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Pulmonary tuberculosis induces a systemic hypercoagulable state

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Summary *Objectives:* Human tuberculosis (TB) remains an important cause of death globally. Bangladesh is one of the most affected countries. We aimed to investigate the impact of pulmonary TB on pro- and anticoagulant mechanisms.
Methods: This prospective study was conducted in Chittagong, Bangladesh. We performed an in-depth analysis of coagulation activation and inhibition in plasma obtained from 64 patients with primary lung TB and 11 patients with recurrent lung TB and compared these with 37 healthy controls. Additionally, in nine patients coagulation activation was studied in bronchoalveolar lavage fluid (BALF) harvested from the site of infection and compared with BALF from a contralateral unaffected lung subsegment.
Results: Relative to uninfected controls, primary and recurrent TB were associated with a systemic net procoagulant state, 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. Coagulation activation could not be detected at the primary site of infection in a subset of TB patients.
Conclusions: Pulmonary TB is associated with a systemic hypercoagulable state.

Introduction

Tuberculosis (TB), caused by the acid-fast bacterium *Mycobacterium* (*M.*) *tuberculosis*, is one of the most devastating infectious diseases worldwide, with one-third of the world population being infected.[1,2] In 2011, globally 8.7 million people became infected and 1.4 million people died from this disease.[2] Bangladesh is one of the most affected countries with an annual incidence in 2011 of 225 new cases per 100,000 inhabitants and an overall mortality rate of 45 per 100,000.[2] Treatment of TB involves prolonged antibiotic regimens. *M. tuberculosis* bacilli that are not fully eradicated from the lungs remain a potential danger to the infected individual and his/her surrounding people.[1,3] This emphasizes the importance of understanding host response mechanisms during TB.

There is ample evidence that during severe acute pulmonary infections, in addition to activation of inflammatory pathways, haemostatic changes occur.[4,5] These changes include increased procoagulant activity, decreased expression of anticoagulant factors, and suppression of the fibrinolytic system, which in most severe cases can result in disseminated intravascular coagulation and microvascular thrombosis.[4,5] In patients with acute lower respiratory tract infections, procoagulant changes are also detected at the primary site of infection, in the bronchoalveolar space.[6–9] Previous investigations have indicated that pulmonary TB may be associated with activation of coagulation in the circulation, as reflected by elevated plasma levels of fibrinogen.[10,11] Some case reports and small series have suggested a link between TB and deep venous thrombosis, pointing to a procoagulant state in these patients.[12–16]

Thus far, detailed analyses of haemostatic disturbances in patients presenting with TB have not been reported. Therefore, in this prospective study we aimed to get more insight into activation of pro- and anticoagulant mechanisms in the circulation of patients with pulmonary TB. In addition, we measured activation of the coagulation system in bronchoalveolar lavage fluid (BALF) obtained from a subset of patients who underwent a diagnostic bronchoscopy because of clinically suspected TB.

Materials and methods

Study design and population

In this observational prospective study we aimed to investigate systemic (Part A) and local (Part B) host responses with respect to coagulation, anticoagulation, and fibrinolysis during active pulmonary TB. Patients were screened at the Tuberculosis Clinic of Chittagong General Hospital, Chittagong, Bangladesh and in the Chittagong Medical College & Hospital, Chittagong, Bangladesh.