td>16.2</td>
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<td>16.5</td>
<td>88</td>
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<td>29</td>
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<td>NA</td>
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<td>89.4</td>
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<td>45</td>
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<td>77</td>
<td>134</td>
<td>4.3</td>
<td>163</td>
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</table>

aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CRP = C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; NA = not available; PCT = procalcitonin.

*Patients in cases 1 and 5 died out of the hospital after a sudden cardiac arrest. Values are either nonexisting (case 1) or taken from a blood gas analysis (case 5).*

### Table 2—Continued

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<thead>
<tr>
<th>Antimicrobial and Coagulation Therapy</th>
<th>D-Dimer</th>
<th>Resulting Agency</th>
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<td>Ref Range &amp; Units</td>
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<tr>
<td></td>
<td>&lt;230 ng/mL DDU</td>
<td>1,346 ^</td>
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<td>Resulting Agency</td>
<td>UNCH MCL</td>
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<tr>
<td></td>
<td>CRP</td>
<td>&lt;10.0 mg/L</td>
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<tr>
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<td>Resulting Agency</td>
<td>UNCH MCL</td>
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<tr>
<td></td>
<td>LDH</td>
<td>338 - 610 U/L</td>
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<tr>
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<td>Resulting Agency</td>
<td>UNCH MCL</td>
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</table>

**UNC Case:**

![UNC Case Diagram](image-url)
CT and Macroscopic Autopsy Findings
Results

• **Antemortem Labs:**
  - Elevated LDH (median 7.83 μkat/L, range 2.71-11.42, ref range 2.00-4.10)
  - Elevated D-dimer (median 495.24 nmol/L, range 20.38-1904.76, ref range <2.7)
  - Elevated C-reactive protein (median 189 mg/L, range 18-348, ref range <5)
  - Mild thrombocytopenia in 40% of patients

• **Autopsy**
  - Massive PE in 4 cases (w/ thrombi from LE deep veins)
  - 3 cases with fresh DVT present in absence of PE
  - All cases with DVT had bilateral LE involvement
  - Lungs were congested and heavy
  - Avg combined lung weight of 1988 g (standard weights: 840g men, 639g women)
  - In all 12 cases, cause of death was found within the lungs or pulmonary vascular system

*data available for only 5 patients*
Results (continued)

• Histology
  • Microthrombi regularly found in small lung arteries, occasionally within prostate, but not in other organs
  • Diffuse alveolar damage seen in 8 cases

• Post-mortem CT
  • Mixed patterns of reticular infiltrates in both lungs in absence of known preexisting pathology

• PCR Results
  • SARS-CoV-2 RNA found in lungs of all 12 and pharynx of 9
  • Six patients with moderate viremia
    • 5 with viral RNA detected in other tissues (heart, liver, kidney) in concentrations exceeding viremia
  • Patients w/o viremia had no or low virus load in other tissues
  • Only 4 patients with detectable viral RNA in brain and saphenous vein
Discussion

• Higher than anticipated incidence of DVT/PE (58%)
  • Correlates with unsuccessful resuscitation of 3 of 4 patients
  • Lack of preclinical evidence of PE or DVT

• Previous studies of deceased COVID-19 (w/o autopsy) do not report increased rates of clinically observed PE

• Reliance of PCR testing and caution in scanning COVID-19 patients contributes to overlooking PE
Discussion (continued)

- Autopsy still the gold standard for identifying cause of death
  - Rates decreasing in past decades, especially now due to fear of COVID-19 contraction
- Proposed mechanisms of COVID-19 predisposing to VTE
  - Virus activate coagulation system (HIV, dengue, Ebola)
  - Endothelial dysfunction (increased vWF)
  - Systemic inflammation (via TLR activation)
  - Procoagulatory state (by tissue factor pathway activation)
  - Cytokine storm
  - Severe hypoxemia can predispose to thrombus (hypoxia inducible TF regulates thrombus formation)
  - Indirectly caused by immune-mediated damage via anti-PL antibodies
- PE should always be suspected when COVID-19 patient undergoes hemodynamic deterioration
- Anticoagulant treatment seems plausible in COVID-19 patients due to autopsy findings and coagulopathy associated with high D-dimer
Hold On!

- Sample size
- Single center study
- Selection bias
- What are anticoagulation goals in COVID-19 patients, considering ½ of the cases with PE as cause of death were on LMWH?
- Was this second ED visit avoidable?
  - PE considered during initial hospitalization due to elevated D-dimer but no further imaging done after an unimpressive POCUS cardiac exam
  - POCUS cardiac exam was over-read as showing RV dilatation, septal flattening c/f R heart increased RV pressures, c/f PE
  - Information was not conveyed to treatment time at that time
Module Outline

I. Case
II. Background
III. Article Overview
IV. Clinical Questions
V. Key Points
Clinical Questions

• Should all COVID-19 positive patients be on increased prophylactic anticoagulant therapy?

• Do all patients who pass away with a recent COVID-19 diagnosis require autopsy?

• How can we optimize communication methods to ensure important clinical findings are communicated through proper channels?
Module Outline

I. Case
II. Background
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V. Key Points
Key Points

• Pulmonary embolism has a myriad of presentations- don’t hesitate to add it to the differential

• Postmortem findings of DVT/PE suggest increasing the anticoagulation regimen in COVID-19 unless contraindicated

• CT(A) chest with IV contrast is best for evaluating patient with high PE suspicion, but don’t forget CXR as a cheaper and lower radiation option to assess for non-PE etiologies

• Further study is required to better understand the association between COVID-19 and hypercoagulability

• The effects of anticoagulants in reducing PE/DVT rates in COVID-19 requires additional study, specifically whether increased prophylactic dose is warranted
References


