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Case Report

Alveolar hemorrhage associated with cocaine consumption

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ABSTRACT

Cocaine is an illegal drug; its abuse and toxicity are a public health problem due to its high morbidity and mortality. Cocaine can affect the cardiovascular, central nervous and respiratory systems. The case of a 42-year-old male without history of chronic or degenerative diseases, but previous cocaine consumption is presented in this report. The patient is admitted to the Emergency Department given that the clinical presentation included hemoptysis and dyspnea with mild to minimal activity, which evolved to orthopnea. Advanced airway management was required and supportive care at the Intensive Care Unit was provided. Imaging studies showed evidence compatible with alveolar hemorrhage diagnosis. In search of an autoimmune etiology, an antibody-screening panel was requested, reporting negative results for autoimmune disorders. The patient management was based on corticosteroid therapy and plasmapheresis to counter the persistent hemoptysis and hemoglobin serum level decline. The management strategy was based on the clinical suspicion of vasculitis and a torpid clinical evolution. Pulmonary sepsis ensued, resulting in patient's death. The necropsy report describes the primary cause of death as diffuse alveolar hemorrhage secondary to diffuse alveolar injury. This case report presents the detailed clinical, imagining and histopathological findings of a patient with alveolar hemorrhage secondary to cocaine consumption, as well as a review of the literature.

Introduction

Alveolar hemorrhage (AH) is a clinical and pathological syndrome characterized by generalized extravasation of red blood cells into the alveolar space. AH is the most common clinical manifestation of pulmonary vasculitis. Among the clinical manifestations are hemoptysis and anemia, as well as respiratory failure. Imaging studies, chest x-ray and/or computed tomography, show evidence of a diffuse alveolar infiltrate. Both autoimmune and non-autoimmune etiologies (e.g. pharmacologic toxicity, infections, idiopathic, and secondary to cocaine use) have been described in the literature. In regards to cocaine-induced AH, acute respiratory symptoms develop within hours of use and include the following: 1) a productive cough; 2) chest pain with or without respiratory distress; 3) hemoptysis; and 4) asthma exacerbation. These symptoms are more common with the continuous use of cocaine.[1] We present the case of a patient who developed AH associated with cocaine consumption; diagnosed clinically and with the assistance of laboratory and imaging studies. AH is an infrequent pathology; nonetheless, it must be considered among patients with hemoptysis and cocaine consumption. Other etiologies must be excluded (e.g. vasculitis, bleeding disorders, idiopathic) and the use of glucocorticoids is controversial. The patient did not respond to glucocorticoid therapy, contrary to other reports.[2] The main aim of reporting this case is to provide evidence of a patient that had a torpid evolution refractory to glucocorticoid therapy resulting in his death.

Case presentation

A 42-year-old male arrived at the Emergency Department complaining of localized pleuritic chest pain with an intensity of 6/10

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on the visual analog scale for pain (VAS). The patient reported hemoptysis on several occasions, profuse diaphoresis, and dyspnea with mild to minimal activity six hours prior to admission. The patient did not allude to any exacerbating or mitigating causes. The patient was resident of León, Guanajuato, Mexico, single, a construction worker, and had not completed elementary school but was literate, as educational attainment. The patient's family history included a mother with type 2 diabetes and arterial hypertension; other relevant aspects of family history were questioned and denied. Among the patient's personal history, he reported alcohol abuse and tobacco consumption for more than 15 years, not being able to quantify the consumption. The patient reported a constant cocaine use but was unable to quantify his usage, having last used hours prior to Emergency Department admission. The patient endorsed the use of industrial solvents such as "Agua celeste" (i.e. heavenly water, the street name for a sky-blue colored solvent) and adhesives; the patient was unable to specify the quantity and length of use. The patient denied a history of allergies, blood transfusions, recent travel, tattoos, and piercings. Two years ago, the patient suffered a mild traumatic brain injury without complications or sequelae. The patient had no history of lung disease, asthma during childhood, chronic or degenerative diseases. Twenty-four hours after admission, the patient developed type one respiratory insufficiency (i.e. vital signs: BP: 120/80 mmHg, HR: 115 bpm, RR: 32 rpm, Temp: 37°C; arterial blood gas test: pH = 7.3, PaO_2 = 55 mmHg, $PaCO_2$ = 25 mmHg, HCO_3^- = 13.9 mEq/L, O_2 content = 70%, Base excess = −11.7 mmol/L), thus requiring invasive artificial airway with an endotracheal tube and admittance to the medical intensive care unit for further test and treatment.

Upon admission, the patient had the following vital signs: BP: 140/70 mmHg; HR: 98 bpm; RR: 28 rpm; SO_2 with noninvasive ventilation at a rate of 3L/min: 90%; Temp: 36°C; weight: 70Kg; height: 170 cm; BMI: 24.2.

Upon initial physical exploration, we found a patient with mucosal and tegumentary paleness, recumbent with freely chosen body position, Glasgow coma score of 15, without focal neurologic deficits nor meningeal sings, aware of his environment, with reference to place, time, and people. Diaphoretic, skin and mucosal membranes dehydrated +/+++, with head and neck exploration without alterations. Upon inspection, the respiratory apparatus with oral ventilation, tachypnea with thoracic and abdominal dissociation. The thorax had decreased expansion without vibrations or fremitus during palpation. No asymmetries or abnormal findings in tone intensity, pitch, duration, and quality through direct percussion. Upon auscultation, disseminated bilateral crepitant crackles and bilateral decreased inspiratory breath sounds at the bases. Precordial auscultation reveals tachycardia, heart sounds of good intensity without extra heart sounds. Abdominal exploration without visceromegaly nor abnormalities upon light and deep palpation. Extremities with filiform pulse augmented in frequency and decreased in amplitude without trophic changes.

Laboratory results at admission are presented in Table 1. Due to the personal history of drug use, the following tests were requested: hepatitis B virus, hepatitis C virus, HIV, and urinalysis for benzodiazepines, barbiturates, cannabis, cocaine, methamphetamines, and opiates; all results except urinalysis for cocaine metabolites were reported as negative. In search of an autoimmune etiology, the following tests were requested: Antineutrophil cytoplasmic antibodies (ANCA), cytoplasmic (cANCA) 0.1 (negative), perinuclear (pANCA) 0.2 (negative), Anti-glomerular basement membrane negative, anti-double-stranded deoxyribonucleic acid 0.9UI/ml, anti-cardiolipin IgM antibody 3.20 U/ml and IgG 3.50 U/ml, cyclic citrullinated peptide antibody <2EU/mL; all reported as negative (Table 2).

Table 1
Laboratory test results upon admission the Emergency Department

Full Blood Count	
Hemoglobin at admission	17.40 g/dL
Hematocrit	51.6%
Erythrocyte count	5.64×10^6 µL
Platelet count	279,000 µL
Mean corpuscular volume	91.40 fL
Mean corpuscular hemoglobin concentration	33.70g/dL
Leukocyte count	35,000 µL
Neutrophils	94.3%
Lymphocytes	3.1%
Monocytes	2.5%
Eosinophils	0.1%
Blood Chemistry	
Glucose	134.40 mg/dL
Creatinine	2.67 mg/dL
Urea nitrogen	88 mg/dL
Blood urea nitrogen	40.92 mg/dL
BUN/creatinine ratio	15.3
Uric acid	6.15 mg/dL
Cholesterol	150 mg/dL
Triglycerides	153 mg/dL
Liver Function Enzymes	
Aspartate transaminase	20.40 U/L
Alanine transaminase	20 U/L
Lactate dehydrogenase	965.5 U/L
Albumin	2.2g/dL
Alkaline phosphatase	80 U/L
Gamma-glutamyl transpeptidase	40 U/L
Blood Coagulation	
Prothrombine time	16.7 sec
Partial thromboplastin time	34.4 sec
International normalized ratio	1.2
Electrolytes	
Sodium	143.1 mEq/L
Potassium	5 mEq/L
Chlorine	111.5 mEq/L
Calcium	8.32 mg/dL
Phosphorus	5.5 mg/dL
Magnesium	1.96 mg/dL

Chest X-ray, posterior-anterior projection, shows bilateral alveolar infiltrate at the bases, with left predominance and bilateral progressive diffusion, compatible with ground glass opacification images (Fig. 1). The computed tomography (CT) of the thorax, shows bilateral posterior and inferior lobular involvement at the alveolar level; images compatible with ground glass opacities and air bronchogram (Fig. 2).

Clinical evolution

During the first week, to treat the anemia (8g/dL), the patient was transfused two blood bags, increasing hemoglobin levels to 10.2g/dL. Under the clinical suspicion of an autoimmune disease, three IV boluses of methylprednisolone 1g IV q24h were administered. Subsequently, insertion of a Mahurkar catheter to initiate plasmapheresis was performed (i.e. three sessions). The patient continued with a torpid evolution secondary to active hemorrhage, which required transfusion of two more blood bags, raising hemoglobin levels from 8.3g/dL to 10.5g/dL. A hemodialysis session is conducted as uremia due to secondary hemorrhage was suspected. Ventilation was progressed with extubation after adequate tolerance was established.

During the second week at the ninth day of hospitalization, the patient developed temporal, spatial, and personal disorientation

Table 2
Supplementary laboratory test results

Follow-up	
Hemoglobin at 24 hours	11.7 g/dL
Hemoglobin at 5 days	8 g/dL
Hemoglobin at 5 days after blood transfusion	10.2 g/dL
Hemoglobin at 8 days	8.3 g/dL
Hemoglobin at 8 days after blood transfusion	10.5 g/dL
Hemoglobin at 15 days	8.1 g/dL
Creatinine at 48 hours	3.7 mg/dL
Urea nitrogen at day 15	170 mg/dL
Creatinine at day 15	3.15 mg/dL
Antibodies	
Cytoplasmic antineutrophil cytoplasmatic antibodies (cANCA)	0.1
Perinuclear antineutrophil cytoplasmatic antibodies (pANCA)	0.2
Anti-glomerular basement membrane	Negative
Anti-double-stranded deoxyribonucleic acid	0.9 UI/ml
Anti-cardiolipin IgM antibody	3.20 U/ml
Anti-cardiolipin IgG	3.50 U/ml
Cyclic citrullinated peptide antibody	<2 EU/mL
Viral panel	
Hepatitis B virus	Negative
Hepatitis C virus	Negative
Human immunodeficiency virus	Negative
Urinalysis	
Appearance	Crystalline
pH	6
Specific gravity	1.011
Proteins	100
Ketones, glucose, and nitrite	Negative
Leukocytes	1 per high power field
Erythrocytes	3 per high power field
Bacteria	2 per high power field
Benzodiazepines	Negative
Barbiturates	Negative
Cannabis	Negative
Cocaine	Positive
Methamphetamines	Negative
Opiates	Negative

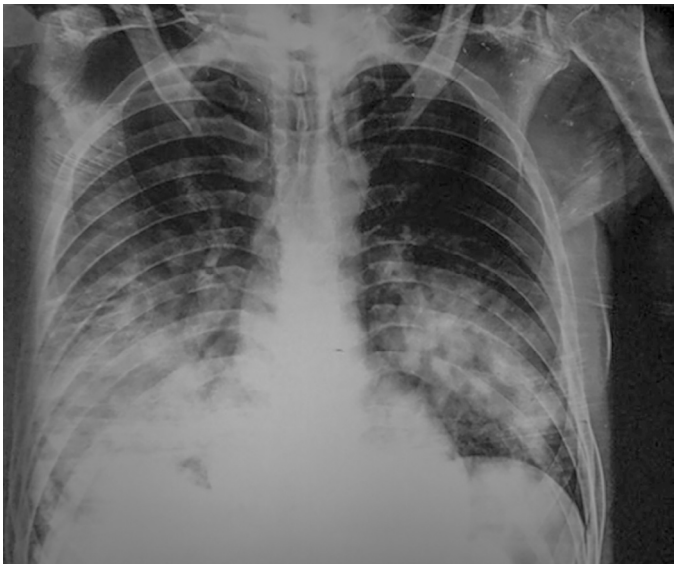

Fig. 1. Chest X-ray. Posterior-anterior projection. Bilateral alveolar infiltrates at the bases, with left predominance and bilateral progressive diffusion, compatible with ground glass opacification images.

without focal neurologic deficits. Polypnea with thoracic and abdominal dissociation elicited reintubation. Persistent fever arose, prompting the implementation of antimicrobial therapy based on clinical suspicion of an infection with pulmonary foci. A hypertensive emergency followed, requiring oral and IV management. On day ten of hospitalization plasmapheresis was initiated. Although laboratory results reported negative antibody count for autoimmune disorders, suspicion of vasculitis remained due to the clinical presentation. Active hemorrhage obliged for the transfusion of one unit of packed red cells and blood derivatives. After isolation of *Enterococcus faecium* from central and peripheral hemocultures, specific antimicrobial therapy was initiated. Two plasmapheresis sessions ensued as result of active alveolar hemorrhage.

During the third week, on day fifteen of hospitalization, tube thoracostomy was performed, placing an endopleural tube on the on the right mid-axillary line due to the presence of pleural effusion. Pleural effusion was examined and the report described the presence of liquid compatible to exudate according to the Light criteria for pleural effusions.[3] Tracheostomy was performed as indicated for prolonged intubation. Since the patient continued with a drop in hemoglobin (8.1g/dL), methylprednisolone was reinitiated. A new hemodialysis session was implemented due to the presence of uremia (i.e. urea nitrogen of 170 mg/dL and creatinine of 3.15 mg/dL). Boluses of methylprednisolone were initiated due to the emergency and severity of the clinical presentation; following the protocol for AH secondary to a probable autoimmune etiology. The patient presented a torpid clinical and paraclinical evolution, thus auxiliary plasmapheresis sessions were added to limit the clinical deterioration. However, due to the persistence of AH, more methylprednisolone boluses were initiated without clinical improvement. The patient continued with a torpid evolution, hence a pulmonary biopsy was requested. Through the histopathological examination of tissue biopsy, the diagnosis was diffuse AH (Fig. 3 and Fig. 4).

On the twentieth day of hospitalization, the patient presented extreme bradycardia (30 BPM), progressing to asystole. Advanced life support protocol was initiated and after 20 minutes without reverting the cardiac arrest; the patient was pronounced deceased. Necropsy examination was performed (Fig. 5). The necropsy report describes the primary cause of death as diffuse alveolar hemorrhage secondary to diffuse alveolar injury. The probable predisposing factor was cocaine consumption. The following findings were concomitant alterations reported in the necropsy report: unspecific acute bronchopneumonia without signs of vasculitis or capillaritis or intraalveolar cocaine crystals; panacinar emphysema; and acute renal failure.

Discussion

Alveolar hemorrhage (AH) is a medical emergency that requires a timely diagnosis and an etiology-specific treatment. Even when AH is appropriately recognized, mortality is high.[4] Symptoms appear throughout the days; however, a subacute onset has also been reported.[5] The clinical presentation involves hemoptysis (i.e. two-thirds of reported cases report it), fever, cough, and dyspnea. Exclusion of common etiologies, as well as the integration of signs, symptoms, blood tests, and auxiliary imaging tests are the basis of the clinical diagnosis. Among the causes of hemoptysis that must be excluded are pneumonia and pulmonary neoplasms.[6,7]

If undiagnosed or treated in a timely manner, diffuse alveolar hemorrhages can have catastrophic results. Small pulmonary vessel vasculitis is the primary source of AH. Alveolar hemorrhages can be classified into three main groups: 1) pauci-immune, generally associated to capillaritis and ANCA positivity; 2) produced by

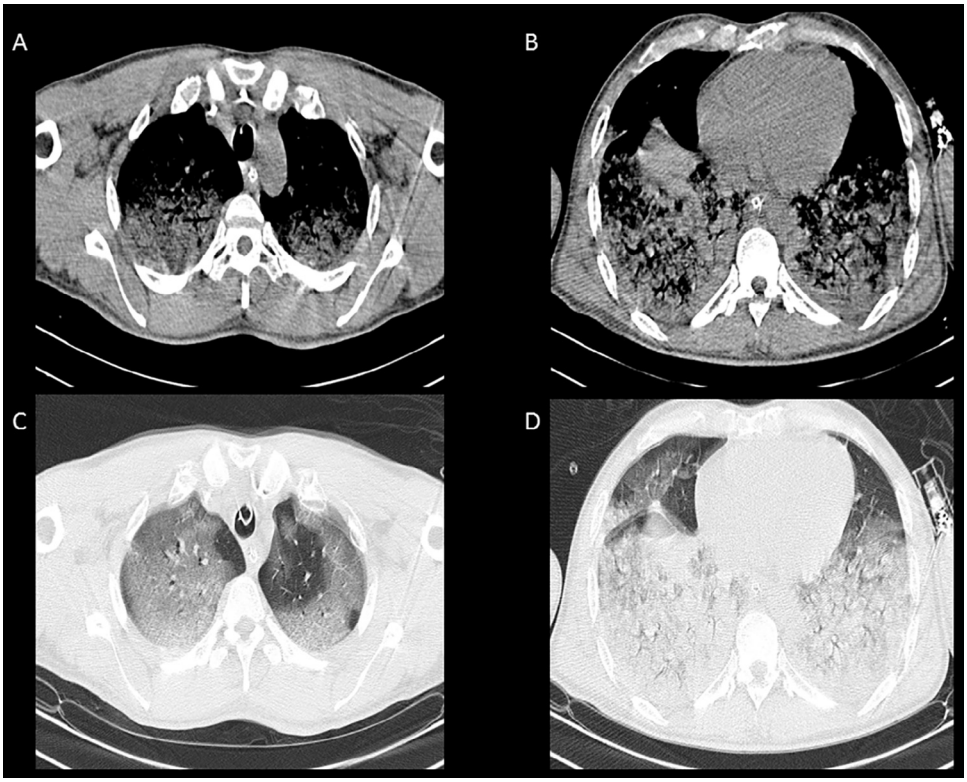

Fig. 2. Computed tomography (CT) of the thorax. Bilateral posterior and inferior lobular involvement at the alveolar level; images compatible with ground glass opacities and air bronchogram. A and B) Axial plane CT without contrast, mediastinal window, areas of alveolar involvement at the posterior and inferior lobules in bilateral hemithorax. B) Regions of consolidation associated with air bronchogram. C and D) Axial plane CT of the thorax without contrast, lung window. C) Pulmonary apical regions with ground glass opacities identified bilaterally. D) Lower level axial planes, where ground glass opacities can also be identified, coalescing into regions of consolidation associated with air bronchogram.

immune deposits, which can be identified by immunofluorescence; and 3) a diverse group, that includes etiologies such as pharmacologic toxicity, infections, and idiopathic causes.[8,9]

Among the infectious etiologies that must be considered are Influenza A virus subtype H1N1, Dengue virus, Leptospirosis, and *Staphylococcus aureus*. Immunosuppressive medication associated with AH are alemtuzumab, cytarabine, azathioprine, bevacizumab, cyclophosphamide, erlotinib, etoposide, rituximab, and mitomycin C, among others.[10,11] Other medications or substances that are reported to have direct pulmonary damage include amiodarone,

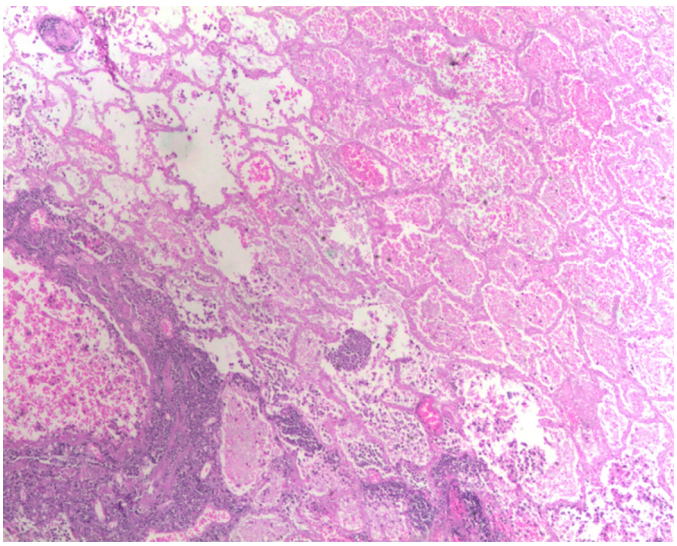

Fig. 3. Histopathology. Lung, 50x, hematoxylin and eosin staining. Diffuse alveolar damage is observed to the right with abundant erythrocytes inside the alveolar spaces. To the lower left of the image, a bronchiole with abundant polymorphonuclear cells are observed. Diffuse alveolar hemorrhage secondary to alveolar injury associated with bronchopneumonia.

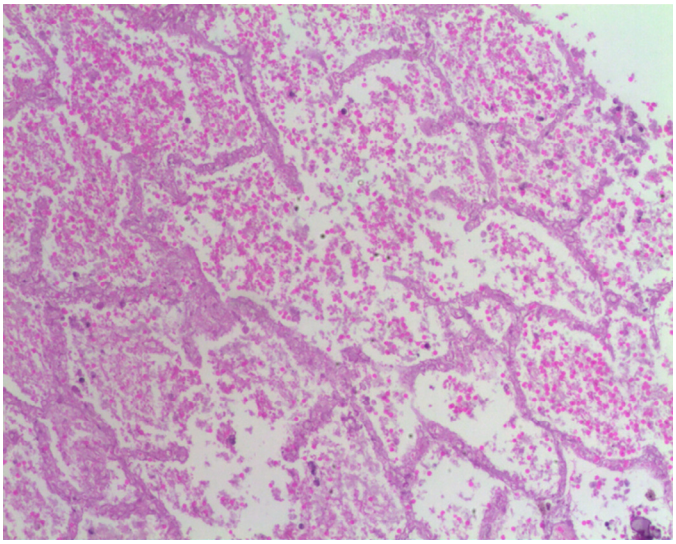

Fig. 4. Histopathology. Lung, 100x, hematoxylin and eosin staining. Diffuse alveolar damage is observed with pneumocyte degeneration and hyaline appearance in the alveolar wall with numerous erythrocytes inside the alveolar spaces.

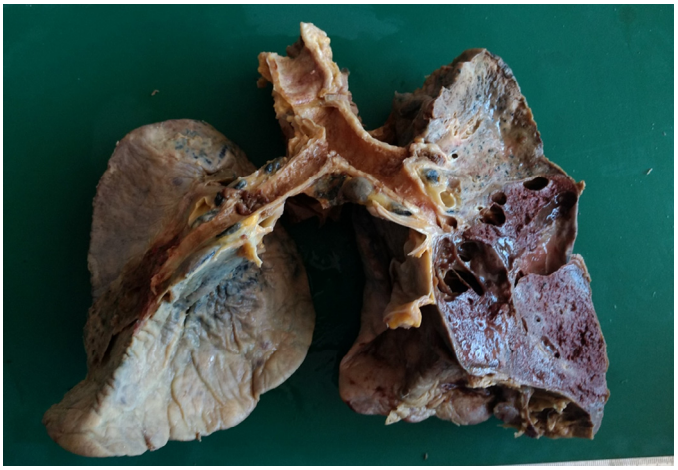

Fig. 5. Necropsy. Lungs. Thickening of the pleura with fibrinopurulent appearance. Parenchyma with several spaces resembling cysts of diverse diameters, with hematic content; present bilaterally with basal predominance.

nitrofurantoin, chemotherapeutic agents, and cocaine, among others.[4,12] Conditions such as thrombocytopenia and hypersensitivity intolerance are associated with AH. Medications that alter blood coagulation such as thrombolytics, anticoagulants, antiaggregant drugs, and dextran 70 are associated with thrombocytopenia. Propylthiouracil, phenytoin, sulfasalazine, hydralazine, carbimazole, leukotriene antagonists, and penicillin are among the medications that have been associated with hypersensitivity reactions.[13]

Cocaine abuse and overdose have a high morbidity and mortality, sustaining damage to the cardiovascular, central nervous and respiratory systems.[14] Cocaine has sympathomimetic, local anesthetic, and vasoconstrictive effects. Endothelial damage secondary to cocaine intake is primarily caused by its vasoconstrictive effects. The vasoconstrictive effect of cocaine results from α-adrenergic receptor stimulation on arteriolar smooth muscle cells, as well as the up-regulation of endothelin-1 and autocrine down-regulation of nitric oxide.[15] These vasoconstrictive properties have been associated with ischemia and endothelial damage in AH.[15] Cocaine has a direct toxic effect over capillary endothelin, thus leading to capillary congestion and pulmonary edema. Subsequent formation of free radicals and production of transforming growth factor beta (TGF-β), can lead to pulmonary fibrosis and pulmonary hypertension; due to the anabolic collagen properties of TGB- β, as well as in situ thrombosis in chronic cocaine users.[16] Other hematologic alterations that have been associated with cocaine consumption are thrombocytopenia and transient protein C and S deficits.[1]

Among the differential diagnoses for acute pulmonary lesions secondary to cocaine consumption are: 1) crack cocaine acute pulmonary toxicity; 2) acute eosinophilic pneumonia; 3) acute respiratory distress syndrome (e.g. infectious, aspiration events, and trauma); 4) pulmonary embolism; 5) heart failure; 6) pneumonia; and 7) acute coronary syndrome.[1,14,17] Toxicity due to chronic cocaine use should be differentially screened for interstitial lung disease (e.g. pneumonia, lymphatic carcinomatosis, and pneumoconiosis), chronic granulomatous disease (e.g. sarcoidosis, berylliosis, and miliary tuberculosis), and chronic obstructive pulmonary disease (e.g. tobacco smoking-induced emphysema).[1,5]

Imaging findings depend on the length of AH presentation. In acute phases, 20% to 50% of cases can have normal lung imaging. Central and basilar opacities might be present in chest x-rays, without costophrenic angle blunting. No interlobular septal thickening is visualized associated with these opacities in a CT scan.[12,17] A bronchoscopy with bronchoalveolar lavage is necessary for AH cases as it provides confirmatory findings of intraalveolar hemorrhage, as well as suitable samples to assess infectious etiologies. Alveolar bleeding with more than 20% of hemosiderin-laden alveolar macrophages (i.e. dust cells) provides additional evidence for AH diagnosis.[8]

Treatment for the pulmonary complications of cocaine abuse is based on the observations made in case reports.[16] Initially, discontinuation of cocaine along with supportive care is provided to the patient.[14] Invasive mechanical ventilation is required in 27% of the cases that present respiratory failure associated with hemodynamic instability, hypervolemia, as well as acute renal injury secondary to AH.[7] The use of corticosteroids is controversial. Some case reports suggest that certain cocaine-induced AH improve with their implementation[5,16]; while other case reports suggest no benefit is gained by the use of corticosteroids.[14]

A vast array of complications associated to cocaine inhalation are described: 1) interstitial pneumonitis; 2) interstitial fibrosis; 3) pulmonary hypertension; 4) diffuse alveolar hemorrhage; 5) diffuse alveolar injury; 6) asthma exacerbation; 7) barotrauma; and 8) airway lesion secondary to thermic insult.[16,18]

Conclusion

Alveolar hemorrhage associated with cocaine consumption is a difficult pathology to diagnose. This non-immune etiology must be considered among the possible causes of AH due to the high consumption and mortality rates of cocaine in the recent decades. This etiology must be suspected in patients with a history of cocaine use, who present hemoptysis, and develop anemia as part of their clinical presentation. Additionally, AH secondary to cocaine consumption should be suspected among patients with imaging studies showing pulmonary infiltrates. This case had a torpid evolution secondary to sepsis, with pulmonary foci, thus progressing to death despite optimal treatment. Previous reports involving cocaine users show an increased risk of infections secondary to decreased lymphocyte and macrophage activity, as well as mucociliary clearance.[19]

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Availability of data and materials: The clinical data supporting the conclusions of this article is included in the article.

Ethics approval and consent to participate: Approval from the ethical committee was not required due to the nature of this case report. Abiding by the Declaration of Helsinki, patient anonymity was guaranteed.

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