Recurrent thrombosis in an HIV-1 infected child

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Abstract

Though thromboembolic complications in HIV infected patients have been described in literature, recurrent thrombosis is very rare. We present a six-year-old HIV infected boy who presented with recurrent thrombosis. He initially had renal artery thrombosis, then middle cerebral artery thrombosis and finally hepatic vein thrombosis that was fatal.

Key words: Children, HIV, recurrence, thrombosis

INTRODUCTION

Thromboembolic complications have been described in HIV infected patients with higher incidence seen in patients with active opportunistic infections (OI) or malignancy, and in patients with acquired immunodeficiency syndrome (AIDS). Incidence of thromboembolism ranges from 0.26% to 7.6%. [1] Various abnormalities predisposing to hypercoagulable state have been reported in AIDS patients including the presence of antiphospholipid antibodies, [2] lupus anticoagulant, deficiencies of proteins C and S, heparin cofactor II, and antithrombin and use of protease inhibitors. [3] Though more than one thrombotic episode has been reported in adults, [4,5] it has rarely been reported in children. [6] We report an HIV infected boy who had three thromboembolic episodes in a matter of 6 months and finally succumbed to the disease.

CASE REPORT

A six-year-old HIV infected boy on 2 drug antiretroviral therapy (ART) consisting of Zidovudine (AZT) and Lamivudine (3TC) for the past 3 years presented with tuberculous meningitis and pulmonary tuberculosis (TB) in December 2004. On investigation, he was also found to have cardiomyopathy (left ventricular dilation with hypertrophy) on echocardiography, elevated liver transaminases, anemia, elevated, basal ganglia calcifications on CT of brain and normal kidney sizes on ultrasound of abdomen (right kidney = 7.9 × 4.1 cm, left kidney = 7.7 × 3.7 cm) and normal renal function tests. His birth history was uneventful. On examination, he was malnourished (weight = 12 kg), had oral thrush, clubbing and hypertension. Other systems were normal. His urine examination showed no proteinuria and ultrasound colour Doppler of renal vessels was normal. He was started on antituberculous therapy (ATT); ART was shifted to AZT, Didanosine (ddI) and Efavirenz (EFV). He also was given Nifedipine for hypertension. His CD4 count was 430 cells/cumm (20%). He was discharged from the hospital. After 3 months in March 2005, he was again hospitalized with convulsion and hypertension. CT of brain showed ring enhancing granulomas in basal ganglia suggestive of toxoplasmosis. His CSF was normal, sputum for acid fast bacilli was negative and chest X-ray had normalized. Hemoglobin had also increased to 16.7 g/dl, and ESR was 15 mm at end of 1 h. Liver transaminases were decreasing (SGOT = 97 IU/L, SGPT = 39 IU/L). However, ultrasound of kidneys showed small left kidney (left kidney = 5.2 × 1.8 cm, right kidney = 9.9 × 4.2 cm). Renal
function tests were normal and urine examination was also normal and serum toxoplasma IgG was positive. DMSA renal scan showed non functioning left kidney. He was treated with sulfadiazine-pyrimethamine for 6 weeks and hypertension was controlled with increasing dose of nifedipine. Colour Doppler of renal vessels showed occlusion of left renal artery. Thus, he was determined to have renal hypertension most likely due to renal artery stenosis. The child was discharged and after 2 months he presented with right-sided hemiplegia and uncontrolled hypertension in May 2005. MRI of brain showed old and new infarcts with angiography showing no flow beyond left middle cerebral artery. He was treated with heparin and then shifted to warfarin. For hypertension control, he additionally required Methyl Dopa, and Atenolol. His urine showed 1+ proteinuria though renal function tests were normal. The child was advised left-sided nephrectomy in view of non functioning kidney and uncontrolled hypertension, which parents refused. He again presented in July 2005 with jaundice, hepatomegaly and ascitis. Ultrasound of abdomen showed thrombosis in hepatic vein leading to Budd–Chiari syndrome. Subsequently, the child developed bacteremia and sepsis and succumbed to the same. Thrombotic workup in form of anticardiolipin antibodies (ACLA), antiphospholipid antibodies (APLA), lupus anticoagulant were negative in this child. Protein C, Protein S and Antithrombin III levels could not be done due to nonaffordability.

**DISCUSSION**

Infection with HIV may lead to hemostatic imbalances. Decrease in natural anticoagulants such as protein C and protein S has been found in HIV infected patients without a thrombotic episode.[17,18] Also presence of APLA, ACLA may also predispose to thrombosis.[2] It appears that CD4 counts <200/mm³, presence of opportunistic infections, AIDS-related neoplasms or autoimmune disorder associated with HIV such as autoimmune hemolytic anemia (AIHA) may predispose to thrombosis.[19] In our patient, though CD4 counts were normal, the child did have advanced HIV disease, had OIs in form of tuberculosis and suspected CNS toxoplasmosis which could have predisposed him to thrombosis. Though his APLA, ACLA were negative, we could not do his protein C and protein S level which would have helped to determine the cause of his recurrent thrombosis. Earlier we had reported a child with APS and cerebral infarct,[5] but recurrent thrombosis inspite of anticoagulation is rarely seen as was seen in our patient. In adults on ART with protease inhibitor, Maj luf-Cruz et al. found that out of 28 adult male homosexuals with AIDS, who had thrombotic episodes, six patients had two thrombotic events.[6] These patients had either deep vein thrombosis, pulmonary thromboembolism or renal vein thrombosis. However, our patient had renal artery thrombosis, followed by middle cerebral artery thrombosis and subsequently hepatic vein thrombosis which has never been reported earlier. Though anticoagulants and/or aspirin have been used to prevent recurrent thrombosis, in our patient inspite of warfarin, the child had a recurrent thrombosis that proved to be fatal.

Our patient initially presented with hypertension, subsequently developed small non-functioning kidney due to renal artery stenosis and proteinuria though he had normal renal function tests on blood examination. A variety of renal abnormalities among HIV-infected patients have been described. These include HIV-associated nephropathy (HIVAN), HIV-related immune complex disease, nephropathy secondary to antiretroviral therapy (ART) or antibiotics, thrombotic microangiopathy, and diseases related to common comorbidities such as opportunistic infections.[9] The broad spectrum of clinical presentation includes acute renal failure (ARF), nephrotic syndrome, progressive chronic renal dysfunction, proteinuria, tubular function abnormalities and electrolyte disturbances.[10] Proteinuria is believed to be the earliest and most consistent clinical finding for the diagnosis of HIV-associated nephropathy. However, our patient presented with hypertension and only later in the disease developed proteinuria suggestive that renal involvement was due to vasculopathy rather than renal involvement of HIV per se. In adults, hypertension in HIV infected patients has been found to be related to increasing age, longer duration of HIV, higher body mass index, and diabetes, with a trend for African American ethnicity.[11] Hypertension has rarely been reported in HIV infected children. We did not get any information on renal artery stenosis in HIV infected children, but postulate that it may be related to thrombotic tendency with HIV infection as the child subsequently had thrombosis in cerebral vessels and also the hepatic veins.

Further studies to elucidate the mechanisms underlying this abnormal hemostatic phenomenon, factors predisposing to recurrent thrombosis are required.

Thus, clinicians caring for HIV infected children should be aware of thromboembolic disease as a possible complication of AIDS.
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FUNCTIONS OF THE COWPERS GLAND
They play an important role in sexual intercourse. When a man becomes sexually aroused, the gland begins to secrete pre-ejaculate fluid. This fluid is a clear lubricating mucus that is similar in composition to semen. Amounts of pre-ejaculate produced varies greatly.

Pre-ejaculate fluid created by the cowper's gland has three functions:
1. It neutralizes the acid levels in the urethra so that sperm can pass through it. Sperm do not thrive in acidic environments. Likewise, pre-ejaculate fluid deposited in the vagina during intercourse can help to lessen the vagina's naturally high acidity, thus increasing the longevity of the sperm.
2. Pre-ejaculate fluid is to remove any foreign material from the urethra before intercourse.
3. It also provides lubrication for sexual intercourse.

The composition of pre-ejaculate fluid is not identical to that of semen, it can sometimes contain small amounts of sperm leftover from previous ejaculations. Therefore, the withdrawal method of birth control where the penis is removed from the vagina prior to ejaculation is not always effective. Sexually transmitted diseases (STDs) can also be transmitted via pre-ejaculate fluid.

Pathology of Cowpers glands
Acute Cowperitis
- Caused by Neisseria gonorrhea
- Abscess formation - unilateral, points towards the perineum

Chronic Cowperitis
- Non gonococcal infection

Potential mimic of Prostate Carcinoma: Differentiated from Prostate Ca by -
Positive Stains: Mucin, smooth muscle actin at periphery of acini
Negative Stains: PSA (variable), PAP, S100, CEA, CK903 (usually)
Electron Microscopy: Acini lined by secretory cell layer, with myoepithelial cells at periphery of acini