Case Report

A Challenging Presentation of Pyrexia and Macroscopic Hematuria in a Kidney Transplant Patient

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Abstract

Kidney transplant kidney transplant (KTx) recipients have increased susceptibility to a spectrum of infections including; bacterial, viral, and fungal pathogens. Many factors contribute to their infection potential risk, in terms of their immunosuppressive state, that result in suppression of their B-and T-lymphocyte repertoire, also to consider certain donor and recipient-related factors, that make them at risk of specific type of infectious complications. In addition kidney transplant patients tolerate poorly infections, which may adversely affect their graft function, by inducing glomerular injury, hence early diagnosis, directed therapy, and careful dosing of antimicrobial agents is of paramount importance in reducing patient's morbidity and mortality. We report a kidney transplant patient, who received her live related kidney graft 7 years earlier (in 2013), she has been with stable graft function in most of her follow up period, until she presented with pyrexia, dyspnea and fatigue associated with deterioration of her graft function.

Keywords: Acute glomerulonephritis, endocarditis, enteroccal endocarditis, kidney transplantation

Introduction

Kidney transplantation (KTx) is the preferred form of renal replacement therapy for end stage renal disease (ESRD) patients, in terms of longer survival and better quality of life compared to dialysis therapy.[1] However KTx patients are at increased risk of intercurrent infections, due to their long-term immunosuppressive state even with improved immunesuppression protocols.[2,3] It was found that 51% of KTx recipients contract infectious complications in the 1st year post transplantation, mostly bacterial and viral infections (31%, 23% respectively).[4] Infectious complications are considered the second most common cause of death with a functioning graft in KTx recipients after cardiovascular mortality.[5] We report a kidney transplant patient, who presented after 7 years of KTx with with pyrexia, dyspnea and fatigue associated with deterioration of her graft function.

Case Report

A 38-year-old female teacher, who had a live related kidney transplant (KTx) in 2013 (donor was her brother), the etiology of her ESRD was chronic glomerulonephritis (GN), patient and her donor were cytomegalovirus IgG-antibody seropositive, her posttransplant course was stable, except for one episode of gastroenteritis 3 years earlier, with transient graft dysfunction that responded to antibiotics and fluid resuscitation. She presented to nephrology clinic at Benghazi Medical Center, in November 28, 2019, with history of exertional dyspnea, dry cough, and fever of 3 days duration associated with remarkable fatigue, no chills or rigors, no history of orthopnea or wheeze, no history of ankle swelling, no history of oliguria or pain at site of her left kidney graft, she had history of watery diarrhea 2–3 times per day, following onset of her febrile illness. Her systems review was uneventful. Her immunosuppressive regimen includes; tacrolimus capsule 1 mg twice daily, and mycophenolate mofetil tablet 500 mg twice daily, her last tacrolimus trough level was 4.2 ng/mL (4–8 ng/mL) in

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October 2019. There was no past medical history of diabetes, hypertension, or connective tissue disease. She was diagnosed in 2010 with rheumatic mitral stenosis, mitral valvuloplasty performed in 2012. She received peritoneal dialysis for several months before proceeding to KTx in 2013. She had history of dental therapy (tooth extraction) 1 month ago; her dentist gave her amoxicillin prophylaxis at that time. Her viral screening is negative for HCV, HBV, and HIV. Her echocardiographic study performed in December 2015 showed; normal systolic and diastolic functions, ejection fraction 68%, with thickened mitral valve and moderate mitral regurgitation, mitral valve area of 1.5 cm^2.

On physical examination: she was dyspneic, dehydrated, and febrile with temperature of 38.8°C, B. P 100/70 mmHg, and body weight 82 kg. Chest examination showed reduced intensity breath sounds on both sides with harsh vesicular character. Pericardial examination revealed regular heart sounds, and tachycardia, with pansystolic murmur at apical area. Abdominal examination: no graft tenderness. Chest X-ray showed increased bronchoalveolar markings on mid and lower zones bilaterally. Her blood counts were; Hemoglobin 11.8 g/dL (12–15), total white blood cells (WBC) 10.5 × 10^3/Ul,(4–11) with 80.2% polymorph neutrophils (45%–70%), platelets 142 × 10^3/Ul (150–450), and blood urea 82 mg/dL (15–50), creatinine 1.8 mg/dL (0.5–1.1) (baseline graft function 4 weeks earlier: blood urea 22 mg/dL, creatinine 1.2 mg/dL).

Provisional diagnosis suggested at this stage; a community acquired atypical pneumonia (pneumocystis jiroveci pneumonia [PJP]*)* with dehydration,[6,7] and patient prescribed azithromycin tablet 500 mg once daily for 3 days, and parenteral fluids were given on outpatient basis for 2 days. On December 2, 2019, patient symptoms worsened, and her new laboratory data showed; hemoglobin 12.4 g/dL, WBC; 12.600/mm^3, with 81.6% polymorphs, platelets 172,000/mm^3, erythrocyte sedimentation rate (ESR) 92 mm/h (0–20), C-reactive protein (CRP) 35 mg/dL (upto 5). Due to her marked respiratory distress, the expected paucity of physical and radiological signs of pneumonia in immunosuppressed patients, and lack of special stain for PJP on brochoalveolar lavage, she was admitted to the hospital, and started therapy with parenteral sulfamethoxazole-trimethoprim in a dose of 10 mg/kg; 400 mg 12 hourly, was started empirically, waiting for further workup. Two days later, patient dyspnea improved partially. A transthoracic echocardiography [Figure.1] showed: mitral valve vegetation. Blood culture in two separate samples; showed enteroccal bacteremia, with sensitivity to vancomycin, and ciprofloxacin. In the meantime she developed macroscopic hematuria with oliguria, despite adequate hydration, and her renal parameters found markedly raised; blood urea 134 mg/dL and creatinine 3.5 mg/dL. Urine sediment showed protein ++, urine protein to creatinine ratio 1.3 (<0.2), WBC 8–10/high-power-field (HPF), red blood cell (RBC) >50/HPF with few granular casts. Serum C3 0.43 g/L (0.9–1.8 g/L), C4 0.13 g/L (0.2–0.5 g/L), antinuclear antibody and anti-ds DNA titer were negative. Cytomegalovirus IgG 3.20 U/

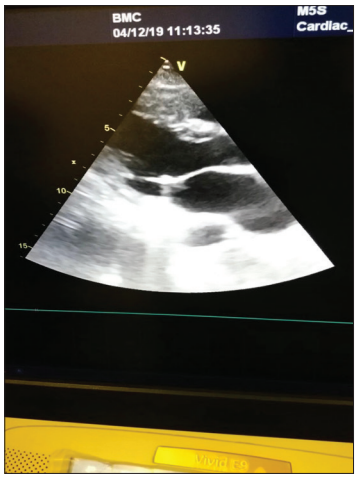

Figure 1: Mitral valve vegetation on transthoracic echocardiography

mL (<0.9 CMV IgM = 0.4U/mL (<0.9), tacrolimus trough level is 4.5 ng/ml (4–8 ng/mL). Ultrasound study of the graft showed; normal size graft with increased echogenicity, Doppler study of graft renal artery didn't show evidence of stenosis with resistive index is <0.6. Diagnosis of infective endocarditis (IE) was made, and her acute kidney injury (AKI) represents an associated acute nephritis.

Patient management at this stage included; combination of vancomycin and ciprofloxacin in modified renal dose, vancomycin intravenous (IV) at dose of 500 mg twice per day for 2 weeks, and ciprofloxacin I. V at a dose of 200 mg once daily for 4 weeks, then oral ciprofloxacin tablet 400 mg once daily for additional 2 weeks, and she was prescribed prednisolone in a moderate dose of 0.5 mg/kg daily for 4 weeks. Patient's dyspnea, fever and fatigue improved after few days, and her macroscopic hematuria resolved after next 3 days. Her laboratory data in January 12, 2020, were as follows: Hb 13.5 g/dL, WBC 12,000/mm^3, ESR 8 mm/hour, CRP 0.7 mg/dL, blood urea 44 mg/dL, creatinine 1.3 mg/dL, C3 0.98 g/L, C4 0.28 g/L, urine sediment; urine protein +, WBC 2–4/HPF, RBC 8–10/HP, with complete resolution of her mitral vegetation, and blood culture became negative 1 week after starting therapy. Patient was followed on daily basis for 2 weeks before her discharge in good condition. Her graft function showed progressive improvement over 2 weeks of time, returning to her baseline level after 4 weeks; in January 27, 2020, with blood urea 32 mg/dL, creatinine 1.2 mg/day, and plain urine sediment.

Discussion

KTx recipients are prone to a variety of infectious complications, with increased susceptibility to intercurrent infections of bacterial, viral, or fungal origin. Many factors contribute to this infection potential risk; including mandatory long-term immunosuppressive state, and recipient factors; such as preexisting cardiac lesions that make patients vulnerable to specific infections as IE. In developed countries, it has been

found that, the incidence of IE ranges from 3.6 to 7 cases per 100,000 populations per year, while the incidence rates of IE per 1000 patient has been reported 2.6 among deceased-donor transplant recipients and 1.8 among living-donor transplant recipients.[8]

Our case has previously manipulated mitral valve (valvuloplasty), and history of tooth extraction, 1 month prior to her presentation, making her at increasing risk for developing native valve IE, this is further supplemented by echocardiographic finding of mitral valve vegetation, blood culture report of enteroccal bacteremia (on two separate occasions),[9] patient was febrile (38.8°C) at presentation, and presence of a predisposing cardiac valve lesion; meeting definite diagnosis of IE according to modified Duke's criteria; having two major and two minor criteria.[10] Enterococcal endocarditis is well known in KTx patients occurring in up to 31%–50% of IE episodes, particularly in patients with prosthetic valve or previously manipulated valves.[11] Clinical presentation is characterized by occurrence of gastrointestinal symptoms, such as nondysenteric diarrhea. She was started on combination antibiotic therapy according to culture sensitivity report in modified renal dose, based on modification of diet in renal disease formula.[12]

Furthermore, patient developed acute renal dysfunction (nonoliguric), 3 days after onset of her IE symptoms with Subnephrotic proteinuria, macroscopic hematuria, active urine sediment, and reduced C3 and C4 levels. Her immunological screening profile was negative for anti-nuclear antibodies, anti-ds DNA or anti-neutrophil cytoplasmic antibodies, and color Doppler study of her graft renal vasculature was normal. These finding pointed toward occurrence of acute GN episode, which mandates treatment with moderate dose of oral prednisolone 0.5 mg/kg for 4 weeks, considering active endocardial infection, with dramatic response of her renal parameters and urine sediment activity within 1 week of starting steroid therapy. Because of this significant improvement of graft function to moderate steroid dose, we had switched our suspicion of recurrent primary glomerular disease to be a case of IE associated GN and this had deferred the decision of doing graft biopsy.

The occurrence of IE in KTx patients has been a talking point in the literature. In a retrospective study conducted by Pereira *et al*.[13] between 1992–2012 in Portugal, with a total of 1065 kidney transplant patient's files reviewed. Seven IE episodes were recorded, most cases occurred in males (71.4%), blood culture negative was found in 42.9% of cases, while blood culture positive reports were mostly gram-positive cocci; enterococcus and streptococcus. One case had renal allograft function loss due to sepsis and the patient died with a failed transplant. Of the remaining cases, three had reversible acute allograft dysfunction and three had no allograft dysfunction, and this study demonstrated 30 days mortality rate of 16.7%. In many studies renal dysfunction due IE is well known, it had been found that 80% of cases are due to focal or diffuse endocapillary proliferative GN, the remainder are either septic emboli or drug induced acute AKI, due to prolonged antimicrobial therapy.[14,15] In a large biopsy-based clinico-pathological study on IE associated acute GN, by Boils CL, *et al*.,[16] the most common presenting feature was AKI due to GN, and the most prevailing biopsy finding was necrotizing and crescentic GN in 53%, followed by endocapillary proliferative GN in 37%. C3 deposition was prominent in all cases, whe
reas IgG deposition was seen in 30% of kidney biopsies, with hypocomplementemia was seen in 56% of patients.

Conclusion

Nephrologists have to be aware of common infectious complications in KTx patients. IE should be suspected when KTx patient presents with triad of fever, dyspnea, with underlying cardiac valve disease. The occurrence of renal dysfunction associated with subnephrotic proteinuria, hematuria and hypocomplementemia (C3, C4) is an evidence to suspect diagnosis of concurrent episode of acute GN. Appropriate antimicrobial therapy for 4–6 weeks in tailored dosage, is essential to treat IE episode, and the addition of moderate dose of prednisolone for 8 weeks proved to be sufficient to overcome IE associated acute GN, with good recovery of graft dysfunction.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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