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MASSIVE HAEMOPTYSIS AND CARDIOPULMONARY ARREST SECONDARY TO ACUTE PULMONARY HISTOPLASMOSIS IN A TRAVELLER FROM CHINA SUCCESSFULLY MANAGED WITH CRYOEXTRACTION

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ABSTRACT

Histoplasma capsulatum is a dimorphic fungus that grows as a mould in the environment and as a yeast in human tissues causing histoplasmosis. Histoplasmosis varies in clinical presentations and severities of the illness and is endemic in certain areas of North, Central, and South America, Africa, and Asia. A 47-year-old previously healthy male presented with a sudden onset of massive haemoptysis requiring emergent intubation in the emergency department. Bronchoscopy revealed blood clots within the endotracheal tube extending into both main bronchi with active bleeding from both airways. Subsequently, the patient experienced a cardiac arrest with asystole, requiring three rounds of cardiopulmonary resuscitation before achieving return of spontaneous circulation. A computed tomography scan of the chest demonstrated diffuse ground-glass opacities. Collateral information obtained from the patient's family indicated travel to Southeast China two months prior to hospitalization. Histoplasma antigen testing returned positive, and antifungal therapy was initiated. Along with serial suctioning and forceps use via fibreoptic bronchoscopy, cryoextraction of blood clots from the bronchi was performed, leading to successful extubation and hospital discharge. This case highlights the need to consider histoplasmosis in patients who have travelled to endemic areas and present with severe respiratory symptoms.

KEYWORDS

Massive haemoptysis, histoplasmosis, Histoplasma capsulatum, acute respiratory distress syndrome, ARDS

LEARNING POINTS

- Acute pulmonary histoplasmosis can present with life-threatening complications such as massive haemoptysis, even in immunocompetent individuals.
- A thorough travel and occupational history are critical for diagnosing histoplasmosis, especially in non-endemic regions.
- Combined management with antifungal therapy and bronchoscopic cryoextraction can be effective in severe pulmonary histoplasmosis with airway obstruction.

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INTRODUCTION

Histoplasmosis, caused by the dimorphic fungus *Histoplasma capsulatum*, is one of the fungal infections that can present with a variety of symptoms depending on the severity. Traditionally recognized in Ohio and Mississippi River valleys in the United States, *H. capsulatum* is now acknowledged as a global fungus with reported cases in parts of Asia, including southwestern China[1]. Common symptoms of acute pulmonary histoplasmosis include cough, chest pain, fever, and weight loss. However, massive haemoptysis is a rare symptom[2], and only one paediatric case has been documented so far[3].

We report the first known case of acute pulmonary histoplasmosis complicated by massive haemoptysis leading to cardiopulmonary arrest, successfully managed by combined treatment with antifungal treatment and serial bronchoscopic cryoextraction of blood clots from the airway. This case underscores the importance of a thorough travel history in diagnosing histoplasmosis and demonstrates successful management through comprehensive management.

CASE DESCRIPTION

A 47-year-old non-smoker Chinese male with no significant past medical history, including pulmonary disease, presented to the emergency department with acute massive haemoptysis. The patient reported being in his usual state of health until one day prior to admission, when he developed a low-grade fever and dry cough. He experienced mild shortness of breath but denied wheezing, night sweats,

Haematology	
WBC (/μl)	9,500
Neutrophils (%)	45
Eosinophils (%)	2
Monocytes (%)	8
Lymphocytes (%)	44
RBC (×10⁶/μl)	4.75
Haemoglobin (g/dl)	14.8
Haematocrit (%)	42.1
Platelet (×10⁴/μl)	32.3
Biochemistry	
Total bilirubin (mg/dl)	0.3
AST (U/l)	28
ALT (U/l)	24
ALP (U/l)	46
LDH (U/l)	415
BUN (mg/dl)	13
Creatinine (mg/dl)	0.76
Na (mEq/l)	138
K (mEq/l)	4.2
Cl (mEq/l)	100
Blood sugar (mg/dl)	175
HbA1c	8.2
Coagulation	
PT-INR	0.91
APTT (s)	31
Fibrinogen (mg/dl)	200

Serology and Immunology	
CRP (mg/dl)	<0.3
ESR (mm/hr)	2
ANA	<40
C3 (mg/dl)	99
C4 (mg/dl)	16
Complement activity level (U/ml)	65.4
RF	-
MPO-ANCA	-
PR3-ANCA	-
Jo-1 Antibody	-
Anti-Sm Antibody	-
Anti-SSA Antibody	-
Anti-SSB Antibody	-
Anti-Proteinase-3	-
Beta-2 Glycoprotein IgG/	-
Beta-2 Glycoprotein IgM	-
Anti-myeloperoxidase	-
Centromere Antibody	-
IgG (mg/dl)	543
IgA (mg/dl)	117
IgM (mg/dl)	34
Tissue TGlutaminase IgA (FLU)	<1.0

Abbreviations: WBC, white blood cells; RBC, red blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; HbA1c, haemoglobin A1c; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody; RF, rheumatoid factor; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; Tissue TGlutaminase IgA, tissue transglutaminase immunoglobulin A; PT-INR, prothrombin time - international normalized ratio; APTT, activated partial thromboplastin time.

Table 1. Blood test on admission.

weight loss, or loss of appetite. A thorough travel history was obtained from the patient who had returned from a one-month trip to southwest China one month prior to this presentation. He had engaged in farming activities and nature excursions, including visits to mountainous regions during his trip. He explicitly denied cave exploration or exposure to bats.

On the day of hospitalization, the patient experienced a sudden onset of large-volume haemoptysis, with an estimated total blood loss of approximately 200 ml over the preceding 24 hours. Upon arrival at the emergency department, the patient had significant hypoxemia with an oxygen saturation of 77% on ambient air. Other vital signs were within normal limits. Physical examination showed laboured breathing with the use of accessory muscles. Auscultation of the chest revealed decreased breath sounds and rhonchi diffusely.

Given the severity of his hypoxemia and ongoing haemoptysis, the patient was emergently intubated. A bronchoscopy performed shortly thereafter revealed copious amounts of blood obstructing both the left and right mainstem bronchi. Despite initial stabilization, the patient experienced a cardiac arrest due to hypoxemia during the bronchoscopy. Three cycles of cardiopulmonary resuscitation were required to achieve a return of spontaneous circulation.

Initial laboratory studies were notable for a haemoglobin level of 14.8 g/dl, which dropped to 11 g/dl within the first four hours despite receiving 3 units of packed red blood cell *(Table 1)*. A broad diagnostic workup was initiated to identify the aetiology of the haemoptysis. Chest X-ray showed diffuse patchy area bilaterally and chest computed tomography (CT) scan showed diffuse ground glass opacities, which worsened on day 2 *(Fig. 1)*.

Diagnostic bronchoscopy showed mucosal erosion and fibrotic changes in the entire trachea with active bleeding from bronchi. Serial bronchoalveolar lavages were not progressively more haemorrhagic, not indicative of diffuse alveolar haemorrhage. The clinical course was further complicated by severe acute respiratory distress syndrome (ARDS) with a partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio of 92.5, necessitating the use of paralytics and prone positioning after maximizing the ventilation setting.

On hospital day 4, the histoplasma antigen testing returned positive, confirming the diagnosis of pulmonary histoplasmosis. Antifungal therapy with itraconazole 200 mg twice daily due to concern about using amphotericin B in a patient with kidney injury. However, due to the severity of the ARDS, antifungal therapy was transitioned to amphotericin B 400 mg daily based on the most recent guideline and infectious disease specialist's guidance[4]. Although the patient's respiratory status mildly improved with antifungal therapy and serial fibreoptic suctioning, he remained hypoxic which prompted cryoextraction of blood clots from the bronchi on hospital day 6. The procedure was performed once by a pulmonologist in the intensive care unit. Standard

Infection markers	
SARS-CoV-2	Negative
Influenza A/B	Negative
Varicella Zoster PCR	Negative
RSV	Negative
Leptospira antibody	Negative
HIV-1/2Ab	Negative
Aspergillus galactomannan antigen	Negative
Fungitell 1,3-Beta-D-Glucan	Negative
Histoplasma antigen	Positive
Microbiology test	
Sputum culture	Normal flora
Blood culture	-
AFB culture and smear	-

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; HIV, human immunodeficiency virus; AFB, acid fast bacilli.

Table 2. Infection markers and microbiology test.

Olympus flex bronchoscopy 1T180® (Olympus Europa SR & Co. KG, Hamburg, Germany) was inserted through the endotracheal tube. During the procedure, no active bleeding was identified in the airways. Large blood clots were found in the lingula and left upper and lower lobes, which were attempted to suction but unsuccessful. Radial jaw® 4 forceps with needle (Boston Scientific, Marlborough, USA) was used which only removed some clots. Then ERBECRYO® 2 with a 1.1-mm cryoprobe (Erbe Elektromedizin GmbH, Tübingen, Germany) was employed to remove the rest of the clots in the lingula and left upper lobe. Cryoextraction was also performed for the remaining clots in the left lower lobe and eventually most of the clots were successfully removed without complications. Other laboratory tests including testing for tuberculosis returned unremarkable *(Table 2)*. Levels of immunoglobulins and complement factors (complement 3, complement 4, and complement activity) were within normal range. Human immunodeficiency virus (HIV) 1/2 antibody was negative. The patient's respiratory symptoms significantly improved, and he was discharged on hospital day 23 without supplemental oxygen. He was discharged with itraconazole 200 mg twice daily for a total of four weeks and was scheduled for follow-up with the infectious disease clinic.

DISCUSSION

We report the first documented case of acute pulmonary histoplasmosis complicated by massive haemoptysis leading to cardiopulmonary arrest, successfully treated with antifungal therapy and serial bronchoscopic interventions including cryoextraction of airway blood clots. Haemoptysis is a rare presentation for histoplasmosis, but we were able to successfully diagnose this patient by obtaining a thorough

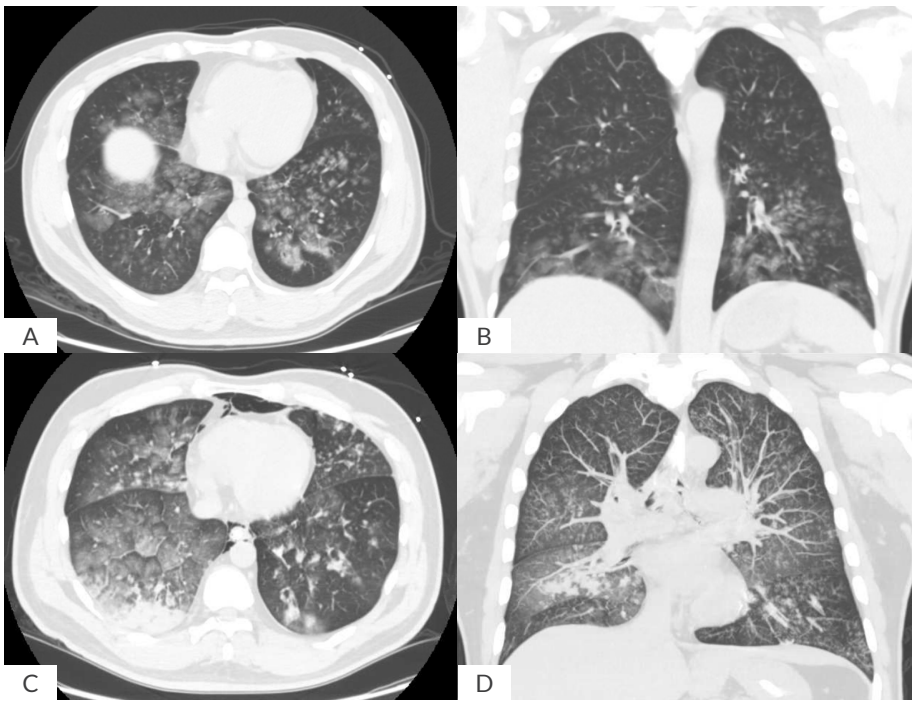


Figure 1. A, B) Computed tomography (CT) imaging on the day of admission shows relatively diffuse small ground glass opacities with a tree-in-bud distribution in the upper lungs that become larger and confluent in the lower lungs without any solid pulmonary nodule or mass to suggest pulmonary neoplasm or bronchiectasis or evidence of pulmonary tuberculosis. C, D) Follow up CT imaging on day 2 shows worsening diffuse ground glass opacities in both lung fields.

travel history and an antigen test. Our thorough workup was negative for other common aetiologies that could cause haemoptysis, including bronchiectasis, tuberculosis, lung cancer, chronic infections, pulmonary vascular diseases, autoimmune diseases, and coagulopathies[5,6]. Massive haemoptysis, defined as 150 ml of blood in a 24-hour period or bleeding at a rate of more than 100 ml/hr[7], is a rare presentation for acute pulmonary histoplasmosis; only one paediatric case solely has been documented in the past[3]. This patient eventually required paralysis and prone positioning for severe ARDS, however, we were able to successfully manage the patient with antifungal agents, serial bronchoscopy, and cryoextraction.

Cryoextraction is an effective technique for removing blood clots in critically ill patients with massive haemoptysis[8]. The cryoextraction device system consists of two main components: a cryogen and a cryotherapy device (cryomachine). The cryomachine includes a cryoprobe—featuring a chamber at its tip that enables the inflow and outflow of gas for rapid cooling—a transfer line that connects the cryoprobe to the liquefied gas container holding the cryogen, and a console that controls the flow of cryogen through the system[9]. During the procedure, the flex bronchoscopy is advanced through endotracheal tube or tracheostoma. Once the bronchoscope tip is positioned approximately 0.5-1 cm proximal to the target area, the cryoprobe is inserted through the working channel and placed in direct perpendicular or tangential contact with the lesion. Activation is achieved via a foot pedal, typically for 30 seconds. After deactivation, thawing occurs passively. This freeze-thaw cycle is generally repeated two to three times at each site before proceeding to the next area[10].

Cryotherapy has become more widely used since the introduction of the flexible cryoprobe, particularly in patients with malignancies[9]. While it may help avoid the need for more invasive interventions such as extracorporeal membrane oxygenation, evidence supporting its use specifically in patients with histoplasmosis remains limited. Our literature review found that there are no previous case reports describing histoplasmosis and massive haemoptysis treated with cryoextraction. This highlights the novelty of our histoplasmosis case presenting with massive haemoptysis successfully treated with cryoextraction.

The gold standard method of diagnosis for histoplasmosis is culture, though overall sensitivity is low[11]. Alternatively, other modalities have been used for the diagnosis including urine antigen test as this case. Histoplasma urine antigen test has 91.8% sensitivity and 99.0% specificity for acute pulmonary histoplasmosis[12,13], and this has been more commonly used to diagnose histoplasmosis.

There are some reports of severe forms of disease in immunocompetent patients[14,15]. They suggest a correlation between the amount of spores and the severity of disease. Our patient did not have any significant conditions causing immunodeficiency such as cancer or HIV infection but had newly diagnosed mild type 2 diabetes mellitus. The patient travelled to the endemic area and engaged in farming activities, which could have exposed the patient to large amounts of spores.

Histoplasmosis is relatively rare and not well-documented. In China, however, although histoplasmosis is considered rare, sporadic cases have been reported, particularly in regions along the Yangtze River[1,16]. In this case, the patient had a significant history of travel to one of the branches of Yangtze River in southwest China, with exposure during farming activities and nature excursions. Additionally, it has been reported that certain occupations, such as poultry farming, construction, and other jobs involving soil and bird or bat droppings, can increase the risk of exposure to *Histoplasma capsulatum*[16,17]. Given these factors, our patient's farming

activities likely increased his risk of developing a severe form of histoplasmosis.

This case provides the important insight that histoplasmosis should be included in the differential diagnosis for cases of massive haemoptysis if patients have a history of travel to endemic areas, even though massive haemoptysis is a rare presentation. Delay in diagnosis can be fatal and thorough history taking and broad workup is needed in patients at risk. This case also highlights the success of comprehensive management with antifungal treatment and cryoextraction.

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