Annals of Internal Medicine

ORIGINAL RESEARCH

Autopsy Findings and Venous Thromboembolism in Patients With COVID-19

A Prospective Cohort Study

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Journal Club 6/9/20

UNC SCHOOL OF MEDICINE Radiology

Learning Objectives

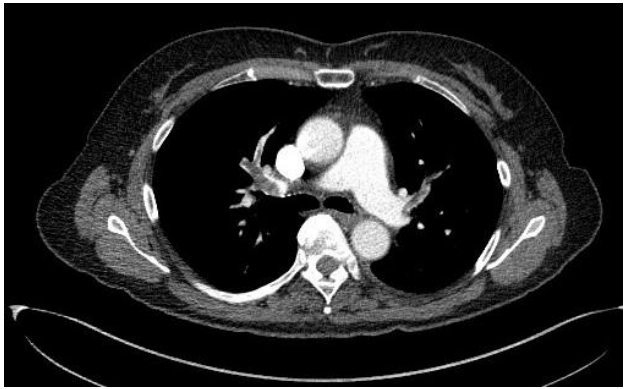
By the end of this journal club, participants will be able to:

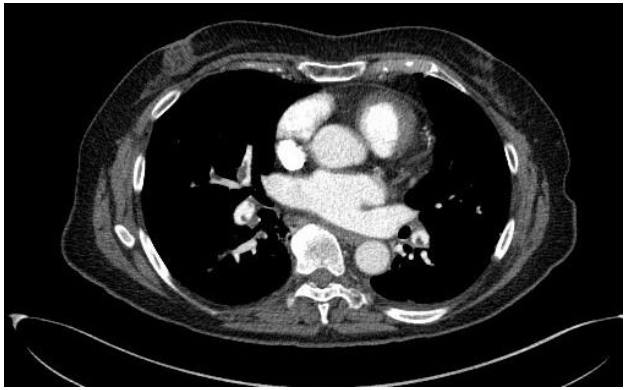
1. Identify which imaging modality to use based on PE pretest probability
2. List genetic, provoking, and non-provoking risk factors for PE
3. Know both ‘classic’ and atypical presentations of acute PE
4. Understand why PE suspicion should be higher in COVID-19 patients

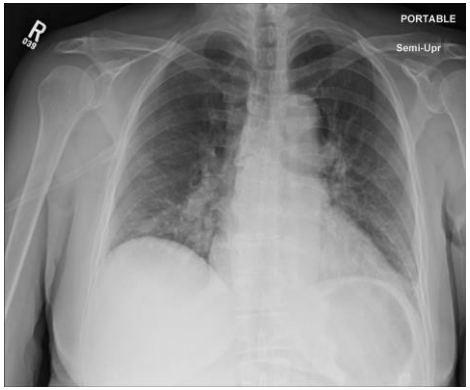
Module Outline

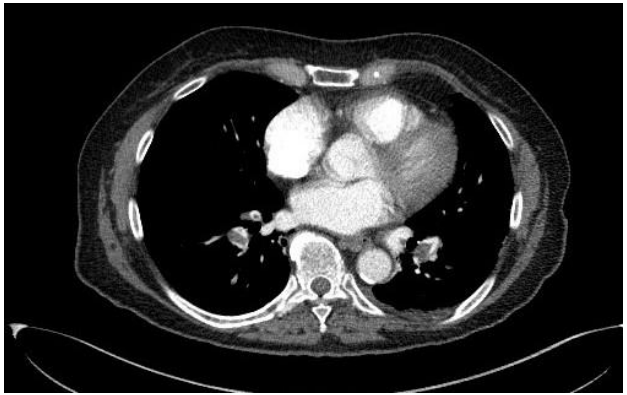
I. **Case**
II. Background
III. Article Overview
IV. Clinical Questions
V. Key Points

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).



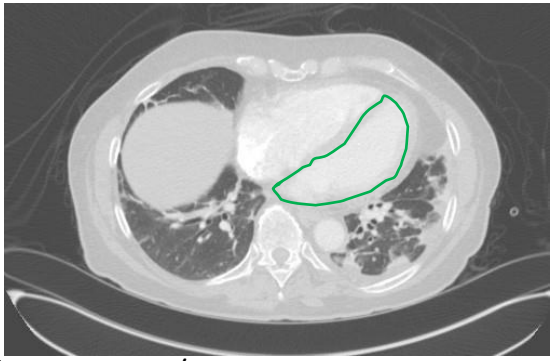




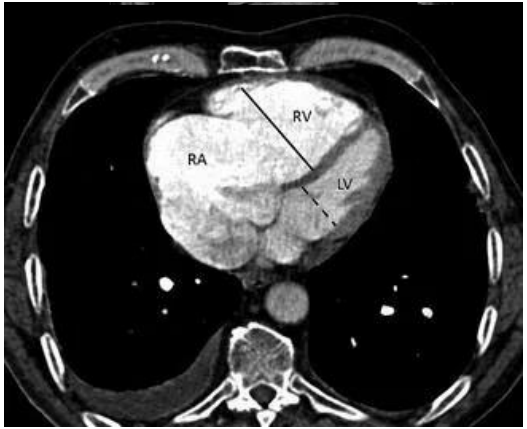


1. Which imaging studies would you like to order?
2. Are the emboli bilateral or unilateral?
3. Why would you hesitate to order a V/Q scan in this case?

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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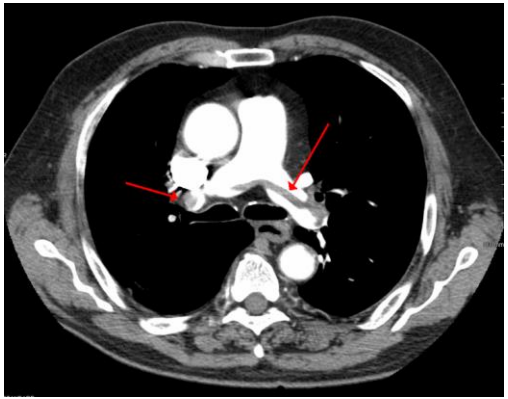
Background on Pulmonary Embolism

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:

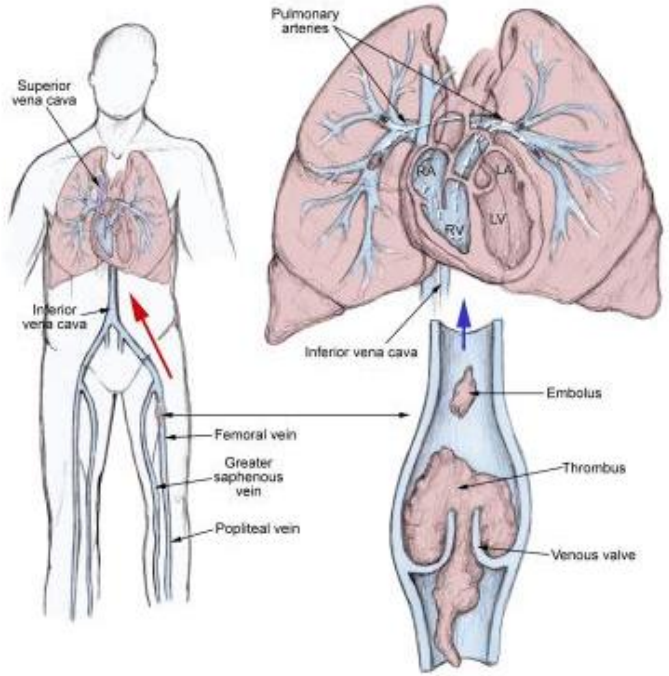
- Believed to have been underreported until 1990's (with CTPA and D-dimer testing)
- Increased incidence in males and with increasing age
- Accounts for 100,000 deaths in US annually

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 → increased pulmonary vascular resistance → 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.**

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9		☢
CTA chest with IV contrast	5	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.	☢☢☢
CT chest with IV contrast	3	This procedure should be optimized for pulmonary arterial enhancement.	☢☢☢
US duplex Doppler lower extremity	3	This procedure has a low yield in the absence of symptoms of DVT.	O
CT chest without IV contrast	2		☢☢☢
Tc-99m V/Q scan lung	2		☢☢☢
CTA chest with IV contrast with CT venography lower extremities	2		☢☢☢
MRA chest without and with IV contrast	2		O
US echocardiography transthoracic resting	2		O
CT chest without and with IV contrast	1		☢☢☢
Arteriography pulmonary with right heart catheterization	1		☢☢☢☢
MRA chest without IV contrast	1		O
US echocardiography transesophageal	1		O

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

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

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9		☢
CTA chest with IV contrast	9	This procedure should be optimized for pulmonary circulation.	☢☢☢
CT chest with IV contrast	9	This procedure should be optimized for pulmonary circulation. This procedure may be an alternative to CTA, but both should not be performed.	☢☢☢
Tc-99m V/Q scan lung	7	This procedure may be an alternative to CTA, but both should not be performed.	☢☢☢
US duplex Doppler lower extremity	7	This procedure may be an initial study prior to CTA.	O
MRA chest without and with IV contrast	6		O
CTA chest with IV contrast with CT venography lower extremities	5		☢☢☢
Arteriography pulmonary with right heart catheterization	3		☢☢☢☢
US echocardiography transthoracic resting	3		O
CT chest without IV contrast	2		☢☢☢
CT chest without and with IV contrast	2		☢☢☢
MRA chest without IV contrast	2	This procedure has limited sensitivity and may be indicated for rare situations or certain contraindications for a specific patient.	O
US echocardiography transesophageal	2		O

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

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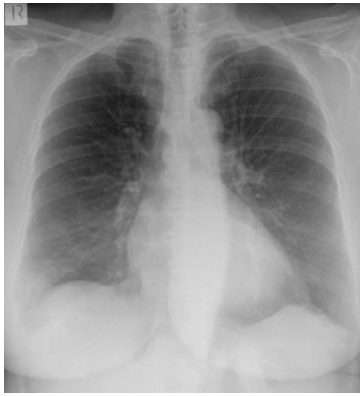
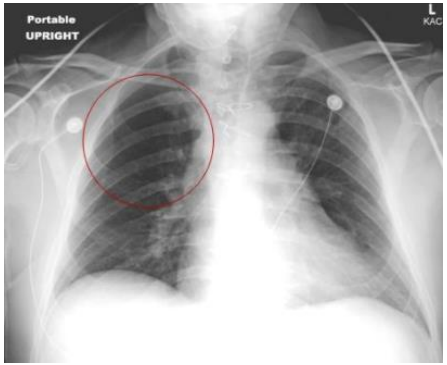
CXR and PE

- 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%)



Hampton’s hump



Westermark sign

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 1. Patient Characteristics and Autopsy Findings

Case Number	Age, y	Sex	Preexisting Medical Conditions	Treatment	BMI, kg/m²	Clinical Cause of Death	PMI, d
1	52	Male	Obesity	CPR	38.8	Sudden cardiac death	1
2	70	Male	Parkinson disease, CHD, PAD, CKD	BSC	22.2	Respiratory failure, pneumonia	1
3	71	Male	AH, nicotine abusus, granulomatous pneumopathy	CA, MV	36.8	Respiratory failure, pneumonia	2
4	63	Male	T2DM, obesity, bronchial asthma	CA, MV, lysis of right ventricular thrombus, CPR	37.3	Cardiorespiratory fa[illegible]e, PE	1
5	66	Male	CHD	CPR	25.3	Sudden cardiac death	2
6	54	Female	Dementia, epilepsy, trisomy 21	BSC	29.6	Respiratory failure, aspiration pneumonia	1
7	75	Female	Atrial fibrillation, CHD, nicotine abusus	NIV	26.3	Respiratory failure, viral pneumonia	4
8	82	Male	Parkinson disease, T2DM, CHD	BSC	27.8	Respiratory failure, viral pneumonia	1
9	87	Female	Non–small cell lung cancer, COPD, CHD, CKD	BSC	15.4	Respiratory failure, viral pneumonia	4
10	84	Male	T2DM, AH, ulcerative colitis	BSC	20.7	Respiratory failure, viral pneumonia	5
11	85	Male	CHD, AH, bronchial asthma, atrial fibrillation	CA, MV, RRT	30.0	Cardiac arrest due to respiratory failure	2
12	76	Male	Obesity	CA, MV, CPR	34.[illegible]	PE	3

Table 1–Continued

Cause of Death	Main Pathologic Findings	PMCT (Lungs)	Histology (Lungs)
PE, pneumonia	PE, DVT, pneumonia, obesity, cardiomegaly (660 g), splenomegaly (500 g), hepatomegaly (3880 g), shock organs (liver, kidneys), atherosclerosis	Diffuse bilateral pulmonary consolidations in each lobe	DAD: aPC, FB, GC, sparse HM, slight fibrosis Additional findings: Co, Thr
Pneumonia with bronchopneumonia	Pneumonia, CHD (stents in LAD and RCA, status post MI, cardiac aneurysm), contractures (with Parkinson syndrome), purulent bronchitis, cardiomegaly (515 g), shock liver	No PMCT	DAD: aPC, HM, sparse LC Additional findings: focal Gra, CB, AB
PE, pneumonia	PE, DVT, pneumonia, status post VATS (due to unspecified granuloma), CHD, anasarca, atherosclerosis	Emphysema; fine reticular pattern in each lobe; consolidations in the right lower and left lower lobes	DAD: SM, FB, aPC, HM Additional findings: Thr
PE, pneumonia	PE, DVT, pneumonia, obesity, cardiomegaly (605 g), ischemic colitis, shock liver	No PMCT	DAD: FB, aPC, HM, SM Additional findings: HI, Thr
Pneumonia	Pneumonia, DVT, CHD, status post MI	Consolidations in each lobe; reticular pattern in the right upper and lower lobes and in each left lobe	DAD: aPC, FB, HM, necrosis, LC Additional findings: surrounding small vessels, Thr
Pneumonia	Pneumonia, kidney infarctions, PEG tube	Consolidations in the right upper and middle lobes and in parts of the left upper and lower lobes; ground glass opacities in the right upper and lower lobes and in the left upper lobe; reticular pattern in the right middle and lower lobes and in each left lobe	Gra, AB, Co (no DAD)
Pneumonia	Pneumonia, lung emphysema, CHD, left cardiac dilatation, calcification of the mitral ring, cardiac pacemaker, atherosclerosis	Reticular pattern in each lobe; small areas of consolidation in the right lower, left upper, and left lower lobes	DAD: HM, aPC, SM Additional findings: emphysema, Co
Bronchopneumonia	Pneumonia, emphysema, DVT, CHD, status post ACVB, status post MI with left cardiac aneurysm, atherosclerosis	Emphysema; diffuse consolidations in each lobe; reticular pattern in the right upper and lower lobes and in the left lower lobe; bilateral pleural effusion	Gra, emphysema (no DAD)
Purulent bronchitis	Pneumonia, purulent bronchitis, CHD, status post MI, cachexia, bullous emphysema, NET in the lung, atherosclerosis	Emphysema; round tumor in the right lower lobe; small areas of consolidation in the right upper and lower lobes and in the left upper lobe; reticular pattern in the right upper and lower lobes and in each left lobe	Gra, AB, emphysema (no DAD) Additional findings: NET composed of small cells
Pneumonia, septic encephalopathy	Pneumonia, emphysema, septicemia, status post MI, atrophic kidneys	Reticular pattern in the right upper and lower lobes and in each left lobe; consolidations in the right middle and lower lobes and in each left lobe; ground glass opacities in the right upper and middle lobes and in parts of the left upper lobe; bilateral pleural effusion	Emphysema, Co, Gra, CB, fibrosis (no DAD)
Pneumonia	Pneumonia, DVT, minor PE, emphysema, CHD, cardiomegaly (650 g), atherosclerosis	Diffuse consolidations in each lobe; reticular pattern in the right middle and lower lobes and in each left lobe; ground glass opacities in the right upper and middle lobes and in the left upper lobe; bilateral pleural effusion	DAD: HM (sparse), GC, aPC Additional findings: emphysema, Co, Gra
PE	PE with lung infarctions, DVT, pneumonia, purulent tracheobronchitis, pneumonia, cardiomegaly (745 g), emphysema, obesity	No residual ventilation in either lung except for small areas in the right upper and middle lobes and in the left upper and lower lobes; bilateral pleural effusion	DAD: HM, aPC, fibrosis Additional findings: LC, PIC, HI, Thr, Co

Table 2

Table 2. Overview of Laboratory Results Taken at the Time of Hospitalization*

Case Number	Hemoglobin, g/dL	MCV, fL	Platelets, × 10⁹/L	Leukocytes, × 10⁹/L	INR	aPTT, s	D-dimer, µg/L	LDH, µkat/L	Creatinine, µmol/L
Normal range	14.0–17.5	80.0–94.0	150–400	3.8–11.0	–	23–30	<500	2.00–4.10	53.4–99.1
1	NA	NA	NA	NA	NA	NA	NA	NA	NA
2	12.1	92	144	7.4	1.3	NA	NA	5.92	228.8
3	14.9	100	190	9.2	2.1	42	NA	6.32	102.9
4	13.3	88	478	7.1	1.1	21	23,100	11.07	65.6
5	14.4	NA	NA	NA	NA	NA	NA	NA	NA
6	14.0	95	135	3.4	1.0	30	NA	6.12	59.5
7	12.1	98	125	6.9	1.5	57	28,800	7.97	76.3
8	14.8	79	186	7.1	1.2	29	2100	9.84	99.1
9	10.7	98	210	5.3	1.0	23	NA	2.70	99.1
10	16.5	88	219	15.5	1.1	29	>200,000	10.50	129.6
11	9.9	78	304	11.6	1.1	45	5700	11.40	83.9
12	16.8	90	141	3.8	0.95	32	NA	6.32	67.1

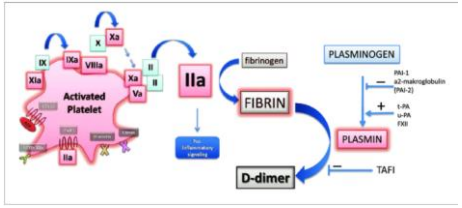
Table 2–Continued

AST, U/L	Sodium, mmol/L	Potassium, mmol/L	CRP, mg/L	PCT, mg/L	Antimicrobial and Coagulation Therapy
<50	135–145	3.6–4.6	<5	<0.5	
NA	NA	NA	NA	NA	None
54	154	4.6	303	NA	Rivaroxaban: 20 mg once daily Piperacillin/tazobactam: 4.5 g three times daily
52	139	4.45	304	NA	Meropenem: 1 g three times daily Levofloxacin: 400 mg twice daily Enoxaparin: 4000 IU once daily
54	139	3.5	133	0.1	Cefpodoxime: 200 mg twice daily
NA	141	8.7	NA	NA	None
NA	132	4.4	18	0.2	None
97	141	3.8	213	0.3	Edoxaban: 30 mg once daily
NA	141	4.6	92	NA	None
NA	135	4.6	39	NA	None
NA	140	3.5	348	16.2	None
77	141	4.5	268	0.3	None
77	136	4.3	167	0.5	Certoparin: 3000 IU once daily

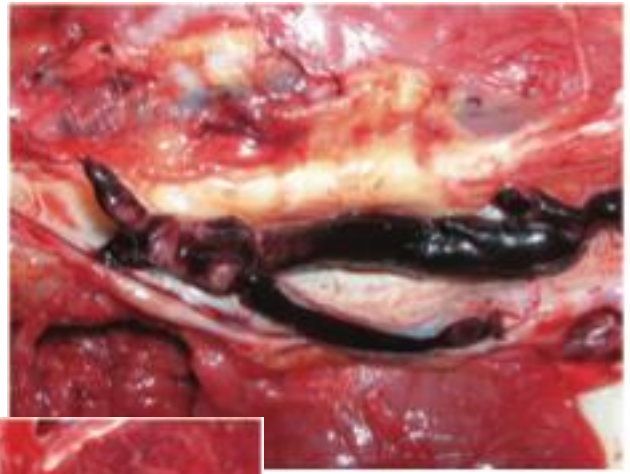
aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CRP = C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; NA = not available; PCT = procalcitonin.
* Patients in cases 1 and 5 died out of the hospital after a sudden cardiac arrest. Values are either nonexisting (case 1) or taken from a blood gas analysis (case 5).

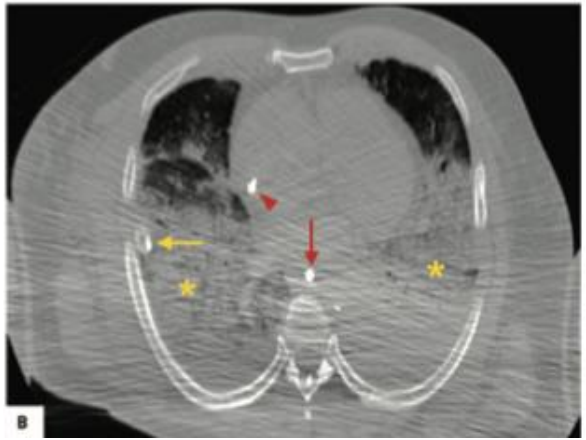
UNC Case:

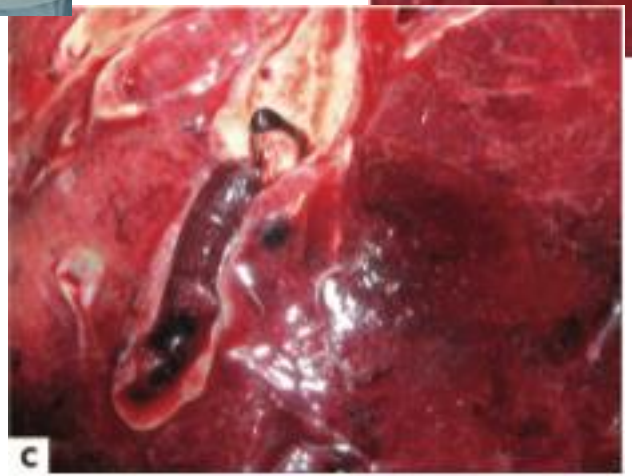
	Ref Range & Units	4/10/20 0721	4/9/20 0447	4/5/20 0358
D-Dimer	<230 ng/mL DDU	1,348 ^	2,309 ^	2,994 ^
Resulting Agency		UNCH MCL	UNCH MCL	UNCH MCL
	Ref Range & Units	4/10/20 0721	4/9/20 0447	4/5/20 0358
CRP	<10.0 mg/L	61.2 ^	25.9 ^	19.1 ^
Resulting Agency		UNCH MCL	UNCH MCL	UNCH MCL
	Ref Range & Units	4/10/20 0721	4/9/20 0447	4/4/20 0446
LDH	338 - 610 U/L	581	676 ^	682 ^
Resulting Agency		UNCH MCL	UNCH MCL	UNCH MCL



CT and Macroscopic Autopsy Findings







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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

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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?

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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

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