RadioGraphics

Pulmonary Complications from Cocaine and Cocaine-based Substances: Imaging Manifestations[1]

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CME FEATURE

See accompanying test at http://www.rsna.org/education/rg_cme.html

LEARNING OBJECTIVES FOR TEST 2

After reading this article and taking the test, the reader will be able to:

- List the various pulmonary complications associated with cocaine abuse.
- Describe the radiologic and histopathologic findings associated with cocaine abuse.
- Discuss the various pathophysiologic events that result from cocaine abuse.

TEACHING POINTS

See last page

Cocaine is the illicit drug whose abuse most often results in cardiopulmonary symptoms and emergency treatment. Habitual smoking of alkaloidal cocaine ("freebase," "crack") has replaced nasal insufflation as the most common method of abuse. Smoking of cocaine exposes the lung directly to the volatilized drug as well as to the other combustion products of the smoked mixture, thereby increasing the risk of adverse pulmonary effects. A wide variety of pulmonary complications including interstitial pneumonitis, fibrosis, pulmonary hypertension, alveolar hemorrhage, asthma exacerbation, barotrauma, thermal airway injury, hilar lymphadenopathies, and bullous emphysema may be associated with the inhalation of crack cocaine or of associated substances such as talc, silica, and lactose. Cocaine abuse represents one of the most serious medical and social problems of our time. Radiologists should be familiar with the various pleuropulmonary complications associated with the abuse of illicit drugs in general and of cocaine in particular to ensure correct diagnosis and appropriate treatment planning in patients with respiratory manifestations associated with such abuse.

Abbreviations: AIDS = acquired immunodeficiency syndrome, BAL = bronchoalveolar lavage, HIV = human immunodeficiency virus

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See also the article by Hagan and Burney (pp 919–940) in this issue.

Introduction

Diagnosing drug-induced pulmonary and cardiovascular diseases remains a challenge for clinicians and radiologists, especially in urban hospitals. Cocaine use keeps growing and has reached epidemic proportions. According to the U.S. Department of Health and Human Services, in 2003, 34.9 million Americans 12 years of age and older reported having used cocaine at some point during their lifetime, with 7.9 million having used "crack"; about 5.9 million reported having used cocaine in the past year, with 1.4 million having used crack; and about 2.3 million reported having used cocaine in the past 30 days, with 604,000 having used crack (1). Cocaine is the most commonly used illicit drug among patients seen in hospital emergency departments and the most frequent cause of drug-related deaths reported by medical examiners.

Teaching Point

Pulmonary complications of cocaine are influenced by administration method, dose size, and the presence of associated substances (eg, heroin, talc). These complications include acute respiratory symptoms; barotrauma; airway injury; asthma; pulmonary edema; hemoptysis and pulmonary hemorrhage; "crack lung" and eosinophilic lung disease; bronchiolitis obliterans with organized pneumonia and bronchiolitis; talcosis, silicosis, and interstitial lung disease; pulmonary hypertension; emphysema; infection and aspiration pneumonia; and tumors (Table). In this article, we describe cocaine and its abuse, after which we discuss and illustrate the pathophysiologic and imaging features of the aforementioned complications.

Pulmonary Complications of Cocaine Abuse

Chest pain
Airway injury
Pneumothorax
Pneumomediastinum
Pneumopericardium
Pulmonary edema
Exacerbation of asthma
Pulmonary hemorrhage
Bronchiolitis obliterans
Crack lung
Eosinophilic lung disease
Focal airspace disease and atelectasis
Pneumonia
Emphysema
Pulmonary hypertension
Pulmonary infarction
Enlarged lymph nodes

Cocaine

Cocaine hydrochloride, or benzoylmethylecgonine ($C_{17}H_{21}NO_4$), is a naturally occurring alkaloid that is extracted from the leaf of the *Erythroxylon coca* plant (Fig 1) after a relatively complex chemical process. The plant, which is botanically classified as a shrub, grows primarily in South America. The *Erythroxylon* plant contains cocaine (average, 0.8% relative to dry leaf weight; range, 0.3%–1.5%) as the principal alkaloid (2). Cocaine is available in four forms: hydrochloride salt, "freebase," crack, and "bazuco."

The hydrochloride form is a fine white powder that is prepared by dissolving the alkaloid in hydrochloric acid and that decomposes at high temperatures. It can be taken orally, intravenously (occasionally mixed with heroin), or intranasally. Cocaine hydrochloride is not heat stable and cannot be smoked.

Freebase and crack cocaine have the same chemical form but have different manifestations and are obtained by different methods. The freebase form is obtained by dissolving cocaine hydrochloride in water, then adding a base (eg, ammonia) and a solvent (ether or alcohol) (3). Crack cocaine is obtained by dissolving cocaine hydrochloride in water with sodium bicarbonate (baking soda) to extract the hydrochloride and make the substrate heat stable. The cocaine base precipitates, forming hard masses or rocks that melt when dry and vaporize at high temperatures (98°C) and can be smoked. The name "crack" is an onomatopoeia for the sound the substance makes when it is heated. Crack is considered to be the most potent and addictive form of cocaine, and because the euphoric effects of smoking crack cocaine are obtained within seconds, smoking is the preferred method for many drug users (4,5).

Adulterants are found in all street samples of cocaine and result in additional toxicity for this form of substance abuse. Chemical analysis of street samples shows that their purity ranges from

Figure 1. Photograph illustrates the *E coca* plant, a shrub that is native to South America and grows in a variety of areas, including Venezuela, Colombia, Ecuador, Peru, Bolivia, Brazil, and northern Argentina.

14% to 75% (average, 40%). Among the most common adulterants are local anesthetics (lidocaine, benzocaine), sugars (mannitol, lactose, sucrose), stimulants (caffeine, ephedrine), toxins (quinine, strychnine), and inert compounds (inositol, talc, cornstarch) as well as other substances (eg, flour, calcium, aspirin, plaster) (6). A highly impure form of cocaine paste known as "bazooka" or bazuco and consisting of a crude extract of coca leaves mixed with other substances such as water, kerosene, gasoline, sulfuric acid, flour, sand, talc, sugar, and so on is commonly smoked in South America but is not widely used in the United States (2,3,7).

Pathophysiologic Events Resulting from Cocaine Abuse

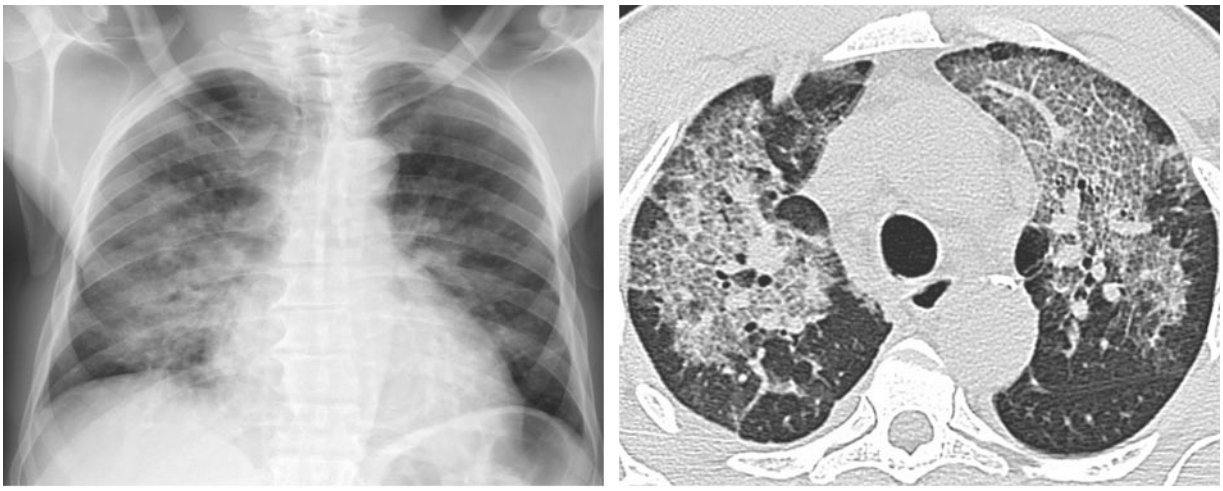
Pulmonary complications resulting from cocaine abuse depend on the method of administration (oral, nasal, intravenous), dose size, frequency of exposure, and presence of associated substances (eg, tobacco, heroin, talc). Respiratory symptoms are quite common after cocaine exposure, particularly after exposure to the combustion products of crack cocaine. The average size of generated particles is 2.3 μm, which is small enough to result in the deposition of particles in the alveolar region of the lung (8). Respiratory symptoms include cough with production of carbonaceous material, chest pain, dyspnea, hemoptysis, wheezing, and exacerbation of asthma (4). Massive quantities of carbon pigment are often found at bronchoalveolar lavage (BAL) in patients with a history of crack cocaine abuse. During the smoking of crack, a dark and tarry residue is formed, which many addicts collect and then resmoke along with more crack. During the inhalation of these impurities, there is extensive accumulation of large amounts of intracellular (macrophages) and extracellular carbon pigment (9).

When applied locally, cocaine acts as an anesthetic because it inhibits membrane permeability to sodium during depolarization of cell membranes, blocking the initiation and transmission of electrical impulses. When systemically administered, cocaine affects synaptic transmission, blocking the presynaptic reuptake of norepinephrine and dopamine and acting as a potent sympathomimetic agent (5). This mechanism is particularly important pathophysiologically in cardiovascular complications resulting from cocaine abuse (eg, pulmonary hypertension, myocardial ischemia). Cocaine-associated ischemic injury has been documented in many organs, including (among others) the liver, kidneys, bowel, brain, heart, and placenta.

A decrease in diffusion capacity secondary to damage to the alveolar-capillary membrane has been reported (10,11). This phenomenon is probably related to other factors as well, including damage to the pulmonary vascular bed and interstitial lung disease due to concurrent intravenous drug abuse (4).

Acute Respiratory Symptoms

Because the combustion products of crack cocaine principally affect the lungs and related airways, it is not surprising that a significant number of crack users experience respiratory symptoms that prompt them to seek medical care. In a series of patients with a history of crack cocaine abuse who were seen at a major city hospital for respiratory complaints, more than one-half had abnormal chest radiographs (12). Cough with sputum production (61% of cases), wheezing (50%), and dyspnea (44%) are the most common complaints (13). A common complaint among cocaine smokers is the presence of cough with production of black sputum (40% of cases) (11). Although cocaine alkaloids are volatilized with heating, large amounts of particulate matter and impurities can



a. b.

Figure 2. Acute chest syndrome in a 49-year-old man who presented with progressive shortness of breath and fever after an intravenous cocaine binge. **(a)** Chest radiograph shows abnormal bilateral parenchymal opacities, which are more confluent in the right midlung zone. **(b)** High-resolution computed tomographic (CT) scan demonstrates diffuse bilateral reticular opacities with superimposed thickening of inter- and intralobular interstitium ("crazy paving pattern").

also be inhaled. The dark, tarry residue formed during "freebasing" that accumulates in the bowl or barrel of the smoker's pipe is considered by many smokers to be concentrated cocaine and is recovered, reheated, and resmoked. Frequent deep inhalation of these nonvolatilized impurities overloads the macrophage-clearing mechanism of the lung and results in the accumulation of large amounts of intra- and extracellular carbon pigment (9,14). In many of these patients, radiologic examination demonstrates patchy alveolar infiltrates affecting the upper and lower lobes of both lungs (Fig 2), a finding that may be associated with pleural fluid. Carbon-laden macrophages have also been identified in the pleural fluid of crack smokers (15).

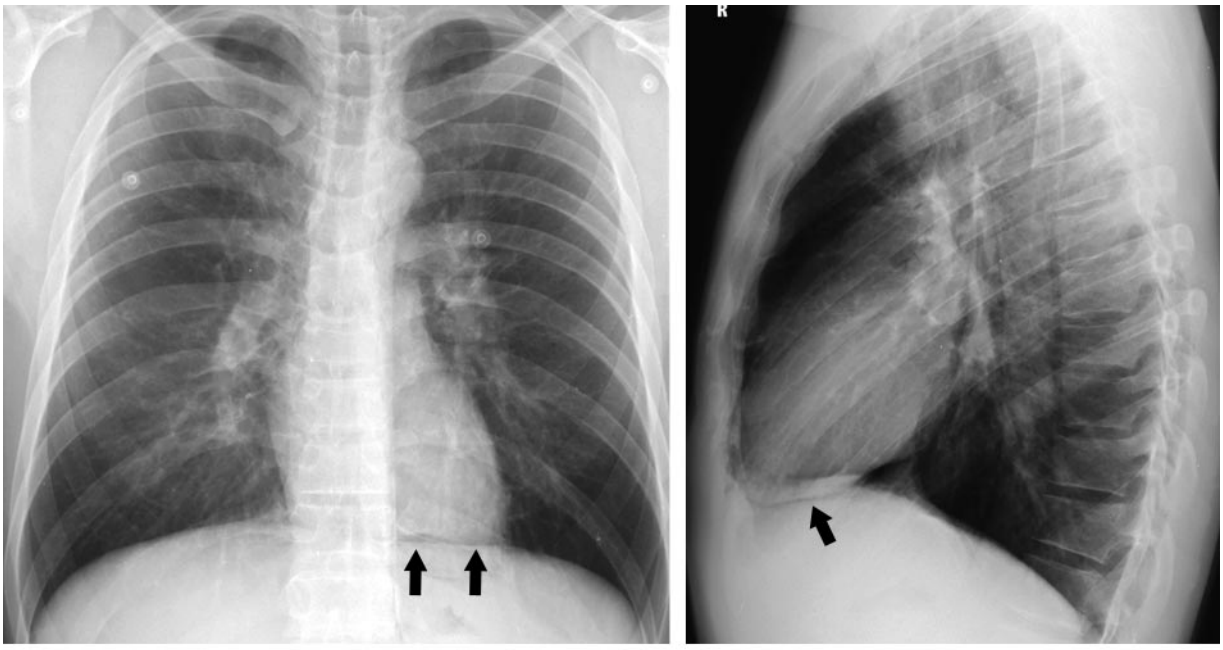
Teaching Point

Cardiopulmonary complaints are the most common manifestation of disease in patients seeking treatment for acute or chronic cocaine-associated medical problems (56% of cases). Among these cardiopulmonary complaints, chest pain is the most common (16). Between 14% and 25% of patients who present to the emergency department in urban hospitals with nontraumatic chest pain have detectable levels of cocaine or cocaine metabolites in the urine (17), and 6% will have enzymatic evidence of myocardial infarction (18). The majority of patients are young, nonwhite male cigarette smokers with no risk factors for atherosclerotic disease and a previous history of cocaine abuse. Other cardiovascular complications resulting from cocaine abuse are ventricular arrhythmias, congestive heart failure, aortic dissection, intramural hematoma of the aorta, dilated cardiomyopathy, and sudden death (5,19–21). Imaging examinations are particularly important if aortic dissection is suspected and are prompted by signs of cardiac tamponade in young patients with chest pain, circulatory compromise, and a history of cocaine abuse. Imaging findings in such cases are well known and include an enlarged mediastinum and aortic dissection, which may be associated with the presence of pericardial blood.

Chest pain is quite common after crack cocaine smoking. In a study by Tashkin et al (11), 39% of patients experienced chest pain within 12 hours of smoking. It has been proposed that chest pain may represent a local sensory response to acute airway irritation from the high concentration of cocaine in the inhaled smoke itself, or from other substances produced by the combustion of crack (4).

Barotrauma

Barotrauma, manifesting as either pneumothorax, pneumomediastinum, pneumopericardium, or subcutaneous emphysema, is a well-known complication of crack cocaine smoking (4). The mechanism seems to be related to increased intraalveolar pressure caused by either *(a)* deep inhalation followed by the Valsalva maneuver, *(b)* the severe cough triggered by cocaine smoke inhalation, or *(c)* mouth-to-mouth positive pressure applied by an accomplice (4,22). In a series of 71 patients who had shortness of breath or chest pain after smoking crack cocaine, findings consistent with barotrauma were among the most common findings at chest radiography (Figs 3, 4)



a. b.

Figure 3. Pneumomediastinum in a 28-year-old patient who presented with retrosternal chest pain after smoking crack cocaine. Posteroanterior **(a)** and lateral **(b)** chest radiographs show a lucent line extending into the anterior mediastinum (arrows).

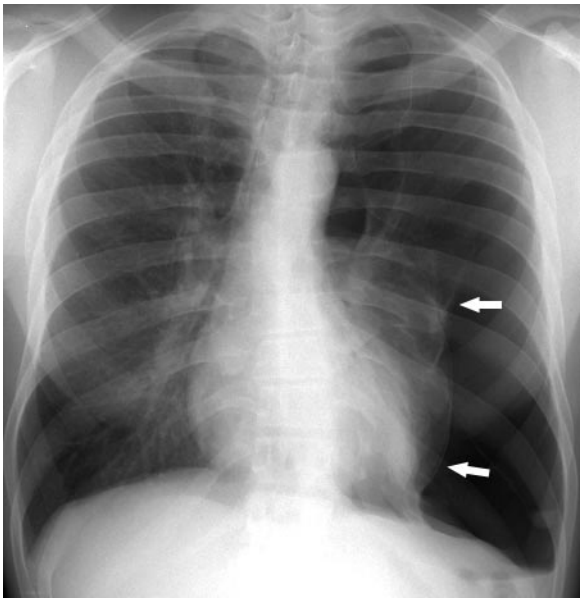


Figure 4. Spontaneous left-sided pneumothorax in a 33-year-old man who had been smoking crack cocaine. The patient presented with chest pain and had no history of trauma. Chest radiograph demonstrates hyperlucency of the left hemithorax and clearly depicts the visceral pleural line (arrows).

(23). CT may also show associated parenchymal opacities and pulmonary interstitial emphysema due to alveolar rupture (24).

In long-term intravenous drug abusers, the inevitable long-term effect of repeated injection of contaminated substances is inflammation and sclerosis of the peripheral veins, which forces the drug abuser to seek new access sites such as the great vessels of the neck ("pocket shot"). One of the common complications of this practice is pneumothorax, which results from injection into either the internal jugular vein or the subclavian vein and can be associated with laceration of the lung apex (12).

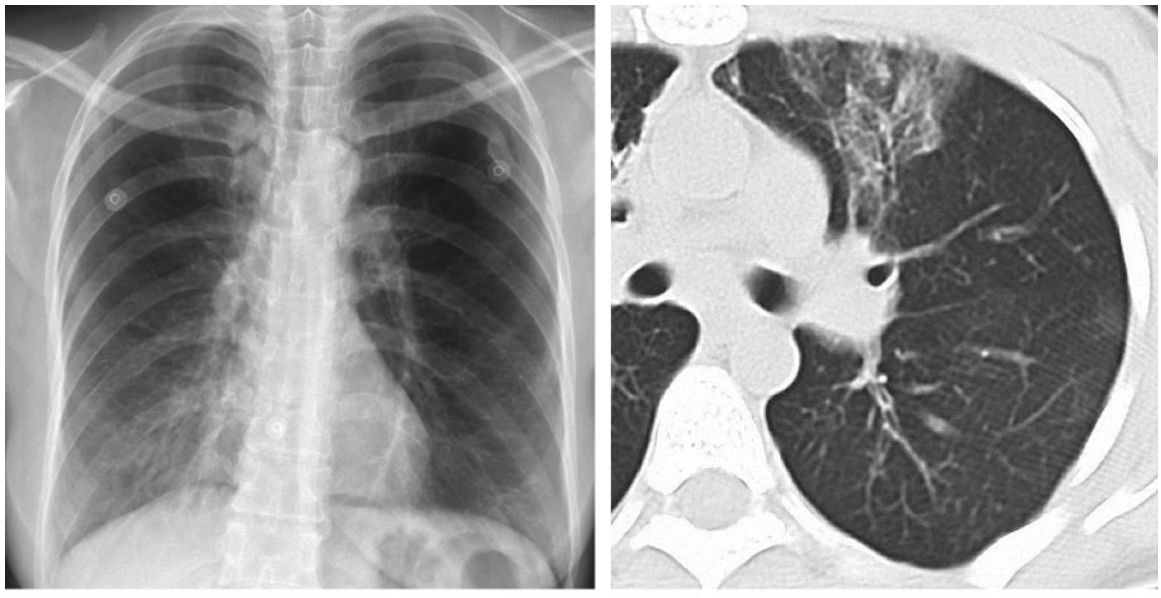
Airway Injury

Habitual nasal insufflation of cocaine may cause mucosal lesions of the nose and upper airways that extend to the perichondrium, with ischemic necrosis and destruction of the septal cartilage, lateral nasal wall, sinuses, turbinates, and palate. These conditions mimic the clinical picture of other diseases associated with necrotizing midfacial lesions, but with even more severe destruction (25).

Thermal airway injury secondary to freebase cocaine smoking and leading to tracheal stenosis may result from either *(a)* inhalation injury from chemical byproducts transported in the smoke, or *(b)* intratracheal combustion of highly inflammable solvents used in the production process (4,26).

Asthma

Cocaine abuse, whether in the form of smoking or nasal inhalation ("snorting"), is well known to precipitate bronchospasm and wheezing, especially in patients with a previous history of asthma. Wheezing has been reported in 32% of



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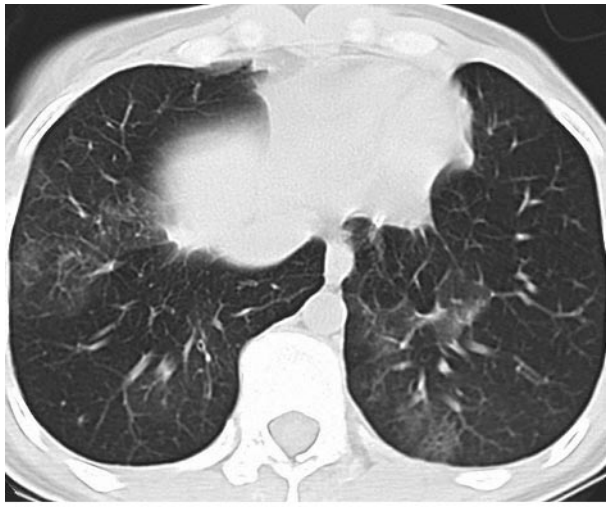


c.

Figure 5. Crack cocaine–induced asthma in a 38-year-old woman. **(a)** Chest radiograph depicts ill-defined peribronchial and parahilar opacities. **(b, c)** CT scans of the anterior segment of the left upper lobe **(b)** and of both lower lobes **(c)** show scattered ground-glass opacities.

habitual crack users during the period of use (27). Smoked cocaine causes acute bronchoconstriction, with an onset within 3 minutes and a duration of at least 15 minutes in healthy individuals with no history of asthma, with plethysmographic evidence of an increase in airway resistance (28). The degree of airway obstruction can be severe, with progression to respiratory failure (29) and death (30,31).

Imaging manifestations are those commonly associated with asthma—namely, increased pulmonary volume and patchy parenchymal opacities (Fig 5)—and usually change over time. Atelectasis or localized parenchymal opacities are among the most common imaging findings in crack cocaine smokers who present with chest pain (23). Whether these findings represent bronchoconstriction or mucosal swelling is not clear.

Cocaine-induced Churg-Strauss vasculitis with new-onset asthma, significant peripheral eosinophilia, alveolar opacities with cavitation at chest radiography, and biopsy-proved eosinophilic infiltrates in small arteries and venules has been reported in an adult patient (32).

Pulmonary Edema

Both cardiogenic and noncardiogenic pulmonary edema have been reported in association with intravenous cocaine abuse and crack cocaine smoking and are common findings at autopsies of drug addicts, especially heroin users (33,34). Pulmonary edema has been demonstrated in 77%–85% of cocaine-related deaths in autopsy series (30, 35).

Teaching Point

The pathogenesis of cocaine-induced pulmonary edema is complex and multifactorial. Myocardial ischemia and infarction, myocardial dysfunction, arrhythmia, and dilated cardiomyopathy may be contributing factors in cardiogenic edema. Damage to the pulmonary capillary endothelium with increased permeability may play a role in noncardiogenic edema (36). It has been postulated that the mechanism may be similar to that of heroin toxicity, with increased endothelial permeability of capillaries and an elevated protein content in BAL fluid.

The radiologic manifestations of cardiogenic pulmonary edema typically include variable de-

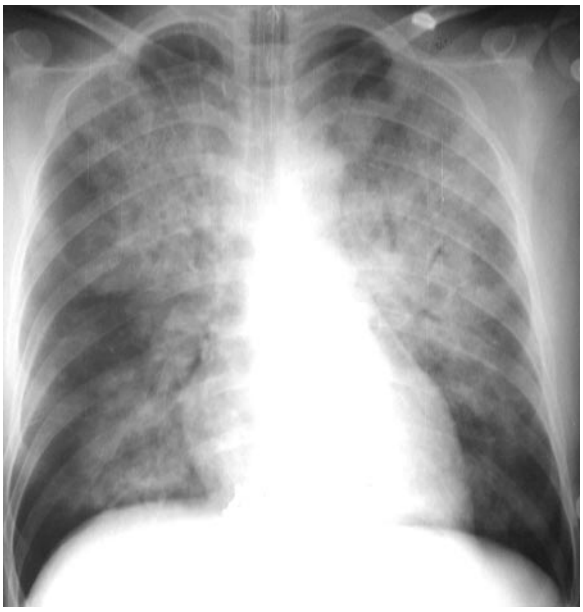


Figure 6. Cardiogenic pulmonary edema in a 36-year-old woman who presented with shortness of breath and chest pain after smoking crack cocaine. Initial chest radiograph shows extensive bilateral heterogeneous central and parahilar opacities.

grees of cardiomegaly, interlobular septal thickening, peribronchovascular edema, pleural fluid, and, in severe cases, parenchymal opacities with airspace disease and consolidation (Figs 6, 7).

In a series of five patients who developed pulmonary edema after smoking cocaine, the typical chest radiographic pattern consisted of bilateral perihilar and fairly symmetric interstitial or alveolar infiltrates with a normal-sized heart. These abnormalities resolved within 24–72 hours regardless of whether the patient received treatment (37).

Hemoptysis and Pulmonary Hemorrhage

Hemoptysis has been reported in 6%–26% of crack users and is considered to be either *(a)* secondary to rupture of bronchial or tracheal submucosal blood vessels, or *(b)* parenchymal in origin, arising from injury to the alveolar-capillary membrane (11,27). Diffuse alveolar hemorrhage with hemoptysis secondary to freebase cocaine smoking can be life threatening, with massive bleeding that may require surgery (38). In an autopsy series of 20 patients whose deaths were related to cocaine intoxication, 85% of cases demonstrated pulmonary hemorrhage (35). Numerous hemosiderin-laden macrophages reflecting alveolar hemorrhage that occurred at least 48 hours prior to death were identified in 35% of cases (35). Evidence of acute or chronic alveolar hemorrhage was found at 71% of autopsies of patients in

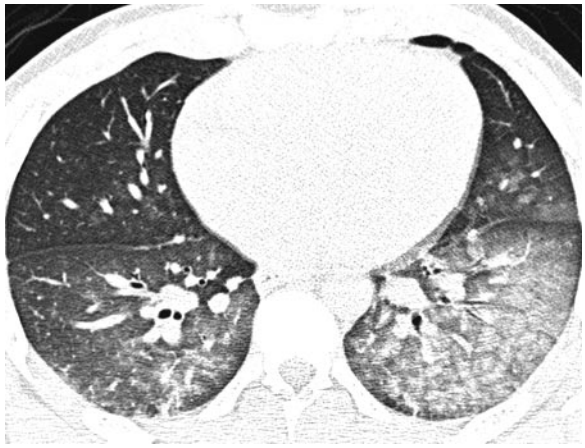


Figure 7. Acute pulmonary edema in a cocaine abuser. CT scan demonstrates bilateral heterogeneous opacities.

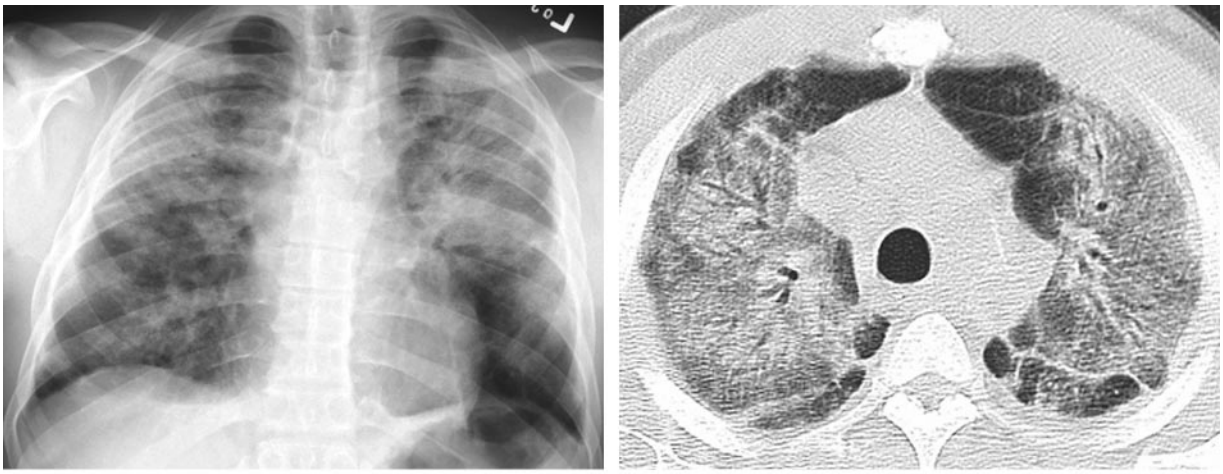
whom toxicologic tests for cocaine conducted by a medical examiner were positive (30).

Occult pulmonary hemorrhage is more common and is found at autopsy in patients who die from an overdose of either cocaine or heroin (4,39,40), as well as in living asymptomatic cocaine smokers. Clinically unapparent alveolar hemorrhage as evidenced by an increased number of hemosiderin-laden alveolar macrophages occurs frequently in otherwise healthy crack cocaine smokers, which suggests that pulmonary hemorrhage is more common than the presence of clinical hemoptysis would indicate (30,41).

Pulmonary hemorrhage manifests radiologically as bilateral multifocal areas of increased opacity. At high-resolution CT, these opacities have a ground-glass appearance that may be centrilobular with interlobular septal thickening.

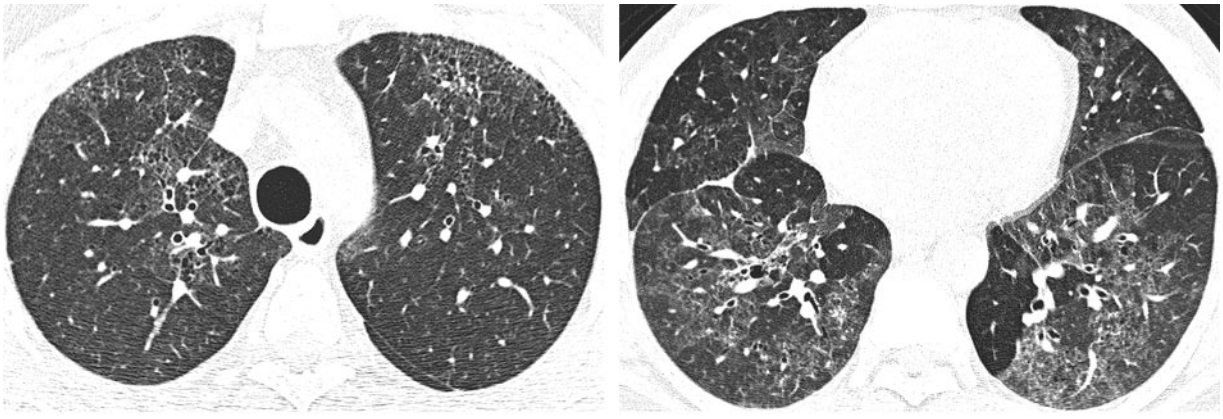
Crack Lung and Cocaine-induced Eosinophilic Lung Disease

The term *crack lung* refers to an acute pulmonary syndrome that occurs after the inhalation of freebase cocaine and is secondary to a prolonged inflammatory pulmonary injury and associated with fever, hypoxemia, hemoptysis, respiratory failure, and diffuse alveolar infiltrates. Lung tissue specimens obtained in affected patients reveal diffuse alveolar damage and alveolar hemorrhage with interstitial and alveolar cell infiltration rich in eosinophils, with deposition of IgE (39,42). Imaging manifestations consist of diffuse interstitial and alveolar parenchymal opacities that affect the upper, middle, and lower lung zones and often involve parahilar regions (39,42,43). Small pleural fluid collections may also be present. The association of alveolar hemorrhage with hypersensitivity



a. b.

Figure 8. Pulmonary eosinophilia in a patient with a history of cocaine abuse. **(a)** Chest radiograph demonstrates bilateral parenchymal opacities with a predominantly peripheral distribution. **(b)** CT scan exhibits extensive bilateral disease with ground-glass opacities and airspace consolidation.



a. b.

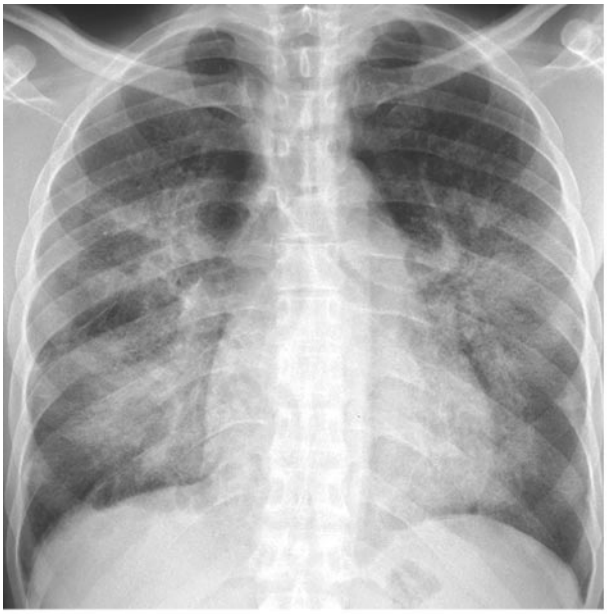
Figure 9. Pulmonary fibrosis in a 38-year-old woman with a long-term history of crack cocaine smoking. **(a)** Chest CT scan demonstrates bilateral, predominantly anterior reticular opacities and honeycombing. **(b)** On a CT scan obtained inferior to **a**, the opacities have a predominantly ground-glass appearance.

pneumonitis has been considered in the pathophysiology of this acute syndrome, which usually responds to corticosteroids.

Pulmonary eosinophilia associated with cocaine inhalation is well known. It has been reported in crack lung as well as in other forms of cocaine-induced eosinophilic lung disease (39,42). Affected patients usually have pulmonary eosinophilia at BAL and a variable degree of peripheral eosinophilia (up to 40% eosinophils in white blood cell count) (44). Imaging findings vary from predominantly interstitial and parahilar opacities (Fig 8) (42) to a more alveolar manifestation with airspace consolidation, with a patchy and random distribution or peripheral predominance (39). Interestingly, eosinophilic "empyema" associated with eosinophilic pneumonitis secondary to crack cocaine smoking has also been reported in the setting of peripheral eosinophilia and eosinophilia in pleural fluid (45). High levels of vascular endothelial growth factor, a leak mediator that is present in eosinophils, and increased levels of interleukins (IL-5, -6, and -8) have been identified in the pleural fluid, findings that suggest a potential role in the development of the effusion (45,46).

Bronchiolitis Obliterans with Organized Pneumonia and Bronchiolitis

Respiratory failure with bronchiolitis obliterans with organized pneumonia documented at open lung biopsy has been reported in young crack cocaine smokers (4,47). Imaging manifestations consist of diffuse bilateral alveolar opacities, and lung biopsies reveal areas of fibroblastic plugs occupying the terminal bronchioles and alveolar spaces, as well as thickened interstitium infiltrated with mononuclear cells, cholesterol clefts, foamy



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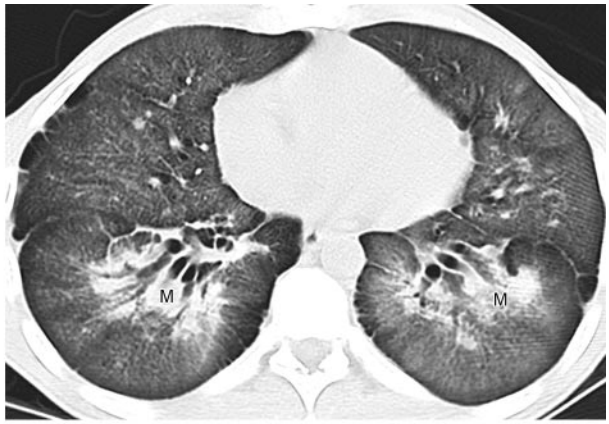


b.

Figure 10. Talc granulomatosis in a patient with a history of intravenous cocaine abuse. **(a)** Chest radiograph demonstrates fine nodular opacities and areas of coalescence. **(b)** CT scan shows tiny diffuse nodules and peribronchovascular conglomerate masses *(M)* in both lungs.

macrophages, multinucleated giant cells, and fibrosis (4). Airway-centered interstitial fibrosis and metaplastic bronchiolar epithelium with heavily muscularized bronchioles, considered to be a distinct form of aggressive diffuse lung disease and a form of bronchiolitis, has also been reported in association with inhaled cocaine (48). Imaging manifestations consist primarily of peribronchovascular interstitial thickening and traction bronchiectasis with thickened airway walls, fibrosis, and a restrictive appearance with small lung fields.

Talcosis, Silicosis, and Interstitial Lung Disease

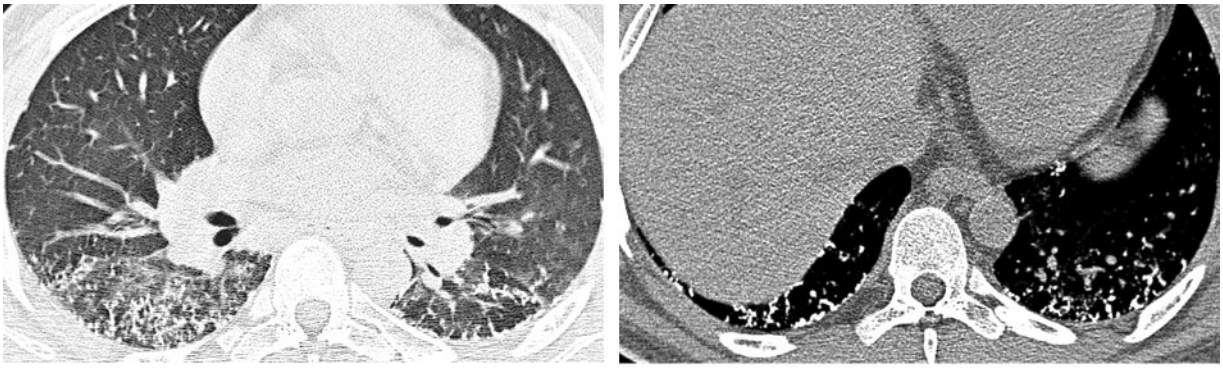
Talc (magnesium silicate) is used for cosmetic purposes and as a lubricant in various consumer goods including pharmaceuticals, in which it is used as a lubricating agent, filler, and diluting agent in oral medications. Intravenous injection of talc results from the intravenous abuse of oral medications. The drug is crushed, dissolved in water, and injected intravenously, resulting in embolism caused by tiny particles of talc that lodge in the pulmonary vascular bed and the interstitium, where they produce a foreign-body granulomatous reaction and fibrosis. This phenomenon has been described in relation to different medications, including pentazocine, methadone, and methylphenidate (49). It may be seen in cocaine users who frequently abuse multiple substances, injecting cocaine in combination with other substances such as heroin, pentazocine, methylphenidate, diazepam, meperidine, and methadone (50). One such combination of drugs involves the intravenous injection of opiates, antihistamines, and cocaine ("speed ball") (30).

Teaching Point

Polarizable foreign material with a histologic appearance consistent with talc and associated microgranulomas was found at 11% of autopsies of cocaine abusers, more commonly in individuals with a history of intravenous drug abuse (30). Talc granulomatosis is rare in "sniffers" and probably results from frequent inhalation of talc used to cut or mix the cocaine sold on the street (51). Similarly, interstitial pneumonitis with extensive accumulation of free silica within histiocytes associated with interstitial fibrosis has been reported in a crack cocaine smoker, findings that indicate frequent aspiration of adulterants in the smoked mixture (52). Frequent inhalation of crack cocaine with crystalline silica may induce the formation of abnormally enlarged lymph nodes with increased serum levels of angiotensin-converting enzyme and increased pulmonary uptake of gallium, findings that manifest as a syndrome mimicking sarcoidosis (53).

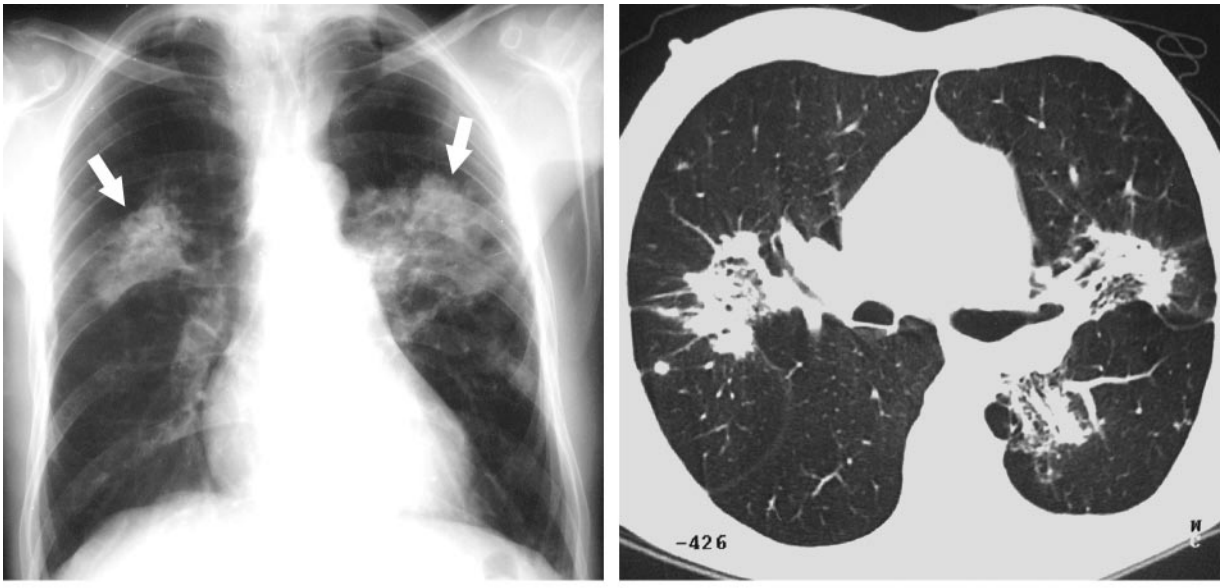
Follow-up of these patients has demonstrated that despite discontinuation of drug abuse, interstitial fibrosis progresses, with development of respiratory insufficiency and significant mortality (52,54). Interstitial pneumonitis or interstitial fibrosis has been reported at 38% of autopsies of patients with a positive toxicologic test for cocaine abuse (Fig 9) (30).

Conventional radiographs show diffuse micronodularity with subsequent progression to conglomerate nodules that resemble progressive massive fibrosis or pneumoconiosis, in particular silicosis. The most common CT findings are interstitial opacities with a diffuse micronodular pattern, lower lobe panacinar emphysema, and ground-glass attenuation (Figs 10–13) (50).



a. b.

Figure 11. Talc granulomatosis in a long-term intravenous cocaine abuser. **(a)** High-resolution chest CT scan (lung windowing) demonstrates peribronchial thickening and numerous bilateral small basilar nodules. **(b)** High-resolution chest CT scan (soft-tissue windowing) shows the nodules with high attenuation.



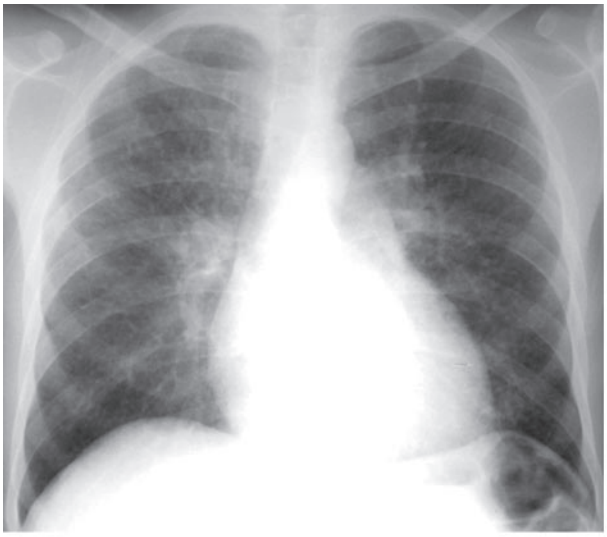
a. b.

Figure 12. Silicotuberculosis in a crack cocaine smoker. **(a)** Chest radiograph shows bilateral, relatively symmetric parahilar masses (arrows). **(b)** CT scan better characterizes the masses.

Foreign-body granulomas secondary to cellulose have also been documented in the lungs of cocaine sniffers, manifesting as bilateral pulmonary micronodules and demonstrating a miliary pattern at chest radiography (55).

Pulmonary Hypertension

As with cocaine-induced pulmonary edema, the mechanism by which cocaine induces pulmonary



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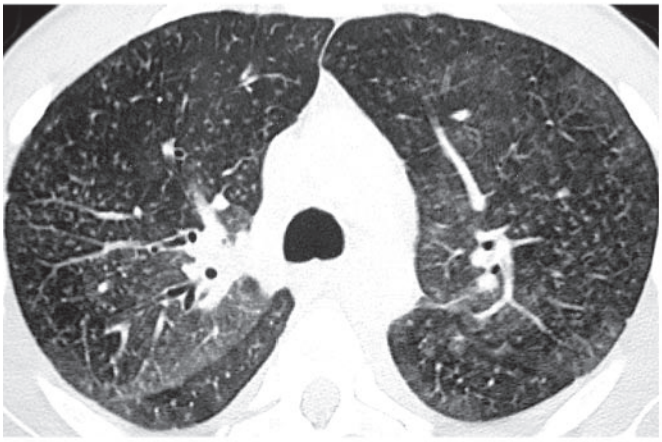

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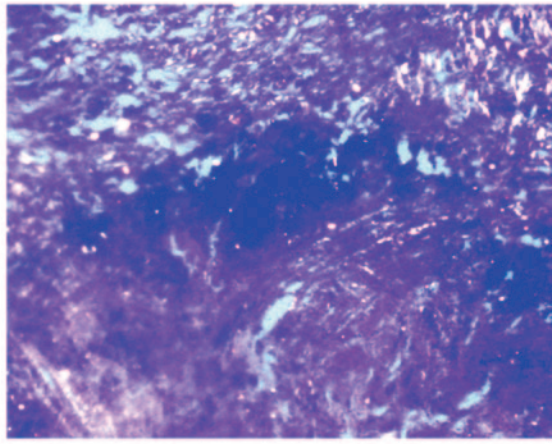


c.

Figure 13. Silicosis in a crack cocaine smoker. **(a)** Chest radiograph shows diffuse bilateral reticulonodular opacities. **(b)** CT scan demonstrates small centrilobular nodules and ground-glass opacities. **(c)** Polarized light microscopic image shows evidence of birefringent particles (pink dots), a finding that represents free silica.

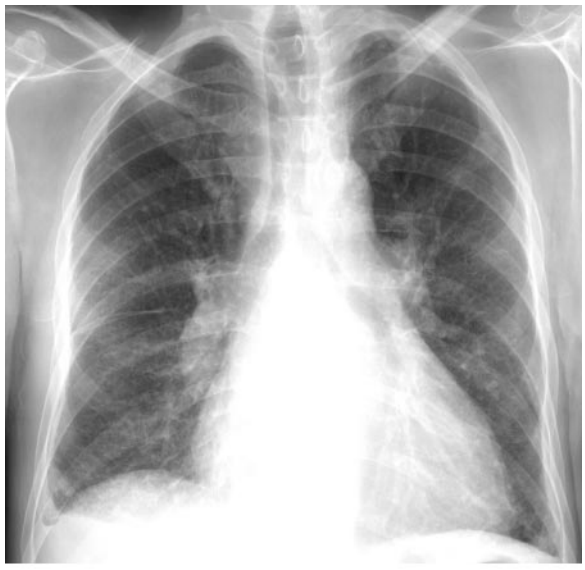
artery hypertension is complex and multifactorial. Intravenous injection of cocaine hydrochloride has not been proved to cause a short-term increase in pulmonary artery pressure or stroke volume index, thereby raising the question as to whether a vasoconstrictor effect on the pulmonary circulation is solely responsible for this complication (56). Initial reports on abnormalities in the pulmonary vasculature in intravenous drug abusers were more related to the associated foreign particle embolization (eg, from talc or other fillers) with significant reduction of the vascular bed caused by the granulomatous process and local chronic inflammation these foreign particles induce (57,58). However, vascular abnormalities have also been reported in the absence of foreign

Teaching Point

particle embolization in crack cocaine users (Fig 14). Pulmonary vascular abnormalities manifesting as medial hypertrophy of the muscular pulmonary arteries and involving both small and medium-sized arteries has been demonstrated at 20% of autopsies of victims of cocaine-related death, despite the young age of these individuals (35).

The vasoconstrictive effect on the pulmonary vasculature can mimic a pulmonary embolism in a crack cocaine smoker who presents with chest pain, with a misleading high-probability ventilation-perfusion lung scan caused by intense pulmonary artery vasospasm (59). Crack cocaine smoking may cause pulmonary infarction secondary to severe local vascular spasm and in situ thrombosis (60).

Endothelin-1, an endothelium-derived vasoconstrictor peptide and a potential indicator of cell damage, has been found at BAL in habitual cocaine users and might be involved in the pathogenesis of pulmonary hypertension. Elevated levels of this entity have been found at BAL in habitual users of crack cocaine (41). Cocaine has also been found to stimulate the release of endothelin-1 in cultured endothelial cells (61,62). Pulmonary hypertension may also be related to alveolar hemorrhage. In a study of four female patients with echocardiographic evidence of elevated pulmonary artery pressure and morphologic changes at open lung biopsy, a large number of hemosiderin-laden macrophages were found at BAL (63).



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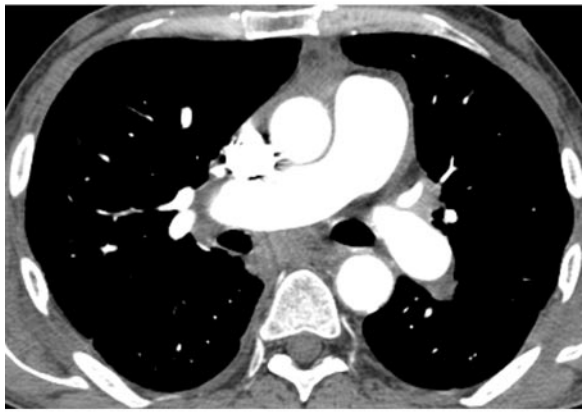
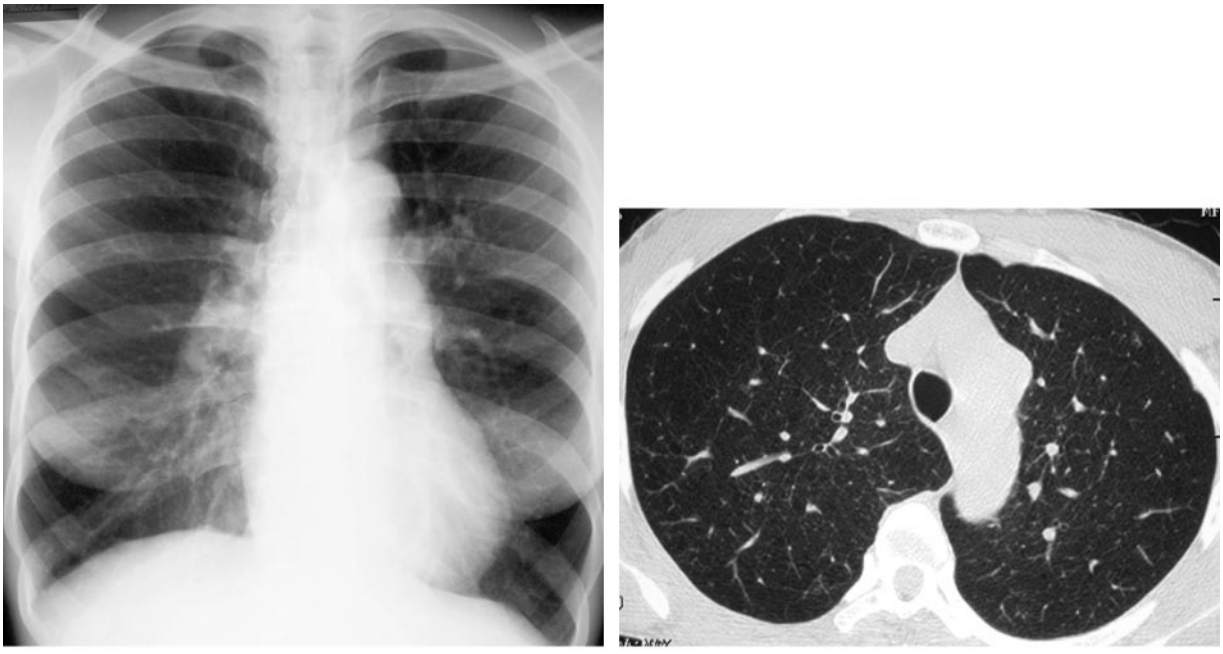


b.

Figure 14. Severe pulmonary hypertension in a 43-year-old man with a history of cocaine abuse. **(a)** Chest radiograph exhibits prominence of the pulmonary arteries. **(b)** Contrast material–enhanced chest CT scan demonstrates dilatation of the main pulmonary arteries.

Emphysema

Pulmonary emphysema, which is characterized by destruction of the alveolar wall as well as permanent enlargement of airspaces distal to the terminal bronchioles, has been reported in 2%–4% of intravenous drug abusers, with an upper lobe predominance and typically affecting young males (64,65). This "precocious" emphysema is a well-known complication of intravenous drug abuse (Fig 15) and is associated in particular with methylphenidate injection (66). Few reports have also mentioned the severe bullous changes associated with cocaine smoking. The pathogenesis of this condition is uncertain but may involve synergism between cigarette smoke, direct toxic effects of the drug, and other combustion products of the smoked mixture (67). The typical distribution of these bullous formations is in the upper lobes of both lungs, especially in the periphery, which re-



a. b.

Figure 15. Advanced emphysema in a relatively young (36-year-old) woman with a history of heavy cocaine abuse and unrelated mitral valve disease. **(a)** Chest radiograph demonstrates hyperinflation of the lungs and signs of pulmonary hypertension. Note the predominance of hyperlucency in the upper lung regions, a finding that suggests a more severe upper lobe disease. **(b)** Chest CT scan reveals diffuse advanced emphysema.

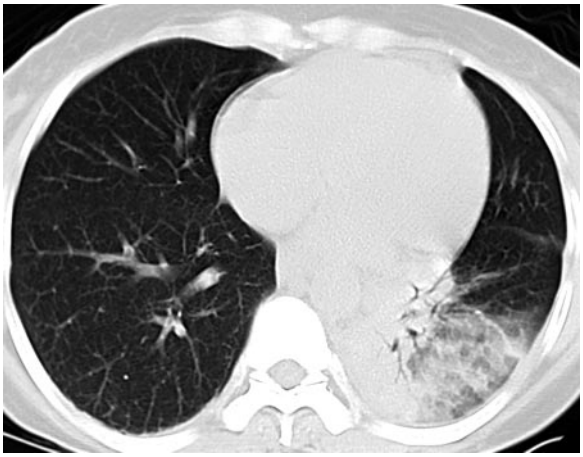


Figure 16. Pneumonia in a cocaine abuser who presented with chest pain, cough, and fever. Chest CT scan demonstrates heterogeneous opacities in the left lower lobe. Posttreatment follow-up CT demonstrated resolution of these opacities.

sults in sparing of the medullary or central portion of the lungs. Pathologic examination of lung biopsy specimens demonstrates intra- and extravascular foreign bodies, angiothrombosis, and areas of acute and chronic inflammation adjacent to the emphysematous bullae (68).

Infection and Aspiration Pneumonia

Septic pulmonary embolism and community-acquired pneumonia are among the most common pulmonary complications seen in intravenous drug abusers (23.5% and 19.6% of cases, respectively) (Fig 16) (69). Smoking of marijuana or crack cocaine alters alveolar macrophage function and cytokine production, severely limiting their ability to kill bacteria and prevent tumor cell growth. Alveolar macrophages in individuals who smoke these substances cannot properly use nitric oxide as an antibacterial agent or molecule, which enhances susceptibility to infectious diseases,

cancer, and acquired immunodeficiency syndrome (AIDS) (70). Crack users have abnormally large amounts of iron and ferritin in the lower respiratory tract secondary to occult alveolar hemorrhage, both within alveolar macrophages and in alveolar epithelial lining fluid, which may contribute to these reported alterations in alveolar macrophage function (16).

Altered mental status ranging from psychosis to coma is commonly reported (27.4% of cases) in acute and chronic cocaine users seeking medical care in emergency departments (71). Central nervous system depression, a common consequence of using certain illicit drugs, particularly opiates, increases the risk for aspiration pneumonia, which characteristically affects the dependent regions of the lungs, especially the superior segments of the lower lobes and the apical and posterior segments of the upper lobes, with a higher prevalence in the right lung. Aspiration pneumonia may manifest radiologically as variable degrees of airspace opacity, with scarring and bronchiectasis in chronic and recurrent cases.

Smoking illicit drugs such as marijuana and crack cocaine has been proved to increase the risk of bacterial pneumonia among human immunodeficiency virus (HIV)–seropositive users of injected drugs (72). In addition, the close association between drug addiction, concomitant use of other intoxicants (especially alcohol), overcrowding, HIV-AIDS, and poor nutrition explains why infections like tuberculosis and sexually transmitted diseases are prevalent in almost epidemic proportions in crack houses located in poor urban areas (73).

Tumors

As with tobacco, marijuana and cocaine smoking have been found to produce a carcinogenic effect on the bronchial epithelium (Fig 17). Several molecular abnormalities (Ki-67, a marker of cell proliferation; epidermal growth factor receptor; globular actin; DNA ploidy) have been demonstrated in the bronchial mucosa of persons who smoke these illicit substances, which suggests that these persons are at an increased risk for the subsequent development of lung cancer (74). In addition, histopathologic abnormalities such as basal cell hyperplasia, stratification, increased nuclear-cytoplasmic ratio, and squamous cell metaplasia—all of which are considered to be precursors of malignancy—have been found substantially more frequently in the lungs of individuals who smoke marijuana and crack cocaine, especially when smoked in conjunction with tobacco, which may have a synergistic effect in the induction of these changes. A solitary fibrous tumor of the nasal cavity in a patient with a long-standing history of cocaine inhalation has also been reported. Chronic irritation with repeated vasoconstriction and vasodilatation as well as chronic inflammation from irritants and solvents have been suggested as contributing factors (75). Nevertheless, further studies are required to clarify the role of cocaine in carcinogenesis.

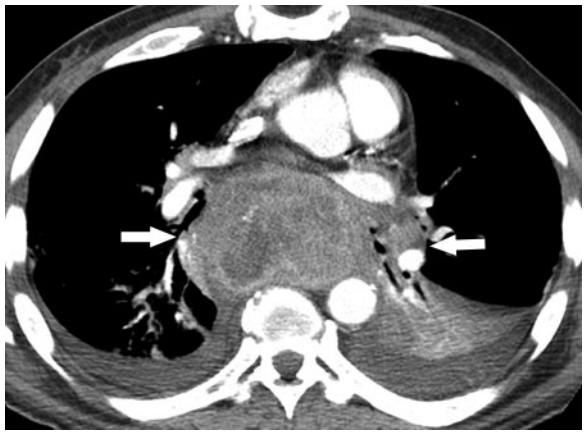


Figure 17. Non–small cell lung cancer in a patient with a 20-year history of crack cocaine abuse. CT scan shows a large, heterogeneous subcarinal and retrocardiac mass with enlarged hilar lymph nodes (arrows).

Conclusions

It is important that radiologists be familiar with the various pleuropulmonary complications associated with illicit drug abuse. In particular, correct diagnosis and appropriate treatment planning in a patient with respiratory manifestations associated with cocaine abuse require familiarity with the wide spectrum of pathologic conditions associated with such abuse, which represents one of the most serious medical and social problems of our time.

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RadioGraphics

Pulmonary Complications from Cocaine and Cocaine-based Substances: Imaging Manifestations

Carlos S. Restrepo, MD et al

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Page 942
Cocaine is the most commonly used illicit drug among patients seen in hospital emergency departments and the most frequent cause of drug-related deaths reported by medical examiners.

Page 944
Cardiopulmonary complaints are the most common manifestation of disease in patients seeking treatment for acute or chronic cocaine-associated medical problems (56% of cases). Among these cardiopulmonary complaints, chest pain is the most common (16).

Page 946
The pathogenesis of cocaine-induced pulmonary edema is complex and multifactorial. Myocardial ischemia and infarction, myocardial dysfunction, arrhythmia, and dilated cardiomyopathy may be contributing factors in cardiogenic edema. Damage to the pulmonary capillary endothelium with increased permeability may play a role in noncardiogenic edema (36).

Page 949
The drug is crushed, dissolved in water, and injected intravenously, resulting in embolism caused by tiny particles of talc that lodge in the pulmonary vascular bed and the interstitium, where they produce a foreign-body granulomatous reaction and fibrosis.

Page 952
Pulmonary vascular abnormalities manifesting as medial hypertrophy of the muscular pulmonary arteries and involving both small and medium-sized arteries has been demonstrated at 20% of autopsies of victims of cocaine-related death, despite the young age of these individuals (35).