Deep Vein Thrombosis and
Pulmonary Thromboembolism ("Pulmonary embolism")

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Background

The most common cause of a pulmonary embolism is pulmonary thromboemboli arising as dislodged clots from the deep veins of the lower extremities (approximately 90% of pulmonary thromboemboli originate in the lower extremities and 10% originate in the upper extremities). This article focuses on pulmonary thromboemboli from deep vein thrombosis. See EMBOLI for a discussion of other embolic phenomena.

While most thrombi in the pulmonary arteries will be embolic from other sites, some thrombi will have formed *in situ*, i.e., pulmonary thrombosis, especially in those with underlying pulmonary pathology such as pulmonary hypertension, emphysema, and/or pulmonary atherosclerosis. These thrombi are not discussed here. (Excellent articles on pulmonary thrombosis arising in pulmonary arteries can be found here and here).

Quick Tips at Time of Autopsy

- Pulmonary thromboemboli are relatively common at hospital autopsy.
- They may not have been known or suspected by the decedent's treating team.
- Small pulmonary thromboemboli can easily be missed by pathologists at the time of autopsy if they are not thinking of the diagnosis.
- Therefore, careful evaluation and sampling for venous thromboembolism is warranted.

Clinical history

- Consider potential risk factors in the decedent's clinical history, as well as the pathophysiology of thrombosis, i.e., Virchow's Triad - hypercoagulability, endothelial damage, and stasis.

Primary (inherited) thrombophilias
Factor V Leiden mutation
Prothrombin G20210A mutation
Protein S deficiency
Protein C deficiency
Antithrombin deficiency
Risk factors for secondary (acquired) thrombophilias

Indwelling lines (e.g., central venous catheter)
Malignancy
Certain cancer therapies (eg, tamoxifen, thalidomide, lenalidomide, asparaginase)
Trauma (e.g., recent hip fracture)
Recent surgery, especially orthopedic procedures
Immobilization
Pregnancy
Oral contraceptive use
Hormone replacement therapy
Heart failure, i.e., venous stasis
Congenital heart disease
Antiphospholipid syndrome
Older age (≥65 years)
Obesity
Severe liver disease
Myeloproliferative neoplasms
Polycythemia vera
Essential thrombocythemia
Paroxysmal nocturnal hemoglobinuria
Inflammatory bowel disease
Nephrotic syndrome
Tobacco smoking

(Modified table from UpToDate: Overview of the causes of venous thrombosis. Accessed here.)

- Review pertinent antemortem laboratory data.
    - Previous laboratory tests of non-therapeutic INR levels measuring therapeutic anti-coagulation may support the diagnosis.

- Ante-mortem D-dimer elevations have a high negative predictive value but are not specific. Post-mortem testing for D-dimer has not been proven reliable.

External examination

- Evaluate for conditions referenced in the above table, e.g., cast on lower extremity suggesting immobility, pregnancy, etc.
- Assess for findings consistent with deep vein thrombosis.
  - **Document asymmetry in calf and thigh circumferences with measurements** (see this video for a demonstration of measuring calf circumference); if upper extremity deep vein thrombosis is suspected arm and forearm circumferences can also be documented.
    - Bilateral leg atrophy may signal paralysis, a risk factor for pulmonary thromboembolism.
  - Document erythema or other dermatologic venous stasis changes consistent with valvular insufficiency.

Gross examination

- The autopsy evisceration technique will determine the optimal method for identifying a large/central pulmonary thromboembolism.
  - Rokitansky/Leteulle method: In situ evaluation for a saddle embolus is performed prior to removing the heart and lungs from the body. After reflecting the pericardial sac to expose the heart and proximal great vessels, incise the proximal pulmonary artery and visually examine and then palpate for thromboembolism. This initial incision can be extended along the right and left pulmonary arteries to the hila to inspect for thomboemboli along all of the major arteries.
  - Virchow method: As the lungs are individually removed visually inspect the pulmonary arteries while they are being cut to identify any clot or thromboembolism which can be dislodged during the procedure.
- Dissection of the deep leg and/or arm veins should be performed when there is either 1) a clinical history of deep vein thrombosis or pulmonary thromboembolism, or 2) when pulmonary embolism is identified at autopsy.
  - The deep leg vein dissection technique is covered in the College of American Pathologists *Special Autopsy Dissections* publication.
  - If the original autopsy consent does not permit this procedure, additional discussion with the next-of-kin should take place to modify the consent and allow for the procedure.

- The funeral director should be notified when unusual incisions such as those used to evaluate the deep veins are used at autopsy.
    - Verbally notify the funeral director.
    - Place a note on the body in the body bag stating that the procedure was performed.
    - Place extra absorbent pads/chucks under the legs in the body bag at the time of transportation.
- When there is a pulmonary thromboembolism and its source is not identified through the usual autopsy incisions (i.e., transecting the iliac veins) and special dissection of the lower extremity deep veins, then the deep veins of the upper extremities should be dissected.

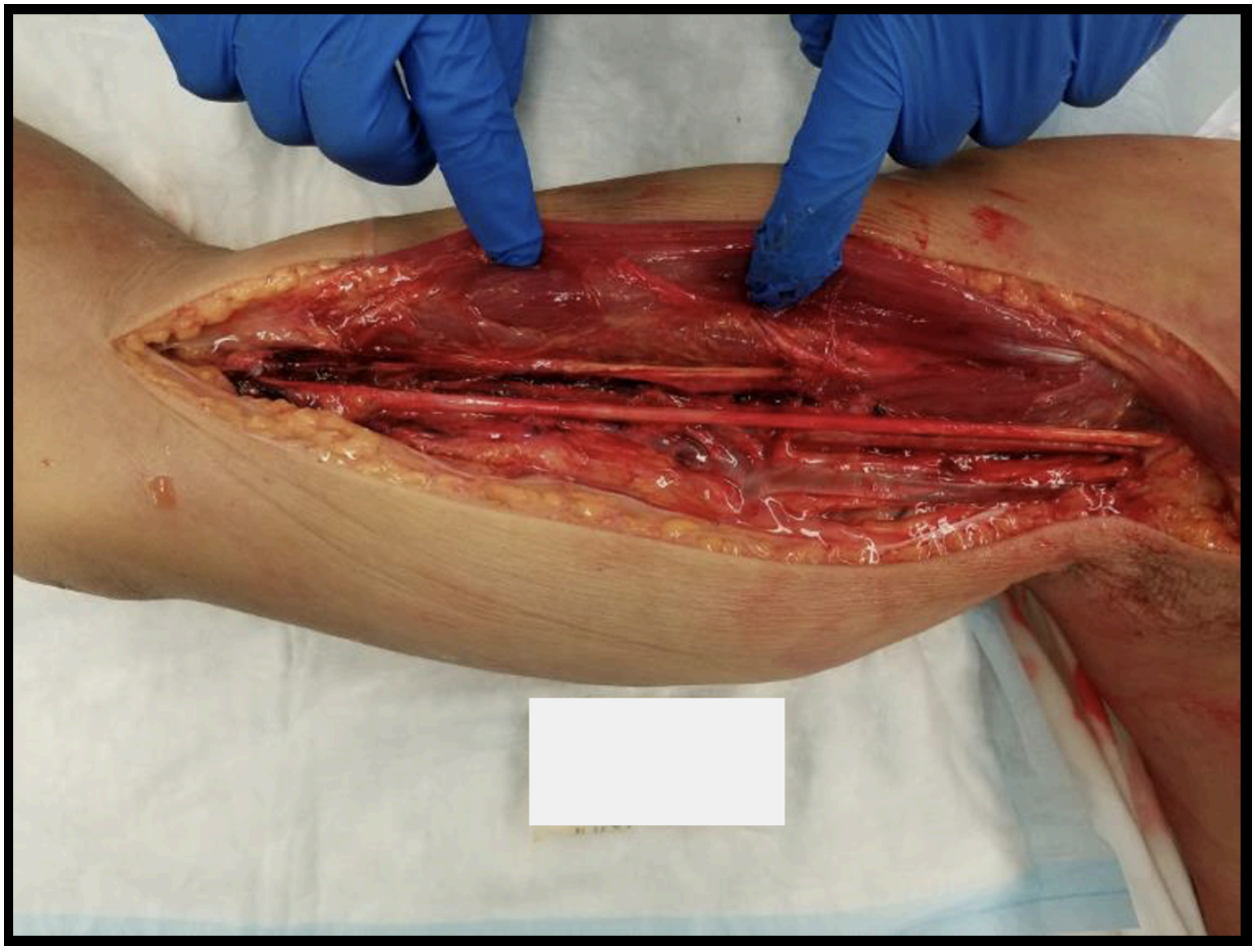


Image: Example of an upper extremity dissection for a thromboembolism. (Image credit: Alex Williamson).

- If the deep leg veins cannot be dissected (e.g., family refuses to modify the consent to allow the procedure), then an acceptable alternative procedure

involves elevating the lower extremities and massaging blood toward the abdomen out of the cut iliac vessels ("milking").

- If blood emanates from the cut iliac vessels then there likely is no thrombus in the iliac vessels.
- Note that approximately 25% of lower extremity deep vein thrombosis are in the iliac veins (Nyamekye 2012), and therefore, 75% are distal to the iliac veins, and so the above "iliac milking" procedure is not sufficient to exclude the majority of lower extremity deep vein thrombosis and these may not demonstrate useful findings.

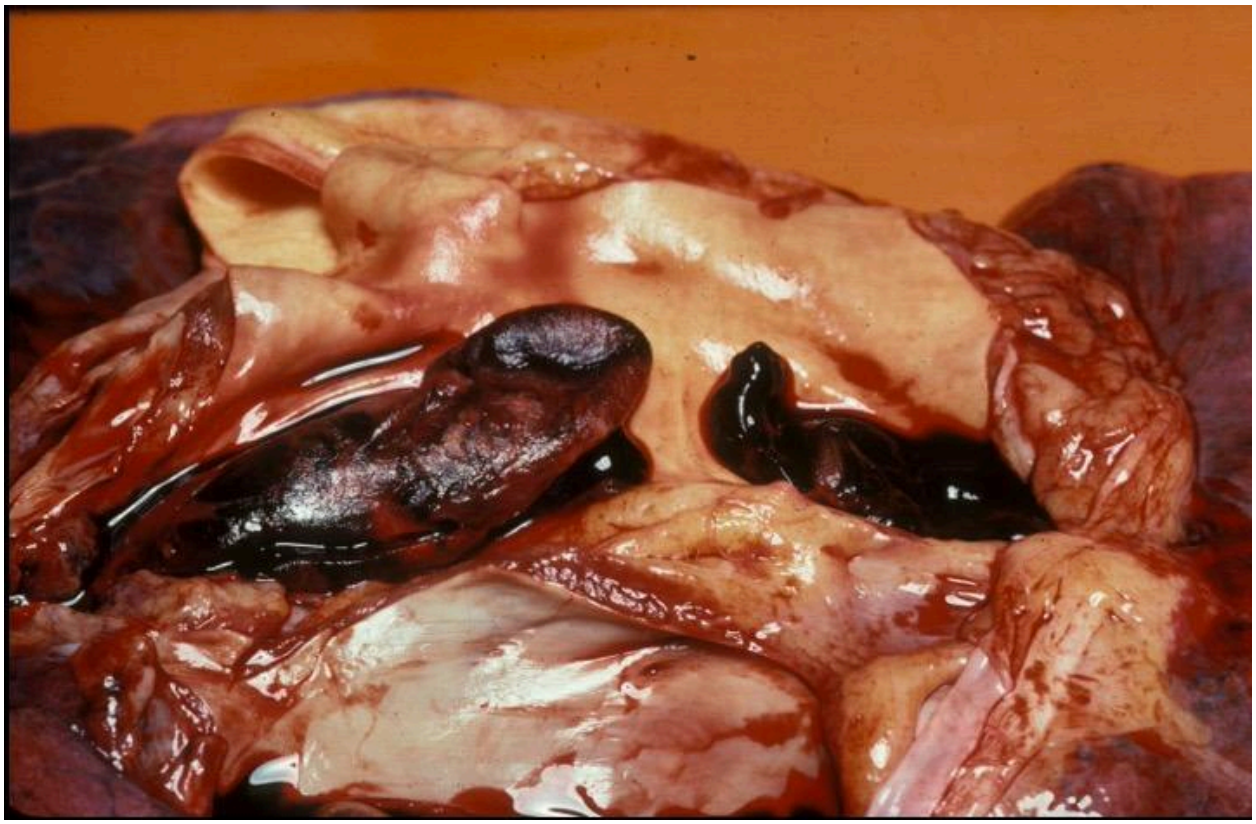


Image: Pulmonary thromboembolism in a large vessel. (Image credit: Corinne Fligner, University of Washington).

- Pointers for evaluating thromboemboli
  - Remember: there can be more than one pulmonary thromboembolism.
  - Most thromboemboli lodge at the bifurcation of a pulmonary artery.
  - "Webs" within a pulmonary artery indicate recanalization of a prior thromboembolism at that site (see photo below).
  - To aid in identifying distal smaller thromboemboli that can be easily missed on initial inspection, the lungs can be inflated with formalin and then sectioned and examined after fixation.

- Other findings often seen in the setting of a pulmonary thromboembolism include
    - Inferior vena cava (IVC) filter
    - Patent foramen ovale
    - Pulmonary infarct(s) in lung(s); these are often wedge shaped and hemorrhagic due to the dual blood supply of the lung.

Image: Hemorrhagic wedge-shaped infarct from a pulmonary thromboembolism. (Image credit: The Internet Pathology Laboratory for Medical Education, University of Utah. Accessed here).

- Distinguishing antemortem vs. postmortem clots.
    - Note: some clots are neither purely antemortem nor purely postmortem, but instead arise in the terminal setting of a “languishing death” (e.g., progressive heart failure, prolonged cardiopulmonary resuscitation) and are therefore best classified as perimortem clots. Overall, they more closely resemble the macroscopic and microscopic features of postmortem clots.

Feature	**Antemortem**	**Postmortem**
Diameter	Smaller, as they form in distal systemic veins	Larger, as they form in the pulmonary artery in which they are found
Color	dark red with variably	separation of red

	prominent tan layering	blood (“currant jelly”) and tan buffy coat/serum (“chicken fat”)
External appearance	granular	shiny
Consistency	firm, may be friable	soft, gelatinous/rubbery
Shape	Tend to coil up on themselves due to their diameter being less than that of their investing pulmonary artery	Tend to fill and/or take the shape of and/or extend along their investing pulmonary artery
Adherence	recent thromboemboli tend not to adhere to their investing pulmonary artery; older thromboemboli adhere to their investing pulmonary artery	“sticky” attachment to their investing pulmonary artery, but easily removed

(Table credit: Alex Williamson).

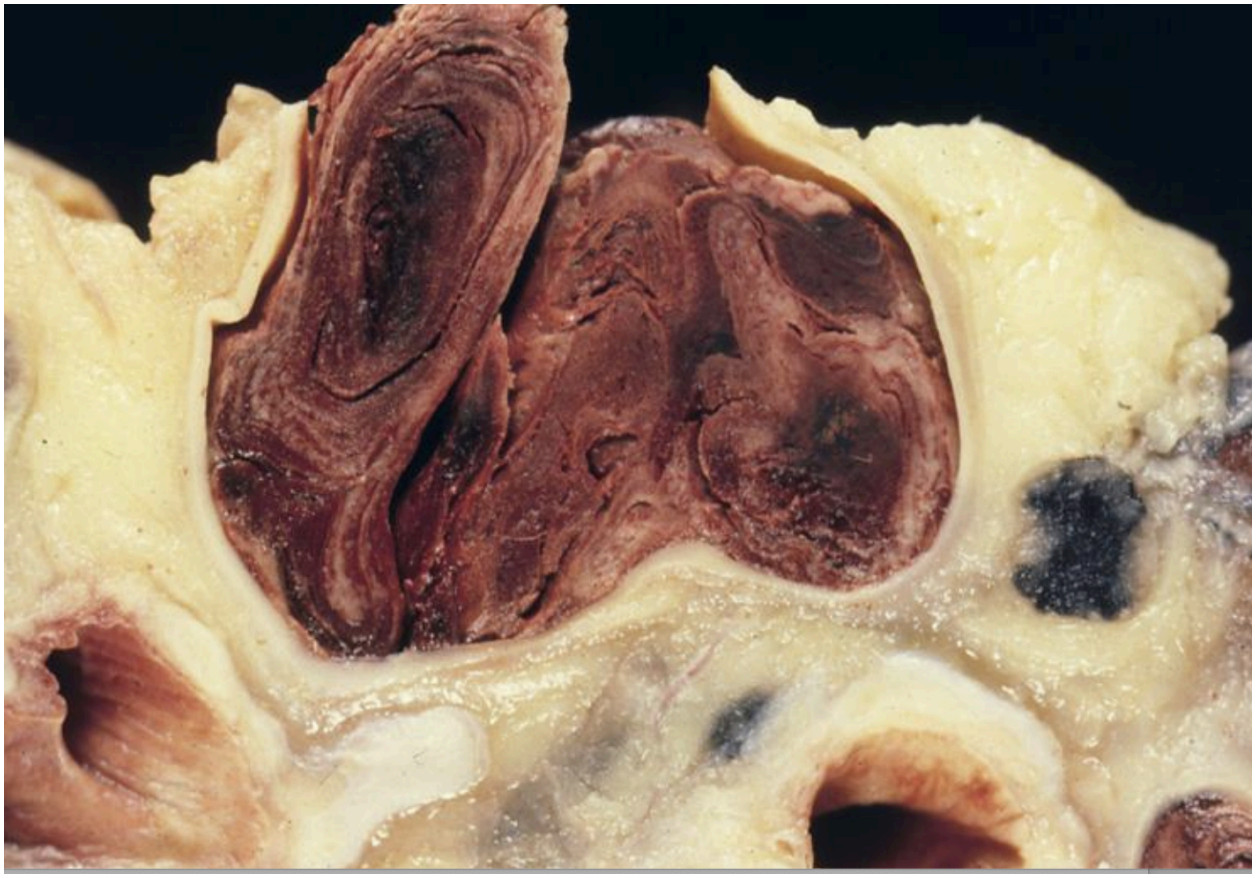


Image: Antemortem PE with clear lines/laminations. (Image credit: Maureen Hoffman. Mechanisms of Thrombosis. Accessed here).

- Sections for histology
    - Note: Thrombi and thromboemboli within vessels should be sectioned for histology after fixation (otherwise the blood clot can fall out of the vessel during transection).
        - Thromboemboli in pulmonary arteries can be kept as part of the whole lung specimen for fixation, or blocked out and separately fixed.
        - A segment of thrombi in systemic veins (approximately 4 cm long) can be blocked out and fixed.
    - Thromboembolus, at least one section to include its investing vessel wall.
    - Thrombus, at least one section to include its investing vessel wall.
    - Lung parenchyma downstream from the thromboembolism may show microthrombi in small vessels, as well as evolving infarction.

Quick Tips at Time of Histology Evaluation

- Postmortem clots (in contrast to antemortem clots/thrombi) will have the following features:

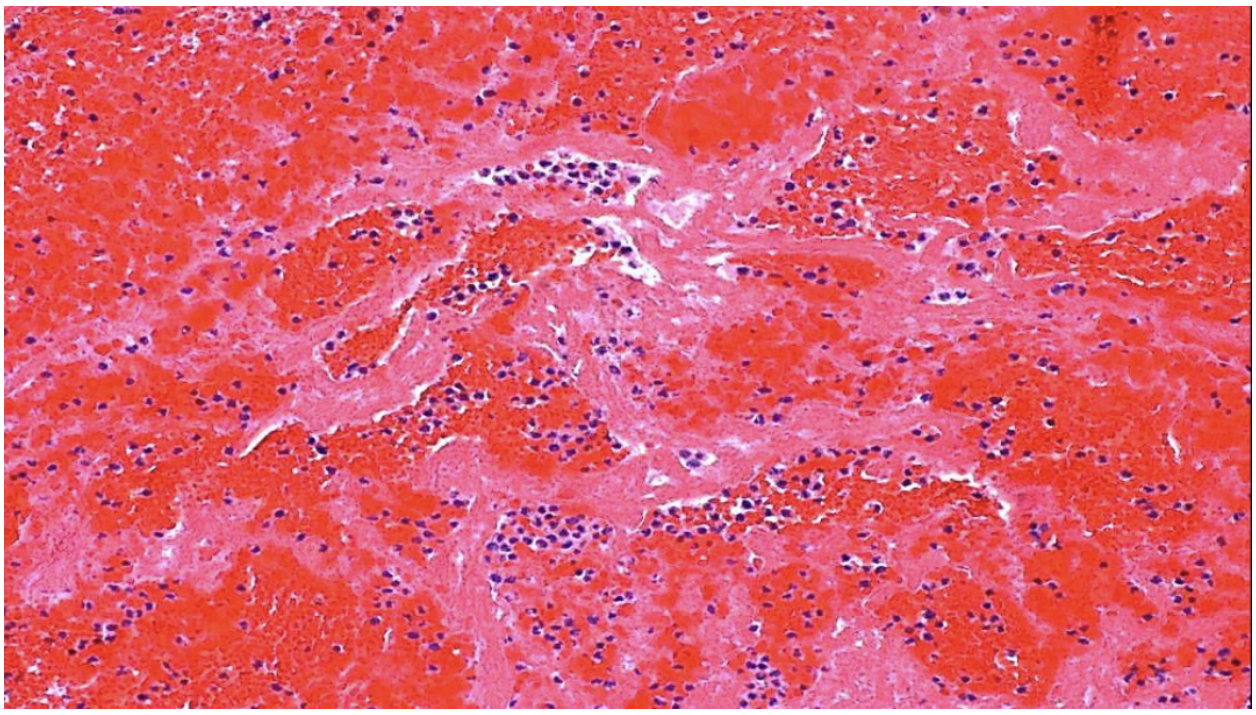
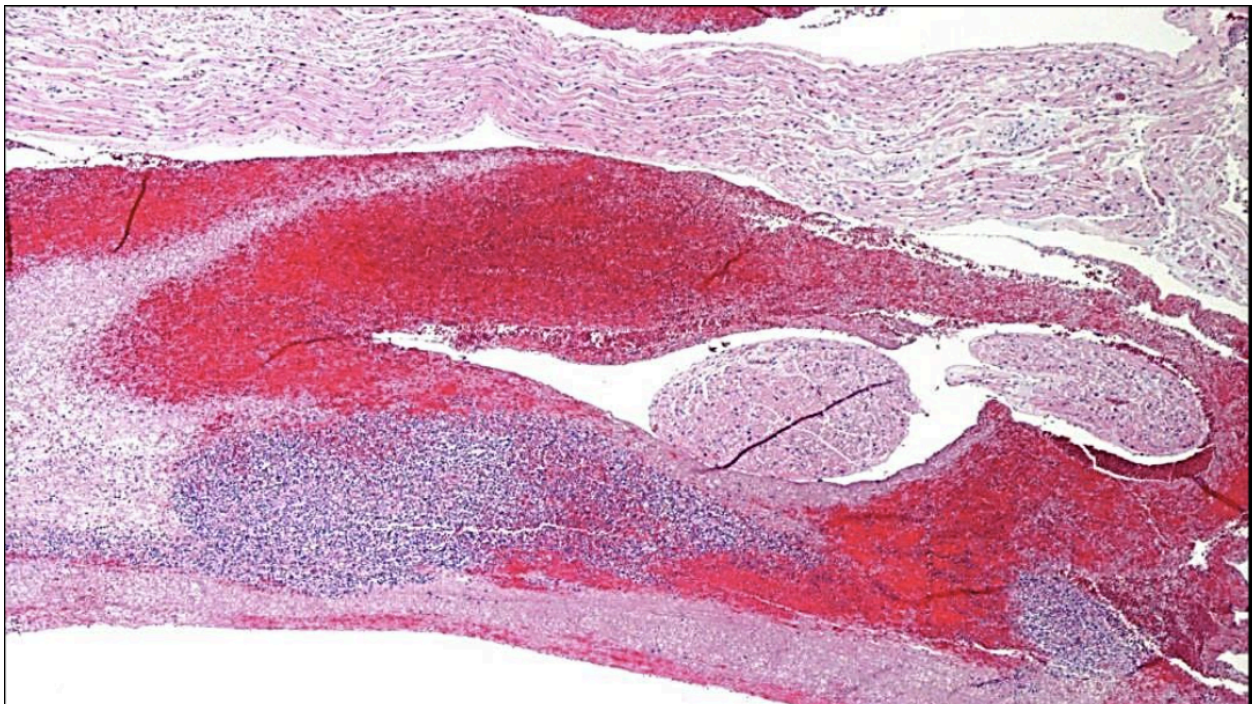


Image: Postmortem blood clot with a random arrangement of RBCs and plasma. (Image credit: Alex Williamson).



Perimortem/chicken fat/agonal blood clot. Of note, “chicken fat” clots are often called post-mortem clots, however they usually form immediately prior to death in the agonal period, especially in cases of death with low cardiac flow such as heart failure where the plasma can partially separate from the RBCs. (Image credit: Alex Williamson).

- Postmortem thrombi have the following histologic findings based on age. Of note, Precise dating of thromboemboli is not possible. The following is a typical sequence of events with approximate timelines as documented in scientific studies (modified from Irninger 1963)

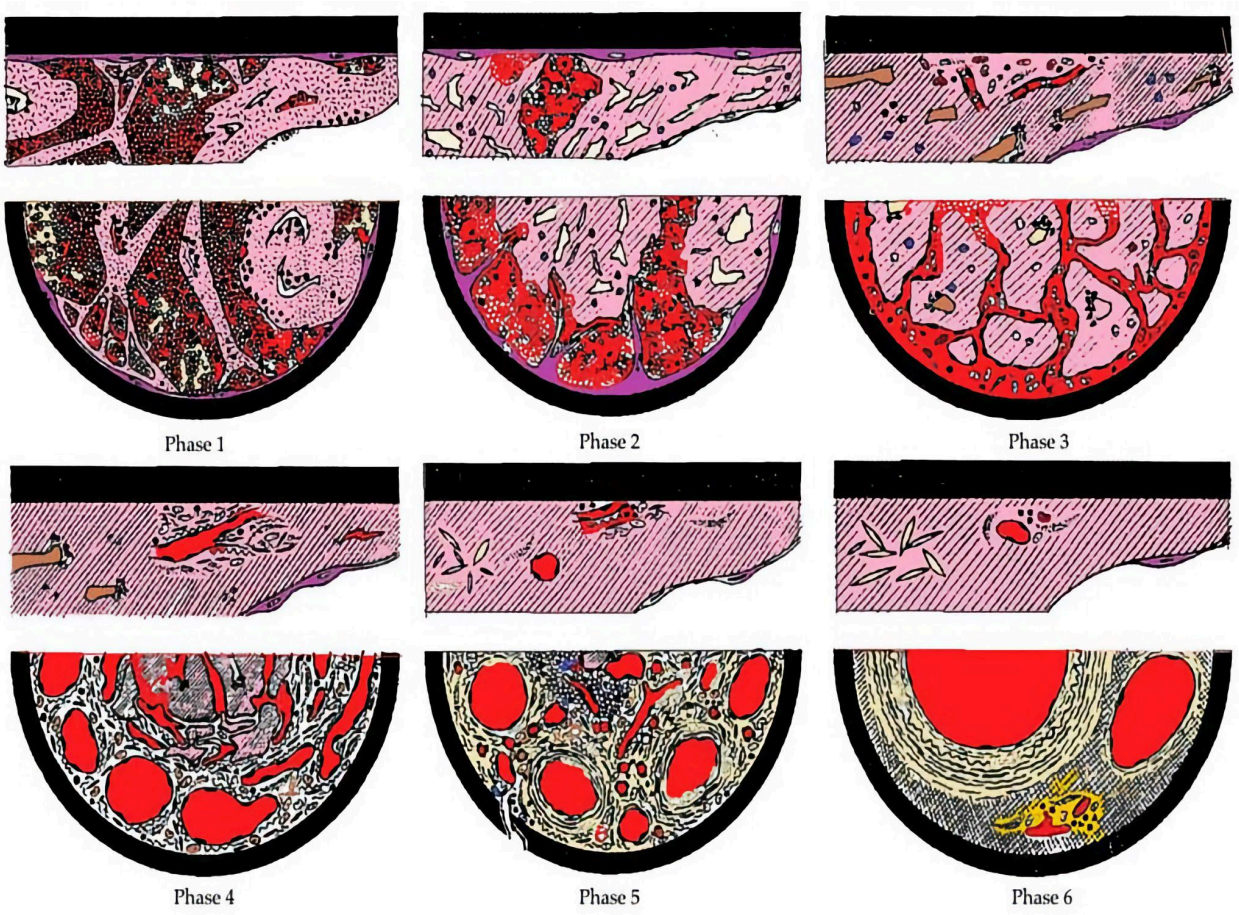
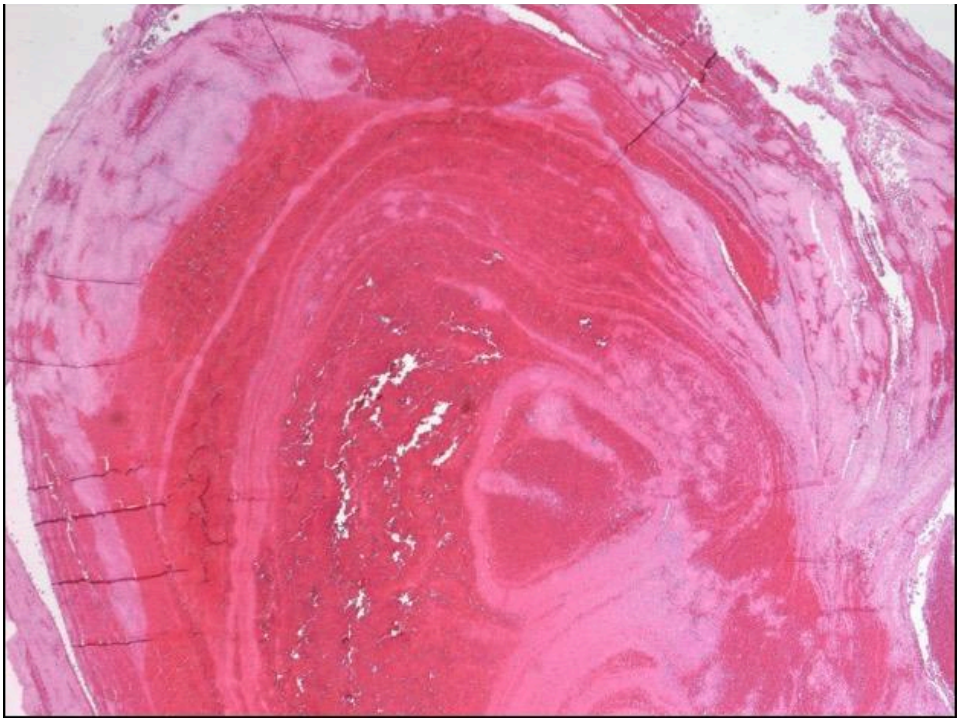


Image: 6 stages of thrombus organization cover approximately 12 months. (Image credit: DiFazio 2021).

- Phase 1: Absence of reaction between endothelium and thrombus; leukocytes, platelets, and fibrin streaks are unaffected; erythrocytes agglomerated centrally and scattered peripherally.



Recent antemortem blood clot with lines of Zhan (layering of RBCs and plasma). (Image credit: Corine Fligner, University of Washington).

- Phase 2: At day five, penetration of endothelial buds; initial hyalinization, mainly central; pyknotic leukocytes and mononuclear cells enlarged; thrombus contraction may create fissures and cavities with erythrocytes inside.

- Phase 3: By day 10, first capillaries, fibroblasts, mesenchymal cells and histiocytes with accumulations of hemosiderin; thrombus hyalinized and divided into large clumps; residual leukocyte nuclei.

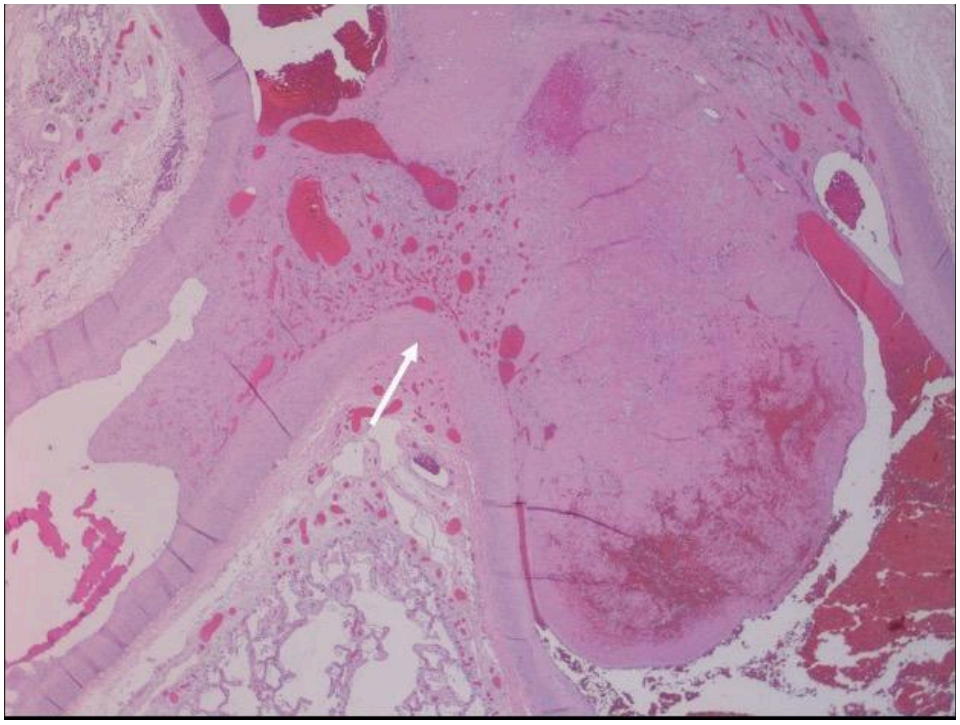


Image: Pulmonary thromboembolism with attachment to vessel wall and microvascular proliferation (both at arrow). (Image credit: Corine Fligner, University of Washington).

- Phase 4: From week four, argyrophilic fibers and collagen; numerous capillaries.
- Phase 5: From the eighth week to the eighth month, completely hyalinized thrombus and presence of fusiform cholesterol crystals; vascularized loose connective tissue; centrally sinuous spaces traversable by fresh blood.

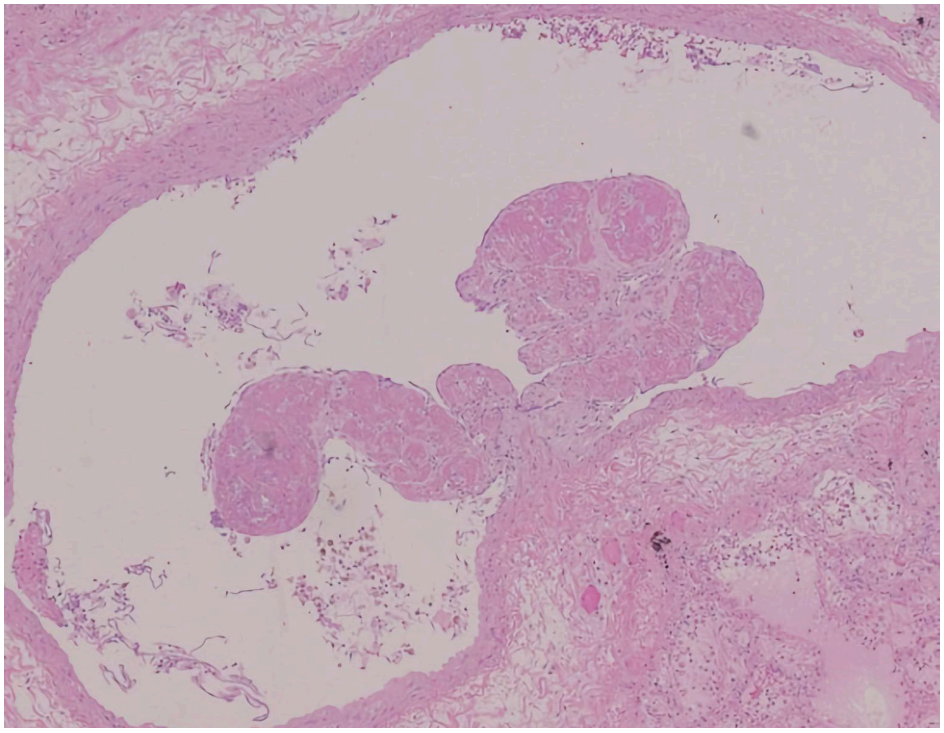


Image: Organizing thromboembolism with endothelialization. (Image credit: Dr. Corine Fligner, University of Washington)

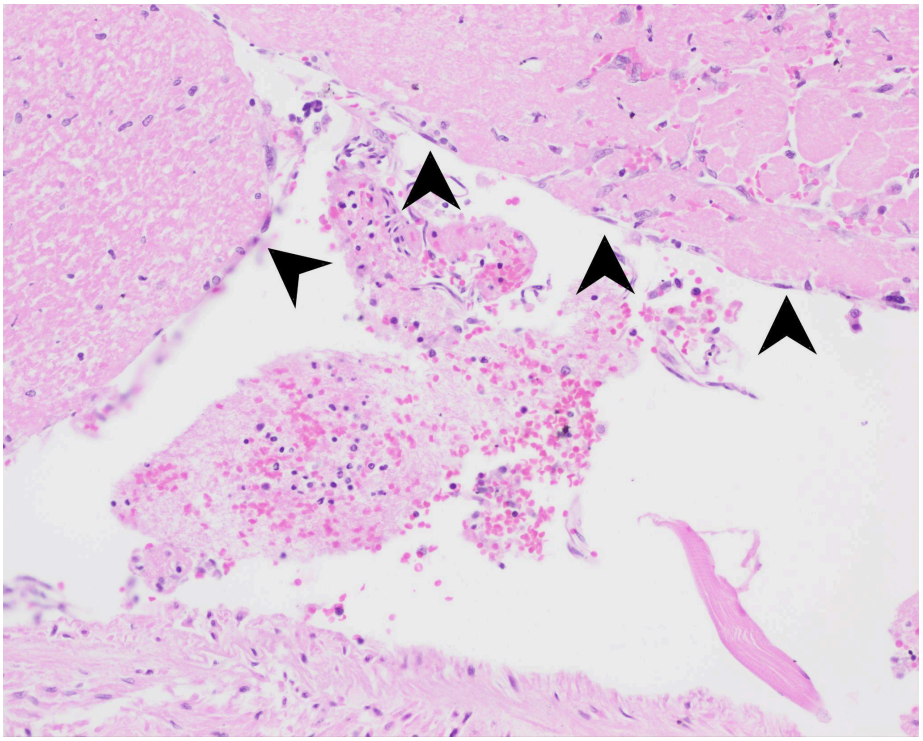


Image: Organized thrombus with epithelial layer (arrows pointing to thin, basophilic endothelial nuclei) and hyalinized thrombus with organizing fibroblasts. H&E 20x. (Image credit: Meagan Chambers, University of Washington).

- Phase 6: After the sixth month, almost complete recanalization through large vessels separated by compact, fibrous connective tissue poor in cellular elements

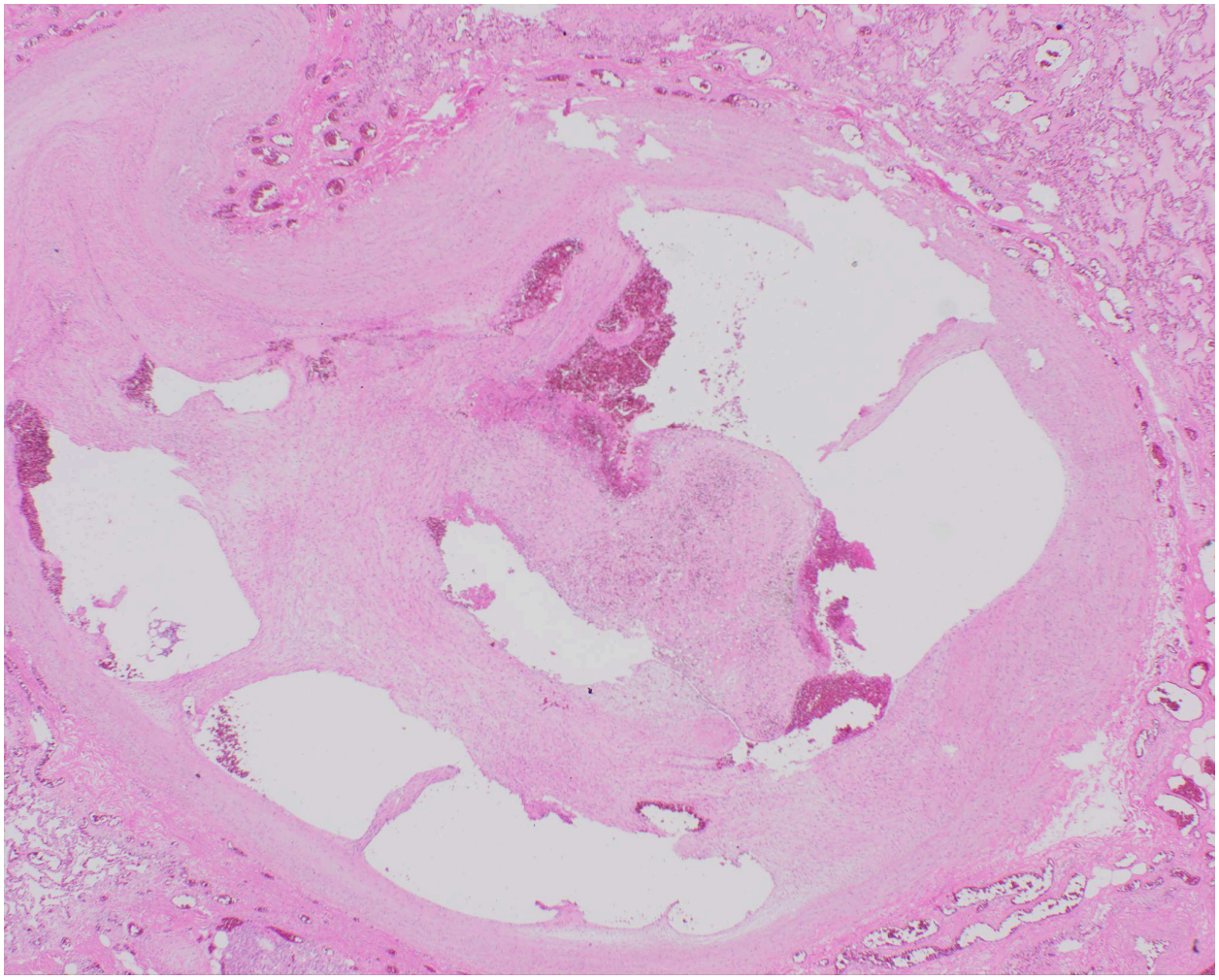


Image: a recanalized pulmonary artery; grossly the septa can look like webs within the vessel. (Image credit: Meagan Chambers, University of Washington).

Due to the imprecision of dating, a three stage dating system has also been proposed:

1st Phase (1–7 Days)	Flowing blood on an eroded endothelium, eliciting a platelet plug and fibrin deposition with a layered growth (Zahn's lines). No reaction between endothelium and thrombus is visible. Erythrocytes are preserved and agglomerated. Initial white blood cells pyknosis. Monocytes cells with enlarged nuclei. Calcium is observed as precipitates with von Kossa stain. The thrombus at its initiation is firmly attached to a small portion of the vessel wall and is not easily removed to leave fragments in situ. On the contrary, a coagulum maintains the usual blood composition (i.e., prevailing red cells plus leukocytes and platelets and a fine network of fibrin), is not attached to the endothelium, and can be easily removed.
2nd Phase (2–8 Weeks)	Endothelial budding and proliferative changes of the medial ring are represented by the penetration of fibroblasts. Macrophages containing hemosiderin predominate, red blood cells ghosts and fibrinous transformation. The ribbons of fibrin changing to coalescences, trapping white cells. The free surface of thrombus is covered by the endothelium. Scattered nuclear debris of white blood cells
3rd Phase (More than 2 Months)	Completely hyalinized thrombus with central sinuous cavities and more advanced recanalizing neo-formed larger vessels with fresh flowing blood. Few white cells are visible between compact, fiber-rich and cell-deficient connective tissue.

(Table modified from DiFazio 2021 and Fineschi 2009)

- Layering ("Lines of Zhan") of recent PEs can be subtle, thin, or limited to the periphery.

Immunohistochemistry:

- Suspected thromboemboli can be stained with CD61, which stains platelets; antemortem clots will demonstrate layering of platelets (Lines of Zhan) while postmortem clots will have a random distribution of platelets.

Quick Tips for Autopsy Report

- Report the presence and location and histologic appearance of venous and pulmonary thromboemboli including whether it was segmental, subsegmental, etc.
- Underlying risk factors identified in the clinical history or at autopsy can be included in the diagnosis/summary/etc.
- Generally, a thrombus occluding >60% of blood flow is considered sufficient to result in sudden death.
- Example cause of death statements
    - Myocardial infarct due to coronary artery atherosclerosis. Contributing conditions include diabetes and smoking.
    - Myocardial infarct due to coronary artery dissection arising in pregnancy.
    - Myocardial infarct due to coronary artery involvement in Kawasaki disease.

Clinical Tid Bits:

- Over half of all venous thromboemboli are healthcare associated (occurring during or shortly after a hospital admission) making them an important finding to document for quality improvement

Recommended References:

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Additional references:

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Additional Photos:

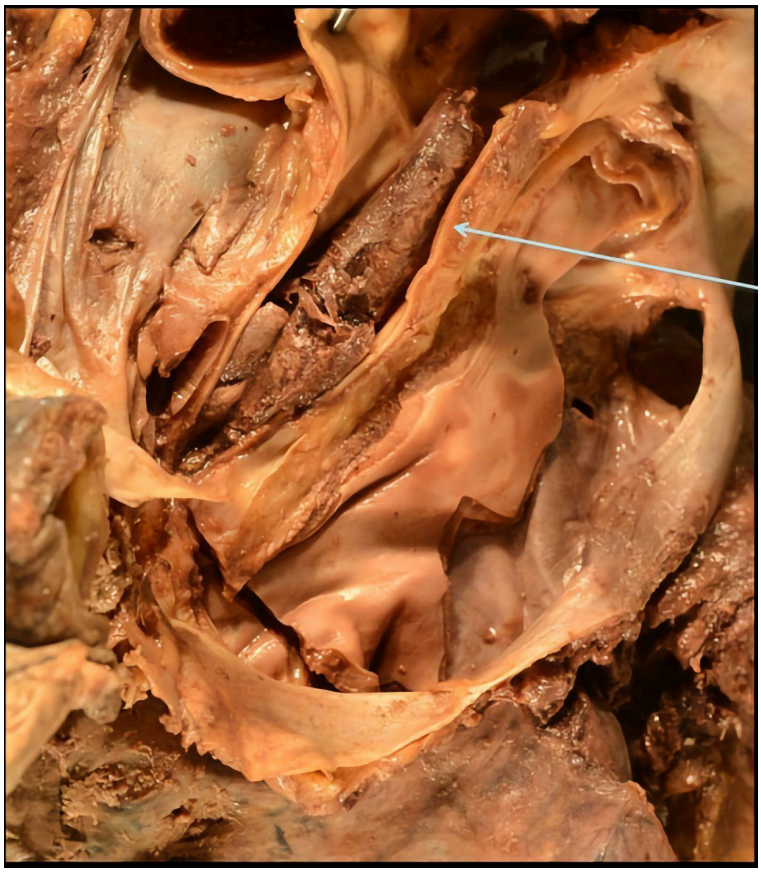

Image: Large pulmonary embolus. (Image credit: Dr. Corine Fligner, University of Washington)

Image: Pulmonary thromboembolism (at arrow and in above vessel) adjacent to anthracotic lymph nodes. (Image credit: Dr. Corine Fligner, University of Washington)