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Cytomegalovirus-Induced Adrenal Insufficiency in a Renal Transplant Recipient

M. Ardalan and M.M. Shoja

ABSTRACT

Cytomegalovirus (CMV) is an important pathogen in organ-transplant recipients. There have been frequent reports of CMV-induced adrenal insufficiency in patients with human immunodeficiency virus infection. Herein, we report CMV-induced renal insufficiency in a renal transplant recipient. A 24-year-old woman had gradual onset of weakness, anorexia, nausea, hypotension, and skin hyperpigmentation at 5 months after renal transplantation. The immunosuppression regimen included cyclosporine, mycophenolate mofetil, and corticosteroid (prednisolone, 5 mg/d). Recent history included acute CMV infection, which was treated with ganciclovir. Basal serum cortisol concentration was 4 μg/dL, and stimulated serum cortisol concentration was less than 10 μg/dL. All clinical signs and symptoms and hypotension gradually improved after the oral prednisolone dose was increased to 10 mg/d. Clinicians must be aware of the possibility of CMV-induced adrenal insufficiency in renal transplant recipients. The condition may be symptomatic despite low-dose prednisolone therapy.

CYTOMEGALOVIRUS (CMV) is the most important pathogen that affects solid-organ transplant recipients. It involves various organ systems including the lungs, liver, retina, and renal allografts. Seronegative recipients who receive an organ from a seropositive donor are at greatest risk. The risk of CMV infection increases with progression of immunosuppression.[1,2]

In primary adrenal insufficiency, the entire adrenal cortex is destroyed, with loss of both glucocorticoid and mineralocorticoid activity. Acute insufficiency is characterized by orthostatic hypotension and circulatory collapse. Autoimmune disease, infections, infiltrating disease, drugs, and toxins may produce chronic adrenal insufficiency with a longer history of malaise, anorexia, weight loss, abdominal pain, and darkening of the skin and mucosa. There have been frequent reports of CMV-induced adrenal insufficiency in patients with human immunodeficiency virus (HIV) infection. The adrenal gland is the most frequently affected CMV-infected organ in these patients.[3,4] In addition to CMV, myriad infectious agents may infect the adrenal gland, in particular in immunocompromised individuals; however, this issue continues to be underrecognized.[5]

Herein, we describe adrenal failure associated with CMV infection in a renal transplant recipient.

CASE REPORT

A 24-year-old woman underwent living unrelated kidney transplantation. Immunosuppression included cyclosporine, mycophenolate mofetil, and corticosteroid. Both donor and recipient tested positive for anti-CMV IgG and negative for IgM antibodies. Serum

From the Nephrology Department, Tabriz University of Medical Sciences (M.A.) and the Tuberculosis and Lung Disease Research Center (M.M.S.), Tabriz, Iran.

Address reprint requests to Mohammadreza Ardalan, MD, Department of Nephrology, Tabriz University of Medical Sciences, PO Box 51665-356, Tabriz, Iran. E-mail: ardalan34@yahoo.com

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creatinine (SCr) concentration was 1.2 mg/dL at 18 days posttransplantation. At day 22, the SCr concentration increased to 3 mg/d, and a 6-day course of antithymocyte globulin therapy was administered; the SCr concentration decreased to 1.5 mg/dL by day 30. However, in the sixth week posttransplantation, the SCr concentration was again increased, to 2.2 mg/dL. A serologic study revealed positive anti-CMV IgM and IgG antibodies. Intravenous ganciclovir was given for 12 days. At the beginning the fifth month posttransplantation, the patient experienced gradual onset of weakness, anorexia, weight loss, vague abdominal pain, and muscle cramping. Physical examination reveal hypotension (blood pressure, 85/60 mm Hg), which was aggravated by standing; hyperpigmentation of the brow, palmar creases, and transplantation scar but not the buccal mucosa; and loss of axillary and pubic hair. Laboratory findings included the following: while blood cell count, 6900/μL; hemoglobin, 12 mg/dL; Scr, 1.5 mg/dL; fasting blood glucose concentration, 95 mg/dL; serum sodium concentration, 136 mEq/L; and serum potassium concentration, 5 mEq/L. The patient was receiving prednisolone, 5 mg/d; cyclosporine; and mycophenolate mofetil. Prednisolone therapy was changed to oral hydrocortisone, 15 mg/d. After 2 weeks, the basal free cortisol concentration determined at 24 hours after administration of hydrocortisone was 4 μg/dL. Adrenal reserve capacity was determined at 30 minutes and at 6 and 24 hours after intramuscular injection of tetracosactide, 1 mg (Synacthen; Novartis Pharma AG, Basel, Switzerland); serum cortisol concentrations were 8, 7, and 7 μg/dL, respectively. A diagnosis of primary adrenal insufficiency was made. Hydrocortisone therapy was discontinued, and oral prednisolone, 10 μg/d, was initiated, and the patient was encouraged to ingest a liberal amount of salt. The constitutional symptoms and hypotension gradually improved, as did hyperpigmentation over the following months.

DISCUSSION

In our patient, the combination of physical signs and symptoms, laboratory findings, and dramatic clinical response to corticosteroid therapy was compatible with adrenal insufficiency, with onset a few months after active CMV infection. A random cortisol value of less than 400 nmol/L (15 μg/dL) is suggestive of corticosteroid insufficiency; in our patient, the value was less than 5 mg/dL. An adrenocorticotropin hormone–stimulated serum cortisol concentration less than 550 nmol/L (<20 mg/dL) also confirmed primary adrenal insufficiency. Skin pigmentation was compatible with primary adrenal insufficiency.[6]

At transplantation, neither the donor nor the recipient had active CMV infection. The CMV infection may have been a new infection, reactivation of infection, or donor-origin superinfection. Intensification of immunosuppression with antithymoglobulin therapy could have triggered CMV infection; it has been reported in patients with AIDS who developed CMV-induced adrenal failure after administration of high-dose steroid therapy.[7,8]

Cytomegalovirus infection was first proposed as a suspected cause of adrenal insufficiency by Manz et al.[9] Glasgow et al[10] considered CMV as the cause of adrenal insufficiency in patients with AIDS. Later studies suggested that the adrenal gland is the organ most frequently affected by CMV infection in patients with AIDS.[3] Despite the high incidence of adrenal gland involvement, clinical adrenal insufficiency has been reported in 5% to 8% of HIV-infected patients. In addition to CMV, *Mycobacterium avium-intracellulare, Cryptococcus,* microsporidia, and Kaposi sarcoma have been reported as causing adrenal insufficiency in patients with HIV infection.[5] Pathogenic fungi such as *Histoplasma capsulatum, Paracoccidiodes brasiliensis,* and less commonly *Blastomyces dermatitidis* and *Cryptococcus neoformans* can infect the adrenal gland, in particular in individuals with impaired cell-mediated immunity. Tuberculosis and herpes simplex virus infection also may infect the adrenal gland in immunocompetent individuals.[5] In addition, hemorrhagic viruses such as Ebola virus, Marburg virus, and Lassa virus, and respiratory syndrome–associated coronavirus and H5N1 avian influenza A virus may infect the adrenal gland in immunocompetent individuals. Acute adrenal hemorrhage may occur due to infection with *Neisseria meningitidis* (Waterhouse-Friderichsen syndrome), group A streptococci, pneumococci, and *Haemophilus influenzae.*[5]

In conclusion, an analogy may be made between renal transplant recipients and patients with AIDS because both have impaired cellular immune responses and are susceptible to the same pathogenic organisms, some of which, such as CMV, potentially can invade the adrenal gland. Corticosteroid therapy as part of the immunosuppression regimen may mask the signs and symptoms of underlying adrenal insufficiency. Low-dose corticosteroid therapy (eg, prednisolone, 5 mg/d) may be inadequate in some renal transplant recipients with underlying adrenal insufficiency, in particular during stress from medical conditions and major surgery. Awareness of this issue is also important when prescribing steroid-free immunosuppression regimens. Awareness of CMV-induced adrenal insufficiency is particularly important in transplantation centers with inadequate CMV prophylaxis.

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