Deep Venous Thrombosis Associated with Pulmonary Tuberculosis and Transient Protein S Deficiency

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Vascular complications associated with Mycobacterium tuberculosis infection have rarely been reported in children. We describe a case of deep venous thrombosis of the left leg in association with pulmonary tuberculosis. The patient had transient protein S deficiency and anticardiolipin IgG and IgM antibodies were also present. The pathogenesis of the hypercoagulable state in tuberculosis is discussed.

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INTRODUCTION

Venous thrombosis is rare in young children and usually occurs secondary to the placement of a central venous catheter or to states of congenital or acquired hypercoagulability associated with an underlying disease (1, 2). Tuberculosis (TB) may be a risk factor for venous thrombosis. The link between inflammation and vascular complications may be found in the acute-phase reaction and hemostatic changes occurring during pulmonary TB (PTB) that may facilitate the development of a hypercoagulable state (3). However, there are very few cases involving acquired protein S deficiency (4) and we have not found any reported in children. We present herein a case of deep vein thrombosis (DVT) in the left leg in association with PTB and transient deficiency of protein S.

CASE REPORT

A 4-y-old boy was admitted with a 48-h history of fever, pain and swelling in the left leg. There were no traumatic antecedents. His medical and family histories were unremarkable.

Physical examination confirmed that the child was ill. His body temperature was 38.2°C and his oxygen saturation was 97% in room air. Skin color was good and there was no respiratory distress. Lung fields were clear on bilateral auscultation. Examination of the extremities revealed swelling up to the groin, pitting edema in the lower left leg and increased skin temperature. Homan and Payr signs were present. Other physical findings were unremarkable.

A Doppler ultrasound study of all 4 extremities revealed thrombosis of the left iliac vein, common femoral artery and the surface and deep femoral arteries. A chest X-ray showed condensation in the mid lobe and bilateral hilar adenopathies. Chest CT revealed alveolar condensation in the mid lobe and the superior and anterior segments of the left lower lobe, as well as subcarinal, right paratracheal and bilateral hilar adenopathies. Flexible bronchoscopy revealed bilateral endobronchial TB. A ventilation–perfusion scan discounted pulmonary embolism. A tuberculin skin test (Mantoux method) was positive.

Laboratory examinations revealed the following results: hemoglobin level 11.7 g/dl; white blood cell count 16,100/mm^3, with 80.7% neutrophils, 9.5% lymphocytes and 8.6% monocytes; platelet count 202,000/mm^3, prothrombin time 12.4 s (normal range 10.9–13.9 s); activated partial thromboplastin time 30.3 s (normal range 28–43 s); fibrinogen level 213 mg/dl; and dimers $>$ 7,000 µg/ml. Results of biochemical tests, an arterial blood gas test and a lipidogram were normal. Anti-nuclear antibodies, anti-double-stranded antibodies, rheumatoid factor, C3, C4, CH50 and immunoglobulins were within normal ranges. An evaluation for thrombophilia was done and the results are shown in Table I. Full thrombophilia testing was performed on the parents and 3 siblings, with no anomalies being found.

The boy initially received low molecular weight heparin (enoxaparin), 1 mg/kg twice a day. Maintenance warfarin therapy was started 48 h after initiation of treatment with enoxaparin, with a target international normalized ratio of 2.0–3.0. Therapy was also started with isoniazid, rifampicin, pyrazinamide and streptomycin because the possible adult source of the infection was a patient with HIV infection and TB resistant to isoniazid. For this reason we employed this 4-drug regimen daily for 2 months, and then admin-

Table I. *Results of laboratory evaluation of the patient. Normal values are shown in parentheses*

Test	Result
Dilute Russell's viper venom time (s)	32.8 (25–37)
Lupus anticoagulant assay (LA-Confirm ratio)	1 ($\leq$1)
Factor VIII (% normal)	74 (50–200)
Protein C activity (% normal)	92 (68–144)
Protein C antigen (% normal)	88 (80–120)
Total protein S antigen (% normal)	64 (73–99)
Free protein S antigen (% normal)	39.8 (60–87)
Activated protein C resistance ratio	2.7 ($>$2.3)
Antithrombin (% normal)	101 (85–125)
Plasminogen activity (U/dl)	91 (80–130)
Homocysteine (mmol/l)	6.46 (5–15)
Anticardiolipin IgG (GPL units)	40 ($<$10)
Anticardiolipin IgM (MPL units)	116 ($<$7)
Prothrombin G20210A	Homozygous normal
Factor V Leiden	Homozygous normal
Methylenetetrahydrofolate reductase C677T	Homozygous normal

istered isoniazid and rifampin for a further 4 months. In addition, steroids were given for 6 weeks.

Warfarin was continued for 14 months following admission. We stopped antithrombotic therapy because anticardiolipin antibody was persistently absent for 7 months. Protein S levels returned to normal within the first 5 months. At present, 9 months after cessation of anticoagulation therapy, the patient remains free of symptoms.

DISCUSSION

Thrombosis manifests itself as a multicausal disease most clearly in children. In the rare event of thrombosis in children, several acquired and genetic risk factors are usually present simultaneously (2, 5). Various mechanisms have been suggested by which infection may cause DVT. These include local invasion of the surrounding tissues by the infectious agent, induction of inflammation by the infectious process, direct endothelial damage and the induction of a transient hypercoagulable state (3, 6).

In PTB, previously described hematological changes that may facilitate the development of DVT include: elevated plasma levels of fibrinogen; the presence of fibrinogen degradation products and tissue plasminogen activator and inhibitor; thrombocytosis; and decreased levels of antithrombin (3). The presence of anticardiolipin antibodies has also been reported (7). However, it would seem that at least 2 concurrent anomalies in the naturally occurring anticoagulant pathway are required for venous thrombosis to develop.

In our case, in addition to the presence of anticardiolipin antibodies, a transient deficiency in protein S was detected. However, Mycobacterium tuberculosis may cause direct or indirect endothelial damage by means of toxins or cytokines (8).

Protein S is a vitamin K-dependent cofactor for the activated protein C-mediated cleavage of FVIIIa and FVa. Normally, 60% of protein S in plasma is bound to C4b-binding protein (C4bBP). C4bBP is an acute-phase reactant; changes in its concentration in inflammatory diseases can alter the concentration of free protein S, thus contributing further to the hypercoagulable state (9). Experimental studies have shown that peripheral blood mononuclear cells in PTB can be readily induced to produce IL-1 and tumor necrosis factor-α. The secretion of IL-6 is also very marked in vitro (8). TNF-α has been demonstrated to cause downregulation of the protein C/protein S system during sepsis (9). However, the exact mechanism by which this deficiency is produced in TB has not been studied.

In conclusion, TB may be associated with an acquired hypercoagulable state in which anticardiolipin antibodies and other acquired hematological disorders may be present. In our patient 2 acquired disorders were present.

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An Extremely Uncommon Infection: Candida glabrata Arthritis after Total Knee Arthroplasty

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Prosthetic arthritis caused by Candida species is extremely rare. Of 30 such cases reported in the English literature, only 3 were due to Candida glabrata. We present herein a fourth case; to the best of our knowledge this is the first example of knee arthroplasty infection caused by C. glabrata.

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