Thrombotic Microangiopathy in Patients with Acquired Immunodeficiency Syndrome Before and During the Era of Introduction of Highly Active Antiretroviral Therapy

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The incidence of thrombotic microangiopathy (TMA) was retrospectively evaluated in a cohort of 1223 patients with acquired immunodeficiency syndrome (AIDS) who were observed from January 1985 through December 1996 (before the era of highly active antiretroviral therapy [HAART]), and the incidence was prospectively assessed for 347 patients with AIDS during the period of January 1997 through December 2000 (during the HAART era). Seventeen cases were reported in the former cohort (1.4%). The increased risk of developing TMA was statistically significant in patients with cryptosporidiosis or AIDS-related cancer but not in those with other diseases. In the 1997–2000 cohort, no cases were observed during follow-up. TMA is associated with conditions observed in the advanced phases of human immunodeficiency virus infection. The disappearance of TMA during the HAART era may be explained by the lower percentage of patients with long-lasting CD4+ T cell depletion, advanced AIDS, or cryptosporidiosis or who have undergone multiple courses of chemotherapy for treatment of cancer.

Thrombotic microangiopathy (TMA) is a clinical syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, microvascular thrombosis, and multiple organ dysfunction. In the clinical spectrum of TMA, thrombotic thrombocytopenic purpura (TTP) is associated with up to 5 symptoms, including fever, neurological abnormalities, anemia, thrombocytopenia, and renal failure, all of which (except cerebral involvement) also occur in patients with hemolytic uremic syndrome (HUS) [1, 2].

Although the pathogenesis of TMA is still unclear, systemic endothelial damage is thought to be an important factor in the microangiopathic process. In line with this interpretation, bacterial endotoxins, antibodies, immunocomplexes, and certain drugs are toxic to endothelial cells and are thought to be pivotal in the pathogenesis of the disease [1, 3].

TMA is a possible complication of HIV-1 infection [4–10], and this association has been reported to account for up to 30% of TMA cases that involve hospitalization [10, 11]. No information is currently available regarding the prevalence of TMA in patients with AIDS, and there are no reports concerning the effect of HAART on the onset or course of the disease; furthermore, the roles of underlying diseases and epidemiological factors in affecting the risk of developing TMA are still unclear.

The aim of our study was to assess the incidence of TMA in a retrospective cohort of patients with AIDS who attended our institute during the era before...
HAART was introduced (1985–1996) and in a prospective cohort of patients with AIDS recruited after the introduction of HAART into clinical practice (1997–2000). We also evaluated the characteristics of, treatment administered to, and outcomes for patients with TMA and the risk of developing TMA in relation to the patients’ clinical history and pathological kidney alterations revealed by immunohistochemistry and electron microscopy.

**PATIENTS AND METHODS**

**Patients.** In the retrospective study, we evaluated for a consecutive series of patients who had AIDS diagnosed at the University of Milan’s Institute of Infectious Diseases and Tropical Medicine (Milan, Italy) during the period of January 1984 through December 1996. The prospective investigation involved a consecutive series of patients with AIDS who were treated at our institution during the period of January 1997 through December 2000. Until 1992, diagnosis of AIDS was made in accordance with the 1987 criteria of the Centers for Disease Control and Prevention [12]; thereafter, diagnosis was made on the basis of the revised criteria [13].

The institute’s standardized database contains the following patient data: complete clinical history (including autopsy records, when available), demographic and laboratory data (including complete blood cell counts, the levels of blood urea nitrogen [BUN], serum creatinine, lactate dehydrogenase [LDH], bilirubin, and haptoglobin; blood clotting times; urinalysis findings; CD4⁺ T cell counts; HIV antigen levels or HIV genemia [p65 Ag] and viremia [as determined by use of the p72 shell vial assay]), the results of tests of stool samples for bacteria and parasites, and the findings of pathological examinations, as available.

The clinical records were retrospectively reviewed (in the pre-HAART cohort) or actively surveyed (in the 1997–2000 cohort) with the aim of identifying cases that met the following clinical criteria for a diagnosis of TMA: (1) hemolytic anemia (a rapid reduction in the hemoglobin level to <7.5 g/dL, with a very low haptoglobin level [<30 mg/dL], the presence of high numbers of schizocytes in peripheral blood smears, and a negative Coombs’ test result); (2) acute severe thrombocytopenia (platelet count, <60,000 platelets/mm³), with or without purpura and with normal blood clotting times in subjects with previous platelet counts of >100,000 platelets/mm³; (3) temperature of >38°C; plus (4) acute renal dysfunction (defined as a serum creatinine level of ≥2 mg/dL and/or a BUN level of >100 mg/dL) and/or (5) CNS involvement, revealed by the acute onset of neurological symptoms (headache, confusion, or disorientation). TTP was defined as TMA with purpura and neurological dysfunction unrelated to the gravity of renal impairment; HUS was defined as TMA with significant renal impairment and few or no purpura or neurological abnormalities.

Before 1995, the therapeutic protocol for TMA at our institute consisted of the administration of large volumes of fresh frozen plasma (loading dose, 30–40 mL/kg, followed by a daily dose of 15–20 mL/kg) and the management of anemia (by blood transfusions) and renal failure (by hemodialysis), when necessary. Since 1995, plasmapheresis has been adopted as standard treatment. Adjunctive therapies (heparin, 10,000–20,000 U q.d.; acetylsalicylic acid, 325–1500 mg q.d.; γ-globulin, 400 mg/kg q.d.; and methylprednisolone, 100 mg q.d.) were administered at the discretion of the physicians. “Remission” was defined as the normalization of platelet counts noted at ≥3 consecutive weekly control examinations, an improvement in anemia, and the resolution of renal failure and/or acute neurological events.

**Pathological analysis.** Ten sections from kidney samples (biopsy and/or autopsy specimens) were processed for light microscopy by means of hematoxylin-eosin, periodic acid–Schiff, and acid fucsin–orange 6 trichrome staining. Ultrastructural examinations were performed for selected areas of routinely processed renal tissues obtained from paraffin-embedded samples. Immunohistochemical analysis was performed by use of mouse anti-CMV (1:20; Dako) and anti-p24 HIV core protein (1:50; Dako). The sections were pretreated by means of proteolytic digestion (pronase type XIV 0.5 mg/mL for 7 min at 37°C; Sigma) or heating in a microwave oven (twice for 5 min at 780 W in 0.01 M citrate buffer), to identify CMV and HIV antigens. Double indirect immunoperoxidase was used, with a 3,3-diaminobenzidine–free base as chromogen.

**Statistical analysis.** The statistical analyses were performed by use of SPSS software, version 7.5 (SPSS). The statistical significance of the between-group differences for all variables was calculated with use of 2-tailed Fisher’s exact test. Crude relative risks and 95% CIs were calculated from logistic regression coefficients.

**RESULTS**

**Incidence, correlates of risk, and outcomes of TMA.** The retrospective survey involved 1223 patients with AIDS, and the longitudinal investigation involved 347 patients with AIDS (table 1). None of the patients in the retrospective cohort received HAART, whereas 295 patients (85%) in the prospective cohort received HAART for >6 months during the study period.

In the retrospective survey, 17 patients (14 men and 3 women) had cases that met the criteria for TMA, for a cumulative incidence of 1.4%; none of the patients in the longitudinal study showed any signs or symptoms of TMA. Because, according to the χ² test, 3.76 events were expected in the prospective cohort, the difference between the 2 cohorts
The cumulative incidence of TMA was 3.9% among homosexual patients (2 of 256 patients), 0.6% among heterosexual patients (10 of 158), and 0.6% among injection heroin abusers (2 of 149 patients). There were no cases of TMA among the patients with other AIDS-index diseases.

Seven of 9 patients with AIDS-related tumors were receiving systemic antineoplastic treatment at the time of TMA onset: 5 patients with Kaposi sarcoma were receiving bleomycin and etoposide, and the 2 patients with NHL were receiving the CHOP (cyclophosphamide-doxorubicin-vincristine-prednisone) regimen. TMA was constantly observed during the first cycle of CHOP but never before the third cycle of bleomycin and etoposide.

The main results of routine laboratory tests performed 45–60 days before and at the onset of TMA are shown in table 2. All patients had rapid decreases in hemoglobin concentration and platelet count; these decreases was associated with increases in LDH, BUN, and serum creatinine levels and reticulocyte and schizocytes counts. At the time of the diagnosis of TMA, bilirubin levels were invariably high and haptoglobin levels were <30 mg/dL (median, 12 mg/dL). All of the patients with HUS had macrohematuria or microhematuria and schizocytes counts. Coagulation parameters, such as prothrombin time, partial thromboplastin time, D-dimers, and fibrinogen, were within the normal range in all of the patients. Tests for detection of CMV were performed for 10 patients, but CMV infection was only found in the patient with CMV colitis.

All of the patients had fever. Persistent watery diarrhea was

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before TMA diagnosis</th>
<th>At onset of TMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin level, g/dL</td>
<td>11 (8.9–12.1)</td>
<td>6 (4–7.2)</td>
</tr>
<tr>
<td>Platelet count, platelets $\times 10^7$/μL</td>
<td>213 (60–410)</td>
<td>20 (1–50)</td>
</tr>
<tr>
<td>Lactate dehydrogenase level, U/L</td>
<td>423 (284–739)</td>
<td>1060 (382–2353)</td>
</tr>
<tr>
<td>Blood urea nitrogen level, mg/dL</td>
<td>20 (12–52)</td>
<td>153 (112–311)</td>
</tr>
<tr>
<td>Serum creatinine level, mg/dL</td>
<td>0.8 (0.3–1.2)</td>
<td>4 (2.6–12)</td>
</tr>
</tbody>
</table>

NOTE. Data are median (range).

* The analyses were performed during a time log ranging from 45 to 60 days before the onset of TMA.
observed in the 6 patients with documented enteric opportunistic infections and in 2 of 6 patients with Kaposi sarcoma. Fourteen patients received standard therapy with fresh frozen plasma infusions in addition to either corticosteroids \((n = 4)\), acetylsalicylic acid \((n = 4)\), heparin \((n = 2)\), or high-dose intravenous γ-globulin \((n = 2)\); 2 patients were treated with plasmapheresis, and 1 patient, who died \(\leq 48\) h after the onset of TMA, did not receive treatment. Three patients required hemodialysis.

Despite receipt of treatment, 13 patients (10 with HUS and 3 with TTP) died within a median of 20 days \(\text{range}, 2–90\) days without achieving any substantial improvement in signs and symptoms. Hemorrhage was the main cause of death in 4 patients \(\text{of 3 patients with TTP developed a fatal intracranial hemorrhage, and the other 2 developed gastrointestinal hemorrhages, and renal failure was the main cause in the other 10. Hemolysis control, a normal platelet count, and improved renal function were achieved by 1 patient who had been treated with plasmapheresis and by 2 patients who had been treated with fresh frozen plasma.}

**Histological and electron microscopy findings.** Pathological findings were available for 15 patients with TMA \(\text{table 3}\). Renal biopsy specimens obtained at the time of HUS onset were available for 2 patients \(\text{patients 1 and 2}\). In both cases, histological examination revealed arteriolar thrombosis and glomerular changes characterized by the retraction of glomerular tufts and a marked thickening and wrinkling of the capillary wall. Although patient 1 still had clinical and laboratory signs of HUS at the time of death, the autopsy examination did not reveal any glomerular or arteriole abnormalities, although there was histological evidence of HIV nephropathy characterized by mesangial hyperplasia and focal segmental glomerulosclerosis. An autopsy examination was not performed for patient 2.

Among the 9 patients with HUS who died of renal failure and for whom autopsy results were available, 6 had glomerular changes, which included an increase in the size of the mesangium \(\text{patients 3–6}\), a thickening of basement membranes \(\text{patients 4 and 6}\), development of subendothelial deposits \(\text{patients 3, 7, and 8}\), and development double contour aspects \(\text{patient 6}\). One patient \(\text{patient 5}\) also had endoluminal thrombi. In patients 9 and 10, who had NHL, the renal structure was entirely destroyed by neoplastic mononuclear cell infiltrates.

The autopsy examinations of patients 13 and 14, who died after the resolution of HUS, revealed aspecific alterations \(\text{sclerotic glomeruli and renal arteries calcifications}\). The renal autopsies of the 3 patients with TTP who died \(\text{patients 15–17}\) did not reveal any significant arteriolar or glomerular changes. The results of immunohistochemical testing for CMV and HIV antigens were negative for all of the tested kidney biopsy and autopsy specimens.

**DISCUSSION**

Our study reveals a relatively low incidence of TMA during the pre-HAART era \(\text{1.4}\%\); moreover, the syndrome mainly occurred in patients with profound immunodepression \(\text{i.e.}, \text{median CD4}^+ \text{T cell count of 50 cells/μL}\), with a higher incidence among homosexual patients that can be explained by the increased incidence of Kaposi sarcoma and cryptosporidiosis \(\text{the diseases more frequently associated with TMA in our case file}\) \(\text{[14, 15]}\).

The pathogenesis and etiology of TMA is still unclear, but pregnancy, infections \(\text{bacterial, fungal, viral, and amebic}\), vascular collagen diseases, malignancies, receipt of chemotherapy, use of medical drugs, and cocaine abuse have all been reported to be possible triggering conditions \(\text{[16–30]}\), although most cases in adults occur without a known precipitating event or associated disease.

CMV inclusions have recently been detected in kidney specimens obtained from HIV-infected patients with TMA, and it has been suggested that the virus may play a causative role \(\text{[8]}\). CMV colitis was present at the time of HUS in one of our patients, and autopsies revealed CMV in the brain of 2 patients and in the adrenal glands of another 2 \(\text{including the patient with CMV colitis}\). However, the results of immunohistochemical studies of biotic and autoptic kidney specimens were negative for CMV in all cases.

CMV is very frequently found in patients with AIDS at autopsy \(\text{72}\%\) of the autopsies of patients with AIDS performed at our hospital \(\text{[31]}\), and a retrospective survey of the clinical records of the patients with renal CMV infection noted at autopsy did not reveal any association between renal CMV infection and a history of TMA \(\text{data not shown}\). Therefore, it seems unlikely that CMV plays a direct causative role in HUS.

On the contrary, 9 \(\text{53}\%\) of the patients with TMA in our files had disseminated malignancies, and endothelial damage due to the release of procoagulant substances into the circulation after tumor lysis is considered a possible trigger of this syndrome \(\text{[26]}\). Moreover, bleomycin, vincristine, mitomycin, and other antineoplastic drugs have been indicated as possible TMA inducers \(\text{[21–24, 32]}\), and high doses of bleomycin have been associated with pulmonary fibrosis, sclerodermatous changes in the hands, and endothelial damage \(\text{[33–35]}\). It is also worth noting that the majority \(\text{5 of 6}\) of our bleomycin-treated patients developed TMA after receiving several courses of bleomycin therapy, thus suggesting that multiple exposures are needed to cause the toxic effect capable of triggering the microangiopathic processes.

A number of cases of TMA in adults have been associated...
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age in years, sex</th>
<th>Risk population</th>
<th>AIDS-associated disease at TMA onset</th>
<th>Clinical presentation</th>
<th>Time from AIDS diagnosis to onset of TMA, months</th>
<th>TMA resolution</th>
<th>Duration of survival from onset of TMA, days</th>
<th>Findings of histological studies of the kidney</th>
<th>Other relevant pathological findings at death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37, M</td>
<td>Homosexual</td>
<td>Kaposi sarcoma</td>
<td>HUS</td>
<td>8</td>
<td>No</td>
<td>12</td>
<td>Focal increase of mesangial areas and subendothelial deposits</td>
<td>Disseminated Kaposi sarcoma, CMV surrenalitis, hemorrhagic gastritis</td>
</tr>
<tr>
<td>2</td>
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<td>Homosexual</td>
<td>Cryptosp</td>
<td>HUS</td>
<td>8</td>
<td>No</td>
<td>42</td>
<td>Increase of mesangial areas, thickening of basement membranes</td>
<td>CMV-associated encephalitis</td>
</tr>
<tr>
<td>3</td>
<td>33, F</td>
<td>Heterosexual</td>
<td>NHL</td>
<td>HUS</td>
<td>2</td>
<td>No</td>
<td>2</td>
<td>Widening of mesangial spaces, rare endoluminal thrombi</td>
<td>Disseminated NHL, pulmonary aspergillosis, CMV encephalitis</td>
</tr>
<tr>
<td>4</td>
<td>53, M</td>
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<td>NHL</td>
<td>HUS</td>
<td>1</td>
<td>No</td>
<td>32</td>
<td>Focal tram-track appearance of basement membranes, moderate increase of mesangium</td>
<td>Disseminated NHL</td>
</tr>
<tr>
<td>5</td>
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<td>Injection drug user</td>
<td>TB</td>
<td>HUS</td>
<td>1</td>
<td>No</td>
<td>29</td>
<td>Mesangial and parietal deposits</td>
<td>Pulmonary TB, brain toxoplasmosis</td>
</tr>
<tr>
<td>6</td>
<td>34, M</td>
<td>Injection drug user</td>
<td>TB</td>
<td>HUS</td>
<td>1</td>
<td>No</td>
<td>15</td>
<td>Mesangial and parietal deposits, renal cryptococcosis</td>
<td>HIV-associated encephalitis, pulmonary TB</td>
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<tr>
<td>7</td>
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<td>NHL</td>
<td>HUS</td>
<td>1</td>
<td>No</td>
<td>16</td>
<td>NHL</td>
<td>Disseminated NHL, disseminated Kaposi sarcoma</td>
</tr>
<tr>
<td>8</td>
<td>60, M</td>
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<td>Kaposi sarcoma</td>
<td>HUS</td>
<td>9</td>
<td>No</td>
<td>40</td>
<td>NHL, multiple bacterial abscesses</td>
<td>NHL, disseminated Kaposi sarcoma</td>
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<tr>
<td>9</td>
<td>25, F</td>
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<td>HUS</td>
<td>2</td>
<td>No</td>
<td>90</td>
<td>Biopsy: arteriolar thrombosis, retraction of glomerular tuft, marked thickening and wrinkling of capillary wall; autopsy: HIV-associated nephropathy</td>
<td>Heart failure</td>
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<td>Biopsy: arteriolar thrombosis, retraction of glomerular tuft, marked thickening and wrinkling of capillary wall</td>
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<tr>
<td>11</td>
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<tr>
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<td>Cryptosp, CMV colitis</td>
<td>HUS</td>
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<td>Yes</td>
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<td>Arterial calcifications</td>
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<td>Homosexual</td>
<td>Kaposi sarcoma</td>
<td>TTP</td>
<td>8</td>
<td>No</td>
<td>15</td>
<td>No relevant kidney abnormalities</td>
<td>Disseminated Kaposi sarcoma, gastrointestinal hemorrhage</td>
</tr>
<tr>
<td>14</td>
<td>27, F</td>
<td>Injection drug user</td>
<td>Cryptosp</td>
<td>TTP</td>
<td>6</td>
<td>No</td>
<td>19</td>
<td>Kidney cryptococcosis</td>
<td>Intracranial hemorrhage</td>
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<tr>
<td>15</td>
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<td>Homosexual</td>
<td>Kaposi sarcoma, cryptosp</td>
<td>TTP</td>
<td>13</td>
<td>No</td>
<td>42</td>
<td>No relevant kidney abnormalities</td>
<td>Disseminated Kaposi sarcoma, pulmonary thrombosis, hemorrhagic gastritis</td>
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<tr>
<td>16</td>
<td>30, M</td>
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<td>Cryptosp</td>
<td>HUS</td>
<td>2</td>
<td>No</td>
<td>35</td>
<td>Not performed</td>
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</tr>
<tr>
<td>17</td>
<td>39, M</td>
<td>Homosexual</td>
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<td>HUS</td>
<td>15</td>
<td>No</td>
<td>20</td>
<td>Not performed</td>
<td>Not performed</td>
</tr>
</tbody>
</table>

**NOTE.** CMV, cytomegalovirus; Cryptosp, cryptosporidiosis; HUS, hemolytic uremic syndrome; NHL, non-Hodgkin lymphoma; TTP, thrombotic thrombocytopenic purpura.
with diarrhea, without there being any evidence of verotoxin-producing *Escherichia coli* infection [36]. The main causative agent of diarrhea in our patients with TMA was *Cryptosporidium parvum*, and dehydration-induced endothelial damage is the most likely pathogenic cause of TMA in these cases.

Two authors have reported cases of TMA associated with cocaine inhalation [28, 29]. The possible mechanisms involved in cocaine-induced TMA include endothelial injury, vasoconstriction and/or impaired vasodilatation, procoagulant activity, and antiplatelet activity. In our 3 patients who had pulmonary TB, cocaine abuse rather than TB itself may have been a triggering factor for TMA. Of interest, the only 2 cases of TMA observed by us during the period of 1987–1996 in HIV-1–infected patients without overt AIDS were diagnosed in 2 injection users of heroin who were also cocaine abusers.

It has also been hypothesized that HIV itself may play a causative role in this syndrome [5, 6]. In particular, the detection of viral p24 antigen in endothelial cells has suggested that HIV may exert a pathogenic role that could range from a direct cytopathic effect to functional impairment of the endothelium [5]. The relatively low frequency of this syndrome among patients with AIDS does not exclude a role of HIV-1 per se in causing TMA, but the pathological studies of the kidneys of our patients revealed the presence of HIV-associated nephropathy in only a single patient, and p24 antigen was never found in kidney cells.

In the time since the start of the HAART era, no cases of TMA have been observed among our patients with AIDS. Furthermore, the recently reported cases have been anecdotal and observed in untreated patients [37–39]. The reasons for this may lie in the lower percentage of patients with advanced disease and the shorter duration of CD4+ T cell count depletion, with the consequently lower risk of developing opportunistic diseases and AIDS-related cancers. In our 1997–2000 cohort, the number of case-file patients with cryptosporidiosis or, to a lesser extent, with Kaposi sarcoma (2 of the conditions more frequently associated with TMA) significantly decreased, and the relative increase in the number of cases of pulmonary TB and NHL was probably not sufficient to balance the decreased risk of TMA. Furthermore, bleomycin was not included in the first-line treatment for the majority of our patients who had Kaposi sarcoma: HAART not only allows shorter chemotherapy cycles but is actually enough to cure Kaposi sarcoma without the use of antineoplastic drugs [40]. Taken together, these considerations can easily explain the disappearance of this condition since the introduction of HAART.

In HIV-negative patients, early diagnosis and an aggressive therapeutic approach may reduce the high mortality rate of TMA [41–43]. Patients with no previous HIV-related symptoms have been reported to respond equally well to adequate therapy [37–41, 44]. On the contrary, the outcome in patients with AIDS is often poor, despite administration of treatment, and is related to the severity of the underlying disease [4, 5, 45, 46]. Our study confirms the high mortality rate (100% for TMA and 71% for HUS) in patients with advanced HIV infection.

Plasma exchange is the treatment of choice for adults with TMA [47, 48], but, although it induces hematologic remission, it is not clear whether plasma therapy also has an effect on renal function. Renal biopsies after plasma infusions in children with HUS have shown the resolution of renal abnormalities [49]. The typical pathological renal findings in TMA, such as arteriolar thrombosis, the retraction of glomerular tufts, and a marked thickening and wrinkling of the capillary wall, were present in the kidney biopsy specimens of our patients at the onset of HUS and in the postmortem specimen from 1 patient who died before starting therapy, but they were absent from postmortem tissue samples obtained from patients who underwent plasma treatment. However, HUS-related signs or symptoms persisted in the majority of patients, and the renal impairment could only be partially explained by the wide range of kidney abnormalities revealed at autopsy. Nevertheless, timely diagnosis and treatment are useful in limiting kidney impairment and obtaining a better outcome.

TMA is a life-threatening medical emergency. Its incidence in patients with AIDS is relatively low, and it is conceivable that combined antiretroviral therapies have significantly reduced the risk of its development. However, the risk of inducing TMA by administration of cancer chemotherapy should still be taken into account in patients with AIDS-associated tumors.

References

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