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High-Resolution Computed Tomographic Findings of Cocaine-Induced Pulmonary Disease: A State of the Art Review

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Abstract Cocaine is the most commonly used illicit drug among patients presenting at hospital emergency departments and the most frequent cause of drug-related deaths reported by medical examiners. Various respiratory problems temporally associated with cocaine use have been reported. Acute and chronic uses also are responsible for lung complications, such as pulmonary edema, alveolar hemorrhage, pulmonary hypertension, organizing pneumonia, emphysema, barotrauma, infection, cancer, eosinophilic disease, and aspiration pneumonia. Although most imaging findings are nonspecific, they may raise suspicion of a cocaine-related etiology when considered together with patients' profiles and medical histories. This literature review describes cocaine-induced diseases with pulmonary involvement, with an emphasis on high-resolution chest computed tomographic findings and patterns.

Keywords Cocaine · Drug abusers · Pulmonary diseases · Computed tomography

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Introduction

Cocaine is an alkaloid found in coca leaves, which belong to the Erythroxylaceae family [1]. It is the second most commonly used and trafficked illicit drug, after cannabis [2]. According to the United Nations Office on Drugs and Crime, 0.3–0.4 % of the global population aged 15–64 years reported having used cocaine at least once in 2012. The prevalence of users in the Americas (1.2 %) is similar to that in Europe [2].

Cocaine is the most commonly used illicit drug among patients presenting at hospital emergency departments and the most frequent cause of drug-related deaths reported by medical examiners [1, 3]. Various respiratory problems temporally associated with cocaine use have been reported [4]. Acute and chronic uses also are responsible for a variety of lung complications [4]. Local or systemic pharmaceutical effects of cocaine may cause changes in the respiratory tract [5]. The diagnosis of cocaine-induced pulmonary diseases remains challenging for clinicians and radiologists, especially in urban hospitals.

Although some articles have reported the findings of cocaine-induced disease on chest radiographs, few studies

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have specifically described computed tomographic findings in this group of patients. In this literature review, we describe cocaine-induced diseases with pulmonary involvement, with an emphasis on chest high-resolution chest computed tomographic (HRCT) findings and patterns.

The Drug

The main routes of cocaine administration are intranasal (snorting), intravenous (injecting), and inhalation (freebase or crack cocaine smoking) [3]. Coca leaves are soaked in a solvent, such as kerosene, until they form a paste, and then treated with hydrochloric acid to produce cocaine hydrochloride salt, which is water soluble and yields a crystalline white powder upon dehydration [1]. This powder is the most common presentation of the drug and it is not smokable because it decomposes at high temperatures [1]. Freebase and crack cocaine are obtained by different methods but have the same chemical form [1]. They are lipid-soluble and resistant to thermal degradation, so that they can be smoked; their rapid absorption via the pulmonary circulation has a near-instantaneous euphoric effect [4]. Because of this property, crack cocaine smoking has largely replaced other forms of recreational cocaine use [4]. The name "crack" is onomatopoeic for the sound that the substance makes when heated [3].

Adulterants are added to cocaine to increase the drug's perceived potency, volume, or toxicity [1]. Adulterants comprise more than 50 % of the cocaine sold on the street [1]. The most frequent adulterants are local anesthetics (lidocaine, benzocaine), sugars (mannitol, lactose, sucrose), stimulants (caffeine, ephedrine), toxins (quinine, strychnine) and other substances (e.g., flour, calcium, aspirin, plaster, levamisole, phenacetin, paracetamol, hydroxyzine), and inert compounds (e.g., inositol, talc, cornstarch, silica) [1]. A highly impure form of cocaine paste known as "bazuco" consists of a crude extract of coca leaves mixed with other substances, such as water, kerosene, gasoline, sulfuric acid, flour, sand, talc, and/or sugar [1].

Cocaine's Mechanism of Injury to the Lung

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 (e.g., tobacco, heroin, talc, silica, cellulose, levamisole) [6]. When applied locally, cocaine acts as an anesthetic, because it blocks the initiation and transmission of electrical impulses [3]. When systemically administered, cocaine affects synaptic transmission, blocking the presynaptic reuptake of norepinephrine and dopamine, and acting as a potent sympathomimetic agent [3]. This mechanism is important pathophysiologically in cardiovascular complications (e.g., myocardial ischemia, infarction, dysfunction; arrhythmia), which may be causative factors in cardiogenic pulmonary edema [3].

The presence of innervated adrenergic receptors in pulmonary vascular smooth muscle has been described, and cocaine administration has been found to increase pulmonary vascular tone [5, 6], manifesting as repeated elevations in pulmonary arterial pressure. Its vasoconstrictive effect can mimic pulmonary embolism in a crack cocaine smoker, caused by intense pulmonary artery (PA) vasospasm [7] and may cause anoxic lung injury and pulmonary infarction [8]. Damage to the pulmonary microvasculature increases the release of endothelin-1 (ET-1) in the microenvironment. ET-1 aids vasoconstriction and the passage of fluid and erythrocytes from injured pulmonary capillaries into alveoli [9]. This mechanism may underlie alveolar hemorrhage and non-cardiogenic pulmonary edema [4]. Furthermore, when crushed oral medications are dissolved and injected intravenously, talc particles embolize small pulmonary vessels, resulting in more occlusion, and then migrate into the pulmonary interstitium, where they induce a foreign-body reaction and fibrosis that can manifest as interstitial lung disease [10]. All of these factors together can explain the development of pulmonary hypertension [10].

Short-term exposure to cocaine has been shown to induce severe bursts of acute inflammatory activity by activating polymorphonuclear neutrophils and their ability to produce interleukin-8, which can cause "crack lung" syndrome [4]. The cumulative effects of these events may contribute to chronic lung damage, characterized by airway-centered interstitial fibrosis and metaplastic bronchiolar epithelium in the spectrum of organizing pneumonia [4]. Ongoing damage can cause destruction of the alveolar wall and permanent enlargement of airspaces distal to the terminal bronchioles, resulting in pulmonary bullous emphysema [3].

Injury caused by the inhalation of chemical byproducts transported in smoke and/or intratracheal combustion of solvents, facilitated by the local anesthetic effect of cocaine in the airways, can lead to severe reactive stenosis [11]. The potent effect of cocaine also may cause necrosis around the mucous membranes in the larynx and perforation [12].

Cocaine primarily affects the ability of pulmonary alveolar macrophages to kill bacteria and tumor cells, possibly by suppressing their ability to generate reactive intermediate molecules, such as nitric oxide [4]. Potential

clinical consequences of this effect may include enhanced susceptibility to infectious disease, cancer, and acquired immunodeficiency syndrome (AIDS) [4]. Nonsterile injection techniques may cause bacteremia, predisposing individuals to tricuspid valve endocarditis or septic thrombophlebitis, and recurrent septic embolization may occur [10].

Clinical Pulmonary Manifestations of Cocaine

"Crack Lung"

The term "crack lung" refers to an acute pulmonary syndrome occurring after the inhalation of freebase cocaine and is associated with fever, hypoxemia, hemoptysis, respiratory failure, and diffuse, eosinophil-rich alveolar infiltrates [3]. Because pulmonary hemorrhage, hypersensitivity pneumonitis, eosinophilic disease, and acute respiratory distress syndrome can be radiographically indistinguishable, the development of respiratory failure with increased opacity in bilateral airspace areas that appears shortly after crack use and clears rapidly after its cessation has been termed "crack lung" [10].

At autopsy, cocaine use is associated with alveolar hemorrhage, the presence of hemosiderin-laden macrophages from previous hemorrhage, congestion and edema, pneumonitis, and interstitial fibrosis. Small-artery medial hypertrophy also may be present. The prominence of intraalveolar macrophages gives the lung an anthracotic appearance [13].

Pulmonary Edema

Cardiogenic and noncardiogenic pulmonary edema has been reported in association with intravenous cocaine abuse and crack cocaine smoking [3].

Cardiogenic Edema

Two radiological phases are recognized in the development of pressure edema: interstitial edema and alveolar edema [14]. The intensity and duration of both phases are determined by the hydrostatic-oncotic pressure ratio [14]. Interstitial edema occurs with an increase of 15–25 mm/Hg in mean transmural arterial pressure (mTAP), appearing on HRCT as smooth thickening of bronchovascular bundles and interlobular septa, and opacities with ground-glass attenuation, which predominate in perihilar regions [15]. mTAP increases >25 mmHg cause the sudden extension of edema into alveolar spaces, manifesting on HRCT as areas of ground-glass opacity and consolidations with a distribution pattern sparing the cortical regions [15] (Fig. 1).

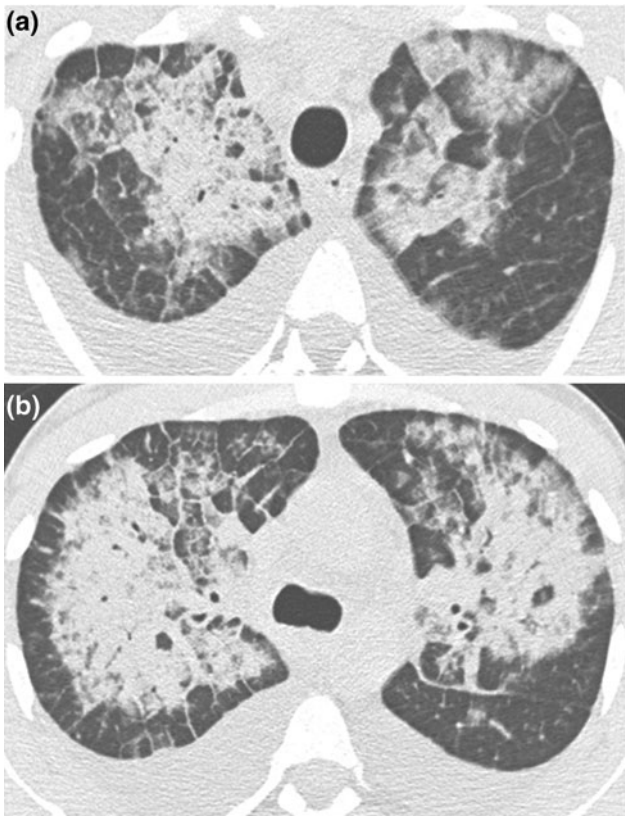

Fig. 1 Acute pulmonary edema in a 29-year-old man presenting with cough, black sputum, and hemoptysis after 9 months of cocaine use. Chest HRCT images (**a**, **b**) show ground-glass opacities associated with smooth interlobular septal thickening (*crazy-paving pattern*) and bilateral pleural effusion. Note in **b** the perihilar distribution of the lesions, with peripheral regions spared

Pleural effusion and increased blood vessel diameter in the upper lobes also may be found [10]. Cardiomegaly may occur, but heart size often is normal because cocaine-induced cardiogenic edema usually involves the acute failure of cardiac function [14].

Noncardiogenic Edema/Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome or noncardiogenic edema is not caused or influenced by concurrent cardiac insufficiency and thus occurs with no increase in pulmonary capillary pressure [14]. This form of edema manifests on HRCT as heterogeneous parenchymal changes. The typical pattern is airspace opacification and inhomogeneous ground-glass appearance, with standard geographical distribution and usually without pleural effusion or cardiomegaly. HRCT also may show diffuse multifocal ground-glass attenuation associated with septal thickening, forming the "crazy-paving" pattern [14].

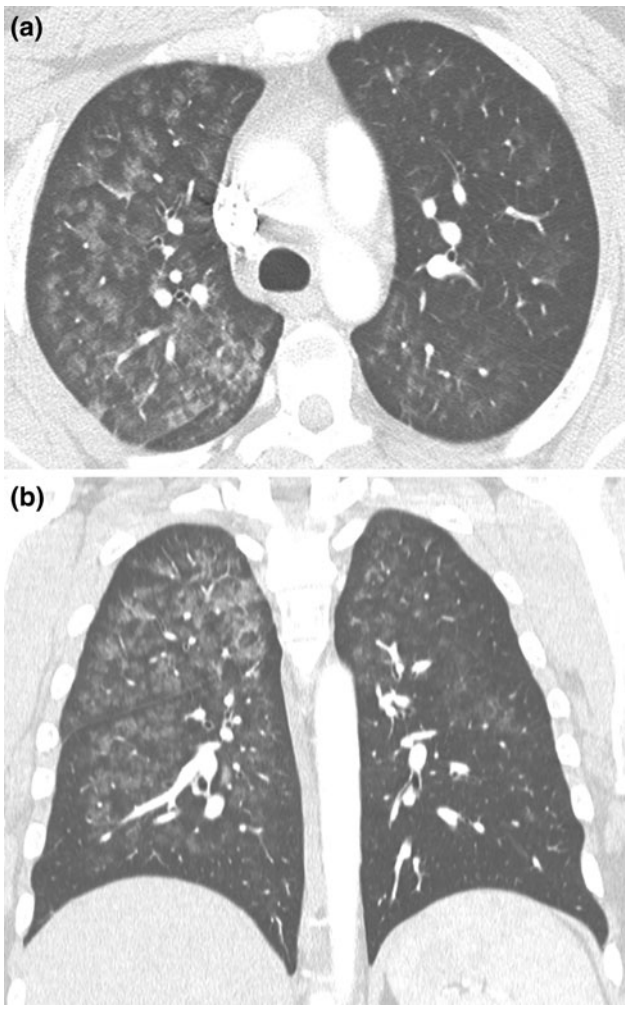

Fig. 2 Pulmonary hemorrhage in a 32-year-old man who presented with hemoptysis after 3 months of crack cocaine use. Axial (**a**) and coronal (**b**) HRCT images show areas of ground-glass opacity with centrilobular distribution, predominantly in the right lung

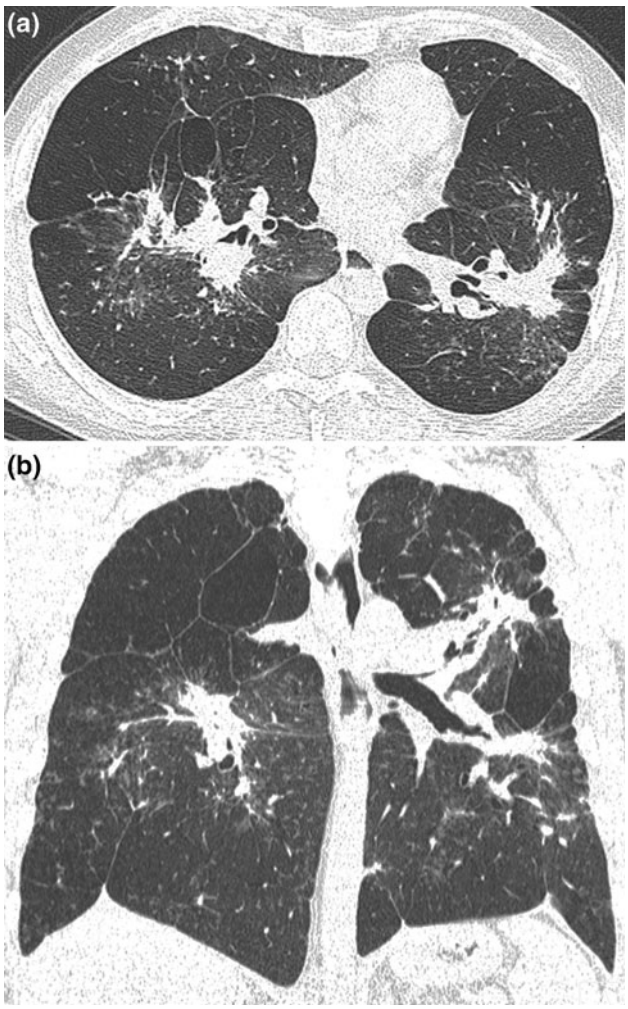

Fig. 3 Talcosis in a 35-year-old man following chronic cocaine injection. Chest X-ray (**a**) shows pulmonary hyperinsufflation and parenchymal opacities with perihilar predominance. HRCT (**b**) shows hypertransparent areas corresponding to emphysema with bullous formations and irregular, conglomerated masses with architectural distortion. Small nodules also are visible

Alveolar Hemorrhage

Cocaine is the most common toxic cause of acute diffuse pulmonary hemorrhage [16]. It may be accompanied by hemoptysis, and occult pulmonary hemorrhage is most common [3]. Levamisole is an immunomodulatory agent previously used to treat cancer. It was removed from the United States market in 2000 because of the common occurrence of agranulocytosis, and its usage is currently restricted to the treatment of parasitosis [17]. It is used illicitly as a cocaine adulterant or bulking agent and has been shown to induce neutrophil mobility and chemotaxis, dendritic cell maturation, T cell proliferation, and circulating autoantibodies [18]. These effects on innate and adaptive immune responses may explain the propensity to induce autoimmunity and vasculitis [18]. McGrath et al. [18] proposed that the clinical syndrome, which includes pulmonary hemorrhage and the presence of antineutrophil cytoplasmic antibodies and the antibody against myeloperoxidase, has arisen due to exposure to levamisole in combination with cocaine. The authors commented that cocaine alone can reportedly induce autoimmunity in the presence of the first antibody but that no report has described a relationship with the second antibody, and the presence of both suggests an association between the two substances [18]. Cocaine abuse can mimic primary systemic vasculitis and seems to be able to induce vasculitis, such as Churg–Strauss [19] or Goodpasture syndrome, which also occur with pulmonary bleeding [19]. Pulmonary hemorrhage manifests on HRCT as ground-glass opacities that may be associated with interlobular septal thickening (crazy-paving pattern; Fig. 2). Centrilobular nodules, in some cases with a tree-in-bud pattern, also may be observed [19].

Interstitial Disease

Talc, silica, and other adulterants are added to cocaine sold on the street [4]. When these inert components are inhaled or smoked, they reach the lower airways and may cause interstitial lung disease [10]. Cellulose granulomatosis is a foreign body granulomatosis from microcrystalline cellulose [20]. It is associated with cocaine inhalation and appears on HRCT as bilateral pulmonary micronodules, often with centrilobular distribution or a tree-in-bud appearance, with subsequent progression to conglomerate nodules that resemble progressive foreign-body granulomas [20]. Similarly, interstitial pneumonitis with extensive accumulation of free silica in histiocytes associated with interstitial fibrosis has been reported in crack cocaine smokers and "sniffers" and may induce the formation of abnormally enlarged lymph nodes with increased serum levels of angiotensin-converting enzyme, manifesting as a syndrome that mimics sarcoidosis [21].

Talc (magnesium silicate) is an insoluble filler used in several oral medications; the inhalation, smoking, or intravenous injection of cocaine adulterated with talc may cause pulmonary disease [10]. Talc inhalation may appear on HRCT as centrilobular or subpleural nodules, conglomerate masses in the upper lobes (Fig. 3), sometimes with high density, and hilar and/or mediastinal lymphadenopathy, which also may contain foci of high attenuation [22]. Injection talcosis can manifest in several patterns on HRCT, including numerous diffuse small nodules with high attenuation and areas of ground-glass attenuation, panacinar emphysema with lower-lobe predominance, and conglomerate perihilar masses [22].

Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is a rare and progressive disease that often leads to right heart failure and premature death. PAH associated with cocaine exposure is a well-recognized subgroup of the disease [23]. The majority of human immunodeficiency virus (HIV)-associated PAH cases occur in individuals with histories of intravenous drug use [24]. The HRCT findings of pulmonary hypertension are marked enlargement of the main PA, prominent interlobar arteries, and the relative paucity of peripheral vascularity. The lung window can show mosaic attenuation, characterized by patchy geographic areas of ground-glass attenuation containing dilated vessels (hyperemia) and areas of decreased attenuation showing minimal vascularity (oligemia) [25]. Contrast-enhanced CT may show dilatation (>29 mm) of the main PA, measured transversely at the level of PA bifurcation on an axial image (mediastinal window); the ratio of PA diameter to ascending aorta diameter exceeds 1 [25].

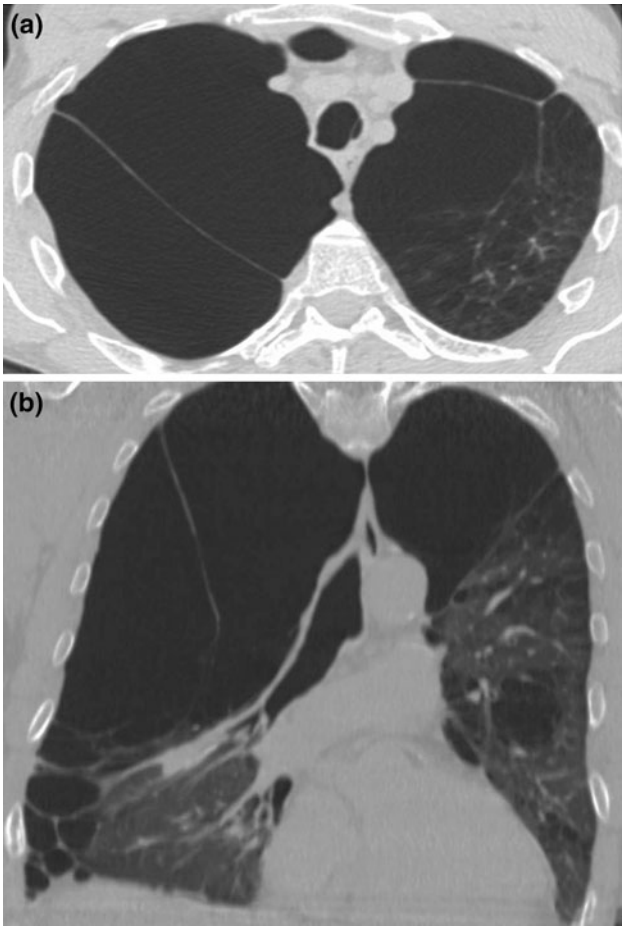

Fig. 4 Bullous emphysema in a 29-year-old male cocaine smoker with dyspnea. Chest HRCT images (**a**, **b**) show *large bullous* formations in the *upper* lobes

Organizing Pneumonia

Organizing pneumonia has been reported in young crack cocaine smokers [26]. HRCT manifestations consist of peribronchovascular interstitial thickening and traction bronchiectasis with thickened airway walls, fibrosis, and a restrictive appearance with small lung fields [3].

Emphysema

Emphysema has been reported in intravenous drug users and typically affects young males [3]. A few reports also have mentioned severe bullous changes associated with cocaine smoking [3]. HRCT reveals bullae and centrilobular emphysema in the upper lobes of both lungs, especially in the periphery and sparing the medullary or central portions of the lungs [3] (Fig. 4). The intravenous abuse of methylphenidate has been connected to the development of a specific pattern of lower-lobe panacinar emphysema [22],

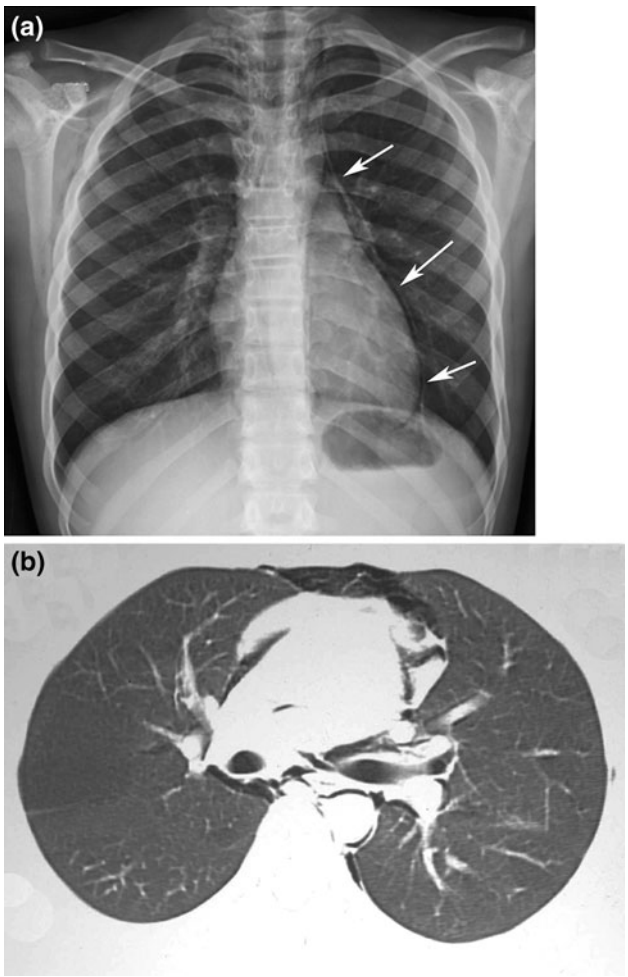

Fig. 5 Pneumomediastinum in a 23-year-old man who had smoked crack cocaine. The patient presented with chest pain and had no history of trauma. **a** Chest X-ray shows a lucent line (*arrows*) extending into the *left* mediastinum. **b** HRCT reveals free air dissecting the mediastinal structures, bronchi, and pulmonary vessels

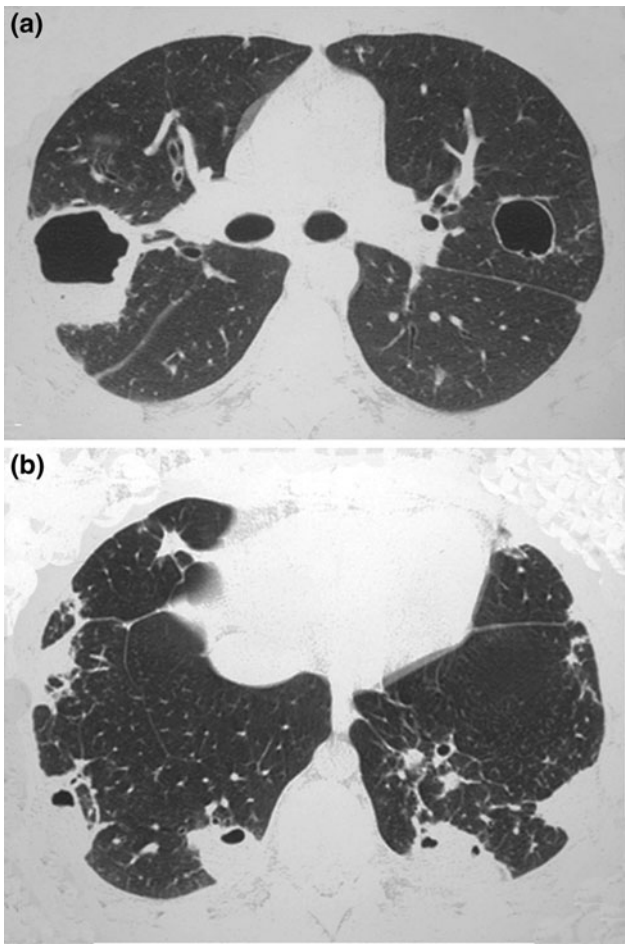

Fig. 6 Pulmonary embolism in a 20-year-old male injected cocaine user with fever, cough, purulent sputum, and hemoptysis. **a** Chest X-ray shows peripheral opacities, some of which are cavitated with air-fluid levels. **b**, **c** HRCT images show cavitated nodules predominating in the peripheral regions of the lungs

although whether it is related mostly to the presence of talc or methylphenidate remains unclear [27]. The occurrence of this pattern in association with the use of other talc-containing drugs, such as cocaine, is possible [28].

Barotrauma

Barotrauma is a well-known complication of crack cocaine smoking and powdered cocaine inhalation [29]. It can manifest as pneumothorax, pneumomediastinum, pneumopericardium, or subcutaneous emphysema [3]. In cocaine users, an increase in pressure is believed to occur after smoking due to forceful coughing or intentional production of a Valsalva maneuver to increase the absorption and maximize the effect of the drug [29]. When alveoli become overdistended against a closed glottis, they may rupture into the interstitium and eventually into the mediastinum, producing pneumomediastinum [10] (Fig. 5). Forceful "snorting" following nasal insufflation of cocaine is believed to cause pneumomediastinum by a similar mechanism [29]. Barotrauma is usually diagnosed with chest radiographs, but chest HRCT can aid diagnosis when chest radiography is inconclusive [30]. Typically, HRCT is performed to evaluate mediastinal fluid collections or hematoma, possible tamponade of the heart or vessels, or small pneumothoraces poorly visualized on chest radiographs [31], but this modality also may show associated parenchymal opacities and pulmonary interstitial emphysema due to alveolar rupture [3]. In young individuals, the presence of mediastinal air in the absence of a history of other etiological factors should raise suspicion of free-based cocaine use [31].

Infection

Septic pulmonary embolism and community-acquired pneumonia are among the most common pulmonary complications seen in intravenous drug users [3]. HIV-related diseases are closely associated with cocaine abuse, especially in intravenous drug users and those who barter sex for drugs [6]. The close associations among drug addiction, concomitant use of other intoxicants (especially alcohol), overcrowding, AIDS, and poor nutrition explain the almost epidemic prevalence of infections, such as tuberculosis and sexually transmitted diseases, in crack houses in poor urban areas [3]. Mechanisms increasing the prevalence of infection in intravenous cocaine users may include the use of contaminated drugs and needles, skin colonization by unusual or virulent organisms from previous hospitalizations, and changes in normal bacterial flora due to self-medication with antibiotics [10]. The tomographic patterns of community-acquired pneumonia can be variable and often are related to the causative agent [32]. Septic emboli characteristically appear on HRCT as multiple, ill-defined, peripherally distributed lung nodules in various phases of excavation and may exhibit areas of septic infarction [10] (Fig. 6). Moreover, cocaine-induced, pulmonary embolization may be associated with exudative pleural or pericardial effusions [33].

Lung Cancer

As with tobacco, marijuana and cocaine smoking have been found to produce a carcinogenic effect on the bronchial epithelium, and this effect is synergic when the two drugs are smoked in conjunction [3].

Eosinophilic Disease

Eosinophilic lung disease is known to be associated with cocaine inhalation and can affect the airways, pleural surface, vasculature, or lung parenchyma [3]. Affected patients usually have pulmonary eosinophilia, detected by BAL, and varying degrees of peripheral eosinophilia [3]. Eosinophilic pneumonia specifically affects the lung parenchyma [34]. HRCT may show diffuse areas of ground-glass attenuation, sometimes with well-defined nodular changes with patchy and random distribution or peripheral predominance [34]. Pleural effusions are common, with eosinophilia in pleural fluid. Eosinophilic "empyema" associated with eosinophilic pneumonitis secondary to crack cocaine smoking has also been reported [35]. When the onset is in the vessels, cocaine use can cause Churg–Strauss vasculitis and excavation areas can be seen on imaging studies [36]. When the onset is in the airways, it causes bronchial hyperreactivity or asthma. A temporal association between heavy crack use and severe acute exacerbation of asthma, including fatal asthma, has been reported [37]. The relationship between the combined use of heroin and cocaine and the development of bronchial hyperreactivity also is well established [38]. This mixture also has specific features, such as the use of ammonia in the preparation of freebase cocaine and the inhalation of the drugs on aluminum foil, known as "rebujo" [38]. HRCT can be normal or show lung hyperinflation signs. It can show increased pulmonary volume and bronchial wall thickening with patchy parenchymal opacities, resulting in the mosaic attenuation pattern, which usually changes over time [3]. Atelectasis also may occur [3].

Aspiration Pneumonia

Another consequence of the combined use of cocaine and heroin, or other opioids, is aspiration pneumonia [15]. Drug users are susceptible to this disease because central nervous system depression impairs airway protection [15]. HRCT reveals consolidations, ground-glass opacities, and airspace nodules in dependent regions of lung tissue, particularly the superior segments of the lower lobes and the apical and posterior segments of the upper lobes, especially when the aspiration event occurs while the patient is recumbent [10]. Atelectasis also may occur [10].

Lipoid Pneumonia

Gurell et al. [39] described lipoid pneumonia in a crack cocaine user who mixed the drug with petroleum jelly to make it last longer. Chest HRCT typically shows ground-glass opacities that may be associated with smooth thickening of interlobular septal and interlobular lines (crazy-paving pattern) and/or consolidations, which may show fat attenuation [39].

Conclusions

Although most HRCT findings of cocaine-induced pulmonary disease are nonspecific, they may raise suspicion of a cocaine-related etiology when considered together with patients' profiles and medical histories. For example, spontaneous barotrauma and pulmonary hemorrhage in a young patient presenting at an emergency department with no history of infection or trauma should prompt the clinician to inquire about drug abuse. Similarly, unusually large bullous emphysema in a young patient, especially with upper lobe predominance, quickly prompts suspicion of illicit drug smoking. The value of this information lies in the reversibility of some cocaine-induced lung injuries with discontinuation of the drug and/or treatment with

corticosteroids. HRCT aids the differentiation of findings that are nonspecific on chest radiographs and the diagnosis of parenchymal abnormalities in symptomatic patients with normal or inconclusive chest radiographs. Thorough knowledge of the spectrum of HRCT findings in cocaine-induced pulmonary disease can result in efficient management of this illness of modern society.

Conflict of interest None.

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