

Thrombotic thrombocytopenic purpura associated with the acquired immune deficiency syndrome

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A KUMAR, J WANG, D SUTTON, EJ BOW. Thrombotic thrombocytopenic purpura associated with the acquired immune deficiency syndrome. *Can J Infect Dis* 1992;3(1):37-41. A bisexual male presented with acute thrombotic thrombocytopenic purpura (TTP) in association with established acquired immune deficiency syndrome. The patient had classic clinical and laboratory findings of TTP and responded well to plasmapheresis therapy. Previously reported cases of TTP in association with human immunodeficiency virus (HIV) infection are briefly reviewed. Basic concepts in the pathogenesis of TTP are examined in reference to HIV infection.

Key Words: *Acquired immune deficiency syndrome, Anemia, Human immunodeficiency virus, Thrombocytopenia, Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura*

Purpura thrombocytopenique thrombotique associé au syndrome d'immunodéficience acquise

RESUME: Un patient bisexuel s'est présenté avec un purpura thrombocytopenique thrombotique aigu (PTT) associé à un syndrome d'immunodéficience acquise diagnostiqué. Les résultats cliniques et trouvaillés de laboratoire étaient classiques et le patient a réagi favorablement à une plasmaphérèse. D'autres cas de PTT associé au syndrome d'immunodéficience acquise sont rapidement évoqués. Les notions fondamentales de la pathogenèse du PTT sont examinées par rapport à l'infection à VIH (virus de l'immunodéficience acquise).

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP), FIRST described by Moscowitz in 1924 (1), is characterized by the pentad of microangiopathic hemolytic anemia, consumptive thrombocytopenia, fluctuating neurological deficits, renal failure and fever. Recently, several cases of TTP associated with human im-

munodeficiency virus (HIV) infection have been reported (2-11). The authors report a case of TTP in association with an established diagnosis of acquired immune deficiency syndrome (AIDS), and briefly review reported cases of TTP associated with HIV infection to date.

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Received for publication April 24, 1990. Accepted November 7, 1990

CASE PRESENTATION

The patient was a 44-year-old HIV seropositive bisexual male whose defining incident for AIDS was an episode of *Pneumocystis carinii* pneumonia eight months prior to the presenting illness. Three days prior to admission, the patient developed diarrhea and vomiting. He subsequently presented to the emergency department of a community hospital with expressive aphasia. Medications on admission included oral acyclovir 200 mg six times daily, oral zidovudine (AZT) 200 mg three times daily, and aerosolized pentamidine by nebulizer 60 mg every two weeks. Two weeks prior to admission, hemoglobin was 110 g/L, platelet count $157 \times 10^9/L$ and leukocyte count $3.0 \times 10^9/L$, with an absolute T4 helper lymphocyte count of $0.08 \times 10^9/L$ and a T4/T8 ratio of 0.23.

On assessment in the emergency department, the patient had an oral temperature of 38.7°C . There were bilateral preretinal hemorrhages, and petechiae were apparent on the hard and soft palate. Apart from expressive aphasia, no other focal neurological deficits were present. Admission laboratory values included a hemoglobin of 61 g/L, platelet count $11 \times 10^9/L$ and leukocyte count $5.8 \times 10^9/L$. Examination of a peripheral blood film revealed many schistocytes, marked polychromasia and few platelets. Prothrombin time was 11 s with a control value of 12 s. Partial thromboplastin time was 31 s with a control value of 30 s.

Blood urea nitrogen and creatinine were significantly elevated at 14 mmol/L and 200 $\mu\text{mol/L}$, respectively. Urinalysis demonstrated hyaline granular casts.

The patient was given six units of platelets, three units of packed red blood cells, and two units of fresh frozen plasma.

Within 12 h of blood product infusion, three generalized seizures occurred. Subsequently, a persistent coma developed. The patient was then transferred to a tertiary care facility.

The patient was unresponsive to noxious stimuli, but pupillary, oculocephalic, corneal and gag reflexes were present. Focal neurological abnormalities were not noted. Otherwise, physical findings were unchanged from the initial assessment. Temperature was 38.6°C orally. Hemoglobin was 68 g/L, platelet count $16 \times 10^9/L$, and leukocyte count $4.8 \times 10^9/L$. Additional laboratory data included lactate dehydrogenase 556 U/L, total bilirubin 44 $\mu\text{mol/L}$, and serum haptoglobin 0.106 g/L. Coagulation studies were normal. Hepatitis B surface and e antigens were present in serum. A computed tomography scan of the head with contrast was normal. Gingival biopsy was nondiagnostic.

Daily plasma exchanges were begun and continued for 13 days. Four to 5 L of plasma were exchanged with fresh frozen plasma daily for the first three days, followed by 3 to 3.5 L exchanges daily to completion. The patient received dipyridamole 400 mg daily and acetylsalicylic acid 325 mg daily, first by nasogastric tube

and then orally for a total of 14 days. Glucocorticoids were not given. Intravenous cefoxitin was given for a right lung infiltrate suspected to be secondary to aspiration.

After the second plasma exchange, the patient awoke but remained confused. Neurological status returned to normal by the fifth day of treatment. The platelet count started to rise after the third day of therapy. Lactate dehydrogenase and bilirubin levels returned to normal. Renal function recovered completely by 10 days of therapy. After 15 days, the patient was discharged with a hemoglobin of 100 g/L and a platelet count of $108 \times 10^9/L$.

DISCUSSION

Individuals with HIV infection exhibit a number of abnormalities and diseases of the hematological system. These include idiopathic thrombocytopenic purpura, lymphopenia, neutropenia, Coombs positive hemolytic anemia, polyclonal hypergammaglobulinemia and high grade lymphomas. Further, bone marrow involvement by secondary infectious processes such as *Mycobacterium avium-intracellulare* may cause anemia. In addition, pharmacological therapy of HIV infection and its secondary infectious complications often results in hematological toxicity. AZT therapy is often dose-limited by anemia and leukopenia. Pentamidine is associated with thrombocytopenia.

Other drugs commonly used for secondary infectious complications of HIV infection (ganciclovir, pyrimethamine, trimethoprim-sulphamethoxazole and foscarnet) also occasionally result in hematological toxicity, particularly thrombocytopenia.

Moschowitz (1) is credited with the first description of the disease now called 'thrombotic thrombocytopenic purpura', but not until 1953, when Monroe and Strauss (12) suggested a microangiopathic process, was the nature of the anemia understood. The hallmarks of this disease are microangiopathic hemolytic anemia, consumptive thrombocytopenia and fluctuating neurological abnormalities. Fever and renal dysfunction were added to the classic triad of TTP by Lukes et al in 1961 (13).

TTP has only recently been reported in association with HIV infection. Jokela et al (2) first reported the association in 1987. Since then, there have been 24 cases described including the present case (3-11). One report (an abstract of six cases [11]), contained limited information and is therefore analyzed only with respect to epidemiological data. Two cases are excluded from review because of insufficient documented evidence of HIV infection (4,9). Of 22 reported cases, 18 occurred in men. Ten of the 13 in whom sexual orientation was mentioned were homosexuals. Intravenous drug use was noted in seven cases including two women. A third woman was the sexual partner of an intravenous drug user. Twelve were documented to be HIV seropositive at

or within weeks after diagnosis of TTP. Nine others were felt to have probable HIV infection based on a combination of persistent generalized lymphadenopathy, secondary infections, secondary malignancies or abnormal T4/T8 lymphocyte ratio and a history of high risk behaviour. One was not diagnosed as being HIV seropositive until one year after presentation with TTP. In total, 10 of 22 cases fit into group II of the Center for Disease Control classification of HIV infection (14) at presentation with TTP. Four others belonged to group III. Group IV was represented by eight patients: five in subgroup C1, three in subgroup C2 and two in subgroup D. Both subgroup D patients were also represented in subgroup C1. Five of the eight group IV cases originated from a single report of six cases from France (11).

The presentation of TTP in these patients is similar to that of HIV-unrelated TTP cases. The most characteristic finding is microangiopathic hemolytic anemia characterized by red blood cell fragments on the peripheral smear. Schistocytes were seen in all 16 cases including the present case. Hemoglobin was typically less than 90 g/L except in one case, where it was 106 g/L. Hematocrit (when noted) was less than 0.26 in all cases. Platelet count averaged $19 \times 10^9/L$. A temperature of greater than $38^\circ C$ was present in 11 of 14 cases in which temperature was noted. Neurological symptoms were present in 13 of 16 cases and varied from confusion to coma. Deficits such as seizures, aphasia and hemiplegia occurred in five cases including the present. Renal dysfunction resulted in a creatinine level of greater than $120 \mu mol/L$ in 10 of 15 cases.

The classic triad of neurological symptoms, consumptive thrombocytopenia and microangiopathic hemolytic anemia occurred in 13 of 16 patients (including the present), but the full pentad was present in only four. Typical hyaline thrombi composed of fibrin and platelets in the small arterioles were noted on either biopsy (lymph node, gingiva or bone marrow) or post mortem pathology in seven of 10 cases in which tissue was available.

Thirteen of 16 reported cases survived on standard treatment with plasmapheresis (2-5,8) or plasma infusion (6,7,9) and glucocorticoids (2-5,7,9,10), acetylsalicylic acid (2-7,9), dipyridamole (2-7,9), high dose gamma globulin (7), vincristine (3,6), or no additional treatment (3,4,8). This is consistent with 81% survival described in combined series of plasmapheresis therapy (15). All three deaths occurred in the first 24 h after presentation and before initiation of plasma-pheresis. Of note in the present patient is the typically early neurological response after initiation of plasma therapy. In addition, the present patient had a sudden and dramatic deterioration after platelet infusion, as has been described in the past. A recent review suggests that platelet transfusions are specifically contraindicated in TTP (16).

The pathogenesis of TTP is not yet clearly delineated. Both the presence of a platelet aggregating factor and the absence of an aggregation inhibitor have been suggested. Lian et al (17) have described a platelet aggregating factor in the plasma of 50% of cases of TTP and a time-dependent inhibition of its platelet aggregating ability by coincubation with normal plasma. Unusually large multimers of von Willebrand factor, which are able to cause platelet aggregation, have been isolated in cases of TTP (18,19). Moake (20) has suggested that these multimers develop due to a deficiency or reduced activity of a specific protease.

Prostacyclin deficiency is another potential cause of the platelet aggregation seen in TTP (21). Other theories of pathogenesis involve antiplatelet antibodies, circulating immune complexes and antiendothelial antibodies (22-26).

Regardless of the pathogenesis of TTP, the immunological perturbations of HIV infection probably underlie the association of the two diseases. HIV infection is known to be associated with a large number of immunological abnormalities apart from an abnormal T4/T8 lymphocyte ratio.

A number of autoimmune phenomena have been associated with HIV infection. These include anti-nuclear, antilymphocyte, antigranulocyte, anti-cardiolipin, antiplatelet and Coombs antibodies, as well as rheumatoid factor and lupus anticoagulant (27,28). Platelet-associated antibodies have been specifically implicated in the pathogenesis of TTP (22,29) and have been isolated in at least one case of TTP associated with HIV infection (3). In addition, it has been suggested that the genesis of Lian's platelet aggregating factor may involve defects in the humoral immune system (30). Further, Moake (20) has noted that processing of the unusually large von Willebrand factor multimers may be deficient due to autoantibodies in some cases of TTP.

In addition, circulating immune complexes are frequently seen in both HIV infection and TTP (23,31). These complexes may promote the formation of microthrombi such that endothelial cell damage leads to prostacyclin deficiency followed by platelet adhesion and aggregation (21,32).

Finally, cytokines such as tumour necrosis factor (TNF)/cachexin and interleukin-1 (IL-1) are elevated in some HIV-infected individuals (33,34). These cytokines have significant procoagulant effects on endothelial cell function, including decreased fibrinolytic activity and decreased activity of protein C and protein S pathways (35). In addition, TNF and IL-1 both increase the production of another substance, platelet activating factor (36,37). This substance has powerful platelet aggregating properties and is known to cause thrombocytopenia in animal models (38,39).

Despite these potential mechanisms of an association, it remains undetermined whether an increased frequency of TTP in HIV-infected individuals exists. The

fact that cases of TTP in association with HIV infection have been reported in the literature so late after the initial description of AIDS suggests at least three possibilities. Clinical expression of the disease in HIV-infected individuals may require a longer period of sub-clinical development than other, more frequent HIV complications. Alternately, the association may be so rare that it is not noted until sufficient numbers of HIV-infected individuals develop (4). Finally, previous TTP manifestations in HIV-infected individuals may have been erroneously ascribed to other causes.

The clinical presentation of TTP in HIV-infected adults is similar to that seen in the absence of HIV infection. The diagnosis of TTP in HIV-infected individuals may, however, be particularly difficult be-

cause individually, fever, thrombocytopenia, anemia, neurological deficits and renal failure can all be caused by HIV infection, various secondary complications and treatment.

Despite these difficulties, thrombocytopenia and anemia in combination with fever, neurological deficits or renal dysfunction in HIV-infected individuals should trigger consideration of TTP. In addition, although the clinical association has been infrequently documented, any patient with evidence of TTP should undergo an HIV antibody test. Plasmapheresis, which is clearly effective in HIV-associated TTP, is the preferred treatment, but appropriate early therapy can only be delivered by prompt recognition of the clinical syndrome.

ACKNOWLEDGEMENTS: The authors gratefully acknowledge the assistance of Armando Susmano, MD, Aparna Kumar, MD, and Darlene Rivera in translation of non-English literature.

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