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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Case Report

A Curious Case of Crazy Cavity

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Abstract

The pulmonary thromboembolism (PTE) can rarely manifest with fever and cavitatory lung lesion. The management of PTE depends on the risk stratification. The novel oral anticoagulation is safe and effective in patients with low to moderate risk.

Keywords: *Pulmonary Thromboembolism (PTE); Chronic Obstructive Pulmonary Disease (COPD)*

Abbreviations

BOOP: Bronchiolitis Obliterans Organizing Pneumonia; COPD: Chronic Obstructive Pulmonary Disease; CT: Computed Tomography; CTPA: Computed Tomography Pulmonary Angiography; CUS: Compression Ultrasonography; DVT: Deep Vein Thrombosis; LMWH: Low Molecular Weight Heparin; MTB: Mycobacterium tuberculosis; NOAC: Non Vitamin K Antagonist Oral Anticoagulant; PET: Positron Emission Tomography; VKA: Vitamin K Antagonist; VTE: Venous Thromboembolism; PESI: Pulmonary Embolism Severity Index; PTE: Pulmonary Thromboembolism; UFH: Unfractionated Heparin

Introduction

The pulmonary thromboembolism (PTE) can rarely manifest with fever and cavitatory lung lesion.

Case Report and Discussion

A 54 year-old man, diagnosed case of chronic obstructive pulmonary disease (COPD) stage IV, Group-D presented with 1 month history of high grade fever, malaise, chest pain, dyspnea and cough with purulent expectoration. There was no history of hemoptysis, joint pain, morning stiffness or skin rash. He worked as a driver. He had history of hospital admission for acute exacerbation of COPD for 4 days 1month ago. He was treated with Levofloxacin and nebulisation at that time. The routine investigations and chest radiograph of the prior admission were normal. The patient had room air saturation of 94% at the time of discharge.

On examination, the patient was febrile with a temperature of 101ºF. His pulse rate was 110/min, the respiratory rate was 24/min, the blood pressure was 120/70 mmHg and the oxygen saturation was 93% on room air. On auscultation of the respiratory system there were rhonchi bilaterally. The examination of the other systems including the ear, nose, throat and musculoskeletal system was unremarkable.

The chest radiograph of the patient is shown in figure 1. The routine blood investigations showed hemoglobin of 11.9 gm/dl and white cell count of 17,800/mm^3. His serum urea was 34 mg/dl, creatinine was 0.7 mg/dl and random blood sugar was 92 mg/dl. The urine routine and microscopic examination revealed no abnormality. The arterial blood gas analysis showed pH of 7.37, PaO_2 of 64 mmHg, $PaCO_2$ of 36 mmHg and bicarbonate of 21 mmol/L. The electrocardiogram was normal. The serum procalcitonin was 0.15 ng/ml (reference ≤ 0.15 ng/ml). The C-reactive protein level was 8 mg/L (reference < 10 mg/L). The pro-brain natriuretic peptide (proBNP) level was 454 pg/ml (reference < 900 pg/mL) and troponin -T was negative. The blood culture did not grow any organisms. His enzyme linked immunosorbent assay for human immunodeficiency virus was non-reactive. The sputum for acid fast bacilli, bacterial and fungal cultures were negative. The sputum Gene Xpert was also negative. The high resolution computed tomography (CT) scan of the chest with contrast enhancement was done in our patient and is shown in figure 2.

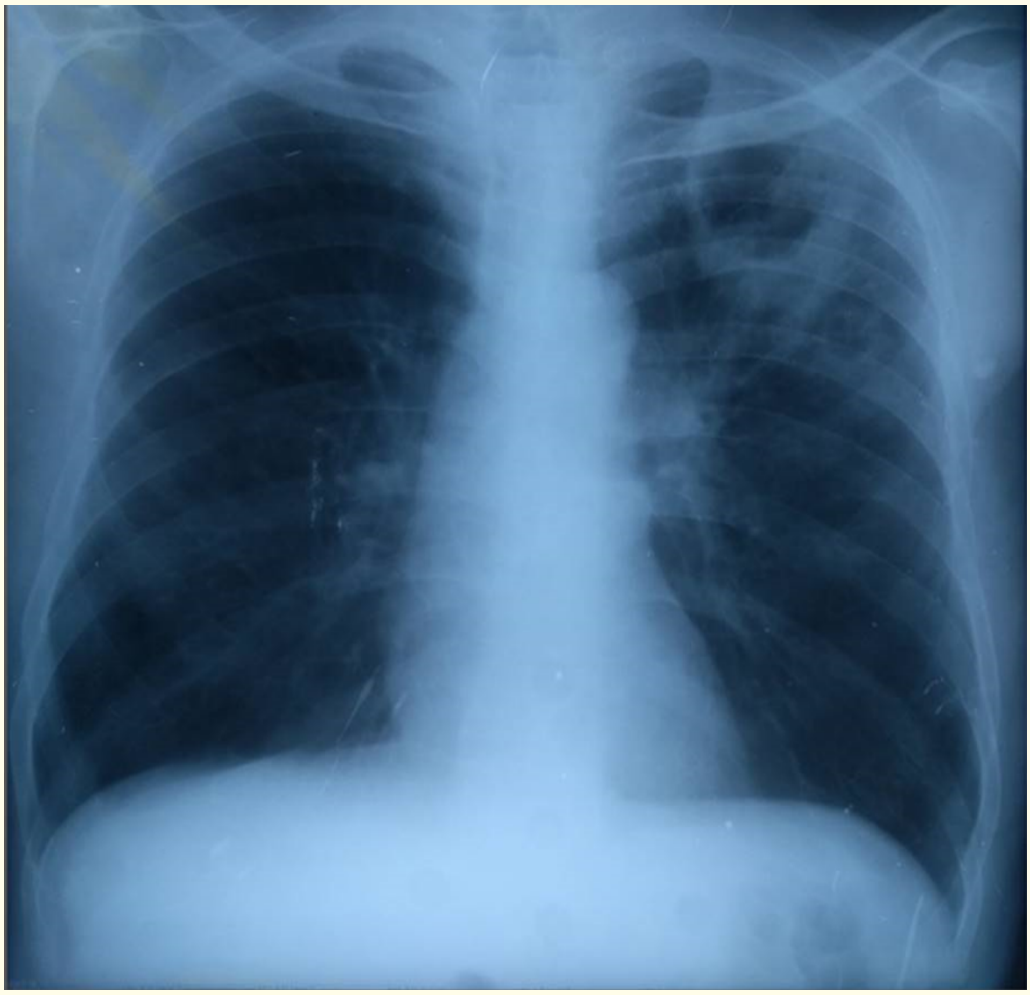

Figure 1: *Chest radiograph of the patient in postero-anterior projection.*

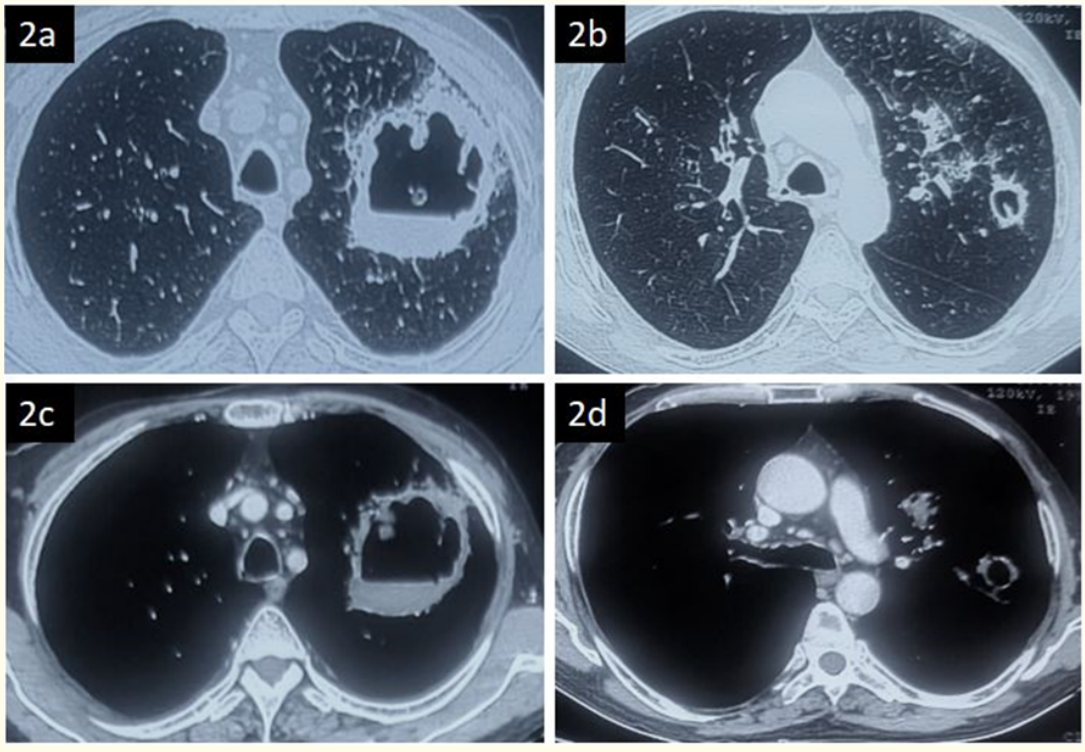

Figure 2: *Computed tomography of chest: figure 2a and 2b - axial section of lung window; figure 2c and 2d -axial sections of mediastinal window at different levels of cross-section.*

Q.1. What is the finding on the chest radiograph and CT scan?

a. Left upper zone cavity

b. Left upper zone bulla

c. Left upper zone cyst

d. Any of the above

Answer 1.a. Left upper zone cavity

A cavity is a gas-filled space, seen as a lucency or low-attenuation area, within pulmonary consolidation, a mass, or a nodule [1]. It has a clearly defined wall > 4 mm thick [2]. A cyst appears as a rounded parenchymal lucency with a well-defined interface with the normal lung. The cysts have variable wall thickness but are usually thin-walled with a wall thickness of < 2 mm [3]. A bulla appears as a rounded focal area of decreased attenuation with size ≥1 cm diameter and bounded by a thin hair-line wall [3].

The CT of the chest is the current imaging of choice for evaluating lung cavities, cysts and bulla as it provides precise information on size, shape, location of lesions, and other characteristics that may not be evident on the chest radiograph [4]. Based on the CT features in combination with an appropriate clinical and laboratory background, the chest physician can narrow the list of possible diagnoses. The CT scan in our patient revealed two ill-defined irregularly thick walled cavities of size 7 cm x 7.4 cm and 2.7 cm x 2.3 cm in the left

upper lobe. The patient was further investigated with fiberoptic bronchoscopy. There was no visible endobronchial growth or narrowing of lumen. The bronchial wash was negative for Gene Xpert, bacterial and fungal culture. It was also negative for malignant cells. The CT guided biopsy of the lung lesion showed reactive fibrosis with inflammatory infiltrate composed of neutrophils, lymphocytes, plasma cells and necrotic debris. The culture of the biopsy material did not grow any organisms. He received an empiric treatment with intravenous amoxicillin-clavulinic acid. But there was no response.

Q.2. What is the likely diagnosis in this patient?

a. Anaerobic lung abscess

b. Pulmonary tuberculosis

c. Primary lung malignancy

d. Necrotising fungal infections

e. Cryptogenic organizing pneumonia (COP)

f. None of above

Answer 2. f. None of the above

The causes of lung cavity are many and can be of infectious and non infectious (Table 1) [5]. A detailed clinical evaluation and appropriate investigations are needed to narrow down the differential diagnoses. The patient was very unlikely to have infectious disease as all the cultures including the lung biopsy specimen were sterile. The malignancy and COP was also unlikely as the biopsy was showing inflammatory cells and fibrosis. On probing he admitted to having intermittent pain in both legs. The lower limb was normal but the clinical examination was positive for the Moses sign and Homan sign in the right leg. He also had new onset of intermittent scanty hemoptysis. The fever had not yet subsided.

Infectious causes		Non-infectious causes
a) Bacterial Infections	**c) Fungal Infections**	**a) Malignancy**
Klebsiella pneumoniae	Aspergillosis	Primary lung malignancy
Streptococcus species	Zygomycosis	Pulmonary metastases
Staphylococcus aureus,	Histoplasmosis	**b) Autoimmunity**
Pseudomonas aeruginosa,	Blastomycosis	Rheumatoid arthritis
Haemophilus influenzae	Cryptococcus neoformans	Granulomatosis with polyangiitis
Acinetobacter species,	Coccidioidomycosis	**c) Miscellaneous Diseases**
Escherichia coli	Paracoccidioidomycosis	Pulmonary embolism
Legionella species	Pneumocystis jiroveci	Bronchiolitis obliterans organizing pneumonia
Actinomycosis	**d) Parasites**	Pulmonary Langerhans cell histiocytosis
Nocardia	Echinococcus	
Burkholderia pseudomallei	Paragonimiasis	
b) Mycobacterial Infections		
Mycobacterium tuberculosis		
Nontuberculous mycobacteria		

Table 1: *Causes of cavitatory lung lesions.*

Q.3. Which of the following next line of investigations will be most helpful in this case?

a. Ventilation perfusion scan.

b. D- Dimer

c. Compression ultrasonography (CUS) of the lower limbs

d. Computed tomography pulmonary angiography (CTPA)

Answer. c and d. Compression ultrasonography (CUS) of the lower limbs and Computed tomography pulmonary angiography (CTPA).

Our patient had the clinical signs of deep vein thrombosis (DVT) of the leg that required confirmation by the CUS of the lower limbs. He also had the risk factors for pulmonary thromboembolism (PTE) like severe COPD, driver by occupation, reduced mobility due to COPD and increasing age [6]. The diagnostic strategy for PTE should be based on the clinical probability assessed either by clinical judgment or by a validated prediction rule such as Wells rule or Geneva rule. Our patient had a high probability of PTE based on the clinical assessment. The D-dimer level is not recommended in patients with a high clinical probability of PTE. This is because a normal result in them does not exclude PTE and a positive result does not confirm PTE. It is useful in patients with low or intermediate probability where a negative result virtually rules out PTE. The confirmation of PTE requires an imaging via ventilation perfusion lung scan or CTPA. The V/Q scan is a relatively inexpensive technique with a low risk of radiation exposure. The finding of an abnormal perfusion scan showing a high probability for PTE confirms the diagnosis. But it is not available in most centers, and the results are inconclusive in 50% of the cases due to high inter-observer variability in interpretation [7]. Also, it will not be useful in this case because of COPD [8]. The CTPA is the imaging method of choice for PTE. It allows adequate visualization of the pulmonary arteries down to the sub-segmental level. Unlike the V/Q scan, the inconclusive results with CTPA is only 3 - 5% and it can provide alternate diagnosis if PTE is excluded. The CTPA has a sensitivity of 83% and a specificity of 96% in PTE diagnosis [7]. So, the CTPA is preferred over V/Q scan.

The need for CTPA in a patient with clinical suspicion of DVT leg and PTE can be assessed based on the CUS results. The diagnosis of PTE is accepted if the CUS shows a proximal DVT. However, in our patient, the pulmonary findings were unusual for PTE. This warranted confirmation with the CTPA along with CUS. The CUS in our patient showed right femoral and popliteal vein thrombosis. The CTPA showed filling defects in the left and right pulmonary arteries supporting a diagnosis of DVT of the right leg with PTE (Figure 3).

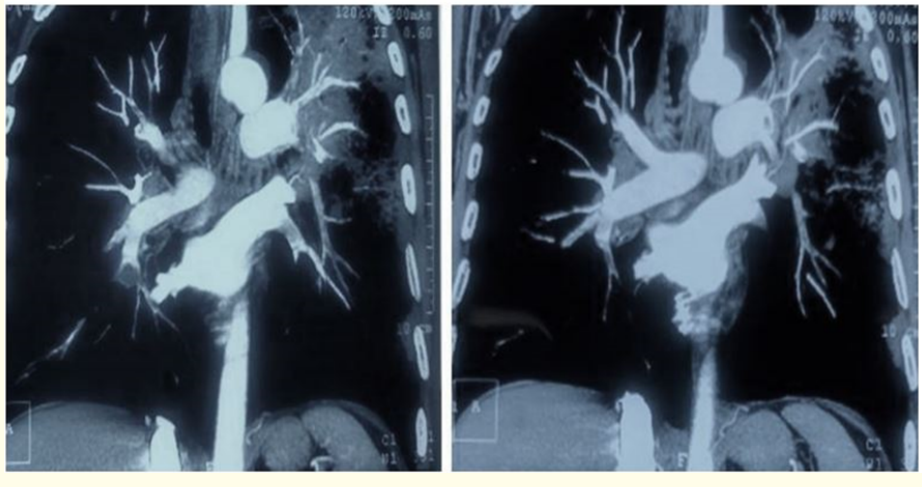

Figure 3: *Computed tomography pulmonary angiography in coronal section.*

Q.4. What should be the ideal management option for this case?

a. Anticoagulation therapy alone

b. Thrombolysis

c. Both antibiotics and anticoagulation therapy

d. Surgical resection

Answer. b. Anticoagulation therapy alone

Once a diagnosis of PTE is confirmed, further optimal management depends on stratifying the patient into classes of disease severity according to the individual's early mortality risk. The clinical tools used to stratify patients into high, intermediate and low risk of early mortality are the presence of hemodynamic instability, Pulmonary Embolism Severity Index (PESI) score and imaging as well as laboratory markers of right ventricular dysfunction. Our patient was hemodynamically stable, PESI clinical score was 94 (class III) and cardiac biomarker troponin-T was negative. He belonged to intermediate-low risk category. Such patients need to be put on anticoagulation and monitored for haemodynamic parameters. For the treatment of PTE without haemodynamic compromise, parenteral or oral anticoagulation without reperfusion techniques is adequate. The rescue thrombolytic therapy is recommended for patients with haemodynamic deterioration on anticoagulation treatment, as the risk of potentially life-threatening bleeding complications are too high for the expected benefits if there is no hemodynamic instability [7].

The fever in PTE responds well with the initiation of anticoagulation alone with resolution achieved within 72 hours in majority of the cases [9]. The previous studies have shown adding antibiotics provided no benefit in PTE [10,11]. In fact physician apprehension towards fever leads to unwarranted use of antibiotics which results in increased adverse events and drug resistance. The lung cavities which do not alleviate by conservative treatment or leads to subsequent lung abscess are managed by surgery [12]. As our patient was hemodynamically stable and fever was due to PTE, anticoagulation therapy alone should be ideal management.

Q 5. Which anticoagulant should be preferred in this patient?

a. Non vitamin K antagonist oral anticoagulant (NOAC)

b. Low molecular weight heparin (LMWH)

c. Fondaparinux

d. Unfractionated heparin (UFH).

Answer. a. Non vitamin K antagonist oral anticoagulant (NOAC)

Anticoagulation is usually done with subcutaneous, weight adjusted low-molecular weight heparin (LMWH) or fondaparinux or intravenous unfractionated heparin (UFH). An equally rapid anticoagulant effect can also be achieved with a NOAC. If anticoagulation is initiated parentally, LMWH or fondaparinux is recommended over UFH. This is because, LMWH or fondaparinux have a fewer recurrent thromboembolic events, carry a lower risk of thrombocytopenia, lower mortality, more predictable pharmacokinetics, a longer plasma half-life making once or twice daily administration possible and do not need routine monitoring compared to UFH. The use of UFH is largely restricted to patients with overt haemodynamic instability or imminent haemodynamic decompensation in whom primary re-

perfusion treatment will be necessary. The UFH is also recommended for patients with serious renal impairment or severe obesity. The dosing of UFH is adjusted based on the activated partial thromboplastin time [7].

When oral anticoagulation is started in a patient with PTE, a NOAC is recommended over vitamin K antagonist (VKA). The NOACs are not inferior to initial LMWH therapy followed by VKA treatment in the prevention of recurrent VTE. Moreover, NOACS do not need monitoring routinely and have a lower all-cause mortality driven primarily by a decrease in fatal intracranial bleeding risks [7]. Therefore, the NOACs have become the agents of first choice in the treatment of acute and extended treatment of PTE for most patients.

Q6. What should be the duration of anticoagulant in this patient?

a. 3 months

b. 6 months

c. 12 months

d. Indefinite duration

Answer. a. 3 months.

The aim of anticoagulation in PTE is to complete the treatment of the acute episode and prevent long-term recurrence. Therapeutic anticoagulation is recommended for ≥ 3 months for all patients with PTE. Beyond this period, the balance between the risk of recurrence after discontinuation of anticoagulant treatment and that of bleeding should be balanced. Table 2 shows the categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long term. Our patient had major transient/reversible risk factor. He was confined to bed in hospital for 4 days due to acute exacerbation of COPD. Thus he had a low risk of recurrence. It is recommended that the treatment for such patient is discontinued after 3 months [7].

a) Major transient or reversible risk factors are associated with >10-fold increased risk for the first VTE event and have low (<3% per year) risk of recurrence. Examples: • Surgery for >30 min under general anaesthesia. • Acute illness or acute exacerbation of a chronic illness enclosed to bed in hospital for ≥ 3 days. b) Minor transient or reversible factors associated with ≤10-fold increased risk for first VTE or no identifiable risk factor have intermediate (3 - 8% per year) risk of recurrence. Examples: • Minor surgery under general anaesthesia for < 30 min. • Admission to hospital for < 3 days with an acute illness. • Oestrogen therapy/contraception. c) Non-malignant persistent risk factors have intermediate (3 - 8%per year) risk of recurrence. Examples: • Inflammatory bowel disease. • Active autoimmune disease. d) Risk factors have high (> 8 per year) risk of recurrence. Examples: • Active cancer. • One or more previous episodes of VTE in the absence of a major transient or reversible factor. • Antiphospholipid antibody syndrome.

Table 2: *Categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long term if anticoagulation is discontinued after the first 3 months.*

Our patient was managed with the NOAC, apixaban at a dose of 10 mg twice daily for 7 days and then discharged with 5 mg twice daily for three months. His fever subsided and the leukocyte count decreased to 9,300/mm^3 by the third day after initiation of apixaban. There was radiological resolution of lung cavities by the seventh day (Figure 4).

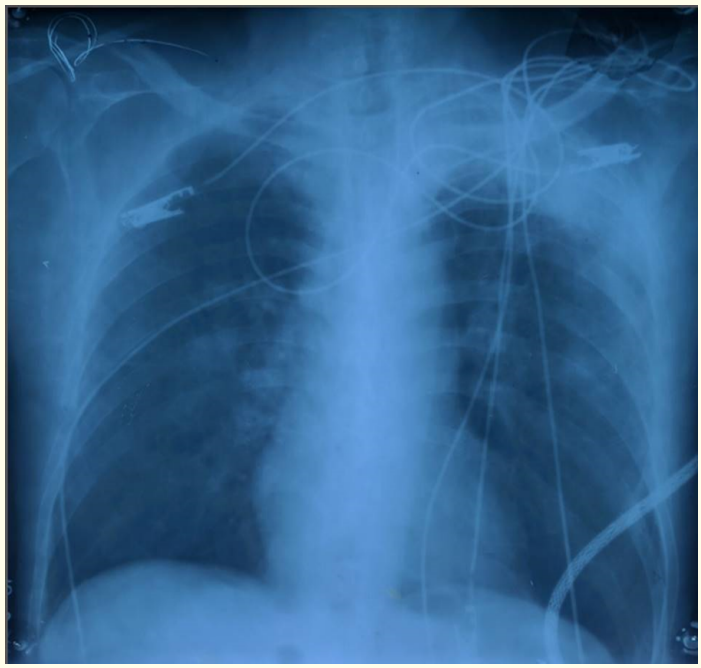

Figure 4: *Chest radiograph of the patient in postero-anterior projection after 7 days of initiation of anticoagulation.*

Discussion

The clinical signs and symptoms of PTE are non-specific. In most cases, the patient presents with dyspnoea, chest pain, pre-syncope or syncope, or haemoptysis. The fever also has long been recognized as an accompanying sign of PTE [13]. The etiology of fever in PTE has not yet been fully clarified. It may be due to local inflammation secondary to vascular irritation and/or the release of chemotactic factors due to tissue necrosis and hemorrhage with occult super-infection [14].

In addition to symptoms, the predisposing factors for PTE are important in determining the clinical probability of PTE. However, in 40% of patients with PTE, no predisposing factors are found [7]. The COPD, prolonged bed rest and prolonged periods of sitting as in drivers are considered risk factors for PTE. The patients with severe COPD have a 1.6-fold higher risk of VTE [6]. The PTE is usually associated with DVT leg. The earlier studies have shown that the CUS showed a DVT in 30 - 50% of patients with suspected PTE and venography showed DVT in 70% of patients with proven PTE. So, finding a proximal DVT inpatients of suspected PTE is considered sufficient to start anticoagulant treatment [7].

Acute PTE leads to pulmonary infarction in only 10% of cases because of the dual blood supply of the lungs. The pulmonary infarction causes cavitation in 4 - 7% of cases [15]. The pulmonary infarct of size > 4 cm, old age and chronic lung disease are risk factors for pulmo-

nary cavitation [16]. The lung cavity may result from either secondary infection of the infarcted tissue or sterile necrosis [17]. The patient in the present case exhibited aseptic cavitation after a sterile pulmonary infarction.

A challenge presented managing cavity with fever in a COPD patient is to exclude an infectious etiology such as community acquired pneumonia, pulmonary tuberculosis, non-tuberculous mycobacteria since all these may present with fever, chest radiograph abnormalities and increased leukocyte counts [4]. This leads to unnecessary use of antibiotics targeting the fever alone. The excessive use of antibiotics leads to increased adverse events and resistance of the microbiota [9]. The majority of patients of pulmonary embolism with fever recover with anticoagulation and early mobilization. The surgical resection is the therapy of choice for lung cavities not responding to conservative treatment or leading to subsequent lung abscess [12].

The choice of anticoagulation frequently depends upon clinician experience and availability, the risks of bleeding, patient comorbidities, preferences, cost, and convenience. The patient values and preferences are critical in selecting a long-term agent for anticoagulation in VTE. Oral agents are preferred for most hemodynamically-stable, non-pregnant patients who do not have renal insufficiency or active cancer. The NOACs have major pharmacologic advantages over warfarin including rapid onset/offset of action, fewer drug interactions and predictable pharmacokinetics [7]. All the patients should be assessed for bleeding risk before and during anticoagulant therapy. The table 3 shows the risk factors associated with bleeding. The bleeding risk evaluation should be used for deciding the duration and regimen/dose of anticoagulant treatment after PTE [7].

S. No.	Risk factor
1	Advanced age (particularly > 75 years).
2	Previous bleeding (if not associated with a reversible or treatable cause) or anaemia
3	Active cancer
4	Previous stroke, either haemorrhagic or ischaemic;
5	Chronic renal or hepatic disease
6	Concomitant antiplatelet therapy or non-steroidal anti-inflammatory drugs (to be avoided, if possible)
7	Other serious acute or chronic illness
8	Poor anticoagulation control

Table 3: *Risk factors for bleeding with anticoagulant therapy.*

Conclusion

The CT of the chest in combination with an appropriate clinical and laboratory background is required in evaluating the lung cavities. Severe COPD and prolonged bed rest are risk factors for PTE. If a patient presents to physician with fever and cavitatory lung lesion with an unclear diagnosis, PTE should be suspected. The CUS and CTPA are the diagnostic modalities of choice for confirming DVT and PTE respectively. The anticoagulation therapy of 3 months duration is adequate in the treatment of cavity due to acute PTE secondary to a major transient or reversible risk factor.

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