Chapter 3
Sudden Death from Pulmonary Causes

Kris S. Cunningham and Michael S. Pollanen

Abstract This chapter seeks to survey many of the common pathological entities identified in the lungs at autopsy and the potential role of pulmonary disease in formulating an opinion regarding the cause of death. Appreciation of pulmonary pathology in the medicolegal context is important as it frequently contributes to the immediate or underlying mechanisms of death. The primacy of the lungs in breathing and their coordinated function with the cardiovascular system means that pulmonary failure can rapidly compromise tissue oxygenation and body chemistry, leading to an alteration in blood pH, hypoxic damage to downstream tissues and ultimately multiorgan failure and death. Moreover, given that the lungs have direct contact with the environment through inhalation and receive approximately 50% of the cardiac output with each beat of the heart, they may be adversely affected by hazardous agents from the outside world or other pathologic processes not primarily located in the lungs. The range of topics discussed herein is limited by design to deaths due to disease and largely foregoes discussion of more forensically relevant issues relating to toxicology or trauma. Furthermore, the content and format of this chapter is not intended to be encyclopedic, but rather attempts to highlight selected issues regarding pulmonary disease of potential relevance to surgical or forensic pathologists who perform medicolegal postmortem examinations.

Keywords Sudden death • Pulmonary pathology • Autopsy • Forensic practice

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Pediatric Pulmonary Pathology

Pulmonary Hypoplasia

Pulmonary hypoplasia in the neonate is an abnormal reduction in mass or volume of the lungs with a normal pattern of lobation. Depending on the extent of hypoplasia and the morphological stage of bronchiolar and alveolar maturation, severe hypoplasia is often incompatible with postnatal life. Multiple developmental and structural anomalies of the thoracic cavity and lungs are associated with pulmonary hypoplasia and neonatal death (Table 3.1) [1]. Co-existing systemic developmental abnormalities may occur with pulmonary hypoplasia. Examples include small or malformed thoracic cavities, hydrops fetalis, oligohydramnios sequence with associated genitourinary disorders, premature rupture of fetal membranes, large intrapulmonary or abdominal mass lesions, diaphragmatic malformations (Fig. 3.1), central nervous system disorders associated with impaired breathing and cardiovascular disorders associated with reduced pulmonary blood flow. In particular, the oligohydramnios or Potter's Sequence highlights the central role of the genitourinary system and its associated production of urine in the staged development of the lung parenchyma. Examples of conditions associated with deficient amniotic fluid production or premature loss include renal agenesis, cystic renal dysplasia, polycystic kidney disease, cloacal agenesis, urethral atresia, posterior urethral valves as well as chronic leakage of amniotic fluid [1].

The neonate with severe pulmonary hypoplasia is hypoxic and eventually develops pulmonary hypertension. This can be exacerbated by concurrent anatomical abnormalities of the heart and brain. Moreover, the degree of respiratory compromise

Table 3.1 Selected conditions associated with severe pulmonary hypoplasia

Hydrops fetalis with large pleural effusions
Oligohydramnios sequence
Congenital diaphragmatic defects with herniation of abdominal contents
Congenital cystic adenomatoid malformations
Pulmonary sequestrations
Congenital muscular dystrophy
Spinal muscular atrophy
Intrauterine hypoxic ischemic encephalopathy with secondary pulmonary hypoplasia
Large foregut cysts
Thanatophoric dysplasia
Osteogenesis imperfecta II
Jeune syndrome/asphyxiating thoracic dystrophy
Achondroplasia
Abdominal mass lesions
Eventration of the diaphragm
Central nervous system lesions associated with decreased breathing
Congenital heart disease associated with decreased pulmonary arterial blood flow
Cytogenetic abnormalities

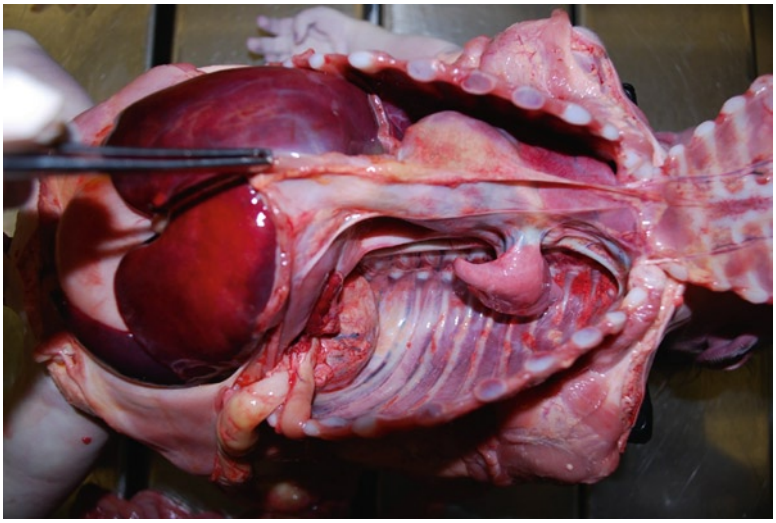

Fig. 3.1 Hypoplastic left lung in an infant with a congenital diaphragmatic hernia (Courtesy of Dr. C. Kepron)

is dependent not only on the reduction in size and volume of the lung, but also on the stage of development of the pulmonary parenchyma. Immature alveolar septae may have limited gas exchange as well as incomplete development of the pulmonary vasculature. Microscopically, the number of alveoli can be reduced with fewer bronchioles, less branching and more alveolar collapse as a consequence of surfactant deficiency. Secondary acute lung injury can develop as sequelae of reduced ventilation, infection or atelectasis.

Examination of the lungs radiologically as part of the skeletal survey can reveal a pneumothorax prior to commencement of the internal examination. This may be particularly true following mechanical ventilation as the hypoplastic lung appears to be more susceptible to barotrauma. In addition, examination of the lungs in situ, prior to evisceration and disruption of the thoracic cavity is suggested to properly assess the underlying anatomy and associated pathology. Unfortunately, the degree of pulmonary hypoplasia necessary to cause clinically significant morbidity or mortality is not precisely defined by the available literature. Thus, correlation of the gross and histological findings with the clinical history is important for correct interpretation of the postmortem findings and evaluating their potential contribution to the ultimate cause of death.

Respiratory Distress Syndrome and Bronchopulmonary Dysplasia

Acute lung injury may occur as a consequence of numerous insults such as infection, shock, drug effects, or assisted ventilation. In the setting of significant prematurity, surfactant deficiency may cause acute lung injury with the development of hyaline

membranes. Depending on the degree of prematurity and the duration of the insult, a spectrum of acute and chronic phases of diffuse alveolar damage (DAD) can be identified, which may ultimately lead to remodeling of the underlying lung architecture and reduced respiratory reserve. In the context of the appropriate clinical history, respiratory distress syndrome (RDS) or surfactant deficiency syndrome is the clinical correlate for hyaline membrane disease identified in the premature infant at autopsy. The histological changes identified in premature infants are mirrored in studies of surfactant-deficient mice (surfactant protein A: SP-A −/− mice) [2]. The microscopic features can include collapsed distal airspaces with hyaline membranes, fibrinous intra-alveolar exudates, pneumocyte hyperplasia, leakage of erythrocytes, acute and chronic alveolar, and interstitial inflammation, as well as collections of siderophages and foamy macrophages. With time organizing pneumonia, granulation tissue plugs within respiratory bronchioles and architectural remodeling of the interstitium may be observed. Neonates born with surfactant deficiency during the late saccular and early alveolar stages (32–36 weeks) usually do not die as a consequence of their prematurity-associated lung disease. However, neonates with extreme prematurity (<28 weeks) in the canalicular stage of lung development (16–28 weeks) or those under 1,000 g are most at risk for RDS and bronchopulmonary dysplasia (BPD) [3].

BPD develops in those infants who have survived the acute phase of lung injury due to surfactant deficiency and develop a chronic fibrosing process of the lung parenchyma that is characterized by patchy, nonspecific, interstitial fibrosis, epithelial regeneration, and parenchymal collapse intermixed with regions of overdistended lung and squamous metaplasia of the distal conducting airways. In addition, medial hypertrophy of pulmonary arteries and arterioles may also be noted in regions of significant parenchymal remodeling (microscopic honeycomb change). Importantly, marked lung injury in infants born before 28 weeks gestation may cause arrest of alveolar development and subsequent deficiency of gas exchange [3]. At autopsy, children with severe BPD may possess firm, consolidated lungs (hepatization), as well as reduced lung volumes and decreased numbers of alveoli.

Severe BPD has been attributed in part to adult-type positive pressure ventilatory techniques; however, current ventilation strategies adapted to neonates appear to limit the severity of BPD with more subtle morphological changes now identified in infants at autopsy. In addition to ventilatory changes, antenatal glucocorticoid administration, surfactant replacement therapy and alteration in ventilation strategies have reduced the incidence of RDS. Moreover, when examining premature lungs by microscopy, amorphous eosinophilic masses within the distal airways may be observed as a consequence of surfactant replacement therapy and should not be confused with alveolar proteinosis [3].

Acute Lung Injury and Ventilator-Associated Trauma

In children with nonspecific acute lung injury, the mortality rate is high and increases in those who go on to develop acute respiratory distress syndrome (up to 50%) [1].

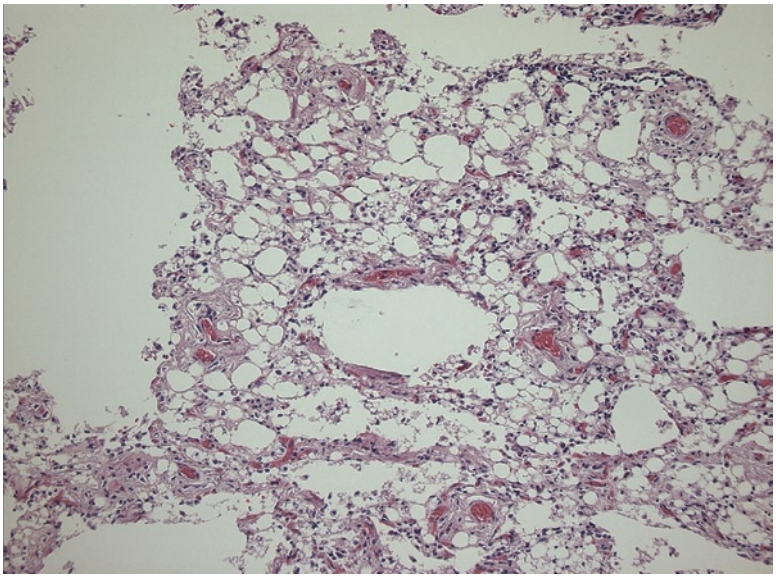

Fig. 3.2 Chronic aspiration with exogenous lipoid pneumonia (orig. mag. 100×)

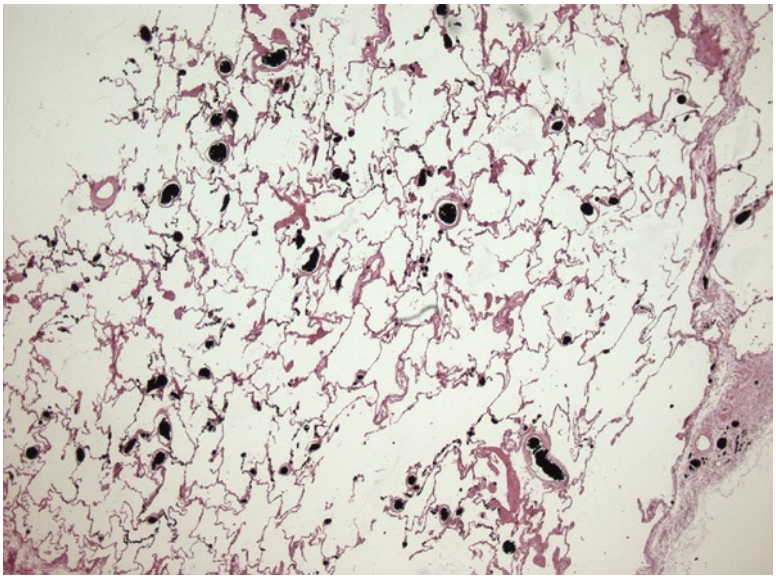

Fig. 3.3 Diffuse intravascular fat emboli highlighted with osmium stain (orig. mag. 25×)

Notwithstanding prematurity-associated surfactant deficiency, acute lung injury (ALI) in the pediatric population may mirror that observed in the adult population and be a consequence of direct or indirect causes. Direct causes of ALI can include infectious pneumonias, eosinophilic pneumonitis, aspiration (Fig. 3.2), fat emboli (Fig. 3.3),

reperfusion injury, cardiovascular disease, severe pulmonary hypertension, pulmonary infarction and malignancy. Indirect causes may include sepsis, shock, transfusion reactions, cardiopulmonary bypass, drug reactions or acute pancreatitis [1].

Ventilation-associated injuries may contribute to respiratory distress syndrome in premature infants or acute lung injury in general. The histological changes induced by chronic positive pressure ventilation frequently overlap with those of the underlying disease and include acute phase diffuse alveolar damage, interstitial edema, and inflammation. Mechanistically, ventilator-induced lung injury is thought to contribute to alveolar damage by multiple mechanisms. These include (1) barotrauma with elevated shear stress on the alveolar lining; (2) volutrauma with large tidal volumes that can disrupt the epithelial–capillary interface; (3) atelectrauma caused by mechanical ventilation-associated stress fracture of the epithelial–capillary interface following repetitive opening and closing of alveoli; and finally, (4) biotrauma, which follows the influx of neutrophils and inflammatory mediators in response to lung injury [1]. Ultimately, ventilatory strategies seek to prevent atelectasis and maintain the patency of airways without overdistention and pressure-related trauma.

Air leak may be seen following ventilation-induced trauma to the parenchyma. Following pressure and volume-associated rupture of bronchiolo-alveolar junctions; intra-alveolar gas may pass into the peribronchovascular spaces and dissect along bronchovascular sheaths, leading to pulmonary interstitial emphysema. Pulmonary interstitial emphysema can potentially extend into adjacent hilar soft tissues, leading to the development of pneumomediastinum, pnueumopericardium, pneumothorax, or rarely air embolism, which has been associated with sudden death. These ventilation-associated injuries may be appreciated radiologically as meandering cystic and tubular lucencies that fail to conform to the predicted pattern of air bronchograms; thin-walled cysts (pneumatoceles) may also be identified [2]. When prominent and unilateral, pulmonary interstitial emphysema, pneumatoceles, and pneumothoracies can rarely cause shift of the mediastinal structures under tension and promote cardiovascular collapse and death.

Born Alive or Dead

Determination of whether a fetus was born alive or was stillborn, not having had a separate living existence from its mother, is a frequent question posed to forensic pathologists. Under the best of circumstances, this determination is difficult. Classically, the flotation or hydrostatic test is utilized, which is based on the premise that *en bloc* lungs or an individual lung placed in water will float if aerated, suggesting that the neonate had at some point breathed or sink if nonaerated, signifying that the fetus was stillborn [4]. Interpretation of the results of this is fraught with difficulty in and it is not recommended to be used in isolation to make a determination of live birth. Potential causes for false-positive results could include air trapping due to attempted resuscitation or the production of postmortem gases by bacteria during putrefactive decomposition. Gas-producing bacteria may be

introduced into the airways, for example, through postdelivery contamination when delivered into a toilet or as a consequence of choramnionitis. Furthermore, we have encountered the circumstance where lungs were examined separately and revealed that one lung sank and the other floated. Moreover, interpreting an increase in the lung's mass as evidence of perimortem breathing, thought to be due to expansion and vascular perfusion of the parenchyma, is also a poor indicator of live birth [4]. Histological sections of the lung may show evidence of alveoli expanded by air following a live birth. However, the results must be tempered by the postmortem interval and the possibility of postmortem gas production by microorganisms. In addition, the presence of diffuse alveolar damage or pneumonia would strongly suggest that the infant was live born.

Further, less stringent physical evidence of potential live birth may include a dirty diaper, food in the stomach, an inflammatory reaction at the umbilical cord stump and the absence of maceration. However, although the history provided to the pathologist at the time of postmortem examination must be considered in the context of the autopsy findings, one must guard against incorporation of circumstantial evidence when making a determination of live birth, as ultimately, in the absence of physical evidence this opinion may not be defendable. Teleologically, the best evidence of live birth is the identification of a clear cause for death.

Sudden Unexpected Death in Infancy and Sudden Infant Death Syndrome

Sudden and unexpected death in infancy (SUDI) is often associated with potentially lethal upper and lower respiratory tract inflammation, most commonly as a consequence of bacterial and/or viral infections [5]. For children who are immunocompromised or from endemic regions, less common infectious agents that could include viruses (cytomegalovirus, herpes simplex virus, varicella zoster virus), fungi (aspergillus, candidiasis, histoplasmosis, blastomycosis, and mucormycosis) or myocobacteria (tuberculosis and mycobacterium avium intracellulare) may be identified within the upper and lower respiratory tract.

Death as a consequence of acute viral pneumonitis and its complications in otherwise "healthy" children is observed. Correlation of the histomorphologic features from a virally infected lung with the results of microbiological culture is a mainstay of assessment. Sampling of the nasopharynx as well as the middle ears for virus may also be considered in addition to lung parenchyma, tracheal tissue, and blood. It has been suggested that in upward of 50–80% of SUDI cases that can be explained after autopsy, respiratory tract infections played a significant role in the ultimate cause of death [5]. Important risk factors for the development of pneumonia to extract from the clinical history could include cytogenetic abnormalities, congenital heart disease, prior aspiration of oropharyngeal or gastric contents, pulmonary masses or fistulas involving the respiratory tract, malignancy, diabetes mellitus, or other causes for a compromised immune system.

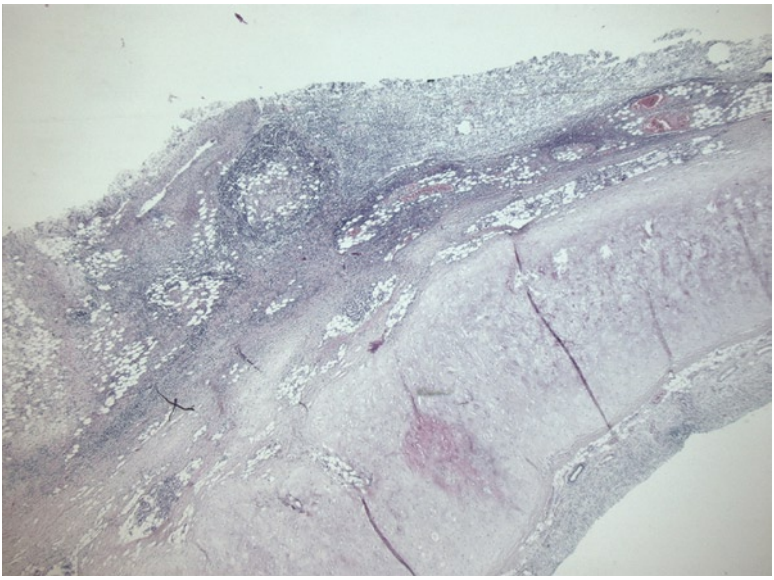

Fig. 3.4 Acute epiglottitis [Courtesy of Dr. J. Tanguay] (orig. mag. 16×)

Acute epiglottitis with swelling and enlargement of the epiglottis may abruptly occlude the airway causing respiratory insufficiency and death. Historically, *Haemophilus influenzae* infection has been implicated; however, immunization protocols have significantly reduced the incidence of acute epiglottitis in children [6]. However, other organisms such as *Pneumococcus* or parainfluenza viruses may also be isolated in both children as well as adults with acute epiglottitis (Fig. 3.4). Occasional cases of vaccinated children who have died from acute epiglottitis who subsequently test positive for *Haemophilus* colonization are identified. Thus, vaccine failure against *Haemophilus influenzae* can occur and must be considered in circumstances of positive postmortem cultures from affected children [7].

Other conditions affecting the upper airways that can lead to sudden death include retropharyngeal abscesses causing acute occlusion or massive hemorrhage within the larynx, tracheomalacea, laryngeal polyps (Fig. 3.5) [8] and bacterial tracheitis. In particular, acute bacterial tracheitis is often superimposed on a preceding viral infection and is associated with suppurative exudates and potentially pseudomembranes within the trachea at autopsy. Complications of bacterial tracheitis include bacterial pneumonitis, sepsis and acute respiratory distress syndrome. Microorganisms associated with acute tracheitis include *S. aureus*, *H. influenzae*, and parainfluenza virus [9].

Respiratory syncytial virus infection (RSV) is the most common cause for acute bronchitis and bronchiolitis (Fig. 3.6). In older children, parainfluenza, rhinovirus, influenza virus (Fig. 3.7), adenovirus and *Mycoplasma pneumoniae* are also commonly observed with clinical bronchitis. Histological findings with RSV include acute and chronic inflammatory infiltrates with airway obstruction by epithelial and inflammatory cell debris, mucus, fibrin, and hyperplastic lymphoid tissues. Occasional

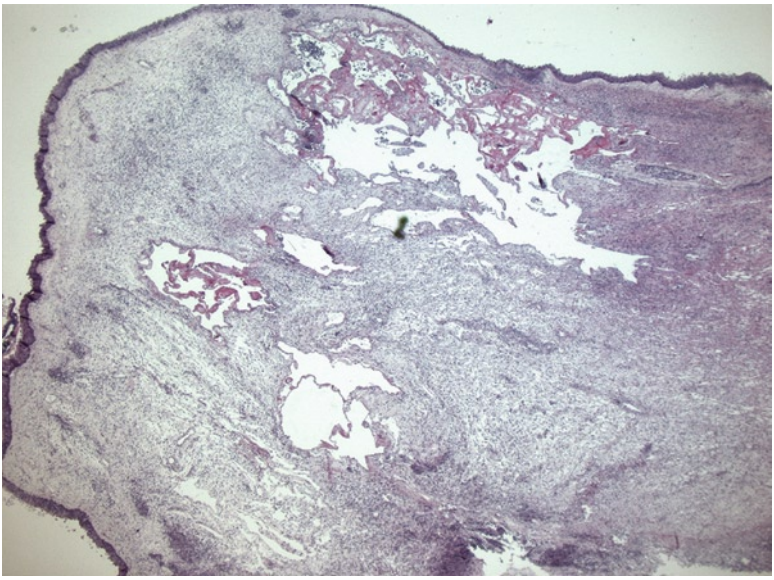

Fig. 3.5 Occlusive laryngeal polyp causing sudden death [Courtesy of Dr. J. Tanguay] (orig. mag. 16×)

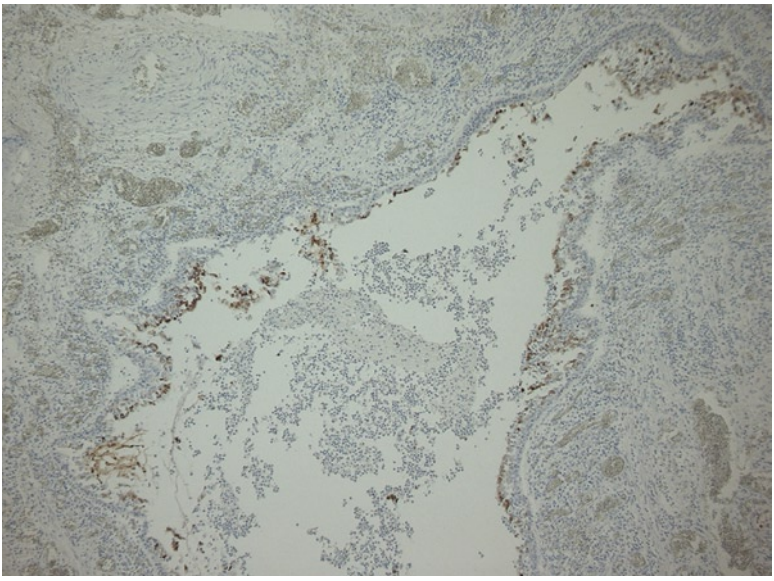

Fig. 3.6 Immunohistochemistry for respiratory syncytial virus highlighting bronchial epithelium (orig. mag. 25×)

multinucleated syncytial cells with viral cytopathic changes may also be observed; however, this finding is uncommon and limited by sampling. Ancillary studies to detect RSV through viral culture, immunofluorescence, immunohistochemistry

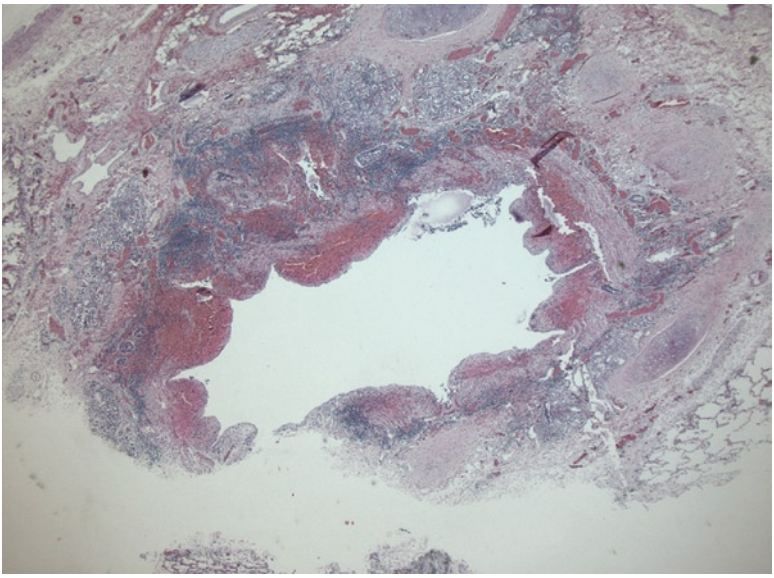

Fig. 3.7 Acute bronchitis/bronchiolitis with influenza A infection [Courtesy of Dr. J. Tanguay] (orig. mag. 16×)

or ELISA-based methods are suggested when possible in appropriate cases [10]. Finally, acute viral bronchitis may be complicated by the development of an acute bacterial pneumonia, particularly by superimposed *S. aureus* infection.

In the circumstance of sudden infant death syndrome (SIDS) the spectrum of pulmonary changes identified are generally nonspecific in their appearance and are not obviously lethal. Typically, the lungs are congested with increased mass and pulmonary edema. It is important to not overinterpret pulmonary edema and congestion at autopsy as evidence of pneumonia. Parenchymal changes may include petechial hemorrhages, particularly in a pleural/subpleural distribution, focal acute congestive hemorrhage with or without occasional siderophages, as well as intra-alveolar and interstitial edema. Atelectasis and focal interstitial emphysema may also be observed in children in whom resuscitation has been attempted [11].

The presence of a protein-rich fluid within centrilobular bronchioles, alveolar ducts, and centrilobular alveoli can be due to aspiration of gastric contents (e.g., milk), which may occur *in extremis* and should not necessarily be interpreted as acute aspiration causing death. Furthermore, depending on the age of the infant, occasional squamous cells (from amniotic fluid) and hyperplastic bronchus-associated lymphoid tissue can be normal for this age group.

In cases of suspected SIDS, multiple sections from each lobe of lung are typically assessed with hematoxylin and eosin staining. In addition, the use of connective tissue stains (elastic trichrome, Movat pentachrome), histochemical stains for microorganisms and immunohistochemical stains to detect inflammatory cells, neuroendocrine hyperplasia [12], viruses, or other microorganisms may be considered for each case.

An assessment of the radial-alveolar index as well as immunohistochemical stains for keratin and endothelial cell distribution may be considered if maturity of the lung and parenchymal architecture is to be assessed [13].

Interstitial and intra-alveolar hemosiderin and siderophages, the presence of which can be confirmed with iron stains, have in the past been used as evidence of asphyxia and in particular, suffocation. Although the nature of this manuscript precludes a detailed discussion of this controversial issue, multiple authors have demonstrated that the amount of hemosiderin does not necessarily indicate that an infant died an asphyxial death. Furthermore, iron in the lungs may be associated with multiple pathophysiological processes as part of natural, accidental or nonaccidental deaths. Thus, the presence of significant hemorrhage and hemosiderin should not be used as an independent predictor in determining the manner of death in an infant [14].

Pulmonary Pathology in the Adult

Pulmonary Infections

A comprehensive review of pulmonary infections is beyond the scope of this chapter. Nevertheless, acute bacterial pneumonia is a common immediate cause of death. However, pneumonia may also arise as a secondary complication of some other underlying disease process. Thus, while pneumonia may contribute to the immediate demise of an individual, the ultimate underlying pathophysiological abnormality or circumstance that initiated the causal chain leading to that pneumonia must be sought.

Both community-acquired pneumonia and nosicomial pneumonia (those cases that develop after 72 h in hospital) are frequently found at postmortem examination (Table 3.2). The nature of the microorganisms identified following histomorphology and/or culture assessment may facilitate the reconstruction of events leading up to death and delineate those risk factors that promoted infection of the lung in the first place. In addition, the macroscopic pattern of inflammation within the lung may also assist with identification of the putative infectious agent and potentially direct the appropriate sampling of tissue for ancillary studies (Table 3.3). Ultimately, it is not necessarily the identification of an acute pneumonia at autopsy that is significant, but rather recognition of the underlying risk factors for that pneumonia that are potentially of medicolegal importance (Tables 3.4 and 3.5).

Any factor that impairs normal respiratory function (e.g., obesity, thoracic cavity anomalies, prolonged immobility, alcoholism); diminishes the host immunological defense against microorganisms (e.g., chronic disease, medications); provides a permissive environment for opportunistic infections (e.g., intrapulmonary cavities, foreign bodies, tracheo-esophageal fistula); increases the risk of aspiration of oropharyngeal or gastric contents (e.g., edentulous state, neuromuscular disease, dementia) (Fig. 3.8) or seeding of the lung with microorganisms from an infected site (e.g., postoperative state, abscesses, endocarditis, intravenous catheters) may

Table 3.2 Classical community-acquired and nosicomial microorganisms

Community acquired	Nosicomial (≥72 h in hospital)
Streptococcus pneumoniae	*Streptococcus pneumoniae*
Haemophilus influenzae	*Haemophilus influenzae*
Legionella pneumophila	*Pseudomonas aeruginosa*
Moraxella catarrhalis	*Enterobacter spp.*
Mycoplasma pneumoniae	*Klebsiella pneumoniae*
Chlamydia psittaci	*Serratia marcescens*
Chlamydia pneumoniae	*Staphalococcus aureus*
Influenza A	*Escherichia coli*
Adenovirus	*Acinetobacter spp.*
Mycobacterium tuberculosis	Anaerobes (*Peptostreptococcus, Fusobacterium, Peptococcus, Bacteroides)*
Fungi (A*spergillus, Candida)*	Fungi (A*spergillus, Candida*)

Table 3.3 Gross patterns of lung involvement with infections

Macroscopic pattern	Possible organism
Patchy, centrilobular or lobar infiltrates	Bacteria, mycobacteria
Nodular with or without cavitation	Fungi, pneumocystis, bacteria, septic emboli, nocardia
Brochiectasis	Mycobacterial, fungal infections
Prominent cavitation	Bacterial abscess, tuberculosis, aspergilloma
Empyema	Bacteria, mycobacteria
Diffuse infiltrates	Pneumocystis, CMV
Enlarged mediastinal lymph nodes	Mycobacteria, histoplasmosis, coccidiomycosis

Table 3.4 Risk factors for pneumonia of potential medicolegal relevance

Mechanical ventilation/tracheostomy
Neuromuscular disease
Dementia
Edentulous
Severe chronic disease (e.g., diabetes mellitus, chronic renal failure, chronic heart failure)
Drug effects/chemotherapy
Acute alcohol consumption/chronic alcoholism
Immunocompromised states
Anatomical anomalies (e.g., Tracheal-esophageal fistulae, sequestrations)
Thrombophlebitis/cellulitis/endocarditis/nonpulmonary abscesses/sepsis
Pulmonary/nonpulmonary neoplasia
Intrapulmonary foreign bodies
Prolonged immobility/atelectasis
Postoperative infection
Thoracic cavity anatomical anomalies (e.g., scoliosis, contractures)
Acute pulmonary infarcts
Morbid obesity
Underlying pulmonary disease (e.g., bronchiectasis, tuberculosis, emphysema)
Intravenous drug abuse
Intravenous catheters

Table 3.5 Histomorphological appearance of selected organisms with hematoxylin and eosin stains

Organism	H&E appearance
Cytomegalovirus	Well-defined intranuclear inclusions (+/− halo)
Adenovirus	Poorly defined intranuclear inclusions (smudge cells)
Herpes virus	Well-defined intranuclear inclusions (multinucleated, large, glassy)
Respiratory syncytial virus	Multinuclear syncytial cells (typically low numbers)
Influenza virus	Nonspecific cytopathic appearance
Histoplasma[a]	2–5 μm; narrow-based budding
Cryptococcus	5–20 μm; narrow-based budding, thick wall
Blastomyces	15–30 μm; broad-based budding
Coccidioides	20–200 μm; endospores
Candida	Yeast and hyphal forms
Aspergillus	Acute angle branching; septate
Zygomces (Mucor)	Right angle branching; broad-based ribbons; few septa

[a]A mature erythrocyte is typically 7–9 μm
Culture, histochemical stains, or immunostains may be used to confirm diagnosis

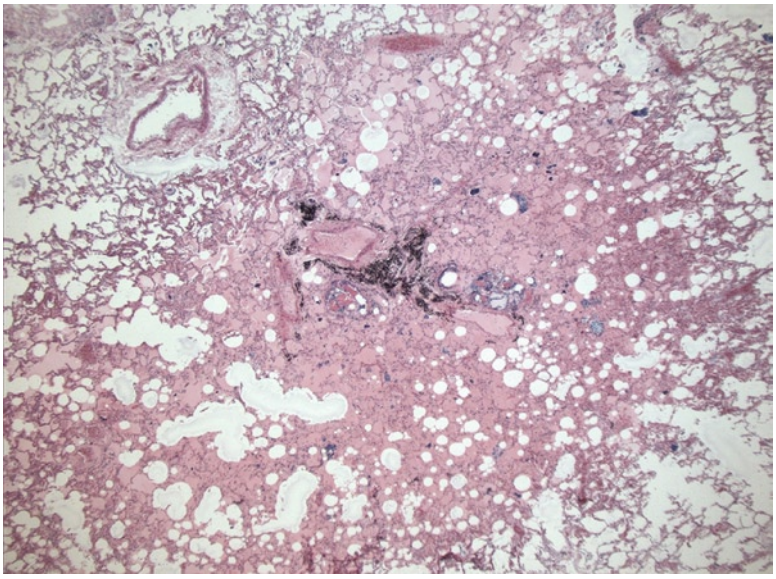

Fig. 3.8 Aspiration of gastric contents. Note concentration of intra-alveolar edema in a centrilobular distribution, adjacent to anthracotic pigment deposition. Fragments of partially digested food, colonies of bacterial microorganisms and acute inflammation are also identified (orig. mag. 16×)

result in a potentially lethal pneumonitis. Moreover, the host reaction against an infectious agent may be associated with significant functional impairment of respiratory function. These changes can include the accumulation of acute and chronic inflammatory infiltrates, interstitial and intra-alveolar pulmonary edema as well as findings of diffuse alveolar damage.

Complications of acute infections may include abscess formation, empyema, bronchopulmonary fistulae, significant hemoptysis, or sepsis. With time, acute infectious pneumonitis with its associated acute lung injury may resolve with complete functional reconstitution of the lung parenchyma. Pneumonitis can also develop into a chronic infection leading to a chronic inflammatory process causing architectural remodeling of the underlying lung parenchyma with impairment of gas exchange. Examples of chronic changes one may observe microscopically or at autopsy can include abscesses formation, nonspecific interstitial fibrosis, stromal and epithelial metaplasia with cyst formation, bronchiectasis, obstructive bronchiolitis, and honeycomb change.

Pneumonia may be due to a compromised immune system. Relevant risk factors may include HIV infection, autoimmune disease, congenital immune deficiency, intravenous drug abuse, medication effects/chemotherapy, transplantation, advanced age, malignancy, chronic alcoholism, neglect, malnourishment, and diabetes mellitus. In some instances, consideration of one or more of these factors may be required when commenting on the significance of a potentially lethal pneumonia at autopsy. Furthermore, multiple conditions that promote acute lung injury such as ventilation may also increase the susceptibility for a secondary bacterial pneumonia. Other examples include antecedent influenza bronchiolitis, inhalational injuries following fire or chemical exposures or a chemical pneumonitis following aspiration of gastric acid.

At the postmortem examination, appropriate sampling of tissues for ancillary testing must be considered. Depending on the clinical circumstances, sampling can include tissue for bacterial, fungal, or viral culture, tissue for snap freezing or electron microscopy, as well as blood for aerobic and anaerobic cultures. If indicated, communication with a public health laboratory or microbiologist before the autopsy may provide guidance to facilitate procurement of tissue specimens for ancillary testing.

Respiratory Infection Outbreaks

For infectious respiratory outbreaks caused by unknown pathogens, institutional protocols should be consulted for an approach to the autopsy that ensures the safety of autopsy staff, outlines the appropriate sampling of tissues for analysis and enables proper handling of tissues to minimize unintended transmission of virulent microorganisms after postmortem examination. It is important to consider undertaking a complete autopsy with sampling of body fluids and tissues examined when investigating an unknown infectious pathogen. This serves two purposes; first, it allows one to confirm that the cause of death was as a result of primary pulmonary disease caused by a putative pathogen, and second, permits procurement of varied tissues for analysis as it is not always clear prior to the autopsy that an unknown pathogen

associated with respiratory failure is best isolated from lung tissue. Moreover, if pneumonia is identified, a complete autopsy may permit one to assess if that infection is primary or perhaps secondary to some other pathologic process, such as bronchial obstruction due to occult carcinoma. Anecdotally, during the SARS (severe acute respiratory syndrome) and Legionella pneumonia outbreaks in Toronto, a number of deaths that were clinically suspected to be due to the infectious agent in question were ultimately determined to be the result of other pathologies. The ultimate cause for death may have been missed had the autopsy been solely restricted to the lungs.

Interpretation of Suspected Aspiration

A controversial finding in many autopsies is the presence of food fragments within the distal airways/alveolar ducts identified at microscopic examination. It is well recognized that gastric contents may contaminate the airways during the postmortem period and potentially migrate deep into the lung parenchyma. In the absence of evidence of a significant host response such as an acute inflammatory infiltrate, it is very difficult to substantiate a diagnosis of perimortem aspiration. Migration of gastric contents into the airways may also occur during attempted resuscitation of the decedent. In addition, even if early acute inflammatory infiltrates are identified in association with foodstuffs in the airway, aspiration of gastric contents can commonly occur *in extremis*. Consequently, these findings should not necessarily be interpreted to mean that airway occlusion by aspirated gastric contents contributed to the death of the individual being autopsied. The number of affected airways, the degree and nature of the host response and the clinical context should all be considered when confronted with this issue.

Cancer and Its Physiological Derangements

Evidence of malignancy within the lungs is commonly observed in medicolegal autopsies and includes both primary pulmonary malignancies as well as metastatic tumor deposits. The traditional risk factors for primary lung carcinoma for which we may find evidence at autopsy includes chronic cigarette smoking, occupation-based pneumoconioses such as asbestosis or silicosis, idiopathic pulmonary fibrosis (or UIP, usual interstitial pneumonitis), coal miner's lung as well as prior solid organ transplantation. Chronic infection with the human immunodeficiency virus (HIV) has also been associated with an increased risk of bronchogenic carcinoma as well as other pulmonary malignancies [15]. The lungs are a frequent site for metastatic disease. Classically, metastatic carcinoma, sarcoma, melanoma, or germ cell tumors present with multiple parenchymal nodules that may be unilateral or bilateral in their distribution, located either centrally or more often peripherally and frequently deposit within the pleura and subpleural tissues.

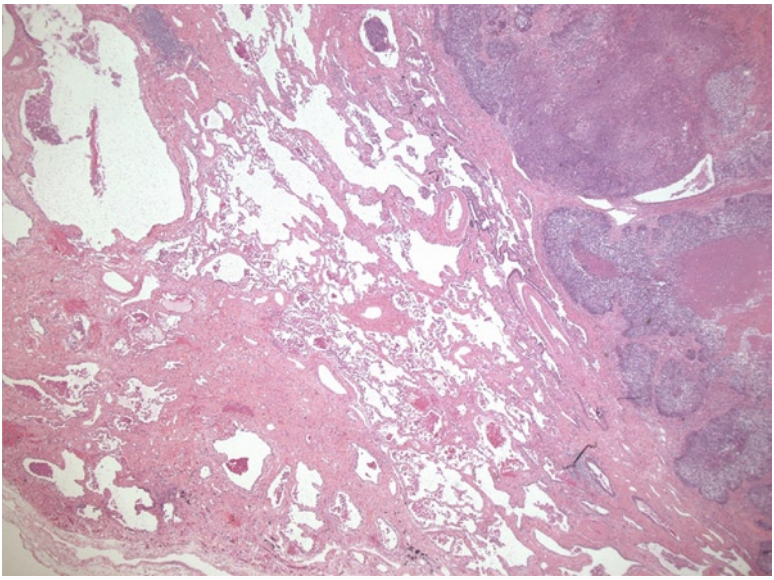

Fig. 3.9 Squamous cell carcinoma arising out of background of usual interstitial pneumonitis (orig. mag. 16×)

Carcinomas may invade the lung parenchyma directly from a contiguous site or enter through the vasculature and lymphatic channels. Lymphatic channels in the lungs are generally identified around the bronchovascular bundles, within the interlobular septae and within the pleura. With a more pronounced lymphangitic pattern of spread, known as lymphangitic carcinomatosis, the gross examination may reveal a number of small nodules bilaterally that are often associated with thickened parenchymal septae and visceral pleura. Microscopically, lymphangitic carcinomatosis may be obvious or very subtle. Sarcomas frequently metastasize to the lungs by hematogenous spread and can infiltrate or arbourize along the vasculature in a serpinginous manner. Occasionally, this pattern of tumor embolization and growth has been found to be fatal [16].

Primary bronchogenic carcinoma may also locally invade the lung parenchyma in atypical patterns. Examples can include restriction to the pleural/subpleural tissues that can mimic mesothelioma or arise from within regions of dense interstitial fibrosis such as with usual interstitial pneumonitis (UIP) (Fig. 3.9), which can be entirely missed macroscopically. Although metastatic bronchogenic carcinoma may metastasize to virtually any anatomical site, it has a predilection for the ipsilateral or contralateral lungs, mediastinal lymph nodes, brain, liver, bone, and adrenal glands.

Given the altered appearance of decomposing tissues and the difficulty in interpreting immunohistochemistry, it is generally not necessary to specifically characterize the nature of the malignancy beyond a general class of neoplasm if possible; such examples would include carcinoma (non-small cell vs. small cell),

sarcoma, lymphoma, melanoma, or germ cell tumor. In the end, however, the questions that may arise out of the case should ultimately dictate the degree of diagnostic detail required.

Lung cancer may cause cachexia and death through numerous physiological derangements. A malignancy can compromise its surrounding anatomy, which may lead to a potentially lethal infection, infarction of surrounding normal tissues or massive hemorrhage. Examples of lethal complications attributable to lung cancer include erosion of tumor into large vascular structures (e.g., intrapulmonary, mediastinal, or cardiac) causing massive hemorrhage and shock; metastasis of tumor to sensitive regions of the heart or brain causing catastrophic organ failure; promotion of intravascular thrombosis with subsequent occlusion of in situ or downstream vasculature; empyema; development of bronchopulmonary fistulae and pneumothorax and finally, occlusion of bronchi with subsequent bacterial and lipoid pneumonias. In addition, recurrent pleural effusions as a result of the malignancy may lead to atelectasis and respiratory embarrassment, which can complicate respiratory function in an individual whom may already have compromised cardiorespiratory reserve.

Metastatic carcinoma can extensively occlude a large percentage of the intrapulmonary microvasculature, which can lead to sudden death. Such pulmonary tumor microemboli have been identified in individuals with occult malignancies who present *in extremis* with apparent respiratory failure. Clinically, this condition can mimic pneumonia, tuberculosis, and interstitial lung disease [17]. Furthermore, the additional presence of numerous microscopic thromboemboli and fibrointimal proliferative lesions within the pulmonary microvasculature may also be observed, a condition referred to as pulmonary tumor thrombotic microangiopathy (Fig. 3.10). This associated condition may lead to potentially lethal pulmonary hypertension and is most commonly linked with metastatic adenocarcinomas from the upper gastrointestinal tract [18].

Bronchogenic carcinomas, especially small cell carcinoma, may be associated with numerous paraneoplastic syndromes that have physical manifestations that can be observed at autopsy and in certain circumstances may contribute to the mechanism of death (Table 3.6). Notable examples include central pontine myelinolysis in the setting of syndrome of inappropriate antidiuretic hormone secretion (SIADH), widespread paraneoplastic pemphigus or coagulopathic anomalies. Interpretation of postmortem physical and biochemical changes from suspected paraneoplastic syndromes requires careful correlation with the antemortem clinical history.

Pulmonary Vascular and Cardiovascular Disease

Pulmonary Thromboembolism

A wide range of pulmonary vascular anomalies may be associated with sudden death. One of the most common causes for sudden and unexpected death is acute,

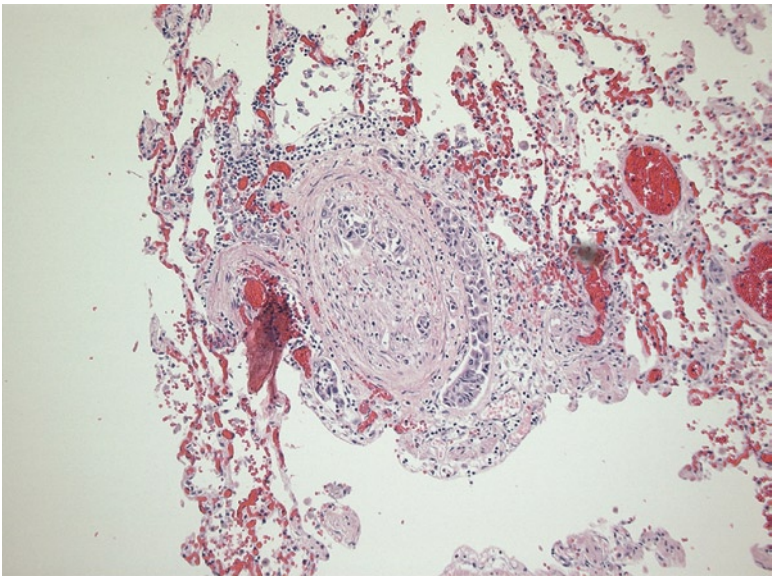

Fig. 3.10 Tumor thrombotic microangiopathy adjacent to tumor-filled lymphatic space (orig. mag. 50×)

Table 3.6 Paraneoplastic syndromes with potential significance to the medicolegal autopsy

Cushing syndrome
Polymyositis-dermatomyositis
Hypercalcemia
Syndrome of inappropriate antidiuretic hormone secretion
Paraneoplastic cerebellar degeneration
Encephalomyelitis
Sweet's syndrome
Pyoderma gangrenosum
Nonbacterial thrombotic endocarditis
Paraneoplastic pemphigus
Disseminated intravascular coagulation
Acquired thrombophelia
Anemia
Membranous glomerulonephritis

occlusive pulmonary arterial thromboembolism. The origin of intravascular thrombi is typically from deep femoral, popliteal, or crural veins. Sometimes thromboemboli originate from deep pelvic veins, the inferior caval vein, hepatic veins, deep veins of the upper extremities or mural thrombi from within the heart. The cause of deep venous thrombi may be a consequence of an identifiable thrombogenic risk factor(s) (Table 3.7).

Table 3.7 Selected risk factors for intravascular thrombus formation of interest to the medicolegal autopsy

Inherited coagulation factor mutations (factor V Leiden, mutations in prothrombin, etc.)
Prolonged immobility
Prolonged restraint
Vascular trauma
Vasculitis/vascular aneurysms/vascular malformations
Pregnancy
Oral contraceptive medications/estrogen replacement/estrogen supplementation
Estrogen producing tumors (e.g., adult granulosa cell tumor)
Postoperative states
Lupus/antiphospholipid antibody syndrome
Malignancy (especially adenocarcinoma)
Nephrotic syndrome
Dilated cardiomyopathy
Acute or remote myocardial infarction/ventricular aneurysm/cardiac tumors
Chronic arrhythmia (e.g., atrial fibrillation, atrial flutter)
Intravascular foreign bodies (catheters, pacemaker leads, prosthetic valves, prosthetic pumps, etc.)
Sepsis/diffuse intravascular coagulation
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome/eclampsia

Acute thromboemboli may cause sudden death through occlusion of one or more large caliber pulmonary arteries. In addition, diffuse occlusion of smaller caliber vessels by thromboemboli, located in the more peripheral zones of the lung may also cause sudden death. The number and/or size of acute thrombi that cause sudden death likely depend on the underlying cardiopulmonary reserve of the affected individual. Any combination of proximal and/or peripherally located thromboemboli that cause an acute rise in the right ventricular systolic pressure by 40–50 mmHg can lead to acute heart failure [19]. Moreover, one may consider microscopically dating intravascular thrombi into, for example, recent, organizing, organized, or old thrombi in order to provide comment about the potential chronicity of the embolic process, which could have medicolegal significance. For example, if an individual dies 4 days following a surgical procedure of pulmonary thromboembolism, yet has evidence of organizing and organized thrombi in their pulmonary arteries and deep veins of their lower legs, one may at least suggest that the decedent had underlying thrombogenic risk factors that preceded the surgical procedure. If such facilities are available, one could consider testing for commonly inherited mutations within the genes of coagulation factors using postmortem blood and include the results within the autopsy report to enable clinical assessment of any first-degree family members.

Pulmonary Hypertension

Pulmonary hypertension may also cause sudden and unexpected death and can be broadly divided into primary and secondary causes (Table 3.8) [20–23]. It is important to recognize that some forms of primary pulmonary hypertension can be inherited and

Table 3.8 Selected factors associated with pulmonary hypertension (PHTN) of interest to the medicolegal autopsy

1. Primary disease of the pulmonary vasculature:	Familial PHTN, idiopathic PHTN, pulmonary veno-occlusive disease, capillary hemangiomatosis, persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension associated with systemic disease:	Collagen vascular disease, HIV infection, medication effects, intravenous drug abuse with foreign body embolization, porto-pulmonary hypertension, sarcoidosis, sickle cell disease, chronic thromboembolic disease, tumor thrombotic microangiopathy, hematological disease, amyloidosis, congenital syndromes (e.g., Alagille syndrome), associated with chronically elevated altitudes, systemic to pulmonary shunts
3. Pulmonary hypertension associated with underlying lung disease:	Chronic fibrosing interstitial lung disease, chronic obstructive lung disease/emphysema, marked architectural remodeling following organizing phase diffuse alveolar damage/bronchopulmonary dysplasia, pulmonary lymphangioleiomyomatosis
4. Pulmonary hypertension associated with underlying heart disease:	Left-sided ventricular failure, aortic or mitral valvular disease, hypertrophic cardiomyopathy, infiltrative heart disease with restrictive physiology (e.g., amyloidosis, hemochromatosis), congenital heart disease with left to right shunts

that one should consider communicating this within the autopsy report; however, secondary causes for pulmonary hypertension are far more frequently detected at autopsy. The morphological changes associated with pulmonary hypertension may be subtle when examining the heart and lungs macroscopically at autopsy. Associated morphological lesions may include "cirrhosis" (cardiac sclerosis), right ventricular hypertrophy, thickening and myxomatous degeneration of the tricuspid and less commonly the pulmonary valves, ectasia of the pulmonary arterial vasculature with or without atherosclerosis, intravascular thrombi, pulmonary infarcts, and nonspecific interstitial fibrous tissue deposition. Microscopically, the lesions may be plexogenic or nonplexogenic in nature and depending on the nature of the underlying cause for hypertension, may involve both arterial and venous vessels. Complications of chronic pulmonary hypertension can include *cor pulmonale*, dissection of the pulmonary arteries [24] and massive intrapulmonary hemorrhage [25].

Pulmonary arteries in central and peripheral locations will often show intimal and medial hyperplasia, reduplication of elastic lamina and incorporation of organized thrombi. Microscopic assessment of peripheral lung tissue for evidence of small vessel disease, plexogenic lesions, remote intrapulmonary hemorrhage, interstitial fibrous tissue deposition and intravascular thrombi supports the diagnosis of chronic pulmonary hypertension (Fig. 3.11). Furthermore, special connective tissue stains such as elastic trichrome or Movat pentachrome will also facilitate the evaluation of underlying architectural changes within the lung.

Rare diseases of the pulmonary vasculature that may also be associated with sudden death include pulmonary artery sarcoma; pulmonary vasculitities such as

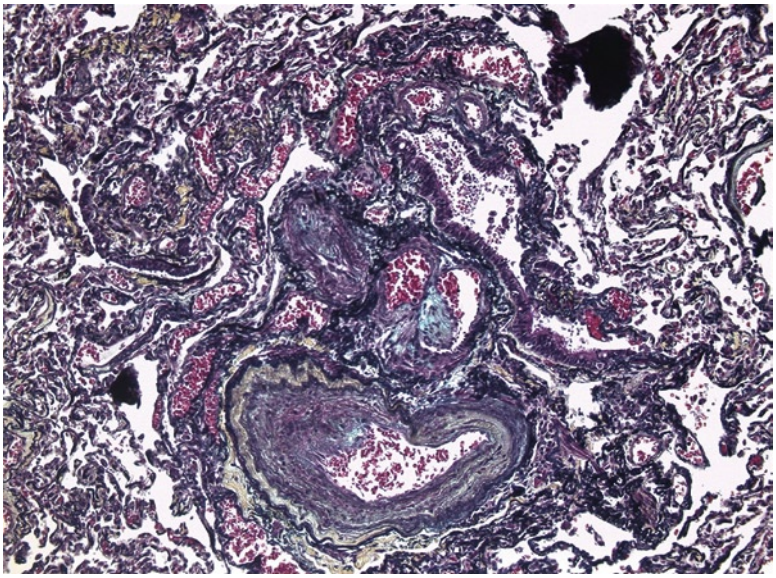

Fig. 3.11 Chronic vascular changes in patient with Eisenmenger Syndrome [movat pentachrome] (orig. mag. 100×)

Goodpasture syndrome, Wegener's granulomatosis, microscopic polyangiitis, and Takayasu's arteritis; as well as rupture of pulmonary artery aneurysms and pulmonary artery dissections (Fig. 3.12) [26, 27].

Emphysema and Asthma

Acute exacerbations of obstructive lung diseases such as chronic obstructive pulmonary disease (COPD) as well as bronchial asthma frequently cause sudden death. With moderate to marked emphysema often associated with long-term smoking or chronic occupational exposures such as coal dust or with α1-antitrypsin deficiency, one may observe secondary pathological changes such as numerous pleural bullae or blebs, pneumothoracies with associated lobar collapse, loss of lung parenchyma in centriacinar, panacinar, or subpleural patterns, as well as diffuse mucus plugging. Histologically, the presence of centriacinar anthracotic pigment deposition, respiratory bronchiolitis and chronic bronchial/bronchiolar inflammation supports a diagnosis of smoking or organic dust-associated COPD. In addition, recent work has suggested that chronic, high quantities of alcohol consumption may also exacerbate the smoking-related risk of developing COPD [28].

Other smoking-related lesions that may occasionally be identified in the lungs of patients with COPD include bronchogenic carcinoma, pulmonary langerhans cell histiocytosis (Fig. 3.13) and desquamative interstitial pneumonitis (DIP). Although

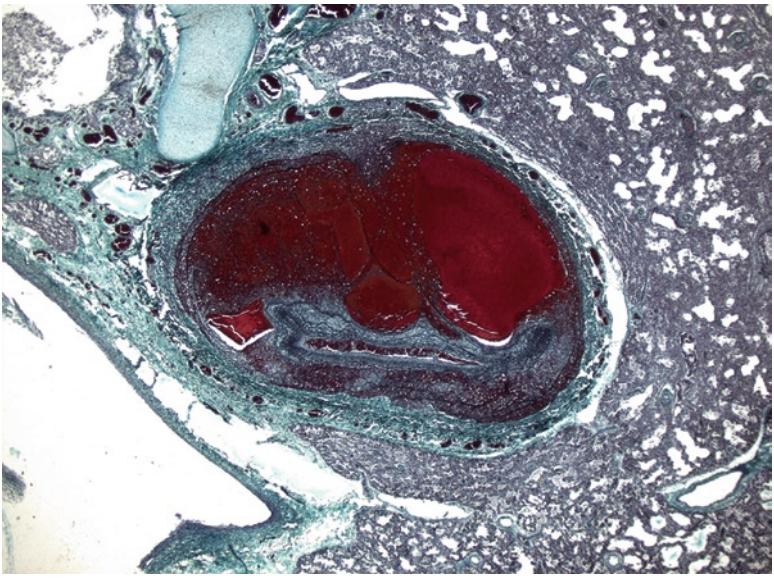

Fig. 3.12 Acute pulmonary artery dissection in 16-day-old infant with complex congenital heart pathology [elastic trichrome] (orig. mag. 16×)

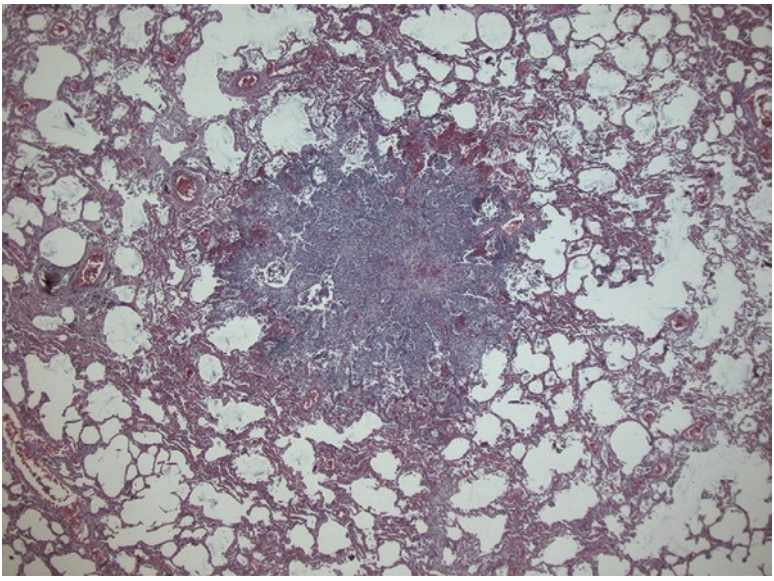

Fig. 3.13 Pulmonary Langerhans Cell Histiocytosis. Note cellular stellate-shaped nodule with Langerhans cells and eosinophils. Smoking-related lesion not to be confused with a malignancy. Immuno: S100+, CD1a+ and Langerin+ (orig. mag. 16×)

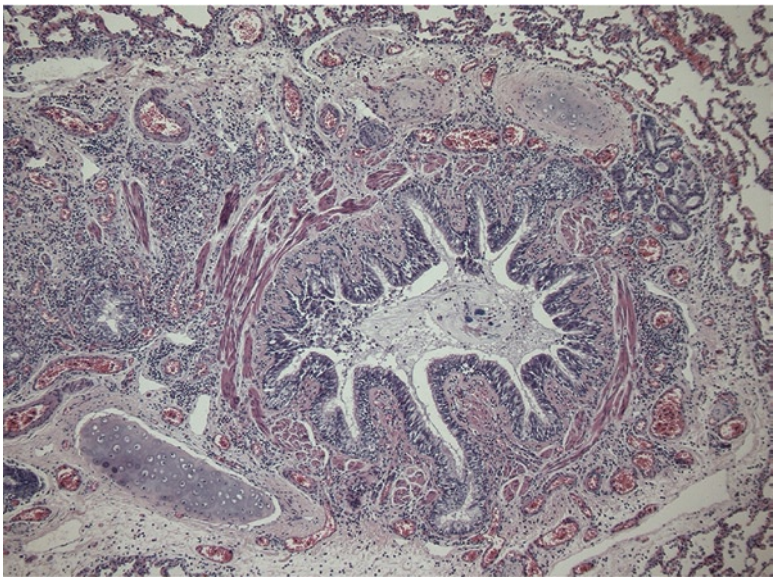

Fig. 3.14 Acute exacerbation of bronchial asthma (orig. mag. 50×)

sudden death may be observed with seemingly stable severe emphysema with or without chronic bronchitis, an inciting pathology such as bronchopneumonia, myocardial ischemia/infarction or aspiration of gastric contents is often identified as an exacerbating factor that can lead to respiratory decompensation, hypoxemia, and sudden death.

Sudden death due to bronchial asthma often correlates with severe, acute respiratory distress and increased usage of β-agonists [29], a delay in seeking medical attention and a clinical history of poorly controlled asthma (Fig. 3.14). It is within this context of multiple bronchial and bronchiolar mucus plugs, submucosal glandular hyperplasia, basement membrane thickening, bronchial/bronchiolar smooth muscle hypertrophy, and increased numbers of intramucosal eosinophils are virtually diagnostic of bronchial asthma. The lungs often appear hyperinflated at autopsy, frequently with overlapping borders of the right and left lungs across the anterior surface of the mediastinum. A frozen section at the time of autopsy may facilitate early diagnosis.

Careful assessment of the history often suggests exposure to a potential trigger prior to respiratory distress. However, sudden and unexpected death is not uncommon in individuals with seemingly well-controlled asthma [30]. Finally, given that some individuals with bronchial asthma may also be at increased risk of systemic anaphylaxis following exposure to specific allergens, the differential diagnosis of systemic anaphylaxis causing acute respiratory distress and sudden death may also be considered when evaluating bronchial asthma as a potential cause for death. Furthermore, submitting serum for immunoglobulin E and tryptase levels in conjunction with other physical findings such as airway angio-edema may facilitate making this distinction in selected cases.

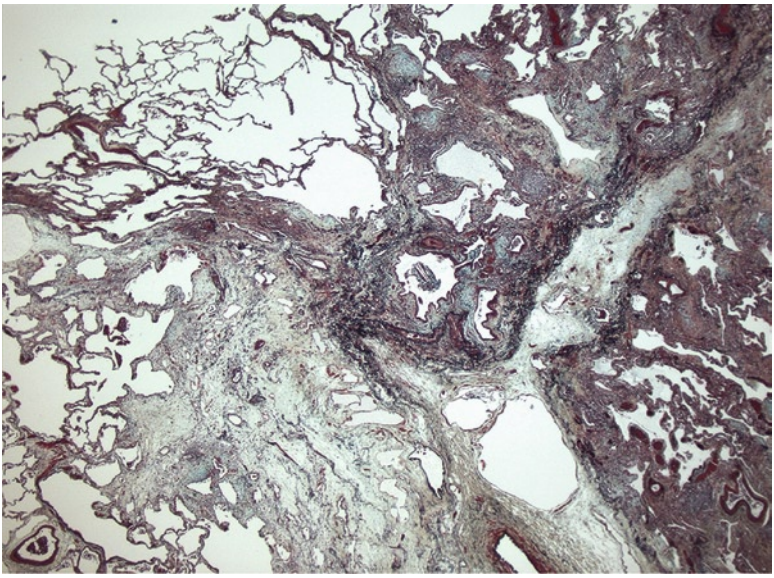

Fig. 3.15 Usual interstitial pneumonitis. Note paraseptal/subpleural distribution of fibrous tissue [spatial heterogeneity of fibrosis], regions of near normal parenchyma adjacent to dense fibrosis as well as fibroblastic foci [temporal heterogeneity of fibrosis] (orig. mag. 16×)

Interstitial Lung Disease

Numerous acute or chronic interstitial lung diseases may be associated with sudden death. Acute conditions can include severe hypersensitivity pneumonitis/eosinophilic pneumonia, Loeffler's pneumonitis, acute allergic bronchopulmonary aspergillosis, and acute interstitial pneumonitis. Conditions that can cause a chronic fibrosing interstitial pneumonitis include usual interstitial pneumonitis (UIP) (Fig. 3.15) and nonspecific interstitial pneumonitis (NSIP). A giant cell interstitial pneumonitis may be observed following chronic heavy metal exposure. Additionally, exposure to asbestos fibers can lead to asbestosis, which typically presents in a UIP pattern of interstitial fibrosis. A nonspecific pattern of interstitial fibrous tissue deposition may also be identified with honeycomb lung, which represents the cystic and fibrosing architectural remodeling of the pulmonary parenchyma in response to various forms of acute lung injury and may occur at the end-stage of a multitude of interstitial and alveolar disease processes.

Widespread interstitial and pleural nodules may occur as a consequence of infectious or noninfectious granulomatous disease, pneumoconioses, pulmonary langerhans cell histiocytosis (PLCH), amyloidosis, bronchocentric granulomatosis and chronic aspiration of oral or gastric contents. Finally, cystic lung changes may be observed in the setting of emphysema, lymphangioleiomyomatosis, PLCH, suppurative abscesses, malignancies, Wegener's granulomatosis pneumatoceles, and bronchogenic cysts.

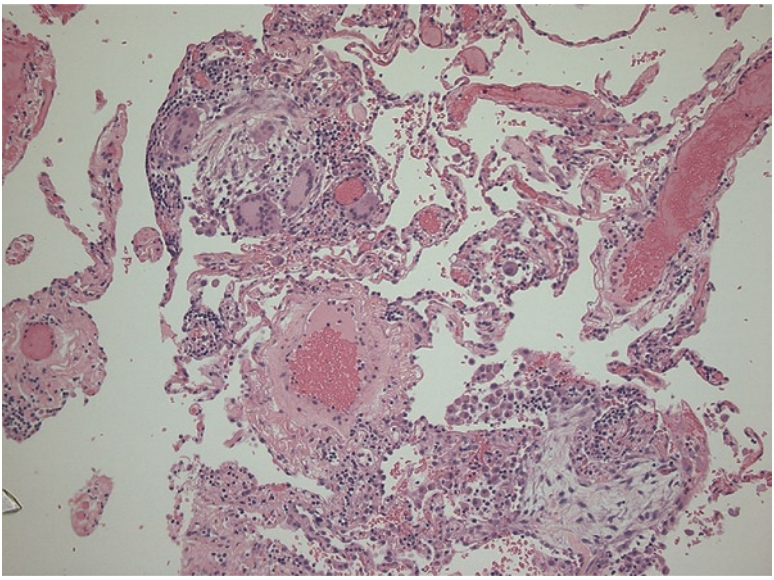

Fig. 3.16 Hypersensitivity pneumonitis. Note poorly formed granulomas, occasional interstitial eosinophils and organizing pneumonia in a centrilobular distribution (orig. mag. 100×)

Diagnostic challenges with interstitial lung disease include identification of major patterns of fibrous tissue deposition, identification of any associated findings such as ferruginous bodies, fragments of aspirated food or inorganic dusts and recognition of secondary changes in the lung such as marked medial and intimal hyperplasia of pulmonary vessels with usual interstitial pneumonitis. It is important to sample less-affected lung tissue that has not gone onto end-stage honeycomb lung, as end-stage pulmonary fibrosis is generally not diagnostically specific and may not facilitate identification of the underlying interstitial pathology.

All lung lobes should be sampled for microscopic assessment as many interstitial lung diseases have a predilection for different regions of the lung or possess a spectrum of histological changes that can be of diagnostic utility, such as with UIP, PLCH, or hypersensitivity pneumonitis (Fig. 3.16). Special connective tissue stains such as elastic trichrome or Movat pentachrome are often of great value in interpreting the underlying architecture of the lung which can aide in interpreting the aberrant pulmonary disease process. Granulomatous disease should prompt the use of special stains to help detect fungi, mycobacteria and bacterial microorganisms. Important information to garner from the history could include the rate of development of the clinical disease, the presence of any autoimmune or collagen vascular diseases, comparison to any prior thoracic radiology and identification of any prior infectious, environmental, occupational, or medicinal exposures. End-stage chronic interstitial pneumonitis is often associated with pulmonary hypertension and *cor pulmonale*. Furthermore, it is not uncommon to identify occult malignancy within regions of dense interstitial fibrous tissue such as with UIP.

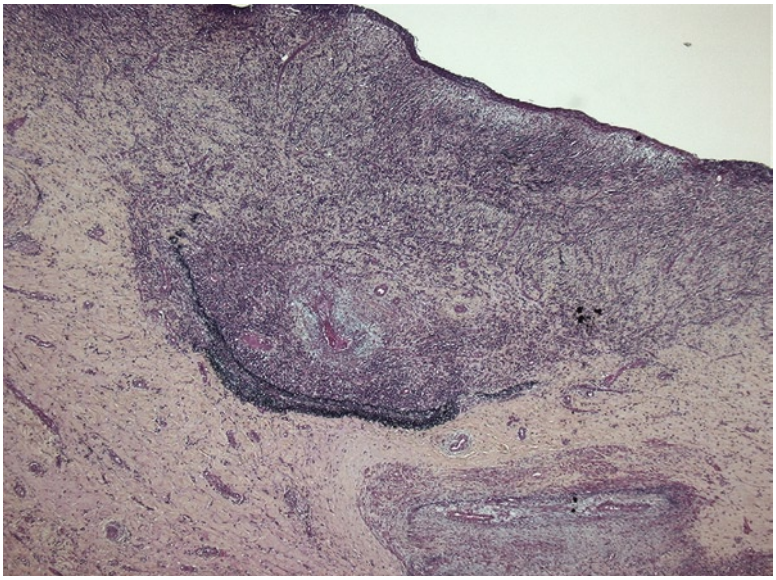

Fig. 3.17 Wall of chronic pulmonary aspergilloma associated with intractable hemoptysis [movat pentachrome]. Note destruction of the underlying vessel wall (orig. mag. 2×)

Contribution of Pulmonary Disease to Systemic Disease Processes

Multiple systemic disease processes involve the lung parenchyma and as such, may cause impairment of respiratory function and potentially contribute to the immediate cause for death. Examples include diffuse alveolar damage associated with systemic shock or "shock lung"; diffuse interstitial thickening as a consequence of collagen vascular disease, amyloidosis or sarcoidosis; hemoaspiration associated with upper digestive tract hemorrhage; aorto-bronchial fistulae; aspergillosis (Fig. 3.17) and bronchiectasis and finally, external restriction or compression of the lungs by chronic fibrous pleuritis, large hydrothoracies, empyema, ascities under tension and morbid obesity. The potential degree of respiratory dysfunction that each one of these conditions may play mechanistically in the immediate or underlying cause for death is highly dependent on the clinical history and the pathological context that these findings are identified.

Conclusions

The identification of pulmonary pathology at autopsy may be central to determining the underlying cause for death. Alternatively, significant disease of the respiratory system may play a secondary role, contributing mechanistically to the more

immediate pathophysiological abnormalities occurring in the period just before death. Recognition of the various patterns of lung disease and appreciation of the differential diagnostic considerations for each of these pathologies will enable pathologists performing medicolegal autopsies to arrange for appropriate ancillary studies and ultimately opine about the immediate and underlying causes for death.

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References

1. Dahlem P, van Aalderen WM, Bos AP (2007) Pediatric acute lung injury. Paediatr Respir Rev 8:348–362
2. DeMello DE (2004) Pulmonary pathology. Semin Neonatol 9:311–329
3. Bendon RW, Coventry S (2004) Non-iatrogenic pathology of the preterm infant. Semin Neonatol 9:281–282
4. Byard RW (ed) (2004) Forensic pathology reviews. Humana Press, Totowa, USA
5. Bajanowski T, Vege A, Byard RW, Krous HF, Arnestad M, Bachs L et al (2007) Sudden infant death syndrome (SIDS) – standardised investigations and classification: recommendations. Forensic Sci Int 165:129–143
6. Gorelick MH, Baker MD (1994) Epiglottitis in children, 1979 through 1992. Effects of Haemophilus influenzae type b immunization. Arch Pediatr Adolesc Med 148:47–50
7. McEwan J, Giridharan W, Clarke RW, Shears P (2003) Paediatric acute epiglottitis: not a disappearing entity. Int J Pediatr Otorhinolaryngol 67:317–321
8. Tanguay J, Pollanen MS (2009) Sudden death by laryngeal polyp: a case report and review of the literature. Forensic Sci Med Pathol 5:17–21
9. Busuttil A, Keeling JW (2009) Paediatric forensic medicine and pathology. Hodder Arnold, London
10. Johnson JE, Gonzales RA, Olson SJ, Wright PF, Graham BS (2007) The histopathology of fatal untreated human respiratory syncytial virus infection. Mod Pathol 20:108–119
11. Valdes-Dapena M, McFeeley PA, Hoffman HJ, Damus KH, Franciosi RR, Allison DJ et al (1993) Histopathological Atlas for the sudden infant death syndrome. Armed Forces Institute of Pathology, Washington, DC
12. Cutz E, Perrin DG, Pan J, Haas EA, Krous HF (2007) Pulmonary neuroendocrine cells and neuroepithelial bodies in sudden infant death syndrome: potential markers of airway chemoreceptor dysfunction. Pediatr Dev Pathol 10:106–116
13. Betz P, Nerlich A, Bussler J, Hausmann R, Eisenmenger W (1997) Radial alveolar count as a tool for the estimation of fetal age. Int J Legal Med 110:52–54
14. Krous HF, Chadwick AE, Haas EA, Stanley C (2007) Pulmonary intra-alveolar hemorrhage in SIDS and suffocation. J Forensic Leg Med 14:461–470
15. Kanmogne GD (2005) Noninfectious pulmonary complications of HIV/AIDS. Curr Opin Pulm Med 11:208–212
16. Ahmed AA, Heller DS (1999) Fatal pulmonary tumor embolism caused by chondroblastic osteosarcoma: report of a case and review of the literature. Arch Pathol Lab Med 123:437–440
17. Jakel J, Ramaswamy A, Kohler U, Barth PJ (2006) Massive pulmonary tumor microembolism from a hepatocellular carcinoma. Pathol Res Pract 202:395–399
18. Chinen K, Kazumoto T, Ohkura Y, Matsubara O, Tsuchiya E (2005) Pulmonary tumor thrombotic microangiopathy caused by a gastric carcinoma expressing vascular endothelial growth factor and tissue factor. Pathol Int 55:27–31

19. Rahimtoola A, Bergin JD (2005) Acute pulmonary embolism: an update on diagnosis and management. Curr Probl Cardiol 30:61–114
20. Montani D, Price LC, Dorfmuller P, Achouh L, Jais X, Yaici A et al (2009) Pulmonary veno-occlusive disease. Eur Respir J 33:189–200
21. Srigley JA, Pollanen MS (2005) Sudden death with clinically undiagnosed pulmonary hypertension. J Clin Forensic Med 12:264–267
22. Diller GP, Gatzoulis MA (2007) Pulmonary vascular disease in adults with congenital heart disease. Circulation 115:1039–1050
23. Chan SY, Loscalzo J (2008) Pathogenic mechanisms of pulmonary arterial hypertension. J Mol Cell Cardiol 44:14–30
24. Arena V, De GF, Abbate A, Capelli A, De MD, Carbone A (2004) Fatal pulmonary arterial dissection and sudden death as initial manifestation of primary pulmonary hypertension: a case report. Cardiovasc Pathol 13:230–232
25. Leung WH, Lau CP, Wong CK, Cheng CH (1990) Fatal massive pulmonary hemorrhage complicating mitral stenosis. Clin Cardiol 13:136–138
26. Marchetti D, La MG, Ranalletta D (1996) Death due to a leiomyosarcoma of the pulmonary artery. Am J Forensic Med Pathol 17:315–318
27. Graham JK, Shehata B (2007) Sudden death due to dissecting pulmonary artery aneurysm: a case report and review of the literature. Am J Forensic Med Pathol 28:342–344
28. Sisson JH (2007) Alcohol and airways function in health and disease. Alcohol 41:293–307
29. Cazzola M, Matera MG, Donner CF (2005) Inhaled beta2-adrenoceptor agonists: cardiovascular safety in patients with obstructive lung disease. Drugs 65:1595–1610
30. Tough SC, Green FH, Paul JE, Wigle DT, Butt JC (1996) Sudden death from asthma in 108 children and young adults. J Asthma 33:179–188