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ORIGINAL ARTICLE

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Fatal cytomegalovirus disease in a high-risk renal transplant recipient

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Abstract The incidence of CMV infection in pediatric renal transplant recipients has increased as immunosuppression levels deepen following the use of newer immunosuppressive agents. It has been thought that 3–5 months of anti-CMV prophylaxis offers sufficient protection for these patients. We present a case of late-onset fatal CMV disease in a pediatric renal transplant recipient who received prolonged anti-CMV prophylaxis while on "quadruple" immunosuppression with daclizumab, mycophenolate, tacrolimus, and prednisone. Our case has prompted us to reassess CMV surveillance, prophylaxis, and immunosuppression levels in our pediatric renal transplant patients.

Keywords CMV · Pediatrics · Daclizumab · Tacrolimus · Kidney · Transplantation · Mycophenolate · Immunosuppression

Introduction

Immunosuppression therapy for pediatric renal transplantation may be complicated by the development of CMV infection, which is either recurrent disease, is introduced within the transplanted organ, or is acquired via community contact [1–3]. Experience with patients on immunosuppressive therapy based on azathioprine, cyclosporine A, and prednisone with or without immunoinduction therapy using earlier monoclonal or polyclonal anti-T-cell antibodies suggests there is up to a 67% incidence of CMV infection in pediatric transplant recipients [4–7]. Infection is usually due to reactivation of prior infection in the recipient or new infection transmitted via the donor organ, irrespective of the recipient's prior CMV immune status [1]. CMV disease requiring hospitalization, occurring in about 5.6% of renal transplant recipients, develops at a mean of 51 days after transplantation, with 90% of cases occurring within the first 5 months post-transplant [1].

Current immunosuppression therapy for pediatric renal transplantation in some centers includes mycophenolate, tacrolimus, and low-dose prednisone. Monoclonal or polyclonal anti-T-cell antibody immunoinduction therapy may be offered as well. The incidence, timing and severity of CMV infections in pediatric renal transplant recipients managed with these newer combined immunosuppression therapies have not yet been determined. Here we present a 5 year-old renal transplant recipient on "quadruple" immunosuppression with daclizumab, mycophenolate, tacrolimus, and prednisone with unexpected delayed onset of fatal CMV disease despite having received prolonged CMV prophylaxis with both CMV hyperimmune globulin and ganciclovir.

Case report

A CMV-negative 5-year-old girl weighing 17 kg received a CMV-positive cadaveric renal graft after 7 months of peritoneal dialysis following hemolytic-uremic syndrome. Donor IgG and IgM antibodies were positive for CMV, while they were negative in the recipient. Her immunosuppression consisted of daclizumab (1 mg/kg/dose, for five doses at 2-weekly intervals), mycophenolate (250 mg po q12 h), tacrolimus (titrated to blood levels of 8–12 ng/ml whole blood), and prednisone. She received methylprednisolone 30 mg/kg on the 1st day after transplantation, and this was tapered to prednisone 1 mg/kg/day on day 8 after transplantation. Reductions of prednisone to 0.7 mg/kg/day were made on day 13, and to 0.5 mg/kg/day on day 19 after transplantation. Prednisone dosage was further reduced to 0.1 mg/kg/day by 18 weeks after transplantation. She received intravenous ganciclovir at 5 mg/kg/day for 1 week and oral ganciclovir at 1500 mg/day through 4 months after transplantation. CMV hyperimmune globulin, at 100 mg/kg/dose for five doses and 50 mg/kg/dose for two doses, was given every 2 weeks for 3 months. Cotrimoxazole was given as prophylaxis against *Pneumocystis carinii*. No acute rejection episodes were noted. Pretransplant WBC counts were in the

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normal range. Post-transplant WBC counts were normal as well, ranging from 6100 to 18,000, with three values above 20,000 on days 12–14 after transplantation and one value of 4100 on day 3 after transplantation.

Four weeks after cessation of ganciclovir she developed chills, fever, and malaise. She presented with a temperature of 38.7°C, RR 23, HR 120/min, BP 120/60 mmHg, and weight 18.1 kg. Her WBC was 2.3×10^9/l, hemoglobin was 7.9 g/l, and platelets were 177×10^3/l. There were mild abnormalities of liver function with alanine aminotransferase 163 units/l and aspartate aminotransferase 166 units/l. She had normal graft function, coagulation profile, and chest X-ray.

Treatment for suspected CMV infection was begun on day 1 with intravenous ganciclovir at 5 mg/kg/day. Mycophenolate was discontinued, tacrolimus dosage was lowered to maintain blood levels of 3–5 ng/ml whole blood, and corticosteroids were maintained at stress doses. On day 2, granulocyte clonal stimulation factor was initiated for neutropenia with WBC 1.3×10^3/l. She defervesced on day 3 and WBC was 8.7×10^3/l. On day 5, she developed chills, fever, and respiratory distress with RR 35/min and good oxygenation. Chest X-ray showed right middle and lower lobe infiltrates. Studies for cold agglutinins, hepatitis A, B, C, Epstein-Barr virus, influenza virus, respiratory syncytial virus, and blood and urine bacterial cultures were negative and liver enzymes returned to normal. CMV DNA was strongly positive with a density reading of 825,000 copies/µg total DNA in peripheral blood.

Chest X-rays showed worsening infiltrates and CMV hyperimmune globulin was given at a dose of 400 mg/kg/dose on day 8. On day 9 she became hypoxic with RR 100/min and assisted mechanical ventilation was begun. Bloody secretions were noted during tracheal intubation. Bronchoscopy was performed and samples were negative for *P. carinii*. CMV hyperimmune globulin was repeated at 200 mg/kg and foscarnet was added. Amphotericin B, liposomal, was initiated. Bone marrow aspirate was negative for fungus, histoplasmosis, mycobacteria, and CMV. CMV resistance to ganciclovir was determined not to be present as no mutations in UL97 codon range (V460, V594, F595, and S595, Viromed Laboratories) were noted. Tacrolimus was discontinued.

On day 12, she developed further pulmonary hemorrhage and required increasing ventilatory support. Her creatinine increased to 149.2 µmol/l from the baseline of 88.4 µmol/l. Graft biopsy on day 12 showed mild acute rejection (grade I, Banhoff Classification) and acute tubular necrosis with negative stains for CMV. Abdominal ultrasound showed pancreatic edema, amylase was 8848 U/l, and lipase 18,450 U/l. On day 17 there was massive pulmonary hemorrhage requiring blood transfusion. Antiglomerular basement antibody was negative. On day 18, hemodialysis, then continuous venovenous hemofiltration was initiated for management of fluid overload. Daily doses of CMV hyperimmune globulin at 200 mg/kg/dose were given on days 18, 19, and 20. By day 20, her pulmonary disease continued to worsen and she was transferred to another institution for high frequency ventilation. Pulmonary hemorrhage persisted through an additional 20 days of high-frequency oscillatory assisted ventilation and she expired from respiratory failure. CMV-DNA assays remained positive despite continuing use of ganciclovir and CMV hyperimmune globulin.

Discussion

This high-risk patient (young, Afro-American, cadaveric graft) on quadruple immunosuppression therapy experienced a late-onset overwhelming CMV infection, leading to pneumonia, multiorgan failure, loss of the graft, and death, despite prolonged anti-CMV prophylaxis. When CMV is found in the donor and/or the recipient, antiviral prophylaxis is offered with some combination of acyclovir, ganciclovir, or CMV hyperimmune globulin [1]. Current general recommendations are to continue prophylaxis for 3–4 months after transplantation [8], although 5 months of prophylaxis has been recommended in pediatric patients [1]. CMV infections in patients who have received prophylaxis are expected to be attenuated as compared to those where prophylaxis was not given, and death has occurred in only 2% of infected patients [1, 9]. High-risk pediatric renal transplant recipients currently receive monoclonal or polyclonal antibody induction, mycophenolate, tacrolimus, and prednisone in many centers. Available data about the incidence and severity of CMV infections in these patients are difficult to interpret where various immunosuppression agents may be used and the existent data may have been developed using older drug combinations.

Mycophenolate, which has largely supplanted azathioprine in current immunosuppression protocols, has been associated with an increased risk of severe CMV infections [10]. Ellis et al. reported that CMV infection could be increased with tacrolimus as compared to cyclosporine A [11]. Daclizumab use has resulted in a slightly decreased overall incidence, but with a significantly delayed onset, of CMV infections [12]. Information about CMV infections in patients receiving combinations of these agents has not been reported.

With rapidly evolving immunosuppression protocols, important information concerning drug safety may be difficult to quickly obtain and interpret. Our case causes us to consider whether current quadruple therapy may be permissive of persistent, more severe CMV infection, which may lead to late-onset, overwhelming CMV disease in some patients. Our response has been to reexamine our CMV prophylaxis protocol and to consider continuing prophylaxis for a much longer time than has been previously thought necessary. Appropriate timing and techniques of monitoring CMV presence in our patients must be sought.

As immunosuppression levels increase, complications from acute rejection episodes have been greatly reduced. However, there is a recent disturbing trend towards a greater overall incidence of CMV infection in pediatric renal transplant recipients [1]. Now, in addition to the higher overall risk of CMV infection, its delayed appearance offers further risks to our patients. Experience with CMV infection following various combinations of induction agents and immunosuppressive agents must be noted carefully as we continue to offer renal transplantation to our pediatric population.

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