Fatal Haemolytic Uraemic Syndrome in an AIDS patient with Disseminated Adenovirus and Cytomegalovirus Co-infection

Sindrome uremico emolitica fatale in una paziente con AIDS affetta da una duplice infezione virale disseminata: adenovirus e cytomegalovirus

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INTRODUCTION

Thrombotic Micro Angiopathies (TMA) are a group of disorders in which intravascular hemolysis and fragmentation of red blood cells occur following a disease of the small vessels. This clinical syndrome has two different forms: Thrombotic Thrombocytopenic Purpura (TTP) and Haemolytic Uraemic Syndrome (HUS) [1].

TTP is an acute disorder of unknown etiology characterised by haemolytic anemia, neurologic and renal pathology. It predominantly affects young adults and is characterized by a sudden onset of fever, renal failure, and neurological signs, such as paralysis, psychiatric disturbances, and coma. In addition, patients tend to develop a generalized purpura and anemia with hemoglobinuria. The hematologic changes are those of a microangiopathy with thrombocytopenia, and sometime evidence of disseminated intravascular coagulation may be observed.

HUS is the presence of acute haemolytic anemia with renal failure in infancy or early childhood. This condition often follows an acute febrile illness or enterohemorrhagic Escherichia coli O157:H7 infection and is characterized by a variable degree of haemolytic anemia with nephritis. Additionally, there is often seen a rapid fall in the hemoglobin levels with marked hemoglobinuria. The condition is also characterized by a severe systemic involvement, with fever, abdominal pain, and renal failure which may eventually progress to complete anuria.

The peripheral blood picture shows the typical microangiopathic appearance which includes: fragmentation and distortion of the red cells, small spherocytes, and marked polychromasia.

A variable degree of thrombocytopenia and leukocytosis generally occurs. Furthermore, there is an elevated blood urea level, and urinalysis provides evidence of nephritis. Before the introduction of highly active antiretroviral therapy, TMA seemed to be a possible complication in advanced phases of HIV-infection [2-3], with an incidence of 1.4% [4], and high mortality rate within 3 months from diagnosis [5]. Although TMA pathogenesis is still unclear, systemic endothelial damage, from many different factors, including viral infections, could be a due of several triggering factors for the microangiopathic process [6-7].

Here, we describe a fatal case of HUS in a woman with AIDS, having systemic cytomegalovirus and adenovirus co-infection.
On 22nd February 2003 a thirty four year old woman from Morocco was admitted to our clinic for a clinical syndrome characterized by fever, nausea, diarrhea and loss of consciousness which begun seven days before. A cerebral CT scan, performed on 15th February, had shown evidence of numerous hypodense lesions.

Based upon a suspicion of cerebral toxoplasmosis, a test for anti-HIV antibodies was given, which resulted positive. Reported risk factor for HIV infection was heterosexual intercourse. Further physical examination revealed a blood pressure of 90/75 mmHg, pulse 98/min, respiratory rate 20/min, temperature 37.2°C. Diarrhea was also a symptom.

Results of the initial laboratory study revealed: Hb 10.9 g/dl, white blood cells 11.700/ mm³, differential leukocyte count: neutrophils 83%, lymphocytes 15%; platelets 288.000/mmc, LDH 552 mU/ml, serum creatinine 0.8 mg/dl, urea 17 mg/dl, CD4+ T cell count was 27/mm³ (2%) and quantitative viral load was >750.000 copies/ml (Cobas Amplicor, Roche).

Direct examination of stools showed the presence of numerous neutrophilic granulocytes. Repeated coprocultures resulted negative for bacteria, mycetes and protozoa and several tests resulted negative also for clostridium toxins. In particular the E. coli O157:H7 resulted negative.

Therapy based on Trimethoprim/Sulfamethoxazole i.v. at the dose of 320/1600 mg b.i.d. was initiated. On the 8th March the patient presented clinical signs of acute abdomen with high fever, being so the patient was placed under urgent surgical care leading to excision of her appendix which resulted having acute catarrhal inflammation. Biopsy of the removed appendix showed presence of giant cells with typical intranuclear “owl’s eye” inclusions, markers for CMV infection. At this time HCMV pp65 antigenemia was tested positive with 150 cells/slide.

Therapy based on Foscarnet 90 mg b.i.d. was started. Over the subsequent days the patient general condition declined with a marked persistence of high fever, abdominal pain and diarrhea, so she was placed on total parenteral nutrition. On 20th March antiretroviral therapy begun with AZT, DDI, Lopinavir/Ritonavir at average recommended dosage.

An abdomen CT scan performed on 21st March showed thickening and enhancement of the small bowel, and colon and mesentery wall, attributable to enteritis and colitis. On 31st March (23rd day of Foscarnet treatment) the pp65 antigenemia was 220 cells/slide. Therefore, Ganciclovir was added to the therapy at the dosage of 5 mg/kg ev b.i.d.

From 10th April the patient developed an acute and severe normochromic normocytic anemia (Hb 6.4 g/dl, Ht 19%), with normal reticuloocytes, low haptoglobin (<5 mg/dl), thrombocytopenia (11000/mm³), and normal blood clotting; schistocytes were present in the blood smear. Fever was present. In the following days the clinical picture became more and more complicated with the appearance of repeated episodes of epistaxis and melena which required the administration of emotransfusions.

In addition, the patient developed renal failure with urea 129 mg/dl and creatinin 2.1 mg/dl. Neither anemia nor thrombocytopenia improved after ganciclovir and HAART withdrawal, which was performed on 18th April. Due to the presence of thrombocytopenia, microangiopathic haemolitic anaemia and acute renal failure (with serum creatinine >2 mg/ml), a diagnosis of HUS was made. No clinical improvement was observed despite the administration of high doses of fresh frozen plasma (20 ml/Kg/die).

The pp65 antigenemia remained persistently positive as did the test for Immediate Early Antigen of CMV (p72) on shell vials. On a plasma sample collected on 20th May, which was positive for pp65 antigenemia with 800 cells/slide, we observed beginning from the tenth day a cytopathogenic effect in long term culture of human embryonal fibroblasts (PEU). The identification, carried out by immunofluorescence with monoclonal antibodies (Argene Biosoft), proved that the cytopathogenic agent was an adenovirus.

Therefore, the patient showed evidence of disseminated CMV/ADV coinfection, the principal location being in the gut. No drugs, which are commonly associated with HUS, had been taken by the patient.

The patient’s condition continued to deteriorate with persistent pancytopenia, kidney failure and gradual development of respiratory disturbances which reflected ARDS as well as high fever. As a result, the patient was moved to the Intensive Care Unit where she passed on 12th June. An autopsy was not performed.
**DISCUSSION**

Although the pathogenesis of HUS remains still unclear, systemic endothelial damage is thought to be a contributing factor in many situations: infections, autoimmune diseases, cancer, and chemotherapy [8]. In this fatal case report we documented three concomitant viral infections: HIV, Cytomegalovirus and Adenovirus, while the other three possible causes (autoimmune diseases, neoplasm or drugs) could had been excluded. HIV alone may play a causative role in this syndrome. The detection of viral p24 antigen in endothelial cells suggests that HIV may exert a pathogenetic role that could range from a direct cytopathogenic effect to functional impairment of the endothelium [9]. In later-stages of HIV disease, a present risk of death from TMA at 1 year is 31-38%, has been described with significant morbidity and mortality and very poor prognosis (45% of AIDS patients die within 2 months of virus detection) [8-10]. Incidence of thrombotic microangiopathy seems to have diminished since the introduction of HAART.

This may be due to the reported lower incidence of opportunistic infections and AIDS related tumours.

Several reports from literature suggested that CMV has significant TMA causative role, although the data do not preclude that cofactors along with CMV contribute to the development of TMA [10-13]. Adenovirus infections by overexpression of I(kappa)B(alpha) in endothelial cells may also play a role in this syndrome [14]. Disseminated adenoviral disease has rarely been associated with TTP after allogenic bone marrow transplantation [15].

It is of our opinion, in this patient with advanced HIV infection, that the adenovirus-cytomegalovirus co-infection might have triggered a fatal form of HUS, with an endothelial cell injury [16].

In conclusion, early identification of disseminated ADV infection could be fundamental in establishing a better treatment strategy, especially within dealing with CMV infection [17].

**Key Words:** Cytomegalovirus, Adenovirus, HIV, Haemolytic Uraemic Syndrome

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**SUMMARY**

We describe a fatal case of haemolytic uremic syndrome in a young woman with AIDS, and disseminated adenovirus (ADV) and cytomegalovirus (CMV) co-infection. We hypothesize that ADV/CMV co-infection may have a causative role in this clinical picture.

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**RIASSUNTO**

Descriviamo un caso fatale di sindrome uremico emolitica occorso in una giovane donna affetta da AIDS, in cui è stata riscontrata una duplice infezione virale disseminata: da adenovirus (ADV) e da cytomegalovirus (CMV). Gli autori ipotizzano che tale co-infezione da ADV/CMV abbia avuto un ruolo nel quadro clinico complessivo.

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**REFERENCES**


