Clots in tuberculosis

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SUMMARY

Tuberculosis (TB) is a common communicable disease. Active TB infection may be complicated by both venous and arterial thrombosis which are often under-recognised. We report two patients with incidental TB associated thrombosis involving different venous systems. Both responded to anticoagulant and anti-tuberculous therapy (ATT). Patients with tuberculosis are at risk of VTE and careful monitoring for venous thromboembolism (VTE) is needed during ATT. Our case illustrates the importance of having a high index of suspicion for silent VTE as it may complicate active TB infection.

INTRODUCTION

TB is a common communicable disease caused by Mycobacterium tuberculosis (MTB). The incidence appears to be rising worldwide.[1] Although all age groups are at risk, the frequency of tuberculosis (TB) appears to be highest in the 34 to 45-year age group, with an increased incidence in the elderly. The majority of patients with TB have involvement of one or more organs. The organs which are frequently involved are the lung, pleura, lymph nodes, gastrointestinal tract, spine, eyes and genitourinary tract. Active TB has been associated with venous thrombosis (VT) and less commonly arterial thrombosis. We report two patients diagnosed with TB who had incidental findings of VT. We describe the investigations, treatment and outcome.

CASE REPORT

Case No. 1

A 39-year-old woman was diagnosed with disseminated TB with involvement of the lungs and peritoneum. She presented with a 2-month history of intermittent fever and abdominal pain. On examination her vital signs were stable with coarse crepitation in the left lower zone of the lung with presence of ascites. The peritoneal fluid was exudative biochemically. Both sputum and peritoneal fluid were positive for MTB polymerase chain reaction. Computed tomography (CT) of the chest showed multiple small lung nodules, ground-glass opacification in both lungs with mediastinal lymphadenopathy (figure 1 A&B).

She was initiated on anti-tuberculous therapy (ATT, AKURIT-4). One week later, she developed acute hepatitis and required bridging therapy with streptomycin, ethambutol and moxifloxacin. Alanine transaminase increased from 44 U/L to 369 U/L with elevated bilirubin of 38 mmol/L. The serum albumin was 30 g/L. The platelet level and fibrinogen level were both normal. Due to persistent hepatitis and prolonged international normalise ratio of up to 2.69, ultrasonography (USG) of the hepatobiliary system (HBS) was performed. This revealed an incidental portal VT with normal liver architecture and the presence of ascites (figure 1 C&D).

Anti-cardiolipin, anti-beta 2 glycoprotein, anti-double-stranded DNA and anti-nuclear antibody tests were negative. We did not initiate anticoagulant therapy due to the presence of prolonged INR. Outpatient review at 2 weeks showed improvement in clinical symptoms with complete resolution of ascites and residual thrombus in the portal vein on ultrasonography (USG) of the abdomen. Oral warfarin was initiated at a dose of 3 mg daily. She achieved the therapeutic international normalise ratio without the need to increase the dose. A repeat USG at 3 months showed complete resolution of the thrombus and the warfarin was discontinued.

Case No. 2

A 55-year-old man with poorly controlled type 2 diabetes mellitus was diagnosed with smear-positive pulmonary TB. He presented with cough for 6 months and a 2-week history of intermittent fever and dyspnoea. On examination his temperature was 39°C, he was tachypnoeic with an oxygen saturation of 94% on room air. There were bronchial breath sounds in the right upper zone, coarse crepitation and stony dullness in the right lower zone of the lung. Chest radiograph revealed a right hydro-pneumothorax with pleural thickening. A small-bore chest drain was inserted.

Laboratory investigation revealed leucocytosis (white cell count of 28.4x109/L), normocytic normochromic anaemia (haemoglobin 10.4 g/dL), Erythrocyte sedimentation rate was 107 mm/hr and C-reactive protein was 11.24mg/dL. Sputum was positive for acid-fast bacilli which were later culture positive. Bacterial sputum and blood cultures were negative. We initiated ATT therapy consisting of isoniazid, ethambutol, rifampicin, and pyrazinamide.

There was persistent fever and poor resolution of the right pleural effusion. A contrast-enhanced computed tomography (CT) of the thorax revealed incidental findings of extensive thrombosis involving the right brachiocephalic, right internal jugular, subclavian and axillary veins (figure 1 E). Further aetiological investigations of thrombosis which included anti-nuclear antibody, protein S, protein C, and anti-thrombin levels were negative. An echocardiogram

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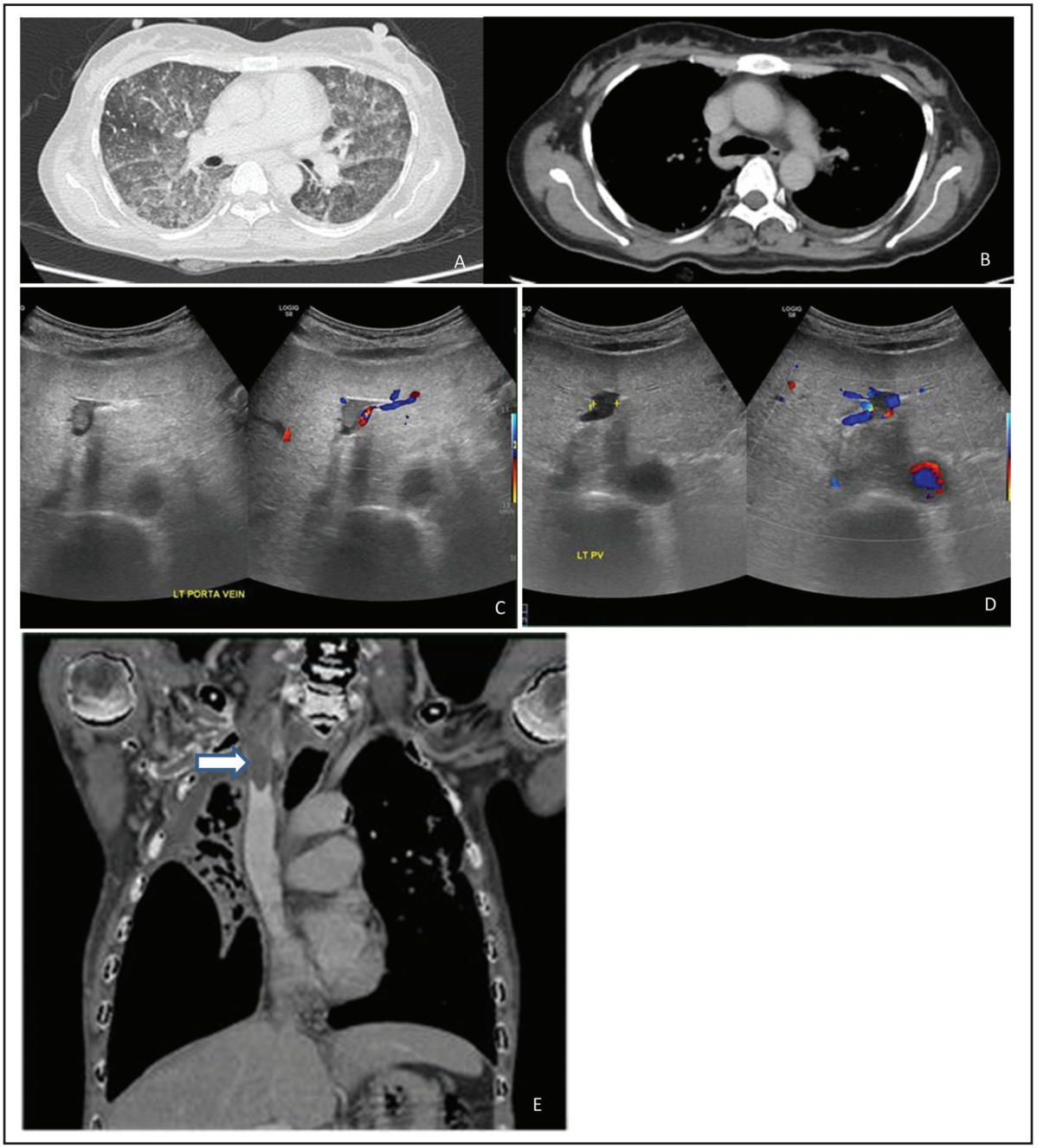

Fig. 1: (A) CECT thorax showed multiple small lung nodules, ground glass opacification in both lungs. (B) . CECT thorax showed mediastinal lymphadenopathy. (C&D) USG Doppler of the portal vein showed residual thrombosis at 2 weeks' interval. (E) CECT thorax showed filling defects in right brachiocephalic, right internal jugular, subclavian and axillary veins.

revealed a normal left ventricular ejection fraction. Ultrasound Doppler of both lower limbs excluded the presence of deep venous thrombosis. We initiated warfarin at a dose of 6 mg daily and continued the ATT for 6 months. He achieved the therapeutic INR. A repeat CT thorax at 6 months showed complete resolution of the thrombosis.

DISCUSSION

Active TB infection can result in a hypercoagulable state leading to an increased risk of both venous and arterial thrombosis. This thrombotic phenomenon is rare with a prevalence of 1.5 to 3.4 % and can occur as either a presenting feature, a complication or sequelae during the course of TB infection.[2] Up to a third of cases occur in the first week of disease.[2] TB is an independent risk factor for thromboembolism with the reported risk almost as high as that of malignancy.[3]

The thrombotic phenomena may involve the portal venous system.[4] This is likely a consequence of the tuberculous inflammation of the porta hepatis or systemic

prothrombotic.[4,5] Other postulations include periportal tuberculous lymphadenitis leading to portal venous thrombosis with portal hypertension.[6] Portal vein thrombosis can cause serious complications such as bowel ischemia and gangrene by extending to the superior mesenteric vein.[6]

It is postulated that TB associated thrombosis is caused by elevation of plasma fibrinogen coupled with impaired fibrinolysis, elevated fibrin degradation products, decreased prothrombin levels, anti-thrombin III and protein C level.[7] Active TB induces the expression of a tissue factor in monocytes-macrophages. It also causes a release of pro-inflammatory cytokines (tumour necrosis factor α, interleukin 1, and interleukin 6 which results in a chromogenic vascular endothelium.[7] Local compression by enlarged lymph nodes may cause venous obstruction or thrombosis. This hypercoagulable state is associated with raised antiphospholipid antibody levels in TB which usually normalises after a month of ATT. Both of our cases had CT evidence of severe pulmonary involvement with the presence of cavities in the second patient indicating a more severe inflammation and hypercoagulable state predisposing the patients to thrombosis.

The prompt initiation of ATT usually results in the improvement of haemostatic abnormalities as early as the first month of treatment.[8] Rifampicin is a potent inducer of hepatic cytochrome P450 and increases the catabolism of warfarin. Co-administration of rifampicin and warfarin may result in higher warfarin dose requirements. Rifampicin itself may induce thrombosis by binding to platelets and erythrocytes to form immune complexes. To date, no reported studies has addressed the benefit of novel anticoagulants in combination with ATT following the failure of vitamin K antagonists to achieve therapeutic INR.

There is a wide variation in treatment regimes in TB related thrombosis from published case reports.[4-8] The commonest reported regime is low molecular weight heparin (LWMH) followed by warfarin.[4-8] The earliest resolution of thrombus was reported at 3 weeks. A retrospective study showed that the majority of patients with concurrent pulmonary TB and deep VT required at least 3 months of anticoagulant treatment for the resolution of thrombus.[2] Both of our patients showed thrombosis in the different venous systems and resolved with warfarin treatment 3 and 6 months, respectively.

There is equipoise in the treatment of portal vein thrombosis (PVT). In cases of non-cirrhotic, non-malignant acute PVT, the American College of Chest Physicians recommends anticoagulation for symptomatic patients, whereas the American Association for the Study of Liver Disease advocates anticoagulation regardless of symptomatology.[9,10]

Our two cases describe silent VTE complicating tuberculosis. Patients with tuberculosis are at risk of VTE and careful monitoring for VTE is needed during the course of ATT.

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