Thrombotic antiphospholipid syndrome in a child with Human Immunodeficiency Virus: A rare Case Report

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Case report

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Abstract

BACKGROUND

Antiphospholipid syndrome (APS) is a noninflammatory autoimmune disorder induced by antiphospholipid antibodies, which exceedingly rarely occurs in pediatric population and even more rarely reported in HIV positive children.

CASE SUMMARY

A 11 years old boy had a sudden onset left lower extremity swelling with pain and the symptoms gradually worsened. Initial one-month topical treatment was ineffective and the symptoms aggravated until suddenly spread to the root of his thigh, accompanied by left lower extremity dyskinesia. Both ultrasonography and vascular CT scan on left lower extremity revealed deep venous thrombosis. His serum aPLs antibodies were tested positive. He experienced a virology failure with substantial HIV viral load (VL) despite receiving regular antiretroviral therapy (ART). The symptoms recovered after aggressive antithrombotic and high-dose corticosteroids treatments.

CONCLUSION

When pediatric individuals develop thrombotic disease, APS also needs to be ruled out. The autoantibodies levels should be routinely tested to look for recurrent thrombosis in children with HIV/AIDS.

Background

APS (also named Hughes Syndrome) is an autoantibodies-induced autoimmune disease characterized by recurrent arterial or venous thrombosis and miscarriage with thrombocytopenia and seropositive (usually moderate-high titer elevated) for anti-phospholipid antibodies (aPLs)(1). The presence of circulating aPLs, including anticardiolipin antibodies (aCLs), lupus anticoagulant (LA) and/or anti-beta 2 glycoprotein I (β2GPI), is a risk factor for developing thrombophilia in asymptomatic individuals. It has been estimated that approximately 39% APS patients coexist with venous thromboembolism(2). The existing studies showed when compared with general population, HIV infected patients have 2-10-fold increase of developing thrombosis(3). However, how the coexistence of APS and HIV infection affect the thrombosis has not been well examined. Herein, we reported a rare case of a coexistence of APS and asymptomatic HIV-infected child who developed left lower extremity thrombosis.

Case Presentation

A 11 years old boy had a sudden onset left lower extremity swelling with pain and the symptoms gradually worsened. No symptoms of fever, headache, cough, chest tightness, chest pain, abdominal pain and diarrhea were reported. His CD4 + T lymphocyte cell count was 522 cells/µL and plasma VL was 943
copies/mL with a blood pressure around 97/69 mmHg at that time. He then initiated one-month topical treatment was ineffective and the symptoms aggravated until suddenly spread to the root of his thigh, accompanied by left lower extremity dyskinesia. The child was first tested positive with HIV at the age of two and was believed to be infected through mother-to-fetus transmission. He had been taken first-line regimen of ART (AZT + 3TC + NVP) since August 2014 with a CD4\(^+\) T lymphocyte cell count of 346 cells/µL at that time. The plasma HIV RNA was undetectable after half a year of ART.

His mother was HIV seropositive. The child had no personal or family history of thrombosis related disease. Nor surgery, trauma, prolonged bed rest, obesity, smoking and other deep vein thrombosis common risk factors were discovered.

On physical examination during hospital admission, the maximum circumference of his left thigh was 38 cm and the right thigh was 34 cm. The maximum circumference of his left calf was 27 cm and the right calf was 24 cm. His left lower extremity thigh was inflamed and swollen, accompanied by tenderness and varicose veins.

Blood test indicated that his white blood cell (WBC) count was \(3.28 \times 10^9/L\) with a CD4\(^+\) T lymphocyte cell count of 430 cells/µL, hemoglobin (Hb) was 126 g/L and platelets was decreased to \(66 \times 10^9/L\). His virology test suggested HIV RNA was 580 copies/mL. The coagulation function test showed PT was 14.0 seconds and activated partial thromboplastin time (APTT) was prolonged to 44.3 seconds. The international normalized ratio (INR) and Fibrinogen (FIB) were 1.16 and 15.1 mg/L respectively. D-dimer was 6.26 mg/L. C-Reactive Protein (CRP) was 32.14 mg/L, procalcitonin (PCT) was 0.029 ng/ml and erythrocyte sedimentation rate (ESR) was 41 mm/h. The aCLs IgG was at 57 (normal < 22), IgM was at 24 (normal < 10). Anti-neutrophil cytoplasmic antibody (pANCA) and anti-β2GPI antibody were tested positive. In addition, some other autoimmune antibodies were also tested positive: ANA (1:100, granular); dsDNA: +; nucleosome: ++; histone: +; mitochondrial M2: +. Other examinations including liver and kidney function were unremarkable.

Ultrasonography of lower vessels revealed deep venous thrombosis in his left lower extremity, accompanied by soft tissue edema and superficial lymphangiectasia. Vascular CT scan on left lower extremity showed extensive mural thrombosis (Figure).

He was diagnosed HIV comminated with thrombotic antiphospholipid syndrome. He was initially treated with low molecular weight heparin (LMWH) calcium 3000 IU every 12 hours for 6 weeks followed by warfarin (1.25 mg/day) for long-term anticoagulant therapy at a target INR of 2.0–3.0. Besides, methylprednisolone (40 mg/day) treatment was also given to the boy for ten days which was substituted with 30 mg/day prednisone after that. The prednisone dosage was gradually reduced by 5 mg each time every 2 weeks until reached 5 mg/d and maintained for another 2 months. Additionally, antiviral regimen was adjusted to ABC + 3TC + LPV/r due to his persistent high HIV viremia.

After one month of treatment, the swelling and pain gradually relieved and repeat vascular ultrasonography showed the blocked vessel was partial recanalized and platelets returned to normal.
After 3 months of treatment, his symptoms continued to be ameliorated. However, the aCLs and β2-GP1 antibody titers were still tested positive. After 6 months of treatment, his left lower extremity blood vessels were returned to normal (Table 1).

**Table 1**

| Age(years)     | 11 years old |
|----------------|--------------|
| Sex            | Male         |
| Personal and family histories | No           |
| January 2009   | Confirmed the diagnosis of HIV infection |
| August 2014    | CD4 count: 346 cells/µL, and initial ART (AZT + 3TC + NVP) |
| February 2015  | HIV RNA: undetectable |
| January 2018   | CD4⁺ T count: 522 cells/µL, HIV RNA: 943 copies/mL |
| February 2018  | CD4⁺ T count: 430 cells/µL, HIV RNA: 580 copies/mL |
| Coagulation function test | PT: 14.0 s (normal, 11–16 s), APTT: 44.3 (normal, 23–40 s), INR: 1.16, FIB: 15.1 mg/L (normal, 2–4 mg/L), D-dimer: 6.26 mg/L (normal, 0–1 mg/L) |
| Other laboratory findings | CRP: 32.14 mg/L (normal, 0–5 g/L), PCT: 0.029 ng/ml (normal, 0-0.046 ng/ml), ESR: 41 mm/h (normal, 0–15 mm/h), WBC: 3.28 × 10⁹/L (normal, 3.5–9.5 × 10⁹/L), Hb: 126 g/L (normal, 130–175 g/L), PLT: 66 × 10⁹/L (normal, 125–350 × 10⁹/L) |
| ACA (+), p-ANCA (+), β2-GP1-Ab (+), aCLs IgG (normal < 22) 57, IgM 24 (normal < 10) |
| Symptoms       | Left lower extremity swelling with pain |
| Signs          | left lower extremity thigh was inflamed and swollen, accompanied by tenderness and varicose veins, |
|                | the maximum circumference of his left thigh was 38 cm and the right thigh was 34 cm. The maximum circumference of his left calf was 27 cm and the right calf was 24 cm. |
| Prognosis      | Thrombotic pediatric antiphospholipid syndrome (PAPS) |
| Treatment      | LMWH followed by warfarin; methyl prednisolone followed by prednisone, ABC + 3TC + LPV/r |
| Evolution      | Left lower extremity revascularized |
Discussion And Conclusions

The etiology of APS is complicated and has not been well delineated. The most popular hypothesis suggested a "two hit" mechanism in pathogenesis of APS. The first hit is the presence of aPLs antibodies and interact with vascular endothelial cells, neutrophils, platelets and monocytes resulting in endothelial dysfunction and injury. The second hit is the facilitation from predisposing factors like infections, contraceptives, malignancies and genetic susceptibility etc which eventually lead to thrombotic events(4, 5). Common infections associated with APS include typhoid bacillus, hepatitis virus, cytomegalovirus and particularly HIV infection (6–8). Among APS patients, the incidence of HIV infection was as high as 17.0%(6).

The HIV virus, as a superantigen that may even resemble some autoantibodies, can induce the APS through possible "molecular mimicry" mechanisms. Moreover, HIV virus can directly damage vascular endothelial cells and subsequent generation of autoimmune antibodies, participating the "double hit" pathway in the development and progress of APS(9, 10). The patient we reported had experienced a virological failure with substantial HIV viral load (VL) despite receiving regular antiretroviral therapy (ART). It has been reported that the manifestation of APS was positively correlated with HIV viral load level [11, 12]. Some studies have even suggested HIV as a direct trigger of APS onset [13]. Therefore, the occurrence of APS may be associated with high levels of HIV viremia in HIV/AIDS patients.

The superimposed HIV infection might even further increase the risk of thrombosis in APS. The existing studies showed when compared with general population, HIV infected patients have 2-10-fold increase of developing thrombosis(8). Firstly, HIV infection often leads to immunosuppression and affecting B cell function result in increasing production of autoantibodies(11). Therefore, HIV-infected patients have higher concentrations of aPLs antibodies(12, 13). Moreover, the CD4+ T count, deficiency of protein C and S and increased platelet activation are risk factors for thrombosis in HIV/AIDS patients (14–16). Additionally, it has been reported that protease inhibitor (PI) in ART regimen might lead to thrombosis event as they could cause major lipid disturbances (17). Therefore, the autoantibody levels should be routinely tested in HIV patients to alert for thrombosis.

APS is the principal cause of thrombotic disease in the pediatric population [20]. When thrombosis occurs in children, especially if it coexists with HIV infection, APS should be considered. Comprehensive review of the literature, only three case of HIV in children with APS is currently reported(18, 19). Other patients that reported with APS and HIV were all adults(2, 7, 20–22). Two of them were dead ultimately. Good result was achieved in our case through aggressive anticoagulant therapy and high-dose corticosteroids therapy.

HIV may induce the occurrence of APS and promote life threatening thrombotic events through several mechanisms. Therefore, the autoantibodies levels should be routinely tested in HIV/AIDS patients, especially in patients with virological failure with high levels of HIV viremia.
Abbreviations

APS
Antiphospholipid Syndrome
VL
Viral Load
ART
Antiretroviral Therapy
aCLs
anticardiolipin antibodies
LA
Lupus Anticoagulant
β2GPI
anti-beta 2 glycoprotein I
WBC
White Blood Cell
Hb
Hemoglobin
APTT
Activated Partial Thromboplastin Time
INR
International Normalized Ratio
FIB
Fibrinogen
CRP
C-Reactive Protein
PCT
Procalcitonin
ESR
Erythrocyte Sedimentation Rate
pANCA
Anti-neutrophil cytoplasmic antibody
LMWH
Low Molecular Weight Heparin

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Committee of the First Affiliated Hospital of Kunming Medical University (2018L-45).
Consent for publication

All presentations of case reports have consent for publication

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

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**Figures**

**Figure 1**

Clinical and Vascular CT three-dimensional reconstruction images of the patient. A.B. His left lower extremity thigh was inflamed and swollen with varicose veins. C.D. Vascular CT three-dimensional reconstruction showed left lower extremity showed extensive mural thrombosis.