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Case Report

Massive pulmonary embolism – what you may be missing?

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ABSTRACT

Our patient is a 68-year-old woman with no known comorbid illnesses, who presented with fever, cough and haemoptysis of 20-days duration. The fever was insidious in onset, intermittent, high grade and was associated with productive cough. There were intermittent episodes of scoughing up of blood-tinged sputum mixed with clots. She was evaluated at another centre and was diagnosed with a pulmonary embolism based on a computed tomographic imaging of the thorax. When she presentation to us, she was hemodynamically stable and her systemic examination was within normal limits. Her computed tomography (CT) scan were reviewed and she was labelled to have an intermediate risk pulmonary embolism. She was initiated on Injection enoxaparin and was simultaneously evaluated for the aetiology of her illness wherein an USG guided supraclavicular lymph node biopsy lead to a diagnosis of extrapulmonary tuberculosis. She was initiated on first line ATT and was discharged on the same. Anticoagulation was continued on discharge. She is currently doing well on follow up. Our objective is to shed light on the association between tuberculosis and pulmonary embolism and to emphasize the need for a thorough evaluation to identify an occult infective focus in patients presenting with venous thromboembolism.

Keywords: Extrapulmonary tuberculosis, Pulmonary embolism, Pyrexia of unknown origin

INTRODUCTION

Pulmonary embolism is a medical emergency and a high index of suspicion is prudent for diagnosis. Patients often present with subtle clinical signs without obvious hemodynamic instability, posing a challenge in arriving at an early diagnosis.[1] Infections are known potent risk factors for the development of deep venous thrombosis and pulmonary embolism. This is attributed to various factors but notably an imbalance between the pro – and anti-coagulant pathways.[2] More often than not, occult long standing infections could be overlooked and no provocating factor is identified. The strong association between tuberculosis and pulmonary embolism has been noted as early as the 1950's in autopsy studies and since then multiple case reports have been published since then proclaiming the same.[3] With advances in the diagnostics of tuberculosis and the increasing identification of extra pulmonary tuberculosis, it is no longer an infection which is difficulty to pick up. The curious clinical mind would not easily label a pulmonary embolism as unprovoked before a meticulous search for all potential triggers.

CASE REPORT

Our patient was a 68-year-old woman who presented with a history of fever and cough for the past 20 days. The fever was insidious in onset, high grade, intermittent, associated with chills and rigors without diurnal variation. The cough was insidious in onset, intermittent, productive with minimal mucoid sputum production occasionally mixed with streaks of blood and clots. There was associated history of gradually worsening breathing difficulty on exertion up to modified medical research council (mMRC) grade 3 during this period with no complaints at rest. She did not give a history of chest pain, palpitations, syncope, bleeding from any other site, abdominal pain, lower urinary tract symptoms, loss of weight or appetite,

headache with neck stiffness, skin rash, altered behaviour or abnormal movements. She presented to another hospital prior to arrival at our centre where her initial electrocardiography (ECG) was within normal limits. Her chest X-ray revealed an upper lobe fibrotic lesion and contrast enhanced computed tomography (CECT) chest showed large thrombi in the right and left main pulmonary arteries, the left gonadal and renal vein. She then arrived at our centre.

Past medical history

There was no history of recent surgeries or immobilisation. There was no history of trauma. She did not give a history of miscarriage. She had no known comorbid illness and there was no past history suggestive of a thromboembolism. Her family history was unremarkable.

Treatment history

She was initiated on injection enoxaparin prior to arrival at our centre.

Clinical examination

On presentation, she was febrile, alert, oriented and not in distress. She was tachycardic with a pulse rate of 110/min. Her blood pressure was 110/70 mm Hg and SpO_2 was 98% on room air. Her general examination revealed an enlarged left supraclavicular node of 1 cm in size which was firm, non-tender, freely mobile and with no overlying skin changes. Her cardiovascular, respiratory, abdominal and central nervous system examination were within normal limits.

Differential diagnosis

Our patient had initially presented with fever and cough with haemoptysis. Her clinical syndrome was suggestive of a lower respiratory tract infection. Given the history of haemoptysis, the possibility of underlying bronchiectasis was considered. Other differentials included pulmonary tuberculosis with bronchial artery invasion, an aspergilloma, lung abscess, necrotising pneumonia or a lung malignancy.

As the patient was already diagnosed with a pulmonary embolism, our focus shifted to the aetiology behind the same. An underlying malignant process was a strong suspicion considering the presence of a left supraclavicular lymph node. It was also prudent to rule out autoimmune disorders like systemic lupus erythematosus (SLE), antiphospholipid antibodies (APLA), antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis and anti-glomerular basement membrane (anti-GBM) disease as the thromboembolism could be the initial manifestation though she had no suggestive history. Though rare considering the late presentation, an inherited thrombophilia was a possibility. An occult infection was last on the cards.

Approach to diagnosis

On evaluation (Table 1), she was found to have a normal complete blood count, renal function and liver functions tests. Her inflammatory markers were elevated: C-reactive protein (CRP) 44 mg/l and erythrocyte sedimentation rate (ESR) 40 mm/1 hour. D-dimer was elevated at 1.31 mg/l. Thrombophilia panel which includes protein C, protein S, MTHFR mutation, pomocysteine levels, beta 2 glycoprotein, anti-cardiolipin and lupus anticoagulant, was sent which was positive for a heterozygous factor V R2 mutation. Homocysteine levels were within normal limits. Urine routine was normal and urine culture sterile. Blood cultures were sterile. HIV antibody test, HbsAg and anti HCV were negative. Sputum gram stain, KOH, AFB and Gene Xpert were negative. Sputum culture was sterile. Her autoimmune workup was within normal limits: ANA by IIF, C- ANCA, P-ANCA and ANA profile was negative. In view of no identifiable trigger for the embolism and the persistence of fever, we went ahead with a whole-body PET CT scan which revealed multiple FDG avid lymph nodes in the axillary- level 1, 2 and 3, abdominal, bilateral supraclavicular and mediastinal regions along with bilateral pleural effusion (Figure 1). A left supraclavicular lymph node biopsy was done under local anesthesia by the surgical team which revealed granulomatous lymphadenitis. Serum ACE levels was normal. The lymph node aspirate was negative for AFB stain, gram stain, KOH mount and routine culture. However, Gene Xpert for Tb was positive.

Table 1: Baseline laboratory investigations.

Laboratory parameter	Value
Hemoglobin (g/dl)	10.7
Total leucocyte count (thou/ul)	11.6
Platelet count (thou/ul)	246
Blood urea nitrogen/serum creatinine (mg/dl)	15.8/1.11
Sodium/potassium (mEq/l)	134/3.64
Total bilirubin/direct bilirubin (mg/dl)	0.7/0.4
AST/ALT (IU/l)	34/37
ALP/GGT (IU/l)	70/72
PT/INR (seconds/1.1)	12.8
APTT (seconds)	38
CRP (mg/l)	49
D dimer (ug/ml)	1.31
Fibrinogen (ug/ml)	2.62

AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; INR: international normalized ratio; MCV: mean corpuscular volume; MCHC: mean corpuscular haemoglobin concentration; MCH: mean corpuscular haemoglobin

SI conversion factors

To convert leukocyte count to 109, multiply by 0.001; haemoglobin to grams per liter, multiply by 10; platelets to 109/l, multiply by 1.0; urea to millimoles per liter, multiply

by 0.357; creatinine to millimoles per liter by 88.4; sodium and potassium to millimoles per litre, multiply by 1; bilirubin to micromoles per litre, multiply by 17.104; ALT, AST to microkatals per liter, multiply by 0.167.

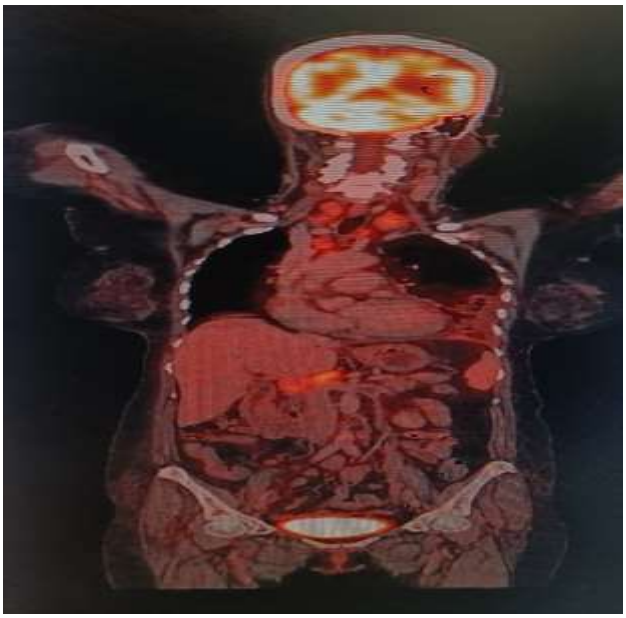

Figure 1: Whole body PET CT showing FDG avid bilateral supraclavicular, mediastinal and para-aortic lymphadenopathy.

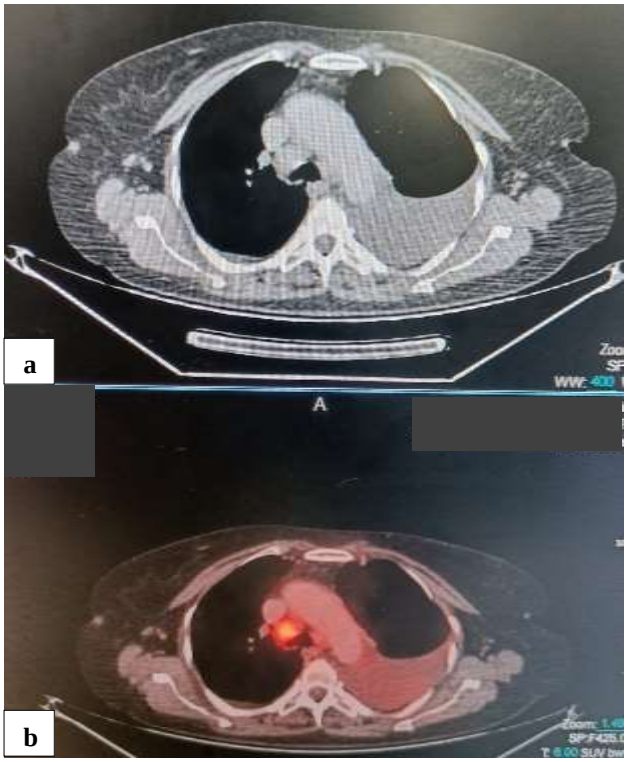

Figure 2: (a) CT chest showing mediational lymphadenopathy and pleural effusion, and (b) PET CT showing increased FDG uptake in the right mediastinal node with no active uptake in the pleural effusion.

Treatment and follow up

She was continued on injection LMWH 0.6 ml subcutaneous twice daily. Despite her massive thrombus load she was hemodynamically stable and was hence risk stratified as an intermediate risk pulmonary embolism patient. There was no indication for a surgical or endovascular intervention or for thrombolysis. She was initiated on first line ATT agents. She tolerated therapy well and was discharged on the same medications.

However, TB Gene Xpert was positive and no rifampicin resistance was detected. At follow up, patient was hemodynamically stable with no complaints of fever or dyspnea on exertion. Her cough had significantly resolved with no further episode of hemoptysis. In view of a deranged LFT, her ATT was modified. After 2 weeks of injectable anticoagulation, she was switched to rivaroxaban which she tolerated well and was put on modified ATT in view of severe gastritis.

DISCUSSION

Pulmonary embolism secondary to active tuberculosis has been well described in literature. The earliest report was an autopsy study from 1958 where among 23.1 percent from a total of 634 autopsies had pulmonary embolism in which 111 cases of tuberculosis were found.[3] The largest pool of evidence is from a retrospective analysis in 2009 by Hyerin et al where among 7905 patients with active tuberculosis, 0.6% has thromboembolism.[4] It is a known fact that infections trigger thromboembolism. However, it is indeed difficult to prove causation as opposed to a temporal relationship between the two. Nevertheless, the pathogenesis of a thromboembolic state in active tuberculosis has been well understood. It has been elucidated that active tuberculosis leads to an imbalance between prothrombotic and antithrombotic factors with elevations in plasma fibrinogen, fibrin degradation products (FDP), tissue plasminogen activator (t-PA) and inhibitor (PAI-1) and depressed antithrombin III levels leading to a prothrombotic state.[5,6] Direct endothelial injuries can be attributed to endovascular spread of tuberculosis coupled with complement mediated cell damage. Further, enlarged lymph nodes lead to direct venous compression.[7,8] In short, tuberculosis fulfils the various components of the Virchow's triad.

Management of pulmonary embolism is based on the 2019 ESC guidelines.[5] Acute managements is based on the severity of the disease where a patient is classified into high, intermediate or low risk. High risk candidates require thrombolysis or surgical intervention. Intermediate risk patients are managed with parenteral anticoagulation and low risk patients can be managed with oral anticoagulation. Duration of treatment is based on the underlying etiology of the embolism. Indefinite duration of anticoagulation is recommended for those with a PE with no identifiable risk factor or with a persistent risk factor such as APLA syndrome. In those with reversible

risk factors, a minimum of 3 months of anticoagulation is recommended. Further extension can be considered in the event based on the underlying risk factor.

The role of NOAC's in pulmonary embolism has been well debated with current guidelines recommending NOAC's as first line for low-risk patients. Rifampicin being a strong inducer of CYP3A4, hinders the use of NOAC's barring rivaroxaban with dose adjustments.[10]

Our patient was risk stratified into the intermediate risk category. She was initiated on injection enoxaparin at therapeutic dose of 60 mg twice daily given subcutaneously. She was subsequently initiated on first line ATT as per the RNTCP guidelines with tablet rifampicin, isoniazid, pyrizinamide and ethambutol with pyridoxine supplementation. She was discharged on the same regimen. Since she required a minimum of 6 months of treatment with ATT for lymph node tuberculosis, it was decided to continue her anticoagulation for the same duration. During follow up, her ATT was modified in view of deranged liver function. Her anticoagulation was switched to tablet rivaroxaban. She is currently doing well on follow up with resolution of the pleural effusion of follow up chest X-ray.

CONCLUSION

In patients who present with a pulmonary embolism without any obvious underlying cause, one should keep a high index of suspicion for tuberculosis especially in India where the burden of the disease is high. A detailed and systematic work up is necessary to rule out known triggers of the same, prior to arriving at a diagnosis of an unprovoked embolism.

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