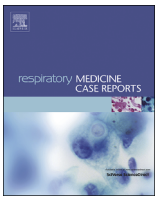
Respiratory Medicine Case Reports 45 (2023) 101884

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

Pleurisy secondary to nonthrombotic pulmonary emboli in a patient with intravenous drug use

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ARTICLE INFO

Keywords:
Nonthrombotic pulmonary emboli
Septic emboli
Patients with injection drug use
NTPE
PWID

ABSTRACT

Patients with injection drug use can have nonthrombotic pulmonary emboli (NTPE) of foreign insoluble particles that are either parts of the equipment used or mixed with the drug as an additive. These foreign particles can become a nidus for infection and inflammation. We present a case of a 31-year-old man with active intravenous drug use who initially presented with signs and symptoms of pleurisy and was found to have NTPE of septic refractile crystalline material as seen on bronchial wash and brush biopsy. We believe our patient likely had embolism of either crack particles, needle fragments or cotton-wool fragments that led to a localized inflammatory reaction and infection. This highlights the importance of obtaining detailed history and diagnostic workup. Once the diagnoses of bacterial endocarditis and thrombophlebitis are ruled out with blood cultures, transthoracic echocardiogram, *trans*-esophageal echocardiogram and/or CT scan (depending on the suspicion), NTPE should be considered and bronchoscopy with bronchoalveolar lavage with biopsy should be performed.

1. Introduction

Septic pulmonary emboli (SPE) are typically infected thrombi that travel through the bloodstream from a distant infectious source and become lodged in the pulmonary vasculature, resulting in obstruction of the vessel, parenchymal infection and/or an inflammatory reaction. Common origins of SPE include cardiovascular infections (e.g., bacterial endocarditis [BE], septic thrombophlebitis, central venous catheter infection) [1,2], infection of implanted devices (e.g., pacemakers [2], defibrillators [3], ventricular-assist devices [4], chronic vascular access device) and periodontal infections [1]. In patients with injection drug use (PWID), tricuspid valve endocarditis appears to be the most common cause of SPE. Rarely, PWID may have nonthrombotic pulmonary emboli (NTPE) of foreign insoluble particles that are mixed with the injection drug as an additive [5,6]. These foreign particles can become a nidus for infection and inflammation. If left untreated, devastating complications may ensue. We present a case of a 31-year-old man with active intravenous drug use who was found to have NTPE of septic refractile crystalline material as seen on bronchial wash and brush biopsy.

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https://doi.org/10.1016/j.rmcr.2023.101884
Received 19 February 2023; Received in revised form 9 May 2023; Accepted 31 May 2023
Available online 4 June 2023

2. Case presentation

A 31-year-old man with a past medical history of intravenous drug use (IVDU), specifically heroin and cocaine, and untreated hepatitis C virus infection presented to the emergency department for the evaluation of chest pain. The patient's chest pain began approximately 5 days prior to presentation as a sharp, non-radiating, persistent pain, which was worse with inspiration and on movement. The pain progressed to 10/10 in intensity below the nipples bilaterally. Our patient endorsed exertional dyspnea mostly because of the inability to inspire without significant pain and subjective fever. He also reported worsening cough productive of light green sputum and, at times, a scant amount of blood. Moreover, approximately a week prior, the patient missed a vein while injecting the drug in the right side of his neck which led to swelling and redness of the area. The remainder of the review of systems was noncontributory. As for his past medical history, our patient reported being informed he was positive for hepatitis C 10 years prior, but he did not seek treatment nor did he follow up with medical providers for the same. The patient has a smoking history of 15 pack years and has been injecting "speedball", a mixture of cocaine and heroin, almost daily for the last 10 years. Our patient reported using "a bundle and a half" of heroin together with "few grams" of cocaine in powder form with water daily. When the patient was not able to acquire cocaine, he used crack which comes in solid "rock" form. He reported crushing the rock form and diluting it with vinegar. He heated the mixture after filtering through cotton-wool before injecting himself using a syringe. The patient generally uses his neck and left arm veins to inject drugs. Our patient used the same syringe for up to a month. He reported that, at times, the needle tip would break off in tiny fragments and it would become difficult to acquire access through it. The patient's last use of these drugs was the day of admission. Our patient admitted to being homeless and has been living on the streets for the last 3 years.

Initial vital signs demonstrated a temperature of 98.7 °F, pulse of 135/min, respiratory rate of 19/min and blood pressure of 108/72 mmHg. He appeared to be in mild distress, with poor inspiratory effort due to pain. Physical examination was significant for poor dentition including a few chipped and missing teeth but no oral lesions or thrush. There was an area of erythema, induration and tenderness on the right side of the neck, about 4 × 10cm in size. Lungs were clear to auscultation bilaterally. Cardiac auscultation revealed normal S1 and S2, with no murmurs, rubs or gallops. Examination of the extremities revealed track marks on left antecubital fossa and onychomycosis of the nail beds. Stigmata of bacterial endocarditis were not seen.

Initial laboratory data was significant for a normal white blood cell (WBC) count of 8.5 K/μL, hemoglobin of 10.2 gm/dL and platelet count of 106 K/μL. The patient's mean corpuscular volume (MCV) was 73.6 fL, with red cell distribution width of 15.3%. Serum sodium was 129 mEq/L, with otherwise unremarkable basic metabolic panel. Serum lactic acid was 1.2 mmol/L (normal 0.5–2.2 mmol/L) and D-dimer was 1197 ng/mL (normal 0–230 ng/mL). Erythrocyte sedimentation rate (ESR) was 95 mm/hr (normal 0–15 mm/hr) and C-reactive protein (CRP) was 15.2 ng/dL (normal <1.0 ng/dL). Urine drug screen was positive for cocaine and opiates but negative for amphetamines. Chest X-ray indicated a patchy increased density in the left lower lobe, lingula, and right middle and lower lobes (Fig. 1). Given a significantly elevated d-dimer in the setting of tachycardia, CT angiography of the chest was performed which excluded pulmonary embolism. However, multiple, fluffy, nodules of varying size and ill-defined margins were seen throughout both lungs (Fig. 2). Some of these nodules were cavitary. Larger coalescent areas were seen in the left lower lobe and the lingula. These findings were concerning for septic emboli or metastatic disease. As a result, CT abdomen and pelvis with contrast was performed which did not show any masses. The only finding was splenomegaly, measuring 18cm in length. Furthermore, given the findings of tenderness on the right side of the neck, CT of the neck with contrast performed to exclude septic jugular vein phlebitis or Lemierre's syndrome was unremarkable.

Meanwhile, blood cultures were drawn and our patient was empirically administered intravenous (IV) Vancomycin 1 g and Piperacillin-Tazobactam 3.375 g. Emergent transthoracic echocardiogram (TTE) was performed which did not show valvular vegetation or abscess. Given a high suspicion of bacterial endocarditis (BE), *trans*-esophageal echocardiogram (TEE) was performed which also did not show any vegetations or abscess. Piperacillin-tazobactam was changed to IV Cefepime 2 g every 12 hours. IV Vancomycin was continued to achieve a therapeutic vancomycin trough level. Pulmonology was consulted and, based on the findings on high resolution CT scan of the chest (Fig. 3), the decision was made to perform navigational bronchoscopy to obtain endobronchial and transbronchial lung biopsies. Specimens were obtained from the right lower lobe using a needle biopsy, and near the pleura using the for-

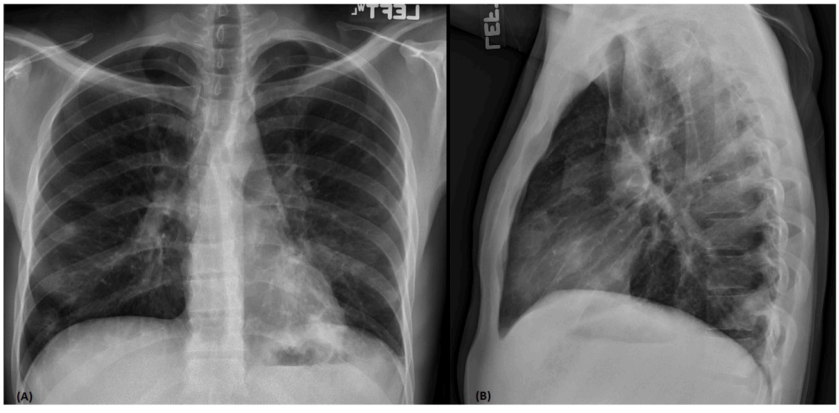

Fig. 1. Chest X-ray showing patchy increased density in the left lower lobe, lingula, and right middle and lower lobes.

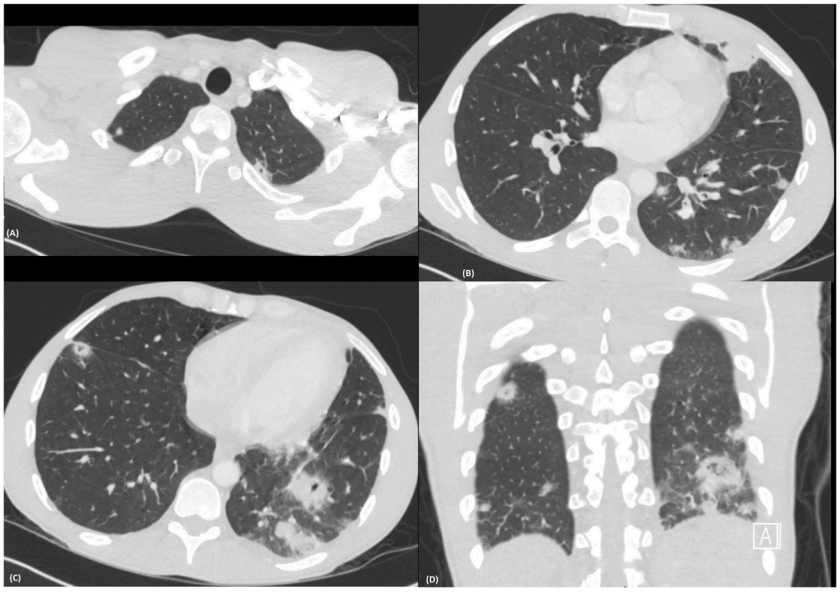

Fig. 2. CT angiography of the chest showing multiple, fluffy, nodules of varying size and ill-defined margins throughout both lungs.

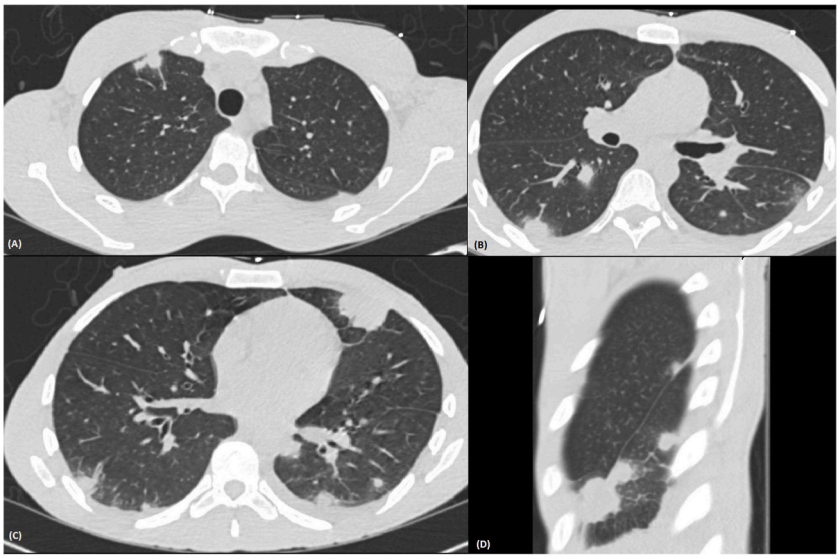

Fig. 3. High resolution CT of the chest remonstrating the nodules with feeding vessel sign.

ceps. A few specimens were also obtained using triple needle brush. In addition, specimens from bronchial washings were sent for cytologic analysis, routine cultures, acid-fast bacilli (AFB) culture and fungal culture.

Additional diagnostic evaluation included HIV testing, QuantiFeron TB, hepatitis panel, rapid plasma reagin (RPR), antinuclear antibody (ANA), anti-double stranded DNA (DsDNA) antibody, anti-glomerular basement membrane (GBM) antibody, anti-neutrophil cytoplasmic antibody (ANCA) and complement levels. Results were unremarkable.

Histopathology report of right lower lobe biopsy specimen was normal with no mononuclear infiltration. A brush tip specimen was also obtained from right lower lobe. Moreover, approximately 55 cc of thick pale orange fluid was obtained via bronchial wash of right lower lobe which showed scattered refractile material surrounded by dense neutrophilic and mononuclear infiltration (Figs. 4 and 5). Gomori methenamine silver (GMS) stain for *Pneumocystis jirovecii* was negative.

The patient's maximum temperature was 100.1 ˚F five days after the admission on antibiotics. The patient's heart rate normalized to 70–90/min and WBC count remained in between 6 and 8 K/μL throughout admission. The patient's chest pain improved over the course of days but mild discomfort with breathing persisted. Blood, respiratory and bronchial wash cultures for bacteria, AFB and fungi remained negative. Because of ongoing concern for bacterial septic emboli, the patient was continued on IV Vancomycin and IV Cefepime for a total of 6 weeks. The patient completed the final 3 weeks of antibiotics at a sub-acute facility.

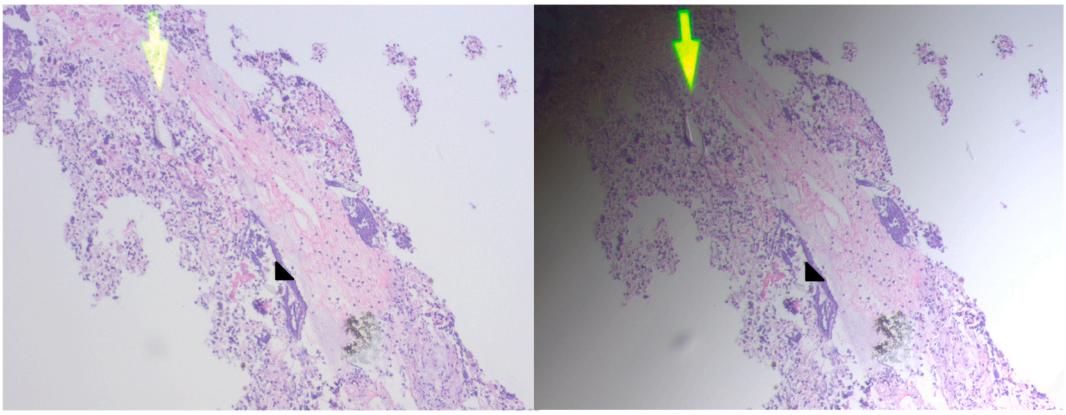

Fig. 4. Crystalline refractile foreign body fragments (arrow and arrowhead) with surrounding dense neutrophilic infiltration.

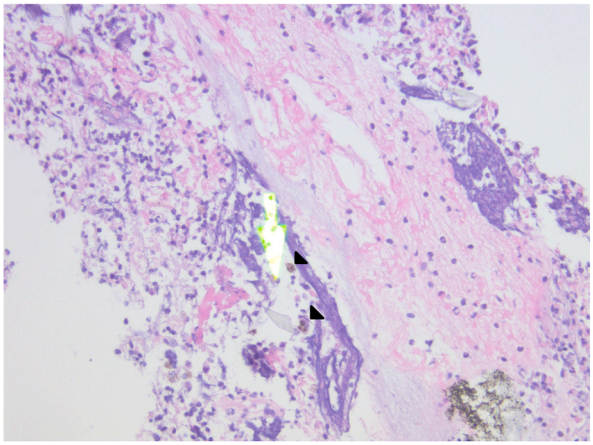

Fig. 5. Higher magnification demonstrated the crystalline foreign body fragment (arrow) with surrounding mononuclear cells (arrowheads).

3. Discussion

Unlike pulmonary thromboembolism, NTPE are rare. Causes of NTPE may be categorized as biological or nonbiological (Table 1). Most of them are iatrogenic or a complication of a disease process. Sometimes, it is a sequala of illicit IVDU. PWID crush tablets intended for oral use, dissolve them in water, and inject them intravenously [6]. These tablets often have a filler agent or additive which can be talc (hydrous magnesium silicate) [8], magnesium trisilicate, microcrystalline cellulose [9], and/or crospovidone [10]. Their particles, when injected into the bloodstream, can become lodged in the pulmonary capillary bed. Sometimes, the needle fragments themselves travel to the pulmonary vasculature [11,12] and can incite an inflammatory response. Persistent mechanical obstruction can lead to a state of chronic inflammation described as "foreign body granulomatosis" [13]. Other complications reported include bullous lung disease, nonspecific interstitial lung disease, and pulmonary hypertension [14].

Table 1
Biological and nonbiological causes of nonthrombotic pulmonary embolism (NTPE).

Iatrogenic	Secondary to a disease process	In patients with IVDU
• Bone and tissue embolism (biologic) • Cholesterol embolism (biologic) • Intraoperative material embolism • Gas embolism • Iodinated oil and glue embolism • Radiotracer embolism • Radioactive seed embolism • Cement embolism • Pacemaker lead embolism • Ventriculoperitoneal shunt embolism • Catheter embolism • Silicone embolism • Hyaluronic acid embolism	• Amniotic fluid embolism (peripartum) • Tumor embolism (cancer-related) • Septic embolism (infectious) • Hydatid embolism (infectious) • Mercury embolism (suicidal) • Bullet embolism (trauma) • Bone and tissue embolism (biologic) • Cholesterol embolism (biologic)	• Talc (hydrous magnesium silicate) • Magnesium trisilicate • Microcrystalline cellulose • Crospovidone • Needle fragments • Cotton-wool fragments

Talc induced pulmonary obstruction has been studied in animal models [15]. When embolized, it has a propensity to cause arteritis which causes an influx of mononuclear infiltrate around the foreign body. The resulting cytokine release can cause thrombosis in pulmonary arteries [16]. This can lead to focal ischemia and alveolar wall necrosis, resulting in focal emphysematous changes [17]. Moreover, when these particles are engulfed by macrophages, multinucleated giant cells replace normal lung tissue and overtime, may lead to fibrosis, depending on the intensity and frequency of the exposure [14]. The same pathophysiology has been seen with other additives.

After pulverizing the tablets, they are often heated and then filtered through cotton-wool before injection. The residual cotton-wool fragments also have the propensity to embolize and incite a giant-cell reaction [18]. Based on the history and histopathology findings, we believe our patient likely had embolism of either crack particles, needle fragments or cotton-wool fragments that led to a localized inflammatory reaction and infection.

Clinical findings in patients with NTPE are variable. While some patients remain asymptomatic, others can experience dyspnea, pleuritic chest pain, cough, increase in sputum production, tachycardia or, in severe cases, sudden death [7,19]. Less commonly, night sweats, weight loss and hemoptysis may be observed. Physical examination findings are also nonspecific which may include crackles in the involved area of the lungs. In patients with longstanding drug use, signs of complications (e.g. pulmonary hypertension) can be seen. Our patient presented with dyspnea and pleuritic chest pain and also complained of having productive cough and intermittent hemoptysis.

Diagnostic evaluation of septic emboli involves radiologic imaging and assessment of pulmonary function. Chest X-ray findings depend on the stage of the disease process. In early acute embolism, hazy opacities or well-defined micronodules in the involved areas of the lungs may be seen [5,20]. The presence of a foreign body may lead to the development of loculated empyema and bronchopleural fistula evident on a chest X-ray [1]. However, it is not uncommon for imaging to illustrate non-specific infiltrates. If the insult is chronic, radiographic studies may show signs of granulomatosis in the form localized deposits and fibrosis. High resolution CT (HRCT) features of NTPE include diffuse ground glass opacities and micronodules, ranging in size from 0.5 to 3.5 cm (representing accumulation of foreign material with adjacent inflammatory reaction), cavitation, air bronchograms within nodules, wedge-shaped pleura-abutting peripheral lesions and/or a feeding vessel sign [21]. There can be areas of infarction near the involved vessel [22]. In the later stages of the disease process, involved areas can progress to interstitial fibrosis [5]. Moreover, confluence of the nodules can lead to the formation of conglomerate masses that destroy the pulmonary architecture, forming bullae and focal emphysematous changes [14,23]. Reactive lymphadenopathy can also be seen. Our patient had patchy densities on chest x-ray that were corresponding to nodules in the lung areas. The nodules in the lower lobes and lingula were coalescing and cavitating on HRCT, raising suspicion for ongoing infection and inflammation.

Treatment depends on the degree of involvement of lung parenchyma and toxicity [1]. To date there are no established guidelines regarding management of NTPE. If the patient appears to be in sepsis and/or respiratory failure, it is reasonable to initiate empiric treatment with antibiotics after obtaining cultures, at least until more common causes of septic emboli (e.g. bacterial endocarditis) are ruled out or the source is controlled (e.g. suppurative thrombophlebitis) [11]. If the patient has empyema, surgical intervention with video-assisted thoracotomy (VATS) or open surgery for decortication and resection of necrotic tissue, may be considered [1]. Since the burden of disease was mild to moderate in our patient, with no signs of systemic toxicity and good response to conservative management, it was decided not to pursue surgical intervention for removal of foreign materials. Close follow up is crucial to monitor for the development of complications described.

4. Conclusion

In patients with symptomatic SPE, common causes such as bacterial endocarditis or septic thrombophlebitis should be considered. Negative findings should raise suspicion for NTPE. Further workup and treatment should be directed to the most likely etiology. In PWID, embolism of foreign insoluble particles like filler agents of pulverized tablets, needle fragments, and/or cotton-wool fragments is a possibility. Treatment with antibiotics is reasonable if the infection is localized. However, the patient should be monitored for response as the development of complications (e.g., bronchopleural fistula, empyema, infarction, fibrosis) is associated with a high rate of morbidity and mortality.

Declaration of competing interest

There are no conflicts of interest to disclose.

Acknowledgements

Special thanks to the pathology department of the hospital, in particular Dr. Fish, Heidi, who provided her valuable input in the pathology slides of the case report.

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