Perspective

Selected Rare, Noninfectious Syndromes Associated With HIV Infection

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Infrequent and sometimes treatable noninfectious syndromes associated with HIV disease include tenofovir-associated Fanconi syndrome, a proximal renal tubular disorder; pulmonary hypertension that appears to be due to HIV-driven inflammation resulting in endothelial proliferation; thrombotic thrombocytopenic purpura, characterized by intravascular coagulopathy; diffuse infiltrative lymphocytosis syndrome, which can affect multiple organs; and Castleman's disease, a lymphoproliferative disorder that usually occurs in a multicentric form with poor prognosis in HIV-infected patients. This article summarizes a presentation on the characteristics, diagnosis, treatment, and prognosis of these disorders by Molly E. Eaton, MD, at the International AIDS Society–USA course in Atlanta in March 2005.

Infrequent and treatable noninfectious syndromes associated with HIV infection include nucleotide reverse transcriptase inhibitor (n*t*RTI)-associated Fanconi syndrome, pulmonary hypertension, thrombotic thrombocytopenic purpura, diffuse infiltrative lymphocytosis syndrome, and Castleman's disease. This review will summarize the characteristics, diagnosis, treatment, and prognosis of these selected disorders.

Nucleotide Reverse Transcriptase-Associated Fanconi Syndrome

Fanconi syndrome is a generalized dysfunction of the proximal tubule with no primary glomerular involvement. It has been observed several weeks after initiation of treatment with the n*t*RTI tenofovir. Tenofovir undergoes renal excretion by active secretion and glomerular filtration; animal studies raised some concerns regarding potential bone and renal toxicity, but clinical trials did not indicate any substantial risk of renal toxicity.

Fanconi syndrome is characterized by variable increase in creatinine levels; proteinuria; normoglycemic glycosuria; phosphaturia and hypophosphatemia; potassium wasting and hypokalemia; HCO_3 wasting and non-anion gap acidosis; and polydipsia, polyuria, and dehydration. Patients with tenofovir-associated Fanconi syndrome often present with fatigue, weight loss, and dry mouth. The workup for proximal renal tubular dysfunction includes serum chemistries to identify abnormal phosphate, potassium, and bicarbonate values; urinalysis to identify proteinuria and glycosuria; and measurement of urine electrolytes (sodium, potassium, chloride) to permit calculation of the urine anion gap. Renal biopsy may be indicated in cases in which symptoms and biochemical abnormalities do not resolve after stopping tenofovir treatment.

The mechanism of this toxic effect is not completely clear. Tenofovir in usual concentrations does not appear to be toxic to renal cells, and the toxic effect may require accumulation of elevated drug levels. Tenofovir is imported into the renal tubule cell via the organic anion transporter 1 (OAT-1) and efflux occurs via the *MRP2* gene-encoded conjugate export pump. It is thought that these transporters may be relatively inefficient in some individuals, allowing accumulation of tenofovir within the proximal tubule. Some protease inhibitors (PIs), such as ritonavir and lopinavir, have been found to inhibit the pump, and this may contribute to tenofovir accumulation, although this interaction has not been proven. Fanconi syndrome is more likely to occur in patients with unrecognized decreased creatinine clearance prior to the start of tenofovir treatment.

Patients on tenofovir should undergo urinalysis and serum phosphate measurement every 6 months. Patients with normal serum creatinine may still have abnormal creatinine clearance, and the latter should be calculated prior to beginning treatment. The drug should be stopped in patients with evidence of acidosis, glycosuria, proteinuria, or hypophosphatemia. Phosphorus supplementation is recommended in cases of isolated low serum phosphate level, although the benefit of such supplementation remains unclear. The toxicity has been found to be mostly reversible. Currently, there are no recommendations regarding reintroduction of tenofovir in a new regimen once the syndrome has resolved.

Pulmonary Hypertension

Pulmonary hypertension is more common in the HIV-infected population than in the general population, with prevalence estimates of 5 per 1000 versus 2 per million (Recusani et al, *AIDS,* 2003). In the general population, pulmonary hypertension is more common in women. Data from cases reported in HIV-infected individuals from 1987 to 1999 indicate that 54% of cases were in men; however, men accounted for the majority of the HIV-infected population during this period as well. No predisposing factor other than HIV infection is recognized in 82% of cases, and there is no correlation of onset with stage of HIV infection (Mehta et al, *Chest,* 2000). Presenting signs and symptoms include fatigue, syncope, and chest pain; progressive shortness of breath has been reported in 85% of cases, pedal edema in 30%, and nonproductive cough in 19%. There usually are signs of right-sided heart failure, including right-sided gallop, loud P2 heart sound, tricuspid regurgitation murmur, increased jugular venous distention, and edema.

Workup for the condition is fairly straightforward after chest x-ray has shown dilated pulmonary vessels and right-sided cardiomegaly. Electrocardiogram may show right ventricular and atrial hypertrophy and right axis deviation. The echocardiogram may show dilated

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right heart chambers, and can exclude valvular lesions that may cause secondary pulmonary hypertension. It can also identify the high mean pulmonary arterial pressure. The elevated pressure should always be confirmed with right-sided catheterization, which also permits assessment of response to vasodilators.

The causes of HIV-associated pulmonary hypertension remain unclear. Histopathology is the same for HIV-related pulmonary hypertension and primary pulmonary hypertension in HIV-uninfected persons, showing overgrowth of the endothelium that leads to obstruction. A mutation in the *BMPR2* gene that results in reduced inhibition of endothelial proliferation in cases of familial primary pulmonary hypertension has not been identified in HIV-associated pulmonary hypertension. In patients with HIV-associated pulmonary hypertension, pulmonary status continues to deteriorate even when viral load is well controlled, suggesting that HIV may be a trigger, but not the sole culprit, in pathogenesis. Further, no HIV is found in lung tissue in affected individuals. It is thus believed that the condition may be caused by increased inflammatory mediators in susceptible individuals, resulting in increased production of endothelin-1 and increased endothelial proliferation. A recent study suggested a role for Kaposi's sarcoma–associated human herpesvirus 8 (HHV-8) in pulmonary hypertension in HIV-uninfected individuals, although the virus could not be identified in 3 patients with HIV-associated pulmonary hypertension included as controls in the study. The findings from this study need to be confirmed.

Therapeutic options in patients with HIV-associated pulmonary hypertension are the same as in HIV-uninfected patients, including vasodilator treatment with calcium channel blockers, phosphodiesterase blockers (eg, sildenafil), or prostacyclins (eg, epoprostenol infusion). Symptomatic relief is crucial and may involve home oxygen use, diuretics, and digoxin. Anticoagulant therapy makes sense in this context, although there are few data on its use. Use of antiretroviral therapy in affected patients is recommended, although there are no data to indicate that it is of benefit in reversing the underlying endothelial proliferation.

Prognosis is very poor for patients with this disorder, with a median time span of 6 months from diagnosis to death. Suppression of viral replication does not improve prognosis. Better New York Heart Association functional classification at the time of diagnosis has been found to be the only predictor of better outcome (Recusani et al, *AIDS,* 2003).

Thrombotic Thrombocytopenic Purpura

The incidence of all cases of thrombotic thrombocytopenic purpura (TTP) increased by 16-fold between 1973 and 1991. The incidence of TTP in the HIV-infected population likely has contributed to this overall increase, but the precise magnitude of this contribution remains unclear. It is imperative to recognize TTP early because response to treatment is generally excellent if intervention is initiated early, and the condition can be fatal if it is not treated promptly (Torok et al, *Am J Hematol,* 1995).

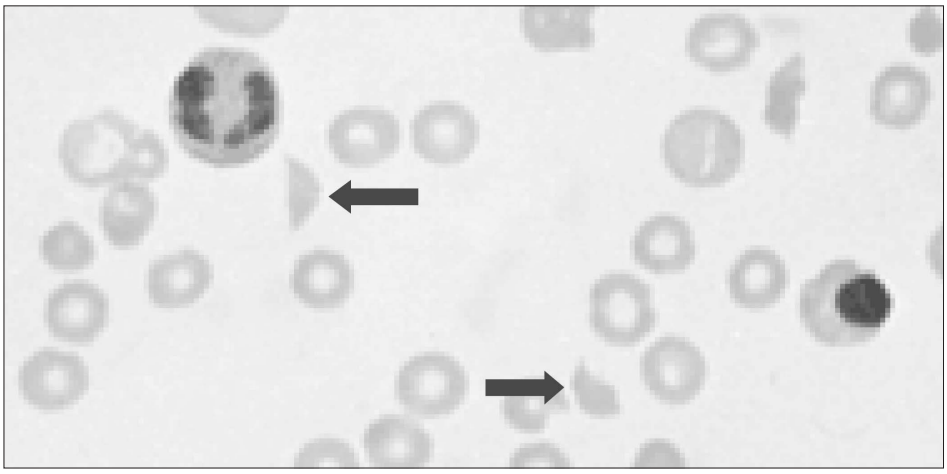

Figure **1.** Schistocytes in blood from patient with thrombotic thrombocytopenic purpura.

The 5 main symptoms of full-blown TTP are thrombocytopenia, anemia, central nervous system abnormalities, renal dysfunction, and fever. The primary dysfunction is intravascular clotting, which consumes platelets and causes an often very marked thrombocytopenia; hemorrhage is nevertheless uncommon. Shearing forces within the clots result in intravascular hemolysis, manifested as high lactate dehydrogenase levels, low haptoglobin, high reticulocyte count, and often a high indirect bilirubin level. Clotting in intracerebral vessels results in ischemia that can present as headache, focal deficits, seizure, and coma. Central nervous system imaging is almost always negative. Clotting in vessels in the kidney can be manifested as hematuria and increased creatinine. Fever is usually but not invariably present; infection must be ruled out in febrile patients. Figure 1 shows the classic finding of schistocytes, fragments of red blood cells that have been torn apart as they move through a clot; platelets are notably absent in the smear.

TTP is associated with large multimers of von Willebrand factor, resulting from a severe deficiency in ADAMTS13, a protease that cleaves von Willebrand factor into smaller multimers. The most common cause of sporadic TTP is an inhibitory antibody that binds ADAMTS13. Because of immune dysregulation, HIV-infected patients make inhibitory antibodies to many blood components, and it is believed that the high incidence of TTP in HIV-infected individuals is associated with high levels of inhibitory antibodies to ADAMTS13 (Tsai, *J Am Soc Nephrol,* 2003).

Treatment is plasmapheresis. After obtaining a hematology consultation and contacting the American Red Cross, plasmapheresis should be performed as soon as possible to reduce risk to the brain and kidney. Plasmapheresis removes the ADAMTS13 inhibitor, infuses large volumes of plasma that dilute inhibitor concentrations, and replenishes ADAMTS13. In cases in which plasmapheresis is not available, plasma infusions may be helpful, although the presence of significant renal failure may prohibit infusion of sufficient volume. The initial response to plasmapheresis usually is excellent. Relapse occurs in approximately 30% of HIV-uninfected patients and probably in a higher per-

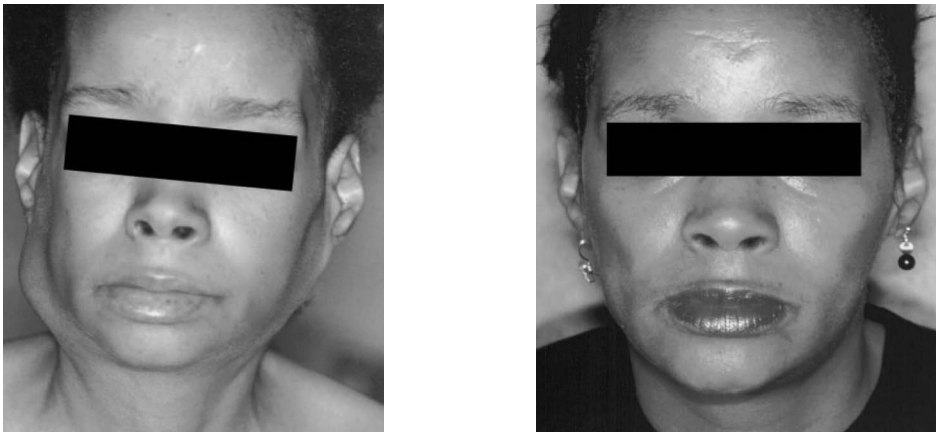

Figure **2.** Patient with diffuse infiltrative lymphocytosis syndrome with characteristic bilateral parotid gland enlargement (left) and after antiretroviral treatment (right).

centage of HIV-infected patients. Antiretroviral therapy, which is believed to remove the antigen drive for antibody production, has been reported to reduce the rate of relapse in case studies. Steroids may also be helpful in this regard. In refractory cases, other options include rituximab, anti-CD20 monoclonal antibody, vincristine, azathioprine, and splenectomy. Despite the severe thrombocytopenia, platelet infusions are contraindicated because they can fuel the intravascular clotting. Overall, survival is greater than 90% if treatment is initiated early in patients receiving plasmapheresis, antiretroviral therapy, and adequate supportive care.

Diffuse Infiltrative Lymphocytosis Syndrome

Diffuse infiltrative lymphocytosis syndrome (DILS) is an autoimmune syndrome characterized by the oligoclonal expansion of CD8+ T lymphocytes in response to HIV antigens. It is often accompanied by lymphocytic infiltration of the salivary glands, as well as of the visceral organs. DILS may be seen in all stages of HIV infection; in one study of 35 patients, 37% of whom had AIDS, diagnosis occurred at a mean CD4+ cell count of 342/µL (range, 44-876/µL; Kazi et al, *AIDS,* 1996). The disorder appears to be more common in populations with major histocompatibility complex (MHC) class 1 and 2 alleles consisting of human leukocyte antigen (HLA)-DR5 and HLA-DRw6. HLA-DR5 and DILS are both more common in African Americans. It is estimated that patients with DILS are more than twice as likely to be African American and 2.8 times more likely to have acquired HIV via homosexual sexual contact than those without DILS.

Table **1.** Visceral Involvement in Diffuse Infiltrative Lymphocytosis Syndrome

- **Parotid involvement**
- **Lung**
  - Lymphocytic interstitial pneumonitis
- **Gastrointestinal tract**
  - Lymphocytic hepatitis
  - Plastica gastric lymphocytic infiltration—linitis
- **Nerve**
  - Cranial nerve palsies
  - Peripheral neuropathies
- **Muscle**
  - Inflammatory myositis

Bilateral parotid gland enlargement, which occurs in approximately 90% to 100% of cases, is the most common presentation of DILS (Figure 2). Patients often have the associated symptoms of dry mouth and dry eyes, similar to that observed in Sjogren syndrome but without anti-Rho or anti-La antibodies. Patients may have extremely high CD8+ cell counts. In one study, the mean CD8+ cell count was 1639/µL, with a range of 560/µL to nearly 5000/µL. Lymphocyte infiltration of extraglandular organs is common (Table 1). Visceral involvement can include the lungs; 31% of patients presented with lymphocytic interstitial pneumonitis in one study (Kazi et al, *AIDS,* 1996).

Patients may be asymptomatic or present with mild to moderate dyspnea on exertion. The pneumonitis is similar to other forms of pneumonitis observed in HIV disease, making it important to perform a diagnostic bronchoscopy with biopsy. Lymphocytic hepatitis may be manifested as elevated liver enzymes but may also progress to frank liver failure. Gastric involvement may need to be differentiated from gastric cancer or syphilis. Peripheral neuropathy is common and resembles HIV-associated neuropathy, although the neuropathy may occur at higher CD4+ cell counts in DILS. Next to effects in the lung, muscle involvement is most common, occurring in 26% of patients. Patients have elevated serum creatine phosphokinase and can have marked symptoms of myalgia and muscle weakness, with the presentation closely resembling polymyositis. In addition to a positive HIV test, diagnosis of DILS involves tissue diagnosis via labial salivary gland biopsy and other tissue biopsies, including bronchoscopy with biopsy and liver biopsy, as well as gallium and computed tomography (CT) scans.

Patients with DILS usually do very well from an HIV disease standpoint. Some data indicate a slower progression of HIV disease in patients with DILS, presumably as a result of the heightened CD8+ cell response to the virus. The goal of treatment is to minimize damage due to the exuberant lymphocyte response. High-dose prednisone can be used to decrease inflammation. The best treatment is antiretroviral therapy, to remove the antigenic drive underlying the inflammatory response. An example of response of the condition to initiation of antiretroviral therapy is shown in Figure 2.

Castleman's Disease

The following case illustrates some of the findings in HIV-associated Castleman's disease.

A 33-year-old African American man with AIDS, CD4+ cell count of 20/µL, was admitted to the hospital with fever and increasing abdominal fullness. He had been diagnosed with disseminated *Mycobacterium avium* complex infection several weeks prior to admission and was taking sulfamethoxazole/trimethoprim, ethambutol, and clarithromycin. He had been unable to tolerate his antiretroviral regimen of efavirenz, lamivudine, and zidovudine. He was toxic and febrile and had massive hep-

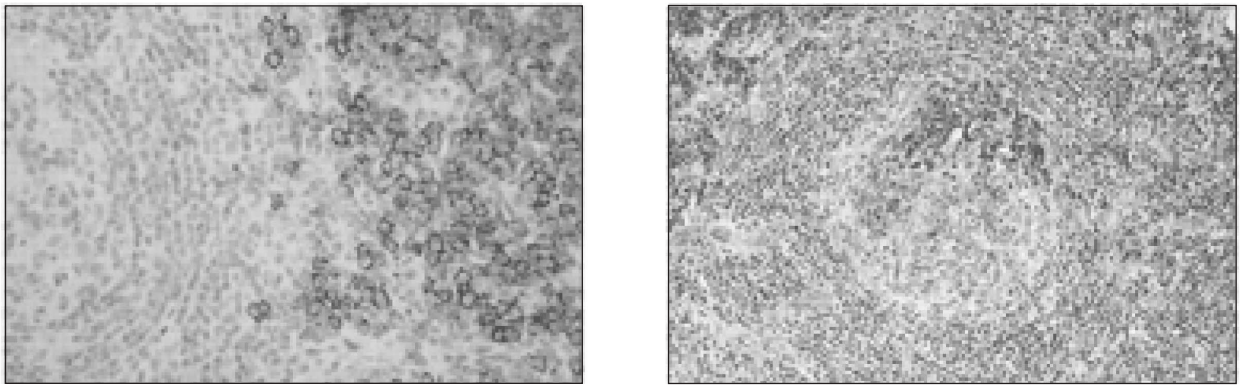

Figure **3.** Histologic variants of Castleman's disease. Left shows plasma cell form, characterized by interfollicular predominance of plasma cells positive for CD138. Right shows hyaline vascular form, characterized by germinal centers with vascularization and an "onion skin" arrangement of mantle-cell lymphocytes. Reproduced with permission from Zietz et al, *N Engl J Med,* 1999.

atomegaly and splenomegaly. Laboratory results showed platelet count of 83,000/µL, hemoglobin 7.5 gm/dL, and lactate dehydrogenase 497 U/L. CT scans showed shotty hilar adenopathy in the lungs, massive hepatosplenomegaly in the abdomen, and scattered small mesenteric lymph nodes. Liver biopsy was normal, and bone marrow biopsy showed no granulomas, fungal elements, or lymphoma. The patient underwent laparotomy with splenectomy. At laparotomy, 3 celiac nodes were removed, with histology being consistent with hyaline vascular Castleman's disease. The patient defervesced and was started on efavirenz, stavudine, and lamivudine. He continues to do well 2 years later. This, however, is not the typical outcome of the disease.

Castleman's disease is a lymphoproliferative disorder seen in HIV-infected and HIV-uninfected patients. It presents with adenopathy, hectic fevers, splenomegaly, hepatomegaly, and polyclonal gammopathy. It can occur as 2 clinical syndromes. Localized Castleman's disease is more common in HIV-uninfected individuals. It may be asymptomatic or it may be associated with symptoms caused by compression of organs by the large lymph node mass. Multicentric disease is more common in HIV-infected patients. It is characterized by numerous enlarged, usually peripheral, lymph nodes; organomegaly; and systemic symptoms such as hectic fever. Lab abnormalities include thrombocytopenia and anemia. The 2 histologic variants of Castleman's disease are the plasma cell form and the hyaline vascular form (Figure 3). The hyaline vascular form is more common in localized Castleman's disease than the plasma cell form; the 2 variants may coexist.

Castleman's disease is highly associated with HHV-8, which is found in 100% of HIV-infected Castleman's disease patients and in 40% of HIV-uninfected Castleman's disease patients. Exacerbation of Castleman's disease is associated with increased HHV-8 viral load and appears to correlate with serum levels of viral interleukin (IL)-6 levels (analogous and homologous with human IL-6). Treatment for localized Castleman's disease is excision of the affected nodes, which is associated with good prognosis. Treatment for multicentric Castleman's disease is not well established, and prognosis remains poor in patients with this form. Steroids, rituximab, and chemotherapy have been used in multicentric disease, but no consistent responses have been observed. Antiretroviral therapy does not consistently alter the course of the disease. Treatments under investigation include a humanized antibody to IL-6 receptor.

The noninfectious syndromes discussed above are not common, but they can mimic more common HIV-associated diseases. Recognizing these syndromes can not only limit unnecessary workup and treatment, but in some cases, such as TTP, can be lifesaving.

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Suggested Reading

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