CLINICAL PRACTICE

Clinical Vignettes

Recurrent Sinopulmonary Infections in a Patient Whose HIV Masked Common Variable Immunodeficiency

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It is generally accepted that persons infected with human immunodeficiency virus (HIV) are at an increased risk of infection due to direct destruction of $CD4^+$ lymphocytes and subsequently impaired cell-mediated immunity. Typically, HIV infection is associated with immunoglobulin elevations, but quantitative deficiencies in immunoglobulins have also been rarely described. We present an unusual case of common variable immunodeficiency (CVID) in a HIV-positive patient with recurrent severe respiratory infections. We review epidemiology, clinical presentation, and treatment of primary immunoglobulin deficiency. We also review the relationship between immunoglobulin deficiency and HIV and highlight the importance of recognizing the coexistence of two distinct immunodeficiency syndromes.

KEY WORDS: HIV/AIDS; diagnosis; immunology.

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CASE

A 34-year-old man with a history of HIV presented with a three-day history of recurrent dyspnea, wheezing, and unproductive cough. Three weeks prior, he had been hospitalized for respiratory failure, requiring Bi-level positive airway pressure support (BiPap), and was diagnosed with viral pneumonia and an asthma exacerbation. His HIV infection was well-controlled, with a recent $CD4^+$ count of 537 cells/mm^3, undetectable HIV RNA, and no prior opportunistic infections. Additional medical history was significant for asthma, chronic rhinosinusitis, major depressive disorder, and six hospitalizations in the last year for recurrent pneumonia and asthma exacerbations. During these hospitalizations, the only causative pathogens recognized were metapneumovirus and rhinovirus. No bacterial or fungal pathogens were identified; however, the patient received empiric antibiotic coverage for community acquired and healthcare-associated pneumonia on multiple occasions. The patient was a former tobacco user, and he intermittently used intravenous methamphetamine and inhaled cocaine. Family history was significant for asthma, alcohol use disorder, and coronary artery disease. His medications included abacavir-lamivudine, raltegravir, albuterol inhaler, fluticasone-salmeterol inhaler, montelukast, buprenorphine-naloxone, clonazepam, citalopram, mirtazapine, and olanzapine. He was allergic to trimethoprim-sulfamethoxazole.

On presentation, his heart rate was 140 beats per minute, blood pressure 130/70 mmHg, respiratory rate 28 breaths per minute, and oxygen saturation was 97% on 4 L of nasal cannula-delivered oxygen. His physical exam was significant for diaphoresis, labored breathing, tachycardia, and diffuse expiratory wheezing. A complete blood count (CBC) and basic metabolic panel (BMP) were unremarkable; lactate dehydrogenase (LDH) was 214 U/L (normal 110 - 205 U/L). Venous blood gas showed pH 7.33, $PaCO_2$ 47 mmHg, and PaO_2 52 mmHg. Chest radiograph and CT angiogram demonstrated bilateral nodular consolidative opacities with tree-in-bud appearance and bilateral pleural wall thickening. The patient was admitted to the intensive care unit, and subsequently treated with vancomycin, piperacillin-tazobactam, azithromycin, pentamidine and methylprednisolone. Bronchoalveolar lavage was performed yielding negative bacterial and respiratory viral studies. *Pneumocystis jiroveci* stain, *Legionella* PCR, *Nocardia* culture, herpes culture, cytomegalovirus culture, and acid-fast bacilli smear were negative. Given the discrepancy between his HIV stage and recurrent pulmonary infections, serum immunoglobulins were measured to explore the possibility of a concurrent underlying deficiency state to better explain his recurrent infections. The results were notable for serum IgA < 5 mg/dL (normal 70–400 mg/dL), IgM 75 mg/dL (normal 40–230 mg/dL), and IgG 432 mg/dL (normal 700–1600 mg/dL) (Table 1). He was discharged on a course of oral antibiotics for healthcare-associated pneumonia, a steroid taper for asthma, and a referral to an immunologist for further management of his newly diagnosed IgA and IgG deficiencies; findings that were most consistent with CVID. Treatment with intravenous immunoglobulin (IVIg) was initiated and scheduled every three weeks. The patient had one additional hospitalization

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Table 1 Mean Ig levels in CVID patients compared with our index patient

	IgA (mg/dL)	IgG (mg/dL)	IgM (mg/dL)
Normal Ig levels	70–400	700–1600	40–230
Mean Ig levels in CVID[1]	28	258	40
Index patient Ig levels	< 5	432	75

for bacterial pneumonia in the subsequent four weeks; however, following his second IVIg infusion, the patient had no further hospital admissions for thirty-six months.

DISCUSSION

We present a case of an HIV-positive patient with a one-year history of recurrent sinopulmonary infections attributed to his HIV infection, ultimately diagnosed with CVID. This case highlights the importance of recognizing the clinical signs and symptoms suggestive of an underlying immune deficiency syndrome. While this case describes the co-occurrence of two distinct immunodeficiency syndromes, the clinical relationship between HIV infection and primary immunoglobulin deficiencies should also be explored.

The hallmark of HIV disease is a profound progressive immunodeficiency resulting primarily from quantitative and qualitative deficiencies in T cell–mediated immunity. Eventually, the HIV-infected host $CD4^+$ lymphocytes are destroyed, leading to a reduction in the $CD4^+$ count. In general, HIV-infected patients are at higher risk for community-acquired bacterial infections as compared with HIV-negative patients, but this is most striking when $CD4^+$ counts fall below 500 cells/μL,[2] and rises in proportion to the decrease in the $CD4^+$ cell count.[3] By framing the index patient in a way that acknowledged that his HIV was virologically suppressed, a new theory was proposed; that an abnormality in humoral immunity could account for the patient's recurrent infections.

The relationship between HIV and humoral immunity is complex, but a common finding in patients infected with HIV is polyclonal hypergammaglobulinemia.[4–6] In a review of 107 patients with HIV infection, serum IgA concentration and serum IgG were elevated in one-third and two-thirds of patients, respectively, and this was strongly associated with HIV disease progression.[7] Another study found a remarkably high level of polyclonal hypergammaglobulinemia (53%) among HIV-positive patients compared with 10% of HIV-negative controls.[8] The mechanism of elevated immunoglobulin levels is multifactorial and may be related to a direct immune response to HIV or other pathogens (such as Epstein-Barr virus), HIV-associated hyperactivation of naïve B cells, and loss of regulation of antibody production.[4–7] The polyclonal gammopathy seen in HIV can lead to an elevation in the paraprotein gap, otherwise known as the gamma gap. The paraprotein gap is the difference between the concentration of serum total protein and serum albumin. A large gap (> 4 g/dL) can be caused by excessive production of immunoglobulins which may reflect an underlying condition: viral infection, malignancy, hematologic disorder, or autoimmune disease.[9]

Given the association between hypergammaglobulinemia and HIV infection, the hypogammaglobulinemia seen in our patient suggested a concomitant primary immunoglobulin deficiency syndrome, which ultimately led to his recurrent sinopulmonary infections. Primary immunoglobulin deficiencies have an estimated prevalence of one in 10,000 people in the general population and are frequently diagnosed in adulthood.[10, 11] Primary immunoglobulin deficiencies should be suspected in patients who present with recurrent bacterial infections of the sinopulmonary tract, including recurrent otitis media, sinusitis, and pneumonia.[12] They should be considered in patients with HIV if the severity or frequency of infections is out of proportion to the degree of HIV infection. For example, the annual incidence of bacterial pneumonia in HIV-positive patients ranges from 5.5 per 100, compared with 0.9 per 100 in HIV-negative patients.[2] Use of antiretroviral therapy and increasing $CD4^+$ count are associated with a significant reduction in the risk of bacterial pneumonia (2.3 and 10.8 episodes per 100 in patients with more than 500 and fewer than 200 $CD4^+$ lymphocytes per cubic millimeter, respectively)[2, 13] Thus, those patients with virologically suppressed HIV presenting with recurrent infections should have laboratory evaluation for immunoglobulin deficiency. One additional clue that may prompt consideration of immunoglobulin deficiency in a patient with HIV is a low or inappropriately normal paraprotein gap. A low paraprotein gap (< 1.9 g/dL) has already been shown to be an effective tool in reducing diagnostic delays for immunoglobulin deficiency syndromes in an adult population.[14, 15] Given the polyclonal gammopathy and corresponding elevation in paraprotein gap seen in patients with HIV, a low or normal paraprotein gap could prompt a clinician to evaluate for immunoglobulin deficiency in the right clinical setting.

Initial laboratory evaluation should include a CBC with differential and serum IgA, IgG, and IgM levels. Evaluation for secondary causes of antibody deficiencies, such as protein-losing enteropathies, malnutrition, chronic kidney disease, hematologic malignances, and drugs (e.g., carbamazepine, phenytoin, disease-modifying antirheumatic drugs), should be considered.[10, 16] Given the undetectable IgA level in the setting of low IgG (Table 1) in our patient, it is worthwhile to juxtapose selective IgA deficiency with CVID.

Selective IgA deficiency is the most common primary immunodeficiency and can be associated with IgG subclass deficiency and progression to CVID.[17] It is characterized by decreased serum IgA concentration (< 0.07 g/L) and normal serum IgM and IgG levels.[18] The majority of patients with this disease are asymptomatic, whereas selected patients suffer from recurrent mucosal infections, allergies, and autoimmune diseases. Patients with selective IgA deficiency who develop recurrent infections should have routine serum IgG and IgM measurements to monitor for progression to CVID.[17]

CVID is a primary antibody deficiency disease characterized by low serum levels of IgG, IgA, and/or IgM, leading to recurrent infections noted mostly in the respiratory and gastrointestinal tract.[17] A study of 224 CVID patients reported the following mean immunoglobulin levels at diagnosis: IgG of 258 mg/dL, IgA of 28 mg/dL, and IgM of 40 mg/dL.[1] In our patient with undetectable IgA and IgG of 432 mg/dL, it was theorized that he initially had selective IgA deficiency that later progressed to CVID. This appears to fit his clinical picture, as the patient's only previous manifestation of humoral immunodeficiency was chronic rhinosinusitis. His sudden development of severe and recurrent respiratory infections was arguably due to progression from selective IgA deficiency to concomitant IgG deficiency.

The standard treatment of CVID is IVIg, administered at a dose of 0.4 to 0.6 g/kg every 3–4 weeks.[19, 20] The dose and frequency are generally adjusted to reach a goal trough IgG level of greater than 500 mg/dL.[19] Supportive care, including consideration of long-term prophylactic antibiotics and pulmonary hygiene, is of utmost importance in the management of CVID.

The clinical improvement witnessed in our patient following the initiation of IVIg gives credence to concomitant humoral immunodeficiency as a paucity of evidence exists showing benefit of IVIg in HIV-infected adults without immunoglobulin deficiencies.[21] Rather, treatment of patients with HIV and concomitant CVID should focus on treating each disease separately. The effect of HIV infection on patients with CVID is not completely understood; however, in rare cases, CVID has been reported to resolve transiently or permanently in patients with HIV infection.[22–26] This resolution is based on the stimulation and recovery of IgG and IgM production following HIV infection in patients with CVID. Notably, IgA levels remained undetectable in these cases—a finding consistent with the concept that specific immunoregulatory and possibly environmental factors are required to induce CVID in patients with select IgA deficiency.[23] Antiretroviral therapy and subsequent virologic suppression do not appear to effect immunoglobulin production, as two of the above cases demonstrated immunoglobulin recovery and resolution of CVID despite treatment.[22, 23] Perhaps the mechanism that leads to polyclonal hypergammaglobulinemia in patients with HIV also leads to immunoglobulin recovery in patients with CVID. This remains a topic of further research that could have implications on treatment of CVID.

In summary, we have presented a case of concurrent CVID in an HIV positive patient, in whom recurrent severe respiratory infections were previously attributed to his HIV. Immunoglobulin deficiency should be considered in all patients with recurrent infections, especially in those patients whose primary medical conditions do not explain the recurrent nature or severity of their infections. The relationship between HIV, immunoglobulin deficiencies, and CVID should be further explored, and it is important to recognize that these distinct immunodeficiency syndromes can coexist.

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Compliance with Ethical Standards:

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