Acute Poststreptococcal Glomerulonephritis: A Manifestation of Immune Reconstitution Inflammatory Syndrome

abstract

Immune reconstitution inflammatory syndrome (IRIS) is a well-described complication of initiation of highly active antiretroviral therapy in HIV-infected patients. As the immune system recovers, an inappropriate inflammatory response often occurs that causes significant disease. It is most commonly seen in patients naïve to therapy with CD4+ T-lymphocyte counts <100 cells/cmm and usually presents as a flare of mycobacterial, cytomegalovirus, or herpes zoster infections. Less commonly, this syndrome occurs in response to noninfectious triggers and results in autoimmune or malignant disease. Here we present the first case of acute poststreptococcal glomerulonephritis associated with varicella zoster virus and IRIS in an adolescent with perinatally acquired HIV and hepatitis C virus infections. Our patient was not naïve to therapy but was starting a new regimen of therapy because of virologic failure and had a relatively high CD4+ T-lymphocyte count. This case report indicates that IRIS remains a concern after initiation of a new highly active antiretroviral therapy regimen in HIV-infected patients with high viral loads, even in the presence of CD4+ T-lymphocyte counts >100 cells/cmm. It may present as infectious, malignant, or autoimmune conditions including poststreptococcal glomerulonephritis. Pediatrics 2012;130:e710–e713

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KEY WORDS

immune reconstitution inflammatory syndrome, glomerulonephritis, HIV, Streptococcus, varicella

ABBREVIATIONS

APSGN—acute poststreptococcal glomerulonephritis
ASO—antistreptolysin O antibody
HART—highly active antiretroviral therapy
IRIS—immune reconstitution inflammatory syndrome
VZV—varicella zoster virus

All authors have made substantive intellectual contributions to the case report and take full responsibility for the entire content of the case report.

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Reconstitution of the immune system occurs once patients are started on effective highly active anti-retroviral therapy (HAART). In children, this process continues years after the therapy is initiated and the patient’s viral load becomes undetectable. Immune reconstitution inflammatory syndrome (IRIS) is an acute process in which a subset of patients experiences clinical deterioration from rapid and dysregulated restoration of antigen-specific immune responses. This creates a “paradoxical” inflammatory reaction to previously treated or subclinical infections, as well as noninfectious stimuli causing autoimmune and malignant diseases. Renal manifestations of IRIS are uncommon and have been primarily described in adult patients with Mycobacterium tuberculosis. Other causes of IRIS-associated renal pathology include granulomatous interstitial nephritis without evidence of tuberculosis, sarcoidosis, and cryptococcal infection. In pediatrics there are only a few case reports of renal IRIS. To date, there have been no published cases of acute renal insufficiency secondary to acute poststreptococcal glomerulonephritis (APSGN) in the setting of IRIS. Here, we present a patient with perinatally acquired HIV and Hepatitis C who developed varicella zoster virus (VZV) and ASPGN after initiation of a new HAART regimen for virologic failure.

**CASE REPORT**

An 18-year-old male Hispanic patient, perinatally infected with HIV and hepatitis C, has been followed in our clinic since birth. He is a long-term non-progressor, having maintained a high CD4+ T-lymphocyte count for most of his life, despite having an elevated viral load in the range of 2000 to 17,000 copies/mL. Because of an unstable social situation, he had a history of poor adherence to HAART. Starting at age 6 years, he was diagnosed with 1 to 3 episodes of symptomatic streptococcal pharyngitis per year. He had documented intercurrent negative throat cultures when well. The patient underwent tonsillectomy at age 10, after a peritonsillar abscess secondary to Streptococcus pyogenes. Otherwise, he has been healthy with normal liver and kidney function and normal urinalyses. At 14 years of age, in the month of June, he was noted to have an increasing HIV viral load with >100,000 copies/mL; CD4+ T-lymphocyte count remained high at 721 cells/cmm. In August, his HAART regimen was changed from stavudine, lamivudine, and nevirapine to didanosine and lopinavir/ritonavir. In October, he was diagnosed with culture-positive streptococcal pharyngitis, which was treated with antibiotics. He presented with back pain in November; 3 months after his medication change and was diagnosed with bilateral herpes zoster infection, which was treated for 7 days with acyclovir. Further laboratory testing at that time revealed hematocrit and proteinuria; elevated creatinine, and a decrease in hemoglobin. His CD4+ T-lymphocyte count decreased but his viral load was undetectable (Table 1). The patient subsequently developed gross hematuria. Additional testing revealed a markedly elevated antistreptolysin O antibody (ASO) titer and mild decrease in complement levels. He never developed swelling, edema, or hypertension. Abdominal ultrasound revealed echogenic kidneys consistent with medical renal disease. Kidney biopsy was suggestive of postinfectious glomerulonephritis without evidence of membranoproliferative disease. It also revealed collapsing glomerulopathy, a condition sometimes seen in HIV and other viral infections. Liver enzyme tests remained normal and hepatitis C viral load was unchanged from baseline.

The patient was continued on his HAART therapy. He was not treated with steroids or any other form of immunosuppression. His gross hematuria resolved and creatinine normalized within 6 months but microscopic hematuria persisted for more than 2 years. He required supplemental erythropoietin for anemia related to acute renal failure. The peripheral blood smear showed no evidence of microangiopathic hemolytic anemia. Repeat throat cultures done 3 months and 2 years after onset of hematuria were both negative. His ASO titer on presentation was extremely elevated at 1927 IU/mL and remains elevated 36 months later at 476 IU/mL. He has otherwise been healthy with good virologic control of his HIV infection.

**DISCUSSION**

Establishing a definitive diagnosis of IRIS can be challenging, as there is no specific laboratory test and diagnostic criteria for IRIS have not been standardized. Although there are several atypical features in this case in terms of IRIS presentation, including normal CD4+ T-lymphocyte count and prior HAART therapy, we feel that our patient’s clinical course is highly suggestive of IRIS by fulfilling previous criteria established by Shelburne et al and French et al. These criteria include the following: HIV-infected patient, receipt of effective HAART as shown by a decrease in HIV RNA concentration from baseline, clinical symptoms consistent with an inflammatory process, short interval between initiation of symptoms and change of HAART regimen, clinical course not consistent with expected course, and spontaneous resolution of disease with continuation of HAART. For this patient, IRIS likely occurred by 2 mechanisms: exaggerated activation of the immune system against persistent streptococcal antigen (paradoxical IRIS) and response to viable pathogens (unmasking IRIS); in this case, the herpes zoster infection. Decrease in viral load was associated with a drop in CD4+ T-lymphocyte count, perhaps...
TABLE 1

Chronological Profile of Patient's Laboratory Findings

<table>
<thead>
<tr>
<th></th>
<th>6 mo Previous (June)</th>
<th>3 mo Previous (Aug)</th>
<th>Onset of Hematuria (Nov)</th>
<th>1 mo Later (Dec)</th>
<th>2 mo Later (Jan)</th>
<th>6 mo Later (May)</th>
<th>1 y Later</th>
<th>2 y Later</th>
<th>3 y Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV viral load</td>
<td>&gt;100,000</td>
<td>50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Medication</td>
<td>D4T, 3TC, NFV</td>
<td>AZT, DDI, LPV RTV</td>
<td>AZT, DDI, LPV RTV</td>
<td>AZT, DDI, LPV RTV</td>
<td>AZT, DDI, LPV RTV</td>
<td>AZT, DDI, LPV RTV</td>
<td>AZT, DDI, LPV RTV</td>
<td>AZT, DDI, LPV RTV</td>
<td>AZT, DDI, LPV RTV</td>
</tr>
<tr>
<td>CD4</td>
<td>721</td>
<td>363</td>
<td>625</td>
<td>192</td>
<td>684</td>
<td>653</td>
<td>563</td>
<td>71.1</td>
<td>70</td>
</tr>
<tr>
<td>C3</td>
<td>72</td>
<td>24</td>
<td>1.27</td>
<td>0.08</td>
<td>0.11</td>
<td>0.08</td>
<td>0.7</td>
<td>0.8</td>
<td>14.7</td>
</tr>
<tr>
<td>C4</td>
<td>7.75</td>
<td>0.59</td>
<td>1.2</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
<td>0.8</td>
<td>15.2</td>
</tr>
<tr>
<td>ASO</td>
<td>1927</td>
<td>22.8</td>
<td>1.2</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
<td>0.8</td>
<td>15.2</td>
</tr>
<tr>
<td>Urine protein/Cr</td>
<td>2.28</td>
<td>0.09</td>
<td>1.27</td>
<td>0.08</td>
<td>0.11</td>
<td>0.08</td>
<td>0.7</td>
<td>0.8</td>
<td>14.7</td>
</tr>
<tr>
<td>Serum Cr</td>
<td>8.4</td>
<td>2.4</td>
<td>1.8</td>
<td>1.2</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
<td>0.8</td>
<td>15.2</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Neg</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Neg</td>
<td>&gt;300</td>
<td>100</td>
<td>Trace</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
</tr>
</tbody>
</table>

3TC, lamivudine; ASO, reference range <250 IU/mL; AZT, zidovudine; C3, reference range 75–140 mg; CD4, cells/μL; Cr, creatinine; DDI, didanosine; D4T, stavudine; HIV viral load, copies/mL; LPV, lopinavir; Neg, negative; NFV, nelﬁnavir; RTV, ritonavir; Proteinuria, mg/dL.

In addition, interstitial inﬁltration secondary to HIV infection may be related to relative immunologic dysfunction. Several atypical features suggesting a more virulent streptococcal strain or streptococcal infections may point to a more virulent streptococcal strain or a history of recent streptococcal infection. Month before marked elevation of functional impairment manifested by AST and mild decrease in complement C3 and C4. Urine and complement C4 and C3 remain slightly abnormal. Although many features of this case are consistent with typical APSGN, there is no history of recent streptococcal infection. Although this patient’s creatinine normalized within 6 months, he continued to have microscopic hematuria for more than 2 years. Although several atypical features such as kidney biopsy and clinical course were most consistent with APSGN, he had sudden hypercalcemia and hypophosphatemia as is seen in APSGN. The morphologic features on light microscopy revealed diffuse mesangial proliferation, as is seen in APSGN. The length of time for the ASO titer to normalize was much longer than what is expected for typical APSGN. This prolonged time to normalization is likely to be related to immune dysregulation. Immune dysregulation secondary to HIV infection may be related to relative immunologic dysfunction. Several atypical features suggesting a more virulent streptococcal strain or streptococcal infections may point to a history of recent streptococcal infection. Month before marked elevation of functional impairment manifested by AST and mild decrease in complement C3 and C4. Urine and complement C4 and C3 remain slightly abnormal. Although many features of this case are consistent with typical APSGN, there is no history of recent streptococcal infection. Although this patient’s creatinine normalized within 6 months, he continued to have microscopic hematuria for more than 2 years. Although several atypical features such as kidney biopsy and clinical course were most consistent with APSGN, he had sudden hypercalcemia and hypophosphatemia as is seen in APSGN. The morphologic features on light microscopy revealed diffuse mesangial proliferation, as is seen in APSGN. The length of time for the ASO titer to normalize was much longer than what is expected for typical APSGN. This prolonged time to normalization is likely to be related to immune dysregulation. Immune dysregulation secondary to HIV infection may be related to relative immunologic dysfunction. Several atypical features suggesting a more virulent streptococcal strain or streptococcal infections may point to a history of recent streptococcal infection. Month before marked elevation of functional impairment manifested by AST and mild decrease in complement C3 and C4. Urine and complement C4 and C3 remain slightly abnormal. Although many features of this case are consistent with typical APSGN, there is no history of recent streptococcal infection. Although this patient’s creatinine normalized within 6 months, he continued to have microscopic hematuria for more than 2 years. Although several atypical features such as kidney biopsy and clinical course were most consistent with APSGN, he had sudden hypercalcemia and hypophosphatemia as is seen in APSGN. The morphologic features on light microscopy revealed diffuse mesangial proliferation, as is seen in APSGN. The length of time for the ASO titer to normalize was much longer than what is expected for typical APSGN. This prolonged time to normalization is likely to be related to immune dysregulation. Immune dysregulation secondary to HIV infection may be related to relative immunologic dysfunction. Several atypical features suggesting a more virulent streptococcal strain or streptococcal infections may point to a history of recent streptococcal infection. Month before marked elevation of functional impairment manifested by AST and mild decrease in complement C3 and C4. Urine and complement C4 and C3 remain slightly abnormal. Although many features of this case are consistent with typical APSGN, there is no history of recent streptococcal infection. Although this patient’s creatinine normalized within 6 months, he continued to have microscopic hematuria for more than 2 years. Although several atypical features such as kidney biopsy and clinical course were most consistent with APSGN, he had sudden hypercalcemia and hypophosphatemia as is seen in APSGN. The morphologic features on light microscopy revealed diffuse mesangial proliferation, as is seen in APSGN. The length of time for the ASO titer to normalize was much longer than what is expected for typical APSGN. This prolonged time to normalization is likely to be related to immune dysregulation. Immune dysregulation secondary to HIV infection may be related to relative immunologic dysfunction. Several atypical features suggesting a more virulent streptococcal strain or streptococcal infections may point to a history of recent streptococcal infection.
not treated with steroids, his HAART therapy was continued, and he improved over time.

Although renal IRIS is relatively rare, renal pathology is very common in HIV-infected patients over the course of their lifetimes with a wide differential diagnosis including HIV and non-HIV-related diseases. IRIS has previously been associated with renal pathology in pediatrics patients in the cases of nephrotic syndrome and renal cryptococcal infection. No cases of renal immune complex deposition associated with IRIS have been reported. Primary varicella infection has been described in the literature to cause both immune complex deposition and exacerbations of APSGN. This association has not been reported with varicella zoster nor has it been described in the HIV-infected population. Here we propose that immune reconstitution after change in antiretroviral treatment regimens led to reactivation of VZV and subsequent prolonged course of APSGN.

In summary, we report the first case of an adolescent with an association of VZV, protracted APSGN, and IRIS, the former 2 probably caused by the latter. Although IRIS has most commonly been described in patients with very low CD4+ T-lymphocyte counts who were previously naive to antiretroviral therapy, this case is highly suggestive of IRIS occurring in the setting of a normal CD4+ T-lymphocyte count at the time of HAART regimen change because of treatment failure. As experience with prolonged HAART treatment and management of treatment failures continues, we are likely to see more patients with this type of IRIS presentation.

REFERENCES

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