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CASE REPORT

Pulmonary Tuberculosis Induced Coagulation Disorder - A Case Series.

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ABSTRACT:
Active pulmonary tuberculosis may be complicated by deep vein thrombosis, pulmonary embolism ,cardiac ischemic events , associated with a hypercoagulable state secondary to the inflammatory state due to by enhanced activation of coagulation (elevated plasma levels of thrombin- antithrombin complexes, D-dimer and fibrinogen) together with impaired anticoagulant mechanisms (reduced plasma levels of antithrombin, protein C activity, free protein S, and protein C inhibitor). Often pulmonary tuberculosis patient associated with reactive thrombocytosis due to increased levels of interleukin 6 the degree of thrombocytosis correlates significantly with the degree of inflammation (21) its also act as attributed risk for hypercoagulability state , Vascular complications associated with infection by *Mycobacterium tuberculosis* have been reported in the literature that occurred in 1.5–3.4% of TB infection [1], One-third of patients with symptomatic venous thromboembolism (VTE) manifest pulmonary embolism, whereas two-thirds manifest deep vein thrombosis (DVT). Overall, 25%–50% of patients with first-time VTE have an idiopathic condition, without a readily identifiable risk factor, and its association with tuberculosis (TB) is a rare occurrence. Deep venous thrombosis has been associated with 1.5%–3.4% cases of TB. Early initiation of anti-TB treatment along with anticoagulant therapy decreases the overall morbidity and mortality associated with the disease. We report Four cases of DVT with pulmonary embolism and one case of ischemic cardiac events (myocardial infarction) associated with pulmonary TB ,who were diagnosed due to high index of suspicion as the risk factors for the development of coagulation disorder were present in these cases.

Keyword's: CTPA, DVT, VTE ,AKT ,MMRC ,HRCT ,2D ECHO etc.

INTRODUCTION:

India is the second most populated country in the world and it contributes to 23% of the incident cases of tuberculosis (TB) annually out of total 9.6 million incident cases of TB worldwide.[2] Being a chronic disease, TB has a long-lasting effect on the human body with complications which are less common and may be life-threatening. Although a rare event, deep vein thrombosis (DVT) has been associated with TB in 1.5%–3.4% of cases.[3] patients who are at high risk of developing venous thromboembolism (VTE). We aimed to investigate the impact of pulmonary tuberculosis on pro- and anticoagulant mechanisms related manifestation as coagulation disorders thrombo-embolism events like deep vein thrombosis, pulmonary embolism, coronary ischemic events .It is pivotal to identify TB patients who are at high risk of developing venous thromboembolism (VTE).

METHODS:

This observational study with analysis done at RCSM GMC in Kolhapur, Maharashtra (INDIA). Indore patient at this tertiary care center, who was diagnosed as pulmonary tuberculosis clinical as well as microbiologically confirmed pulmonary tuberculosis related coagulation disorder, 4 patients with primary lung TB coagulation disorder with its management put forward as a case series.

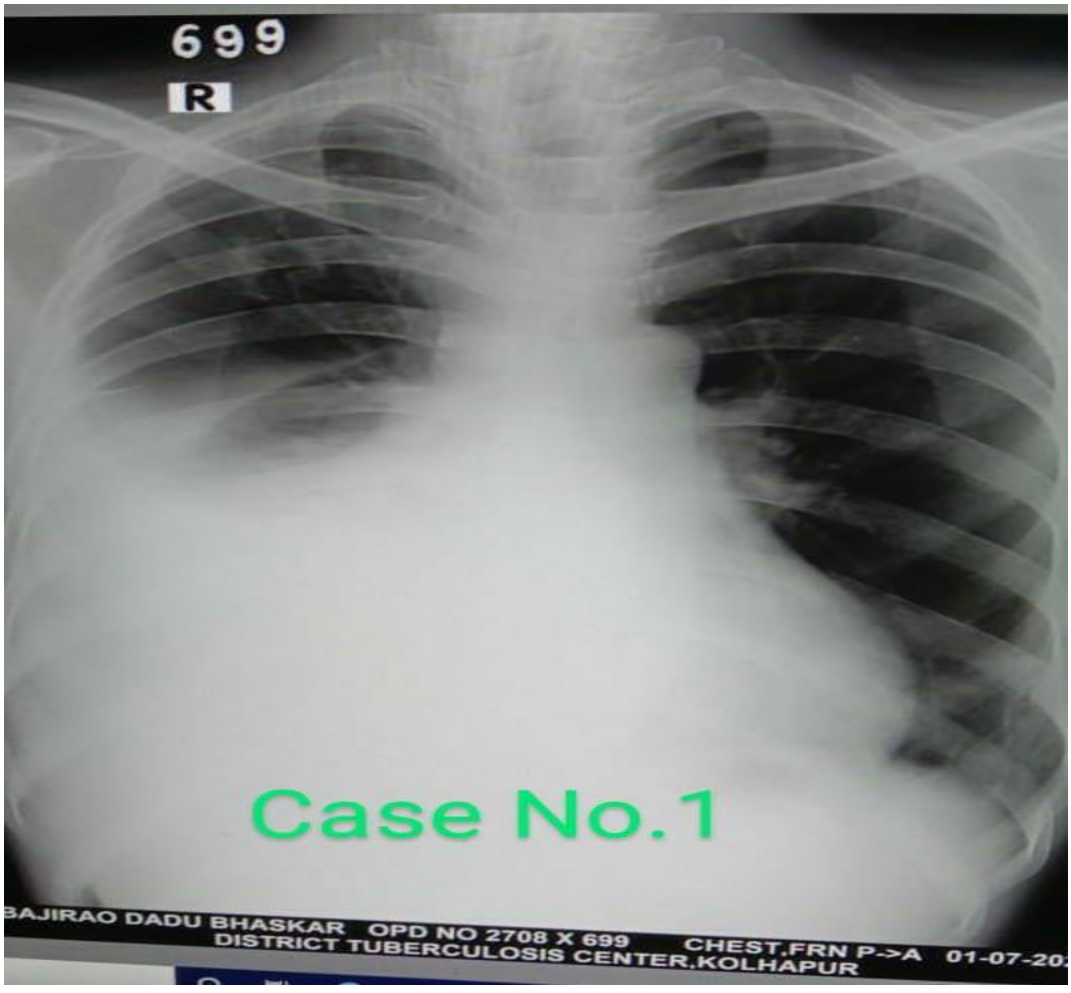
CASE REPORTS:

Case 1:

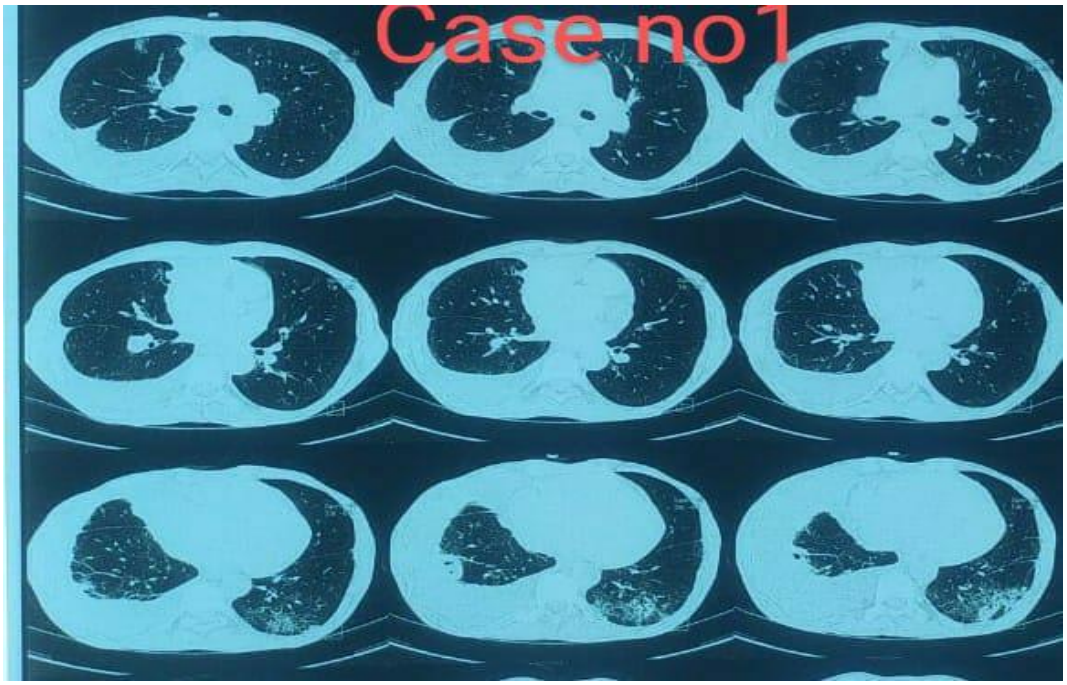
A 50-year-old male, farmer, chronic alcoholic was admitted with exertional breathlessness grade II (MMRC) with cough, bilateral painful swelling of the both lower limb for 5 days duration. He also complained of fever and productive cough for the past 1 months.no major medical, surgical illness in past, **On examination Day 1** Pulse rate 94/min, blood press110/70 Spo2 90%,with bilateral lower limb swelling and JVP more then 10 cm,with respiratory system examination suggest breath sound decreased on right side infra scapular, infra axillary and infra -clavicular area ,Chest X-ray demonstrated right side mid zone and lower zone opacity ,likely of pleural effusion , pleural tapping report suggest exudative &lymphocytic with pleural fluid ADA 60.4 IU/L negative for malignant cells Sputum examination showed acid-fast *bacilli*-positive smear. In view of swelling and tenderness in calf, possibility of DVT was considered. Ultrasound (USG) Doppler of the bilateral lower limb revealed deep venous thrombosis in the left saphenofemoral vein, right common femoral vein, popliteal vein on HRCT plus CTPA study revealed non enhancing filling defect in right pulmonary artery with bilateral lobar & segmental branches (Figure 2) on emergency evolution with 2D ECHO findings are severe pulmonary hypertension (PASP 70 mm of Hg)moderate TR,LVEF 50%,TAPSE 14.5 mm on lab investigation HB 12.2 gm,wbc 12,200 platelet 4.4 lakh ,creatine 1.1, SGOT/SGPT 54/35 d-dimer 7.64 mg/dl, HIV/HBsAg negative ,ECG suggest sinus tachycardia with no ST or T wave changes,

TREATEMENT:

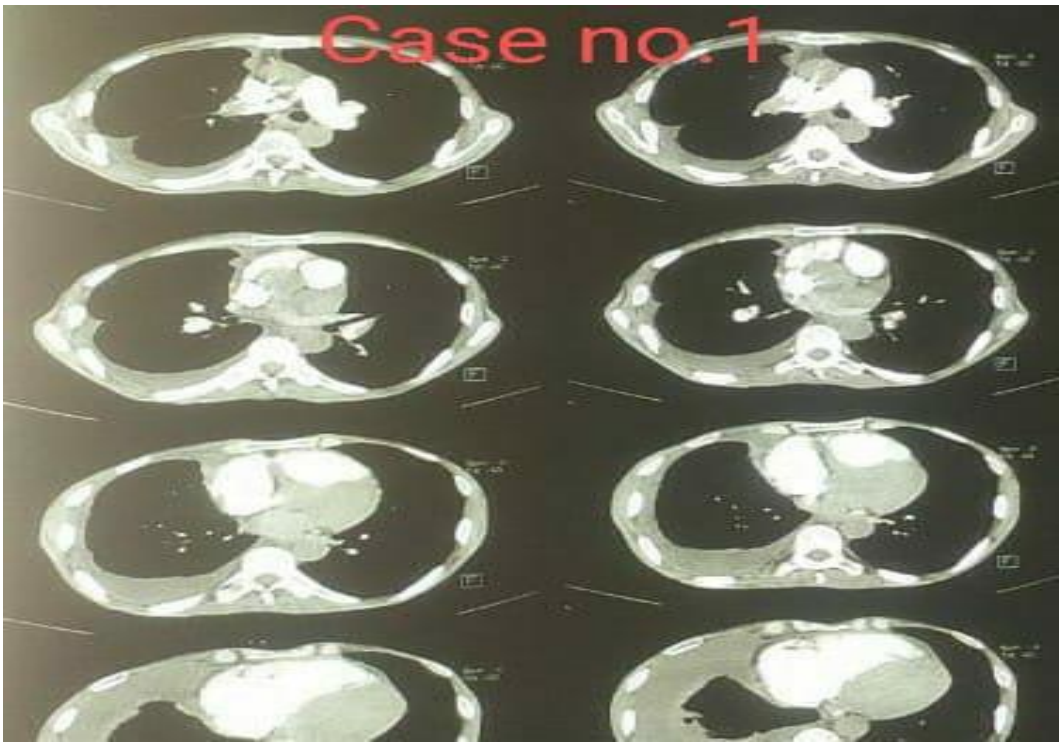
Patient was started on treatment with inject able anticoagulation -heparin infusion drip & oral ant platelet ,Anti-tuberculosis (HRZE) drugs as per weight band ,Vitals after subsequent clinical examination bp fall down to 88/40 mm of Hg with increased respiratory rate 36/min,spo2 86% on room air in ICU was treated with thrombolytic agent streptokinase one bolus dose follow by controlled thrombolytic agent infusion over 24 hr. duration as per cardiologist consultation . was treated with mechanical ventilator support had worsen respiratory failure with cardiogenic shock and died on day 10.



CHEST X-RAY (case no 1) right side mid zone lower zone homogenous opacity - moderate pleural effusion with right upper zone nodular infiltration.



HRCT image (case no .1) right side tuberculosis related pleural effusion with right middle lobe cavitation consolidation & left lower lobe nodular opacity.



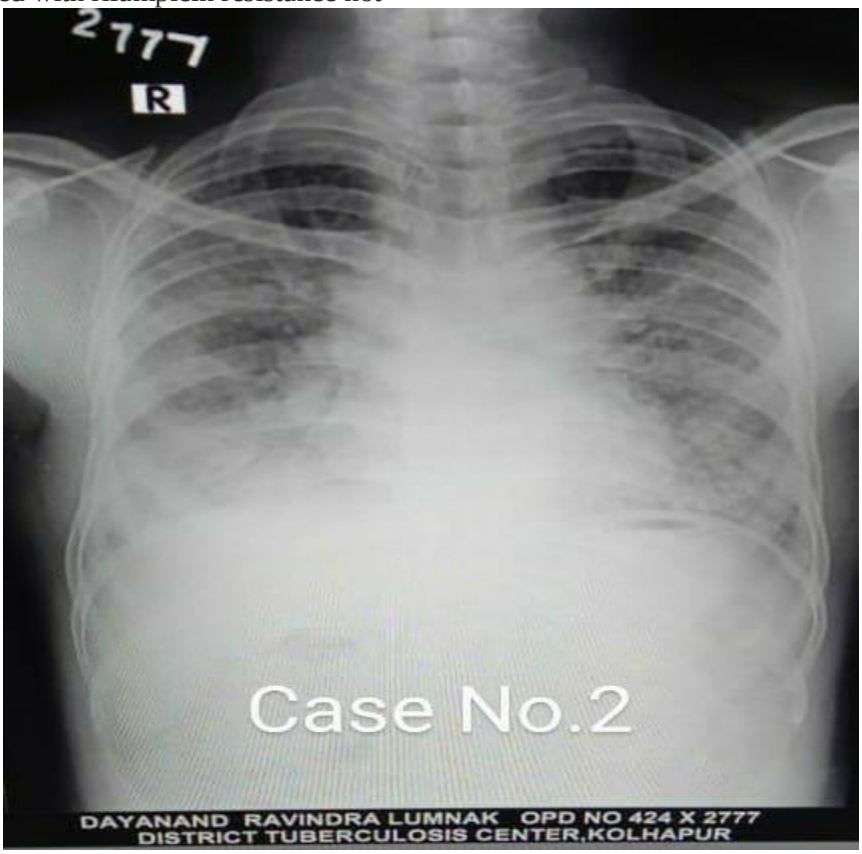
CTPA Image (case no 1) right pulmonary artery hypodense filling defect present with moderate pleural effusion

CASE 2:

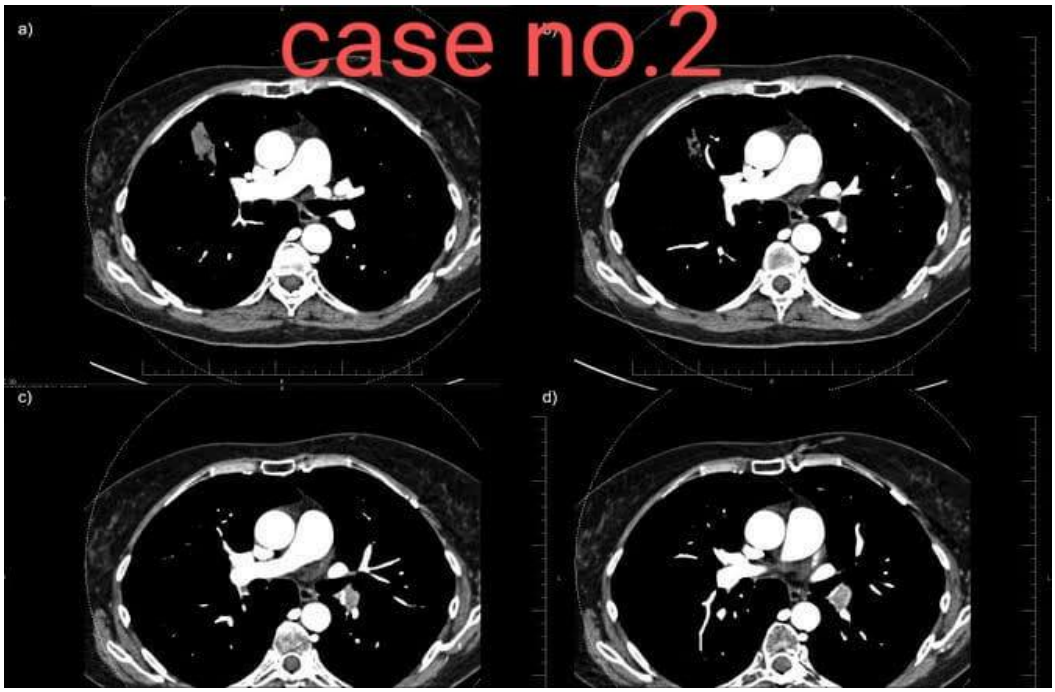
A 38 yrs. male, construction worker, chronic alcoholic, tobacco chewer admitted in view of breathlessness and left lower limb pain in the last 15 days, no history of any comorbidities, On examination pulse rate 120/min, Bp 110/70 mm of Hg, SPO2 90% on room air On auscultation bilateral side infra scapular fine crepitation present Lab investigation: Hb 10.5gm, wbc 8400, platelet 1.0lk, creatinine 0.9 mg, D –dimer 2.3 mg, Chest x ray having, right &left side mid zone, lower zone nodular infiltration. on left lower limb Doppler having complete obstructing thrombus is noted at CFV which is enteding to left PV, SFV, DFV Sputum CBNAAT examination Mtb detected with rifampicin resistance not detected. 2D ECHO , having Good biventricular function, TAPSE 20mm,No RWMA, IVC normal and collapsing, HRCT & CTPA ; Necrotizing pneumonia at right lower lobe suggest infective etiology , Acute Pulmo-thromboembolism in left upper ,lower segmental pulmonary pulmonary arteries

TREATMENT:

Patient started on Anti-tuberculosis drugs(HRZE)as per weight under NTEP and heparin infusion and on overlap with oral anti coagulation on day 3 ,tab. Rivaroxaban was continue patient vitals ,breathlessness improved and discharged in stable condition



Chest x-ray (case no 2) bilateral mid zone lower zone nodular opacity with consolidation .



CTPA (case no. 2) Left side segmental &sub pulmonary artery filling defect (acute pulmonary embolism)

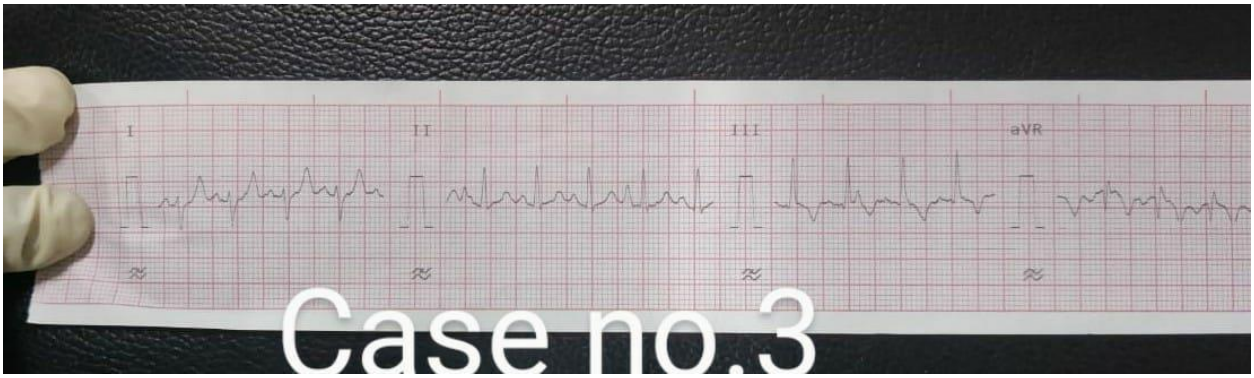
CASE 3:

A 41yr, Male chronic alcoholic, farmer by occupation came to hospital with symptoms of exertion breathlessness, cough with mucopurulent expectoration, had previous history of pulmonary tuberculosis 1yr ago.

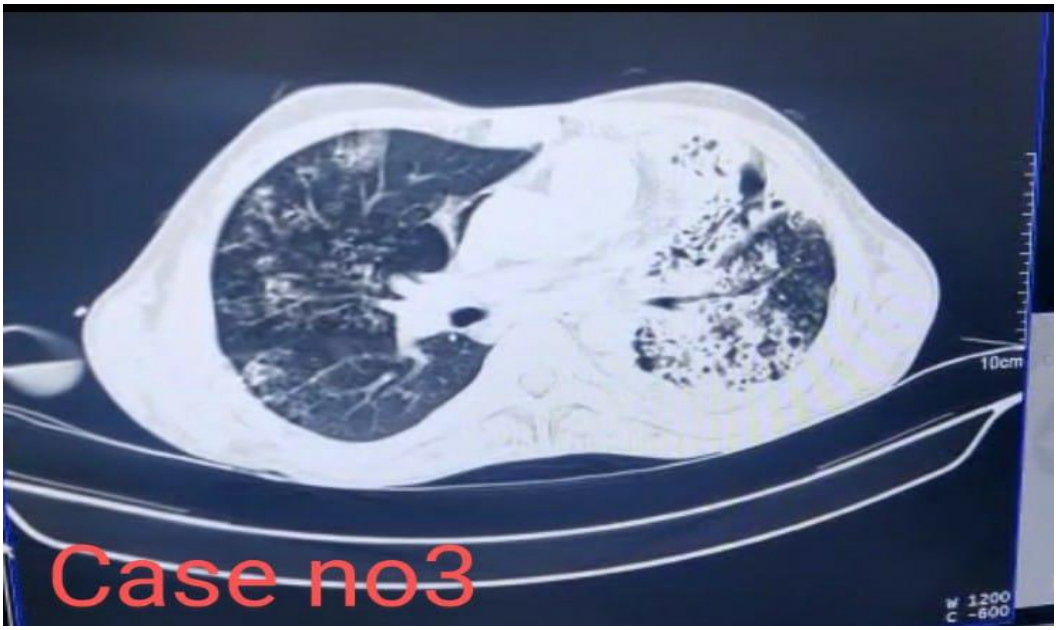
On examination:

Heart rate 122/min, Respiratory rate 30 cycles /min, blood pressure 118/70 mm of Hg,

On Auscultation bilateral fine to coarse crepitation. On chest x-ray, having bilateral lung upper zone fibrotic and cavitation changes, sputum ZN stain AFB bacilli present. HRCT CHEST and CTPA : bilateral upper lobe fibro-bronchiectasis changes, with tree in bud appearances, simultaneously CTPA ,which revealed hypodense filling defect at right main lower lobe branch of pulmonary artery With ECG having typical S1Q3T3 pattern



Lab investigation: Hb 11.5 gm,cbc 17500,platlet 1.5 lakh ,and d –dimer level 7.11 mg/dl 2d echo, normal size RA/RV with no pulmonary hypertension, EF 55% Lower limb Color Doppler filling defect in left distal CSF, CFV, SFV ,Non compressible suggest sub-Acute venous thrombosis Was treated with Anti-tuberculosis drugs (HRZE) FDC as per body weight, with Heparin 5000 IU i.v 6 th hrly then overlap with tab.warfarin 5 mg on day 3 then continue for 6 months Patient was discharged in stable condition on day 10



HRCT CHEST (case no.3) reveled extensive fibro& tractional bronchiectasis opacity with cavitation with upper lobe infectious bronchiolitis (Tree in bud appearance) present .

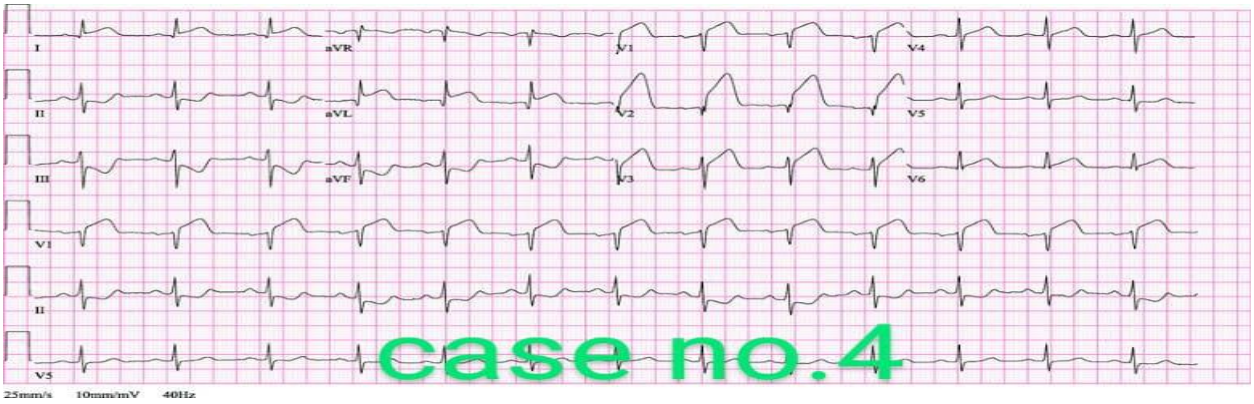
CTPA image (case no 3) Acute pulmonary thromboembolism in right pulmonary artery .

CASE 4:

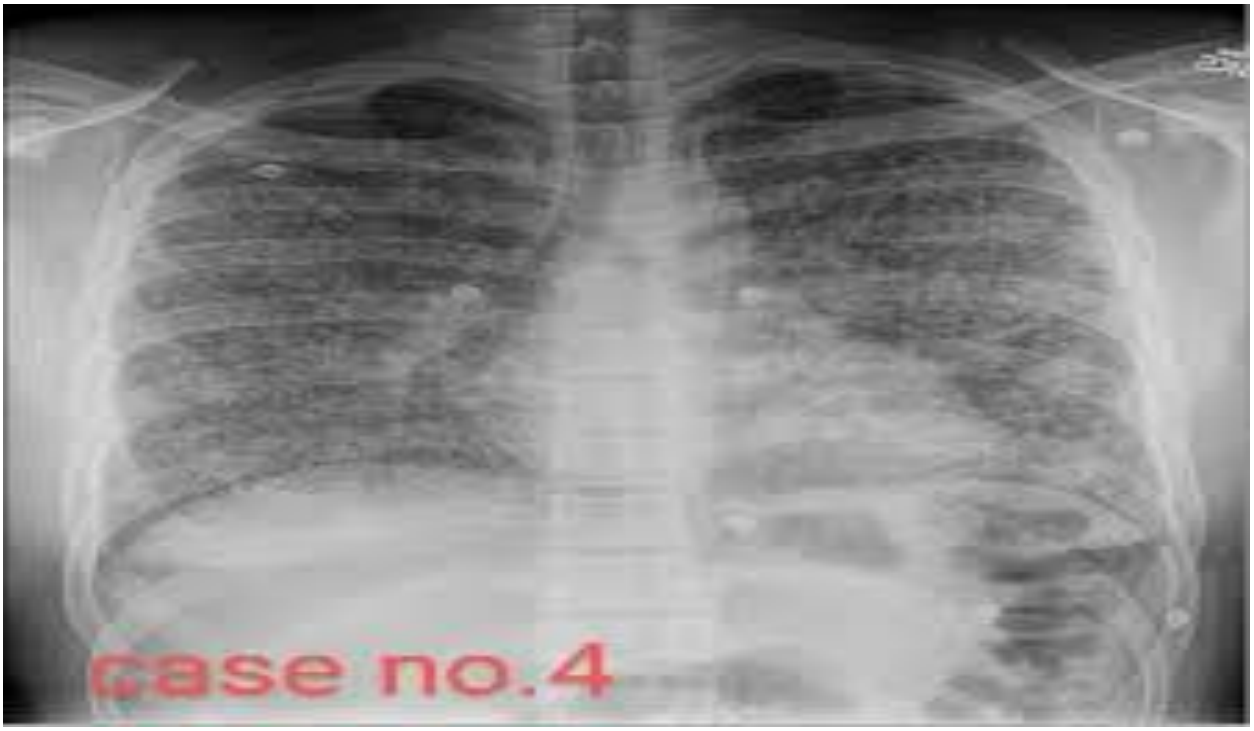
A 36 yrs. male chronic alcoholic, know case of retro viral disease, admitted with complaining of acute onset chest pain for 2 days, cough with expectoration, intermittent fever & weakness for 1 months.

On examination:

Ongoing chest pain present with sweating present, heart rate 136/min, blood pressure 100/70 mm of hg, respiratory rate 36 cycles/min, spo2 78% Ecg suggest acute Acute anterior septal wall myocardial infarct with reciprocal changes (STEMI) was managed by cardiologist with thrombolysis and emergency PTCA done by cardiologist (Angioplasty) . On x ray & HRCT chest suggest bilateral lung Miliary nodular opacity due to active pulmonary tuberculosis. On transfer to pulmonary medicine unit Review with vitals spo2 95% with 1 lit oxygen supplementation, Sputum CBNAAT study MTB detected Rifampicin resistance not detected & On 2d echo, examination Ischemic heart disease, RWMA with mild Apical, anterolateral hypokinesia with no evidence of pulmonary hypertension and EF 35% with no evidence of pulmonary embolism was started anti-tuberculosis drugs (HRZE) With injectable steroid then shifted to oral steroids and Anti-coagulation heparin and anti-platelet, Anti-retro viral drugs discharged in stable condition with Anti- tuberculosis drugs .



ECG (case no 4) Acute anterior septal wall myocardial infarct with reciprocal changes



CHEST XRAY (case no 4) bilateral all zone nodular opacity (miliary mottling) due to miliary tuberculosis present

DISCUSSION:

Pulmonary TB related extensive lung involvement causes severe inflammatory reaction with activation of cytokines & interleukins were associated with a systemic hyper procoagulant state (19), as indicated by enhanced activation of coagulation (elevated plasma levels of thrombin-antithrombin complexes, D-dimer and fibrinogen) together with impaired anticoagulant mechanisms (reduced plasma levels of antithrombin, protein C activity, free protein S, and protein C inhibitor). Activation of coagulation did not correlate with plasma concentrations of established TB biomarkers, Approximately one-third of patients with symptomatic VTE manifest pulmonary embolism (PE), whereas two-thirds manifest DVT alone. (20) VTE recurs frequently in the first few months after the initial event, with a recurrence rate of 7% at 6 months. Overall, 25%–50% of patient with first-time VTE have an idiopathic condition, without a readily identifiable risk factor. Death occurs in 6% of DVT cases and 12% of PE cases within 1 month of diagnosis.[3,4] DVT is commonly seen in postoperative patients and in patients who are admitted to the intensive care unit for a prolonged period. Its association with TB is a rare occurrence, and very few cases have been reported in literature.[5] However, increased awareness along with availability of noninvasive tests such as Doppler USGs, the number of cases of TB with associated DVT are on rise. Our cases showed that VTE may complicate severe pulmonary TB and such events can occur anytime during the disease. A possibility of DVT, CARDIAC ISCHEMIC EVENTS& VTE was kept in all four cases as they were non ambulatory and presented with limb swelling and pain. All of them responded well to the treatment with antitubercular drugs and anticoagulants except one patient worsen in due course due refractory cardiogenic shock with respiratory failure. Peripheral limb edema may be falsely attributed to hypoproteinemia in patients of TB. However, other signs such as pain and increased temperature of the affected limb are important signs that help in diagnosis of DVT. The emphasis should be laid on high index of suspicion, early diagnosis, and management of DVT in such patients. Most of the studies done in the past are retrospective in nature and have not mentioned about the treatment given and duration of treatment. In one study conducted by Kouismi et al.,[11] treatment with LMWH and warfarin was given for 3 months in 25 cases, and in three cases, treatment was extended further for 3 months. In nine patients, only enoxaparin was given due to difficulty in attaining target prothrombin time. In our case one and two, we have used enoxaparin followed by warfarin or acenocoumarol, and in case three, we have only used enoxaparin due to difficulty in attaining target INR. A study done by Bikdeli[8] in 2010 and Marjani et al. [10] in 2012 mentioned the use of color Doppler, D-dimer, and computed tomography CTPA as the diagnostic modality for diagnosis of VTE. We have used USG Doppler for the diagnosis of DVTA & CTPA to confirm site and size of VTE along with it 2D ECHO also done for evaluation of right ventricle function & to check pulmonary hypertension in one case cardiac LVEF was significantly low 35% due to myocardial infarction status due to coronary vascular disease as other means were not available. One retrospective study was done to clarify the association between TB and VTE in a multiethnic population, with a generally good level of public sanitation and low incidence of TB, using data from the United States.. No particular link was found between pulmonary TB and PE or between extrapulmonary TB and DVT. This may suggest the preponderant role of a systemic hypercoagulable state over an intrathoracic venous compression mechanism. In-hospital mortality of patients with both active TB and VTE was higher than mortality of patients with only active TB ($P < 0.001$). The conclusion of the study with all 4 cases was that TB must be considered as a potential risk factor for VTE and should be included in thromboembolism risk evaluation similar to any acute and severe infection.[12] The mechanism responsible for development of DVT in TB is unclear. All the three parts of Virchow's triad, i.e., hypercoagulability, venous stasis, and endothelial dysfunction, may play a role in pathogenesis of the disease. Increase in plasma fibrinogen and factor VIII and reactive thrombocytosis might be reasons of hypercoagulability in TB patients. Hypoprothrombinemia is seen in DVT and one-third of cases of TB have prothrombin deficiency.[7,13,14] Pro-inflammatory cytokines due to the disease process also make the vascular endothelium more thrombogenic which in turn also increase the synthesis of coagulation proteins by liver.[5,14] One study has shown that patients with active PTB have anemia, reactive thrombocytosis, elevations in plasma fibrinogen degradation products, tissue plasminogen activator, and inhibitors with depressed antithrombin III levels which may favor the development of DVT in disseminated TB.[15] Turken et al. [16] also made similar observations regarding these hemostatic disturbances in 45 patients of active TB. High frequency of antiphospholipid antibodies detected in patients with TB is also mentioned in the literature. These hematological

parameters worsen during the first 2 weeks of therapy in many cases, but they normalize after a month of ATT. The return of these hematological parameters to a normal level is a good indicator of disease control.[13] Thrombosis can also result from venous compression by lymph nodes, for example, retroperitoneal adenopathies may cause inferior vena cava thrombosis.[17] Patients of pulmonary TB having extensive disease are not ambulatory for a long duration, which is one of the risk factors of developing VTE. Studies have shown that the risk of developing deep venous thrombosis is proportional to the severity of tubercular disease as there is a close correlation between the hematological abnormalities and the severity of clinical findings of pulmonary TB. The studies have revealed that hematological abnormalities are relatively more common in severe pulmonary TB.[13,18] Studies also demonstrated a possible association between DVT and the use of rifampicin with a relative risk of 4.74 in patients treated with rifampicin-containing regimens.[2] Patient suspected with hypercoagulable state with evidence of DVT ,ECG changes, or CTPA finding suggestive of VTE, should be immediately started supplemented with anticoagulant therapy Thrombolytic agent if require and controlled anticoagulation infusion as per as hemostatic parameters and ,contraindication for thrombolysis (absolute & relative) patient clinical conditions and vitals improve during the 1st month of treatment. The use of anticoagulant therapy in these patients is also of concern due to the interaction of ATT, particularly rifampicin with warfarin analogs, drug induced hepatitis (INH, Rifampicin , pyrazinamide) and its relation with coagulation factor synthesis by liver ,rifampicin induced thrombocytopenia whose efficiency may be reduced due to enzyme induction. The newer Xa inhibitors offer several advantages over traditional therapy with parenteral anticoagulant such as faster onset of action, the lack of need for a heparin lead-in phase, and lesser bleeding events compared with standard therapy. Concomitant use with rifampicin(enzyme inducer action) leads to decrease in the plasma concentration of these drugs by 50%–54%.[29]

CONCLUSION:

In conclusion, in this study we demonstrated that pulmonary TB is associated with systemic activation of coagulation with concurrent impairment of anticoagulant mechanisms, resulting in a net procoagulant state, our cases after clinical evaluation suggest the importance of a high index of suspicion of DVT and VTE in patients of Active pulmonary TB. Early initiation of ATT along with anticoagulant therapy can prevent the potentially fatal complication of the disease unless any contraindications for anti-coagulation. Unfractionated heparin and if require early thrombolysis agent bolus follow by controlled infusion are lifesaving treatment option,LMWH is safer and require minimal monitoring. The overall morbidity and mortality is also decreased. Thus, patients of PTB having predisposing factors for DVT & VTE should be carefully monitored and investigated for an early diagnosis and treatment & manage at critical care unit, pulmonologist , Intensivist &cardiologist have main role in management

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