A 48-Year Old Woman with Recurrent Venous Thromboembolism and Pulmonary Artery Aneurysm

Group 10: Arjun Prasanna, Keaton Mcclure, Shruti Srikumar, Nisha Karwal
Patient History: 15 months prior

- 48 year old woman came in reporting coughing and decreased exercise tolerance
- She received a clinical diagnosis of deep venous thrombosis of the right leg and segmental/subsegmental pulmonary embolism in both lower lobes.
- Blood tests negative for:
  - Factor V Leiden gene mutation
  - Prothrombin gene mutation
  - Antiphospholipid
  - Anticardiolipin
  - $\beta_2$-glycoprotein
- Blood level of protein S was low
- Treatment with warfarin was initiated
Patient History: 12 months prior

- Patient still had persistent cough and dyspnea (labored breathing) upon exertion
- CT scan of chest was performed
  - Pulmonary embolism in the right lung, occlusion of interlobar pulmonary artery that extended into middle and lower lobes, including segmental arteries.
- New focal dilatation of pulmonary artery in the left lower lobe and small right pleural effusion.
- Warfarin discontinued, apixaban initiated.
Question 1

A genetic mutation in which coagulation factor contributes to the Leiden mutation?

A. X
B. Xa
C. XXII
D. V
E. VII
Question 1

A genetic mutation in which coagulation factor contributes to the Leiden mutation?

A. X
B. Xa
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D. V
E. VII
Patient History: 6 months prior

- Previously discovered emboli and dilation had not changed.
- A large pulmonary embolus occluded the distal right main pulmonary artery.
- Since additional thromboembolic events were still occurring after administration of apixaban, medication was discontinued.
- Treatment with therapeutic subcutaneous enoxaparin sodium was initiated, and results of anti-factor Xa assay were within therapeutic range.
Patient History: 2 months prior

- Repeat CT angiograms of the chest were performed.
  - Right main pulmonary artery was completely occluded by thromboembolic material.
  - Dilation seen earlier in left lower lobe progressed into a thrombosed artery.
  - Several areas of lung consolidation => probable infarcts
- A transthoracic echocardiogram was performed
  - Atria and right ventricle were normal
  - Left ventricular ejection fraction was 55% (normal)
- Ventilation-perfusion scan revealed complete absence of perfusion to the right lung, and multiple defects in the left lung.
- Patient was referred to Massachusetts General Hospital
Question 2

Which of the following conditions are NOT part of Virchow’s triad in thrombus development?

A. Endothelial Injury
B. Hypercoagulability
C. Edema
D. Abnormal Blood Flow
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Clinical Presentation

- Patient reported weight loss of 18kg (40 lbs) during previous 3 months but no fever, night sweats, hemoptysis, oral ulcers, genital ulcers, rashes, or eye pain
- No known exposure to tuberculosis
- History of hypothyroidism and seizure disorder
- Medications included enoxaparin sodium, levothyroxine, levetiracetam, phenytoin
- Resided in New England and travelled to Florida in the year before evaluation
- Did not smoke, drink, or use illicit drugs
- Mother had diabetes, but no family history of pulmonary disease, lung cancer, pulmonary embolism, or deep vein thrombosis.
Physical Examination

- Patient was breathing comfortably, both lungs clear
- Heart sounds and pulses normal, without murmurs

<table>
<thead>
<tr>
<th>Test</th>
<th>Observed</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>36.9 C</td>
<td>36.1 - 37.2 C</td>
</tr>
<tr>
<td>Pulse</td>
<td>96 bpm</td>
<td>60-100 bpm</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>20 breaths per min</td>
<td>12-20 breaths per min</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>96%</td>
<td>95-100%</td>
</tr>
<tr>
<td>BMI</td>
<td>17.5</td>
<td>18.5-24.9</td>
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</tbody>
</table>
MRI Results

- MRI performed to investigate thrombus in right main pulmonary artery
- Nearly complete occlusion of distal right main pulmonary artery and bilateral segmental/subsegmental pulmonary arteries indicating thromboembolism
- Enlarging pulmonary infarcts in the right lung with minimal localized pleural fluid
- There is also a new aneurysm (2.4 cm in diameter) on the left lower lobe
Tests upon Admission to Mass Gen

- Electrolyte, blood glucose, blood cell count, and renal/liver function tests were all normal
- Tests for antinuclear and antineutrophil cytoplasmic antibodies were negative
- Tests for HIV type 1 and type 2 were negative
- Blood cultures showed no growth and tests for Treponema bacteria was also negative
- Tests for galactomannan were negative (no mold)
- TB tests (anti interferon-γ) was negative
More Tests

<table>
<thead>
<tr>
<th>Test</th>
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<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3-beta-D-glucan</td>
<td>&lt;31 pg/mL</td>
<td>&lt;60 pg/mL</td>
</tr>
<tr>
<td>Erythrocyte Sedimentation Rate</td>
<td>69 mm/hr</td>
<td>0-20 mm/hr</td>
</tr>
<tr>
<td>C-reactive protein level</td>
<td>106 mg/L</td>
<td>&lt;8 mg/L</td>
</tr>
</tbody>
</table>

- Ultrasonography showed deep vein thrombosis (1.0 cm) in right popliteal vein
Question 3

1,3-beta-D-glucan was used to test for invasive fungal infection. The patient’s lab results appear normal in terms of this measure. However, her erythrocyte sedimentation rate and C-reactive protein levels are both elevated. What condition do elevated readouts in BOTH of these tests most likely indicate?

A. Inflammation
B. Fungal infection
C. Improper clotting function
D. Kidney Failure
E. What??
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Question 4

Which of the following is not a direct symptom of a Deep Vein Thrombosis?

A. Swelling of one or both legs

B. Red/discolored Skin

C. Pain/soreness in calf

D. Sudden Shortness of Breath

E. All of the above are possible symptoms
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Differential Diagnosis

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTPH)

- Condition that on rare occasions can develop from pulmonary embolism and is characterized by obstruction of the pulmonary arteries along with vascular arteriopathy stemming from vascular remodeling and pulmonary hypertension
- Can lead to right ventricular failure and death if untreated
Differential Diagnosis

CTPH is an UNLIKELY diagnosis for several reasons...

- Patient did not have significant pulmonary hypertension since right ventricle and right atrium appeared normal on echocardiography
- Development of thromboembolic disease is unusual without concurrent development of clotting disorder if patient adhered to anticoagulant therapies
- Weight loss, elevated erythrocyte sedimentation rate and C-reactive protein level indicate a systemic disease
Differential Diagnosis

PULMONARY ARTERY ANEURYSMS (PAA)

- A PAA is a focal dilation of all three layers of a vessel wall
- PAAs can be commonly associated with vascular trauma, infection, congenital heart disease, lung cancer, pulmonary hypertension, and systemic inflammatory diseases
- Pseudoaneurysms also cause a bulge in the vessel wall BUT there is not dilation of ALL three layers
Differential Diagnosis

PULMONARY ARTERY ANEURYSMS (PAA)

- HOWEVER... none of these conditions were present in the patient
  - She had no trauma (which is usually caused by catheterization procedures)
  - Infections most commonly associated with PAA include TB and syphilis (recall that both tests were negative)
  - No congenital heart disease or indications of pulmonary hypertension (as mentioned on previously)
  - No indication of lung cancer except weight loss, BUT chest imaging revealed no mass lesions

Conclusion: PAA is also an UNLIKELY diagnosis
What differentiates a Pulmonary Artery Aneurysm from a Pseudoaneurysm?

A. Caused by tissue injury
B. The focal dilation of all three vessel wall layers
C. Associated with a high rate of mortality
D. High probability of rupture
E. Blood is contained by tissue surrounding the vessel
Question 5

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Question 6

Which of the following is NOT a tissue layer of an artery?

(a) Media
(b) Adventitia
(c) Intima
(d) Perimetria
(e) I just don’t know
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Differential Diagnosis

BEÇHET'S DISEASE & HUGHES-STOVIN SYNDROME

- Both are systemic inflammatory diseases
- They are the two vasculitides most commonly associated with pulmonary artery aneurysms
- Hughes-Stovin is thought to be a partially manifested form of Behçet's disease
- Symptoms of complete Behçet's disease include oral ulcers, genital ulcers, eye and skin lesions (none of which were present in patient)

Therefore it is UNLIKELY that the patient has classical Behçet's disease
Differential Diagnosis

- Instead it is PROBABLE that the patient has Hughes-Stovin syndrome alone
- In Hughes-Stovin syndrome, aneurysms can be unilateral or bilateral and typically involve pulmonary or bronchial arteries
- Three phases are described in Hughes Stovin Syndrome:
  - initial phase with venous thrombophlebitis
  - formation of large pulmonary and bronchial aneurysms
  - aneurysmal rupture leading to hemoptysis and death
- There was evidence that the patient had progressed through both phase 1 and 2 (but obviously not phase 3)
- However, Hughes Stovin syndrome is extremely rare (less than 40 reported cases)
Venous Thrombophlebitis can cause which of the following to occur?

A. Abnormal formation of blood clots
B. Deep Vein Thrombosis
C. Superficial Inflammation
D. All of the above
E. None of the above
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Final Diagnosis

- At this point the patient was diagnosed with Hughes-Stovin syndrome
- She had aneurysm in the left pulmonary artery
- She also still had almost full occlusion of the right pulmonary artery (RPA)

This was a bad combination of pathologies for the patient to have and posed high risk if surgical procedures were to be undertaken...

- Since RPA was blocked, the LPA received higher blood volume and was subject to higher pressures which increased risk of aneurysm rupture
- An embolization procedure on the left lung would be “catastrophic” because it would decrease blood flow to the left lung and the right lung would not be able to compensate due to full occlusion
Treatment Strategies

- Biggest concern upon admission → potential for aneurysm rupture

Options...

- Surgical Intervention
  - Primary repair would be feasible IF the aneurysm were in a proximal artery (but it was in a distal artery)
  - Lobectomy of the lower lobe would be an option BUT the only area receiving blood flow would then be the upper left lobe...and that is very risky

- Embolization Procedure - this would require loss of circulation to the entire lower lobe which leads to same concerns as lobectomy

- Pulmonary Thromboendarterectomy - removal of thrombus from pulmonary arteries, which would restore perfusion to the right lung before handling the aneurysm

- Observation with management of the underlying disease
Question 8

Based on information presented on the previous slides, what is the safest and most logical treatment option to pursue?

A. Primary surgical repair
B. Lobectomy of the lower left lobe
C. An embolization procedure to cut off blood supply to the aneurysm
D. Pulmonary thromboendarterectomy of the right lung
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D. Pulmonary thromboendarterectomy of the right lung
E. Observation with management of underlying disease
Intraoperative Course

- Transesophageal echocardiography performed before the thromboendarterectomy procedure showed a mass in the proximal portion of the right pulmonary artery (diagram on right)
- Thromboendarterectomy was performed with cardiopulmonary bypass and hypothermic circulatory arrest
- Material removed from right pulmonary artery was identified to be a thrombus
- Postoperative echocardiography showed no evidence of residual thrombus, but the arterial wall remained abnormally thickened, which is consistent with an inflammatory response
Pathological Discussion

- The biopsy specimen (Panel A) included organizing thrombus and inflammation which in turn included T-lymphocytes, hemosiderin-containing macrophages, and some plasma cells.
- No microorganisms were present and no definitive features of active vasculitis were identified.
- Behçet's disease is characterized by necrotizing vasculitis which *does* show a mixture of inflammatory cells as seen in the patient's pathology.
- Hughes Stovin syndrome, however, typically does not show vasculitis but still displays inflammatory infiltrate consisting of lymphocytes and foamy hemosiderin containing macrophages (Panel C).
- Once again, the thrombus pathology seen in this patient is more consistent with the previous diagnosis of Hughes Stovin syndrome rather than classical Behçet's disease.
Which of the following are AGRANULAR leukocytes?

(a) Lymphocytes
(b) Neutrophils
(c) Eosinophils
(d) Basophils
(e) Mast cells
Question 9

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(d) Basophils
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Discussion of Management

- Since cases of Hughes-Stovin syndrome alone are so rare and treatment strategies are uncertain, the patient was treated similarly to someone with Behçet's disease (BD).
- Since BD is caused by inflammation rather than a hypercoagulable state, immunosuppression is typically the primary management strategy.
- To prevent rupture of the pulmonary artery aneurysm, the patient was given a combo of glucocorticoids and cyclophosphamide.
- The aneurysm did NOT decrease in responses to this treatment.
- As a result, cyclophosphamide was replaced with infliximab (since TNF-α inhibitors had shown efficacy in reducing aneurysms rooted in BD).
- Though the patient recovered well from the thromboendarterectomy procedure, it failed to restore perfusion to the right lung, so surgical action against the left lower lobe aneurysm could not be undertaken.
Question 10

What is the role of TNF (tumor necrosis factor)?

(a) Lyse the cell
(b) Engulf pathogens
(c) Induce inflammation
(d) Dilate blood vessels
(e) Constrict blood vessels
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Postoperative Condition

- The patient's dyspnea and coughing remained stable
- She was treated with prednisone therapy for 6 weeks post op
- Cyclophosphamide was added back after which C-reactive protein and erythrocyte sedimentation remained elevated
- A repeat chest CT then showed an increase in the size of the aneurysm
- The patient then switched back to infliximab after which patient inflammatory markers improved and repeat CT imaging showed modest decrease in aneurysm size
- Overall the aneurysm in the left lower lobe was very difficult to treat due to concurrent occlusion of the right pulmonary artery
Conclusions and Lessons from Case

- Deep vein thrombosis significantly increases risk of pulmonary embolism
- An aneurysm is a balloon-like bulge in the wall of a blood vessel (usually an artery)
- Though pulmonary artery aneurysms are uncommon, they are associated with high morbidity
- Surgical treatment of pulmonary artery aneurysms is highly dependent on the location of the aneurysm
  - Is it in a proximal or distal artery?
  - Is it contained within a distinct lobe?
- It is still unknown what causes Behçet's disease and why it can sometimes only partially manifest as Hughes-Stovin Syndrome