

## HIV-RELATED THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) AS FIRST CLINICAL MANIFESTATION OF INFECTION

Virgilio Cruccu, Elena Parisio, Donata Pedretti, Antonio Villa, Franco Confalonieri

III° Medical Department, Fatebenefratelli-Oftalmico Hospital, Milan, Italy

### ABSTRACT

**A case of thrombotic thrombocytopenic purpura (TTP) in a 40-year-old bisexual man unaware of being HIV positive is reported. The hematologic syndrome represented the first clinical manifestation of this viral infection. The clinical picture, characterized by severe hemolytic microangiopathic anemia, thrombocytopenia, fluctuating neurologic abnormalities and fever, quickly improved after plasma exchange and corticosteroid therapy. Two blood tests showed severe depletion of the CD4+ lymphocyte count and HIV antigenemia was positive. This case represents a clinical epiphenomenon of HIV infection in an advanced phase. According to recent CDC criteria the patient should be considered in AIDS. Antiretroviral treatment was started and after nine months of follow-up there has been no relapse.**

*Key words: thrombotic thrombocytopenic purpura, HIV, AIDS*

Among HIV-associated hematologic manifestations, immune thrombocytopenia (ITP) was the first recognized and the most frequently observed.<sup>1</sup> Many reports are available on the pathogenesis, prognostic meaning and treatment of ITP.

Thrombotic thrombocytopenic purpura (TTP) is another hematologic disorder observed in the context of HIV infection. This syndrome, described by Moschowitz in 1924, is far more unusual than ITP and is characterized by microangiopathic hemolytic anemia, thrombocytopenia, renal dysfunction, fluctuating neurologic abnormalities and fever.

HIV-associated TTP was first described in 1987.<sup>2</sup> The authors also referred to a previously reported case of hemolytic uremic syndrome (a thrombotic microangiopathy closely related to TTP) in an HIV-positive man.<sup>3</sup> Since then, 27 cases (25 from the USA, 2 from Canada) have been published.<sup>4-9</sup>

We describe, for the first time in Europe, a case of HIV-associated TTP. In this case the hematologic disorder represents the first clinical manifestation of the HIV infection.

### Case report

A healthy 40-year-old man suddenly complained of paresthesia in the right hemiface and right upper limb, slight diplopia and visual agnosia. On January 25, 1993 the patient was admitted to our department: he appeared confused, amnesic, with expressive and nominal aphasia, paresthesia had regressed. The patient was febrile (38°). A brain CAT scan proved to be normal; initial laboratory findings showed anemia (Hb 5.8 g/dL; Hct 16.7 L/L) and thrombocytopenia (Plt  $24 \times 10^9/L$ ). Fluctuating neurologic abnormalities were observed in the following hours: faltering speech and deficit of the left facial nerve, reappearance of paresthesia in the perioral area and left limbs, occasional state of confusion, heaviness in the head, continued numbness in the left limbs and, finally, temporospatial disorientation.

Physical examination revealed subicterus, lymphadenopathy in the left laterocervical area and splenomegaly. An electroencephalogram showed slight diffuse reduction in activity with a prevalence of widespread irritative abnormalities in the right temporal region. Examination

of the fundus oculi revealed a plane papilla with indistinct margins, normal vessels and an uninjured retina.

Laboratory analyses on January 26 confirmed severe anemia and thrombocytopenia, with numerous schistocytes in peripheral smears (30%), elevated levels of lactic dehydrogenase (LDH 1875 U/mL) and bilirubin (prevalently indirect: 1.78 mg/dL), an erythrocyte sedimentation rate of 120 mm/hr, reduced haptoglobin (<38.3 mg/dL), absence of antiplatelet antibodies, negative direct/indirect Coombs', normal level of circulating immunocomplexes, microhematuria.

The association of microangiopathic hemolytic anemia, thrombocytopenia, neurologic features and fever suggested a diagnosis of TTP.

We started treating the patient with fresh plasma and a steroid (prednisone 50 mg daily) and acetyl-salicylic acid (500 mg daily): the first plasmapheresis procedure was programmed for January 28.

Since the patient reported having engaged in at risk sexual behavior (homosexual activities), on January 29 we obtained his consent to test for HIV antibodies. The results showed the patient was positive for both HIV antibodies and HIV antigenemia. Skin tests for delayed hypersensitivity (Multitest Merieux) demonstrated severe hypoergy. Two consecutive tests showed severe depletion of CD4<sup>+</sup> lymphocytes: 11% total lymphocytes; absolute counts of 0.101 and 0.108 × 10<sup>9</sup>/L, respectively, and a CD4<sup>+</sup>/CD8<sup>+</sup> ratio of 0.11. Serum β<sub>2</sub>-microglobulin was 3.6 (normal values <3) mg/L.

After the first plasmapheresis treatment platelets rose to 42 × 10<sup>9</sup>/L, after the second to 70 × 10<sup>9</sup>/L and after the third to 183 × 10<sup>9</sup>/L. Hemoglobin and hematocrit improved, and schistocytes gradually disappeared from peripheral smears. Clinically, fever resolved and the neurologic picture improved. The steroid was tapered.

On February 22 the patient was discharged on oral prednisone (37.5 mg daily) and acetyl-salicylic acid (500 mg daily), and enrolled for follow-up in the Day Hospital.

In the following months (March-October) hematocrit and platelets values held steady; nei-

ther neurologic abnormalities nor fever reappeared, and the steroid was tapered to zero on May 25, when the antiaggregant was discontinued too.

Check-ups in April and June confirmed depletion of CD4<sup>+</sup> lymphocytes (respectively, 0.151 and 0.100 × 10<sup>9</sup>/L). Antiretroviral treatment with zidovudine (250 mg twice day) and primary prophylaxis against *Pneumocystis carini* pneumonia was begun with trimethoprim/sulphamethoxazole (160/800 mg daily).

### Discussion

A continuous spectrum of diseases and a wide variety of clinical features are associated with HIV infection. A broad range of hematologic disorders has also been reported: impaired hematopoiesis, cytopenia, coagulation abnormalities. The pathogenesis of these disorders is certainly multifactorial. For instance, cytopenia may result from a direct suppressive effect of HIV, from an opportunistic infection or tumor infiltration in the marrow. The etiology of thrombocytopenia in HIV patients may be due to direct infection of megakaryocytes by the virus, immune-mediated destruction, impaired hematopoiesis, toxic effects from medications and microangiopathic anemia syndromes. While the pathogenesis of ITP is usually considered to be autoimmune, that of TTP remains an enigma.

Our report confirms that TTP can be associated with HIV infection and may constitute its first clinical manifestation. In at least seven of 27 previously described cases, TTP has led to detection of HIV seropositivity;<sup>2-5</sup> in some of these TTP represented the only manifestation of HIV infection for a long time. In three patients TTP was preceded by ITP.<sup>4-6</sup> In at least two others<sup>8</sup> TTP was responsible for the death of the patients: the first was the result of a massive glossal hemorrhage, while in the second it provoked a cardiac arrest before plasmapheresis could be performed.

The positive antigenemia, hypoergy to tests for delayed cutaneous hypersensitivity, severe and confirmed depletion of CD4<sup>+</sup> lymphocytes showed that the infection in our subject was in

an advanced phase. According to recent CDC criteria this patient should be considered in AIDS. Previously described cases belonged to stages II, III and IV (ARC, AIDS) (CDC criteria of August, 1987).

The treatment indicated for this pathology – plasmapheresis, fresh plasma, steroids and antiaggregants – is the same as that used in non HIV-associated cases. Our patient responded well, achieving total remission. Twelve months later, we can say that there has been no relapse.

Among the 27 cases described in the literature, a relapse was reported in two: fourteen<sup>9</sup> and twenty months,<sup>5</sup> respectively, after the first episode of TTP. The follow-up in the above mentioned cases is too inhomogeneous to allow an evaluation of the prognostic meaning of TTP in the natural history of HIV infection. Our opinion is that, like ITP, TTP does not influence the clinical evolution of HIV infection.

The present case and the increasing number of reports on TTP lead us to suggest that HIV serodiagnosis should be performed every time a TTP is observed.

## References

1. Landonio G, Nosari A, Spinelli F, Vigorelli R, Caggese L, Schlacht I. HIV-related thrombocytopenia: four different clinical subsets. *Haematologica* 1992; 77:398-401.
2. Jokela, J, Flynn, T, Henry, K. Thrombotic thrombocytopenic purpura in a human immunodeficiency virus (HIV)-seropositive homosexual man. *Am J Hematol* 1987; 25:341-3.
3. Boccia RV, Gelmann EP, Baker CC, Marti G, Longo DL. A hemolytic-uremic syndrome with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; 101:716-7.
4. Routy JP, Beaulieu R, Monte M, Saint-Louis J, Sauvageau G, Toma E. Immunologic thrombocytopenia followed by thrombotic thrombocytopenic purpura in two HIV-1 patients. *Am J Hematol* 1991; 38:327-8.
5. Thompson CE, Damon LE, Ries CA, Linker CC. Thrombotic microangiopathies in the 1980s: clinical features, response to treatment, and the impact of the human immunodeficiency virus epidemic. *Blood* 1992; 80:1890-5.
6. Manner CE, Gathe J jr, Novak I, Sawyer G, Holder P, Stool E. Thrombotic thrombocytopenic purpura (TTP) in a man with AIDS and prior idiopathic thrombocytopenic purpura (ITP). Abstract presented at the IX International Conference on AIDS, Berlin, 1993: 451.
7. Rarick MU, Espina B, Mocharnuk R, Trilling Y, Levine AM. Thrombotic thrombocytopenic purpura in patients with human immunodeficiency virus infection: a report of three cases and review of literature. *Am J Hematol* 1992; 40:103-9.
8. Leaf AN, Laubenstein LJ, Raphael B, Hochster H, Baez L, Karpatkin S. Thrombotic thrombocytopenic purpura associated with human immunodeficiency virus type 1 (HIV1) infection. *Ann Intern Med* 1988; 109:194-7.
9. Platanias LC, Paiusco D, Bernstein S, Murali MR. Thrombotic thrombocytopenic purpura as the first clinical manifestation of human immunodeficiency virus infection. *Am J Med* 1989; 87:699-700.