TITLE

THE CHANGING FACE OF THROMBOTIC THROMBOCYTOPENIC PURPURA: THE PATHOPHYSIOLOGICAL ROLE OF ENDOTHELIITIS AND COMPLEMENT ACTIVATION IN THE DEVELOPMENT OF HUMAN IMMUNODEFICIENCY VIRUS ASSOCIATED THROMBOTIC THROMBOCYTOPENIC PURPURA

ABSTRACT

Introduction

Human Immunodeficiency virus (HIV) is a described risk factor for secondary thrombotic thrombocytopenic purpura (TTP) (HIV-TTP). The pathogenesis of this thrombotic microangiopathy (TMA) is however still unclear. The micro-thrombotic process in TTP is related to excess ultra-large von Willebrand Factor (ULVWF) multimers produced by the endothelial cells. Autoantibodies to the VWF cleaving protease, a-disintegrin-and-metalloproteinase-with-thrombospondin-motifs 13 (ADAMTS-13), have been postulated to be pivotal in initiating HIV-TTP. Inflammation and complement activation with resultant endothelial dysfunction and excessive release of ULVWF multimers have been implicated in other forms of TMA. These pathophysiological processes were investigated to assess the contribution to the development of HIV-TTP.

Methods

Data were collected from patients presenting with HIV-TTP in an observational cohort study to delineate the routine presenting laboratory parameters and treatment outcomes. The published literature was reviewed to ascertain the documented prevalence, postulated pathogenesis and treatment outcomes of patients with HIV-TTP. An investigational study was performed in patients (n=35) presenting with HIV-TTP. In this study, patient samples were analysed for levels of endothelial activation markers (soluble intracellular adhesion molecule [sICAM] and soluble vascular adhesion molecule [sVCAM]), inflammatory cytokines (tumour necrosis factor alpha [TNF-α] and interleukin-6 [IL-6]), and complement components C3 and 4 and complement Factor H (CFH), an inhibitor of the complement pathway. Published studies were also reviewed to define the baseline biomarker levels of endothelial dysfunction and coagulation activation in people living with HIV (PLWH) without TTP to serve as points of reference. Data were collected from 2 patient cohorts with HIV infection with either disseminated intravascular coagulation (DIC) or with HIV-TTP to assess the utility of scoring systems.

Results

In contrast to published literature which suggests that the prevalence of HIV-TTP is declining, this TMA is prevalent in South African PLWH in Johannesburg with heterogeneous clinical and laboratory presentation. Conventional scoring systems specifically the PLASMIC (reduced platelet count, red blood cell haemolysis, absence of cancer, no history of transplantation, reduced red blood cell volume, preservation of the international normalised ratio and creatinine) score, developed for detection of other acquired forms of TTP, performed inconsistently in the 35 patients assessed with considerable overlap with other TMAs, notably disseminated intravascular coagulation (DIC). ADAMTS-13 levels were undetectable in all patients and all patients had anti-ADAMTS-13 antibodies. The clinical presentation was, however, atypical. To delineate intermediate pathophysiological markers, the complement system, proinflammatory system and coagulation system, as well as markers of endothelial activation were analysed before and after therapeutic plasma exchange

(TPE). Complement components C3 and -4 were consistently at the lower limit of the normal reference range in HIV-TTP patients at presentation. The complement regulatory protein, complement Factor H, was increased. Patients with HIV-TTP had significantly increased levels of proinflammatory cytokines when compared with published results in PLWH without comorbidities. Endothelial activation markers, sICAM and sVCAM, were also significantly increased in the HIV-TTP cohort. Importantly, D-dimer levels were also raised in this cohort of patients.

Conclusions

HIV-TTP remains a cause of HIV-related morbidity and mortality in South African patients. This study reports the findings on 35 PLWH who presented to hospitals in Johannesburg with suspected TTP. The clinical presentation was inconsistent with other secondary forms of TTP i.e., minimal evidence of systemic organ dysfunction. All patients presented with schistocytosis, evidence of haemolysis and thrombocytopaenia and all had low ADAMTS-13 activity levels at presentation with detectable anti-ADAMTS-13 antibodies. Biomarkers of endothelial dysfunction, proinflammatory cytokine levels and markers of coagulation were all significantly increased suggesting that the pathophysiology involves complementary proinflammatory pathways which directly impact secretion of VWF from a compromised endothelium. Activation of the coagulation system, as reflected by increased D-dimer levels, specifically suggests that there may be overlap in the pathophysiology of HIV-TTP and HIV-associated DIC. A potential strategy for differentiation of these disorders with modification of scoring systems is suggested. This study provides compelling evidence of the role of the endothelium in HIV-TTP. Future directions will include validation of the biomarkers described here in more extensive cohorts as well as investigation of these biomarkers in management of these patients.