Pathology of Pulmonary Thromboembolism*

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The incidence of pulmonary thromboembolism is hard to assess by the pathologist as a result of seasonal variation of embolism and disappearance of emboli by thrombolysis. However, the great differences in estimates of the incidence in routine hospital autopsies is mainly related to variation in scrutiny of the investigation and in size of area searched microscopically. Obstruction of major pulmonary arteries almost always results from thromboembolism which is most often found in its acute stage. In chronic major vessel embolism, arterial obstruction by an organized mass may produce pulmonary hypertension. Recanalization of such a mass results in so-called bands and webs. There are no reliable criteria to differentiate between emboli and primary thrombi or their sequelae. In peripheral, particularly muscular pulmonary arteries, thrombi are most likely primary, especially when associated with advanced age and with pulmonary hypertension. However, small arteries may be subject to extensive microembolism following fragmentation of large thromboemboli. Thrombotic arteriopathy is the pulmonary arterial disease based upon either primary thrombosis or embolism. It is often associated with pulmonary hypertension, and characterized by irregular, nonlaminar, often obliteratorive, intimal fibrosis. Recanalization channels, sometimes widening to separate intravascular fibrous septa, are characteristic features. Reversibility of post-thrombotic lesions is very limited.

Pulmonary thromboembolism is a common phenomenon and an important cause of morbidity and mortality. In many respects, it is also an enigmatic disease even with respect to its incidence. Although the clinical diagnosis usually presents great difficulties, the pathologist can hardly provide a reliable estimate of the frequency of pulmonary thromboembolism in routine hospital autopsies. There are several factors that make the pathologic diagnosis elusive. These include seasonal variation in incidence, disappearance of emboli by endogenous thrombolysis, the large variation in size of the emboli, and the impossibility of differentiating morphologically between thrombi embolized to the lungs and those formed in situ.

It has been recognized that pulmonary thromboembolism incidence peaks in spring and autumn.\(^1\) In any study about the incidence of thromboembolism, such a seasonal variation, possibly related to weather conditions, should be taken into account.

The lungs have a certain capacity to dispose of thromboemboli by endogenous thrombolysis. This is probably how a considerable percentage of emboli disappear prior to morphologic investigation. The evidence suggests that large and small thromboemboli can resolve in this manner.

Differences in size of thromboemboli have great consequences not only for the clinical effects and for mortality, but also for the evaluation of the prevalence of pulmonary thromboembolism. Large emboli obstructing pulmonary trunk or main pulmonary arteries will not remain undetected when these vessels are opened at autopsy. However, lobar and segmental pulmonary arteries are not regularly cut systematically, so that emboli in these vessels may escape detection. This explains that the percentage of grossly recognizable emboli in routine autopsies of adult patients varies widely, from 1.5% to almost 30%.\(^3,4\)

Microscopic examination greatly increases the numbers of observed recent and old thromboemboli, so that the percentage of autopsy cases in which they were found rose to 52%\(^5\) or 64%.\(^6\) Since we are dealing with lesions scattered over the lung tissue, the results of such studies depend largely on size and number of tissue blocks taken from each case. In our own experience, the percentage of positive cases may approach 90% when more blocks of lung tissue are studied, and occasional postthrombotic lesions are included in the count.\(^7\)

This, however, raises the question how to distinguish thromboemboli in their various stages from thrombi primarily formed in the pulmonary arteries. Morphologically, such a distinction cannot be made.

Other criteria that can be used for such a differentiation are somewhat vague and certainly not always reliable. Large thrombi present in major elastic pulmonary arteries, are supposed to be embolic in nature as long as there is no underlying disease of the vascular wall in that area. While this is probably an acceptable indication, its usefulness decreases rapidly with the caliber of the pulmonary arteries in which they occur.

Primary thrombi tend to be more common in the upper lobes of the lungs than in the lower lobes, while both large and small thromboemboli are somewhat

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more numerous in the lower lobes.7 The use of this criterion, however, requires a time-consuming counting of lesions in various parts of the lungs, often with doubtful results. When there are numerous thrombotic lesions limited to arterioles, while all larger arteries are patent, it is often assumed that these changes result from primary thrombosis. This is likely to be true in the great majority of the cases.

The inevitable conclusion, however, is that often the pathologist is unable to provide reliable data on the presence of pulmonary thromboembolism.

CLASSIFICATION

A morphologic classification of pulmonary thromboembolism is based on the stage and the size of the emboli. In the acute form of the disease, the thromboemboli are fresh; in chronic thromboembolism, their structure changes gradually to produce a number of more or less characteristic postthrombotic lesions.

For the histologic picture of a thromboembolus, its size is irrelevant. A large thromboembolus in a main pulmonary artery does not differ microscopically from a minute embolus in a peripheral arterial branch, and this applies to the fresh stage of the clot as well as to its sequelae. However, the size of thromboemboli is essential in any classification. For practical reasons, the histologic features will be discussed and demonstrated with respect to small rather than to large thromboemboli.

ORIGINS

The site of origin of thrombi embolizing to the lungs is to be found in the great majority of the cases, in the deep veins of the legs, particularly iliac, femoral, and popliteal veins. The pelvic veins may be the site of thrombosis and a potential source for embolism, especially during and following pregnancy and following operations in that area. The use of intravascular catheters may elicit thrombosis in vena cava and in the veins of the upper extremities. In the heart, the right atrium may be a source of thromboembolism particularly after atrial fibrillation, the tricuspid and pulmonary valves in the presence of valvular endocarditis, and the left ventricle following myocardial infarction.

ACUTE THROMBOEMBOLISM

Acute embolization causing sudden death usually involves obstruction of pulmonary trunk and/or both main pulmonary arteries. Additional thromboemboli may be present in the right side of the heart. Sometimes, unilateral blockage of a main pulmonary artery is instantly fatal, but since pulmonary emboli are usually multiple and thus often bilateral, it is likely that in these instances the embolic attack was preceded by thromboembolism affecting the contralateral lung.

Complete or nearly complete occlusion of a large pulmonary artery may be brought about by a single thromboembolus originating in a large systemic vein, by several smaller emboli, or by folding or twisting of an embolus. A thromboembolus, however, may also be arrested at a bifurcation of pulmonary trunk or at a more peripheral ramification, so that even a large clot fails to occlude the arterial lumen completely and some blood flow remains intact. Such a saddle embolus, therefore, may permit survival after massive pulmonary thromboembolism. Also V-shaped or Y-shaped clots, reflecting their origin from a venous confluence, may allow residual blood flow when impacted into a pulmonary artery.

The morphologic features of a fresh thromboembolus are similar to those of a nondetached thrombus. As it is a cast of the veins in which it originated, it has a roughly cylindrical shape with blunt ends and a smooth surface, sometimes showing the impressions of the venous valves. In contrast to a postmortem clot that is moist, structureless, and rubbery, and that can be removed as a ramifying cast from the pulmonary arterial tree, a thromboembolus is dry and friable. Pale lines of Zahn can be seen on its dark red exposed surface and particularly on its cut surface; these lines represent layers of platelets and fibrin alternating.
with layers of erythrocytes. Since the embolus is forced into a pulmonary artery, the vessel is usually dilated in this area so that its wall is thinner than normal (Fig 1).

That thromboemboli are more often found in the right than in the left lung and more often in the lower than in the upper lobes is clearly related to the flow distribution that favors the right lung and the lower lobes.

**Chronic Major Vessel Embolism**

If the patient survives the initial thromboembolic impact, various processes may determine the fate of a thromboembolus. One of these is endogenous thrombolysis. The capacity of the lungs to remove thromboemboli is great. By enzymatic activity, the fibrin networks within a clot are dissolved and, with this fibrinolysis, particularly small but also larger emboli can be disposed of completely.

Fragmentation of thromboemboli may be mechanical during their transport through the heart and on impact in the pulmonary arteries at sites of ramification. It is likely that endogenous thrombolysis contributes to fragmentation when a clot falls apart after lysis of its fibrin skeleton.

Organization of a thromboembolus can be regarded as a reparative response, characterized by invasion of fibroblasts and capillary buds into the thrombotic mass that becomes adherent to the vascular wall. When the whole embolus is converted into vascularized connective tissue, shrinkage of this mass will restore some of the original lumen. Obstruction of major pulmonary arteries by an organized thromboembolus is sometimes associated with pulmonary hypertension. Surgical correction by thromboendarterectomy may produce significant hemodynamic improvement.

The capillary buds that have invaded a thromboembolus tend to anastomose, forming a network within the organized clot. Some of these channels become very wide at the expense of others. By this recanalization, some blood flow may be restored.

**Figure 2.** Bands and webs (arrow) in main pulmonary artery and its branches. These structures result from organization and recanalization of thromboemboli (original magnification X1.5).
through the obstructive mass. In some instances, the channels become so wide that all that is left of the organized thromboembolus are some fibrous cords that may be single or multiple, forming a network (Fig 2). These so-called bands and webs are not rare; careful inspection of the inside of major pulmonary arteries in routine hospital autopsies will reveal them regularly.9,10

**PULMONARY INFARCTION**

With few exceptions, pulmonary infarction is associated with thromboembolic obstruction of a medium-sized pulmonary artery. It is rarely caused by occlusion of a main pulmonary artery or of a small-caliber elastic or muscular artery. However, infarction is far more uncommon than thromboembolism involving lobar or segmental pulmonary arteries. The reason is that the lung has a dual blood supply and the bronchial arteries, which at a capillary level have an extensive connection with the pulmonary circulation, can prevent serious damage to lung tissue deprived of its pulmonary arterial supply. Collateral blood flow from adjacent pulmonary arteries may contribute to this process.

Therefore, pulmonary infarction is unlikely to occur unless there is an impaired general cardiovascular circulation, particularly an inadequate bronchial circulation or an impediment to the pulmonary venous outflow. Most often, infarctions of lung tissue are found in patients with heart disease, particularly mitral stenosis, and in terminally ill patients. They are very uncommon in individuals younger than 40 years of age.

Infarction implies necrosis of lung tissue, but necrosis is not always an inevitable result of an inadequate blood supply. A mild transient ischemia of lung tissue may result in marked dilatation of capillaries, arterioles, and venules and also in an increased vascular permeability with leakage of fluid and erythrocytes, since the endothelial cells of these vessels are very susceptible to hypoxia.

The resulting pulmonary hemorrhage resembles an infarct, but the structure of the lung tissue is preserved and the preexisting architecture may be restored after resorption of the blood.

Both pulmonary hemorrhage resulting from thromboembolism and pulmonary infarctions may be multiple and are found particularly in the lower lobes. They are usually situated in peripheral lung tissue. They tend to be cone-shaped, that is wedge-shaped on cross section, with the apex pointing in the direction of the thromboembolus and with the base on the pleura. The area is dark red or red-brown and usually well demarcated.

In a pulmonary infarct, the necrotic tissue is almost always hemorrhagic but generally softer than that in pulmonary hemorrhage, while on gross inspection, the original structures of the lung are lost (Fig 3). Microscopic examination, however, is often necessary to tell the two processes apart.

Microscopically, in pulmonary hemorrhage there is prominent congestion. Despite the extensive hemorrhage, the alveolar walls, bronchi, and vessels are intact. In a pulmonary infarct, only a ghost of these structures can be identified. Their cells have become eosinophilic and their nuclei have disappeared. Thrombi are often found in the necrotic vessels. In the outer zone of the infarcted area, the lung tissue is hemorrhagic but intact as a result of the collateral circulation.

In due course, the color of an infarct changes from dark red to dark brown when the erythrocytes in the hemorrhagic area disintegrate and hemosiderin pigment is ingested by macrophages. Later, the color may become grayish when fibrosis sets in and the infarct is converted into a scar. Retraction of this fibrotic area causes a dimple on the pleural surface. However, these scars are often very difficult to demonstrate at autopsy unless the lungs are inflated.

In case of a septic infarct, the color is often grayish white due to lysis of erythrocytes with accumulation of polymorphonuclear granulocytes. Septic infarcts may be due to an infected embolus or to an infectious process in the lungs. In turn, a septic infarct
may produce a lung abscess.

**Small Vessel Thromboembolism: Primary Thrombosis**

Thrombotic lesions in muscular pulmonary arteries can be found in most routine autopsies. Generally, they occur in small numbers but occasionally they can be very numerous, particularly in patients with pulmonary hypertension.

Since there are no histologic differences between embolic and primary thrombi, it usually remains undecided what the nature is of these arterial alterations. At one time, it was presumed that patients with unexplained pulmonary hypertension who had thrombotic lesions in their muscular pulmonary arteries suffered from thromboembolic pulmonary hypertension. These patients generally had no recognizable embolic source in their systemic veins nor did they have a history suggestive of thromboembolism. However, thromboembolic events may remain clinically unnoticed so that the concept of “silent recurrent thromboembolism” can certainly not be dismissed altogether. Such cases, probably based on small emboli, are particularly prone to development of pulmonary hypertension in patients.

However, to produce sustained pulmonary hypertension by microembolism, the number of small emboli has to be extraordinarily large. Therefore, the thrombotic lesions in this form of unexplained pulmonary hypertension may be due to primary thrombosis rather than to thromboembolism.

There can be little doubt that primary thrombosis of peripheral arteries is more common than microembolism. It occurs more often with increasing age and is an almost constant feature in adult patients with pulmonary hypertension by whatever cause.

However, thrombotic microembolism almost certainly may give rise to extensive pulmonary arterial obstruction and to thromboembolic pulmonary hypertension. Cases of widespread peripheral pulmonary arterial occlusion by postthrombotic lesions, which are clearly of embolic origin, may be masquerading as primary pulmonary hypertension. Moreover, thromboemboli may break up into numerous small fragments, either mechanically or during the process of endogenous thrombolysis. Consequently, numerous small vessels can potentially be narrowed or obstructed following organization of these thromboemboli. The pulmonary arterial disease based on thrombotic lesions, whether due to...

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21707/)

**Figure 4.** Fairly recent thromboembolus in muscular pulmonary artery. The embolus is attached to the vascular wall, is lined by endothelial cells (arrows) and shows early organization with proliferation of myofibroblasts (hematoxylin-eosin, original magnification x180).

![Figure 5](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21707/)

**Figure 5.** Longitudinal semithin section of muscular pulmonary artery with postthrombotic intimal fibrosis. Myofibroblasts penetrate the internal elastic lamina (arrows) growing into the patch (toluidine blue, original magnification x230).
primary thrombosis or to embolism, is known as thrombotic arteriopathy; the term implies widespread involvement of the pulmonary arterial tree and should not be used for isolated lesions.

**Thrombotic Arteriopathy**

Contrary to what could be expected, fresh clots easily recognizable as such, whether with or without early signs of organization, are uncommon in thrombotic arteriopathy. Even in patients who died with hypertensive pulmonary vascular disease of this type, recent thrombi may be scarce or completely absent.\(^2\) This indicates that there is a fairly rapid change into an organized plaque.

Organization begins by adherence of the clot to the wall with the formation of a thin lining of endothelial cells over its surface (Fig 4). This is followed by ingrowth of cells from the media together with capillary buds into the thrombus. The cells, myofibroblasts, penetrate the internal elastic lamina of the pulmonary artery (Fig 5) and proliferate within the thrombus, gradually converting this into an irregular fibrous mass (Fig 6). Retraction of this mass produces an eccentric plaque of intimal fibrosis (Fig 7). This does not have a laminar arrangement although sometimes two or more stages in its formation can be recognized.

Relatively often, this postthrombotic intimal fibrosis results in total occlusion and obliteration of an artery (Fig 8). However, most often this alteration extends only over a rather short distance. As a consequence, a single random histologic slide may miss these patches so that the histologic features seem to belie the seriousness of the clinical picture. In judging a lung biopsy specimen from such a patient, it is therefore necessary to study histologic slides at different levels.\(^2\)

Proliferation of capillary buds leads to a plexus of narrow channels within plaques that have occluded the original lumen. Some of these channels widen while others disappear. Recanalization of postthrombotic intimal fibrosis is very characteristic, particularly when the channels become so wide that remnants of the organized thrombus stand out as intravascular fibrous septa, which usually are rather coarse (Fig 9) but may be very delicate (Fig 10). Some restoration of blood flow is provided by these channels.

Deposition of iron pigment within a postthrombotic plaque is an uncommon finding. The same applies to calcification of a thrombus (Fig 11). A very
common change within postthrombotic intimal fibrosis is the development of longitudinal smooth muscle cells in bundles or layers within the plaque (Fig 12). Sometimes, when there is a central lumen, smooth muscle cells form a circular layer around it. This new layer may imitate a "second media" as it may be bounded by elastic laminae.

The reversibility of the alterations in thrombotic arteriopathy is very limited. Retraction and shrinkage of lesions may widen the residual lumen, and recanalization may open up a few channels, but the effect on the restoration of blood flow is generally disappointing. The rationale of anticoagulant therapy is to halt the thrombotic process rather than to bring about regression of the hypertensive pulmonary vascular disease.

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