

Polymicrobial Infections in A Teenaged Renal Transplant Recipient

Inam Danish Khan^{1*}, Pavitra Manu Dogra², Shashi Kumar Ramphal¹, Shazia Khan³, Jayashree Konar⁴, Agnijeet Palit⁵, Namita Srivastava⁶, Prabhav Agrawal⁷, Suboohi Haleem⁸, Saif Alam⁹

¹Department of Pathology, and ²Department of Nephrology and Renal Transplantation, Command Hospital, Kolkata; ³Department of Gynaecology, Nivarini Hospital, Chilka; ⁴ESI Hospital, Joka, Kolkata; ⁵Fortis Hospital, Vasant Kunj, New Delhi; ⁶Department of Microbiology, SN Medical College, Agra; ⁷Maulana Azad Medical College, New Delhi; ⁸Martin and Harris Laboratories, New Delhi; and ⁹GB Pant Hospital, New Delhi, India

Journal of Basic & Clinical Medicine 2015; 4(1):37-39

Abstract

Renal transplantation under effective immunosuppression increases host susceptibility to infections. An unusual case of polymicrobial infection with *Mycobacterium tuberculosis*, Hepatitis B virus, Herpes Simplex Virus, Cytomegalovirus, Varicella Zoster Virus, and *Candida albicans* along with multiple non-infectious comorbidities including graft complications, renal impairment, encephalitis, hypertension, and iron deficiency anemia in a teenaged renal transplant recipient is discussed. Polymicrobial infections present a diagnostic and therapeutic challenge prolonging morbidity and reducing graft and recipient's survival. With the menace of drug resistant infections looming large, such cases require quarantine, containment and long term follow up.

Keywords: Renal transplantation, polymicrobial infections, iatrogenic immunosuppression, infection control

Introduction

Renal transplantation has evolved as a major breakthrough in addressing end stage renal disease. Though modern immunosuppressive regimens have significantly improved graft survival, predisposition to infections has increased. Bacterial infections involving coliforms, *Pseudomonas* and *Staphylococci* are most common and may account for up to 47% of all infections (1). We present an unusual case of polymicrobial infection with *Mycobacterium tuberculosis*, Hepatitis B virus, Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), Varicella Zoster Virus and *Candida albicans* along with multiple noninfectious comorbidities including graft rejection, renal artery stenosis, renal impairment, complicated encephalitis, hypertension, and iron deficiency anemia in a teenaged renal transplant recipient.

Case Report

A 19-year-old male, a case of crescentic glomerulonephritis progressing to end stage renal disease, on maintenance hemodialysis underwent live related renal transplantation in 2005, with mother being voluntary kidney donor. Pretransplant

evaluation included relevant history, clinical profiling, HLA matching and administration of vaccines against Tetanus and Pneumococcus. He was vaccinated with Bacillus Calmette Guerin, Sabin's polio, diphtheria, pertussis, tetanus and measles under universal immunization schedule. Infection screen for both donor and recipient revealed negative serology for Human Immunodeficiency Virus, Hepatitis B surface antigen, antibodies to Hepatitis C and CMV. Screening of recipient for tuberculosis with purified protein derivative (PPD) was negative with a five mm induration. He was given induction with rabbit thymoglobulin, followed by triple drug immunosuppression with mycophenolate mofetil 500 mg twice daily, tacrolimus 2 mg twice daily, and prednisolone 7.5 mg once a day. His tacrolimus trough levels were maintained at 6.1 ng/ml at 12 months post-transplant. In 2006, he developed renal allograft pyelonephritis, acute cellular rejection Banff IIa and was managed with broad spectrum antimicrobials and methylprednisolone pulse for three doses. He later developed gradual increase in serum creatinine and renal allograft biopsy revealed changes suggesting chronic allograft nephropathy.

During the follow up period of nine years post-transplant, he was summated to have multiple episodes of life threatening infections and their complications eventually leading to graft dysfunction (Table 1). The first of these infections was chicken pox seen on day 13 after transplant. In 2009, tubercular lymphadenitis was diagnosed through a lymph node biopsy revealing acid fast bacilli and epithelioid granuloma. He was initiated on four-drug anti-tubercular treatment continuing for 12 months with resolution of lymphadenopathy. In 2011, he developed decreased libido, loss of nocturnal tumescence and decreased facial, axillary, pubic hair and dull ache in scrotum on both sides. Clinically, thickened mildly tender epididymis led to the diagnosis of bilateral epididymo-orchitis which didn't respond to antimicrobials. He eventually developed bilateral testicular abscess and underwent bilateral orchiectomy followed by a three-week course of antimicrobials with adequate response. Histopathological examination of epididymis revealed epithelioid granuloma however no acid fast bacilli were seen. His tacrolimus trough level was 4.8 ng/ml. Subsequently he developed features of hypogonadotropic hypogonadism with undetectable testosterone levels. He was managed with testosterone replacement, erythropoietin and iron supplements. Later in 2011, he was detected to have hepatitis B with e-antigen positivity and viral load of 2 million copies/ml when he presented with jaundice. He was initiated on a two year course of Tenofovir following which viral load became undetectable.

Received: June 18, 2015; Accepted: June 28, 2015

*Correspondence author: Inam Danish Khan: Department of Pathology, Command Hospital (EC), Kolkata 700027, India. Mobile: +91 9836569777; E-mail: titan_afmc@yahoo.com

Table 1: Yearly average values of investigational work up of renal allograft recipient

Test Year	Hemoglobin (g/dl)	Total Leucocytes (/dl)	Differential Count	ESR (mm at 1 h)	Tacrolimus Trough Levels (ng/ml)
Pre-transplant					
2005	14.5	10700	N 73 L 25 E 02	24	-
Post-transplant					
2005	14.0	9800	N 70 L 27 E 03	30	-
2006	13.0	6400	N 70 L 27 E 02 B 01	35	6.1
2007	13.0	4500	N 64 L 33 E 03	35	-
2008	12.5	4200	N 59 L 35 E 04 B 02	42	-
2009	11.0	3500	N 55 L 40 E 03 B 02	45	-
2010	9.5	3700	N 55 L 40 E 03 B 02	46	-
2011	8.5	3200	N 45 L 48 E 05 B 02	48	4.8
2012	8.0	3100	N 45 L 48 E 05 B 02	45	-
2013	7.5	3300	N 51 L 44 E 03 B 02	43	4.0
2014	8.0	3600	N 45 L 48 E 05 B 02	40	-
2015	8.5	3600	N 45 L 48 E 05 B 02	38	-

In 2013, he developed a non-healing ulcer on medial aspect of right leg. Direct smear and biopsy revealed epithelioid granulomas and acid fast bacilli (Fig. 1 and 2). Culture from the ulcer revealed *Mycobacterium tuberculosis* susceptible to Rifampin and Isoniazid. He was initiated on four-drug antitubercular therapy. Three months later, he developed right hemiparesis and global aphasia. Clinically, he had upper motor neuron signs of right half of the body and right 7th upper motor cranial nerve palsy. Cerebrospinal fluid showed 68 leucocytes/high power field, proteins 300 mg/dl, raised globulins and HSV-1 by PCR.

Magnetic resonance revealed extensive chronic infarct of left cerebral hemisphere with encephalomalacia in left middle cerebral artery territory, right ptosis bulbi and encephalitis. Fusiform aneurysms were seen in left middle cerebral and basilar arteries.



Fig. 1: Chronic non-healing tuberculous ulcer on medial aspect of right leg.

He was managed with acyclovir. Motor aphasia is persistent even after motor improvement. Following this episode, he developed progressive weight loss, dysphagia, diarrhea and low grade fever. Renal evaluation showed creatinine 3.4 mg/dl. CMV DNA in serum was 48500 copies. He was treated with injectable Ganciclovir followed by oral valgancyclovir for six months. Upper gastrointestinal endoscopy showed esophageal candidiasis which was managed with oral fluconazole.

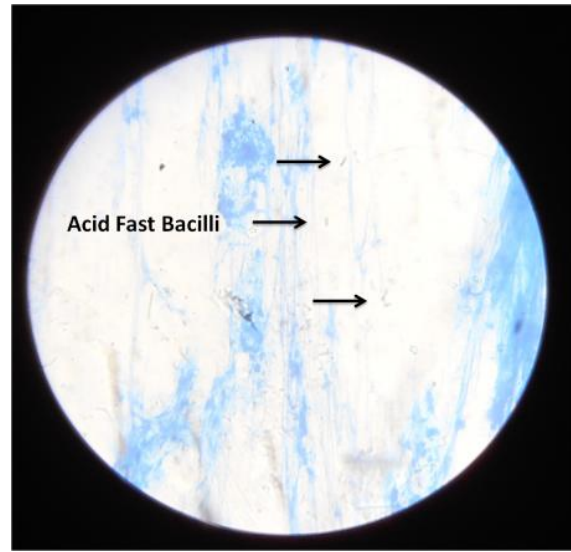


Fig. 2: Smear from non-healing ulcer revealing acid fast bacilli.

His immunosuppression was reduced further by replacing Mycophenolate mofetil with Azathioprine 50 mg per day. Tacrolimus was reduced to 0.5 mg twice a day to keep tacrolimus trough level at 4 ng/ml. He also had an episode of pneumonia which was managed with antimicrobials.

Infection surveillance of his family residence and immediate work environment were not contributory. Yearly analysis of infections from patient clientele hailing from his community did not reveal high prevalence or increased incidence of infections.

Discussion

The patient’s condition involved renal transplantation during teenage, repeated episodes of graft complications, renal

impairment and polymicrobial infections including tuberculosis, viral and fungal infections, complicated encephalitis, hypertension, eye diseases, and iron deficiency anemia. Renal transplantation at such a young age leaves a patient iatrogenically immunosuppressed for a longer duration which increases the risk of infections and other complications. Rejection episode managed with augmented immunosuppressive therapy may have increase host susceptibility and exposure to nosocomial and community acquired infections. They in turn lead to increased exposure to multiple antimicrobials during treatment, leading to development of antimicrobial resistance. While the patient was immunized for tuberculosis and other vaccines under universal immunization in childhood, vaccination for other vaccine preventable diseases was not considered. With the availability of a plethora of vaccines, it may be a tough clinical decision to immunize iatrogenically immunocompromised patients against many diseases. It is also difficult to trace the acquisition of infections in this patient due to community residence along with repeated cycles of hospitalization and interventions. The infections may have been acquired from either the hospital environment or community or even from reactivation of latent tubercle bacilli or viruses (2, 3).

The transplant patient form an ideal host and reservoir for emerging pathogens (4-6), which may persist due to immunosuppression and antimicrobial resistance; and thereby contributes to nosocomial hazard. The complications and sequelae of encephalitis may be due to delayed patient attendance owing to subdued clinical presentation and latency of viruses. Uncontrolled hypertension may have led to retinal detachment and renal dysfunction may have led to anemia.

Transplantation increases host susceptibility to infections owing to iatrogenic immunosuppression, metabolic abnormalities and increased exposure (1). Immunosuppression may be contributed by both immunosuppressive drugs and immunomodulating viruses. Newer immunosuppressive agents are potent although remain nonselective for different components of the immune system, thereby interfering with cellular and humoral immunity. Thymoglobulin depletes lymphocytes, mycophenolate mofetil causes neutropenia, steroids suppress inflammatory response and combined immunosuppressive regimen can cause renal failure (7). Viruses may differently modulate the immune system (8). Nosocomial infections may be acquired from the allograft, transfusions, parenteral access, catheters, drains or activation of latent flora (1, 9). Lifestyle determined environmental exposures due to occupation, travel, sexual, drug and dietary habits are also contributory (10). Polymicrobial infections in transplant recipients present a diagnostic and therapeutic challenge due to subdued clinical presentation, weak immunological reaction and antimicrobial resistance (11). Both transplantation and microbial infections independently elicit a chronic albeit altered inflammatory response (12). Polymicrobial infections may prolong morbidity, increase hospital stay, reduce graft survival, promote furtherance of antimicrobial resistance and lead to complications such as sepsis and mortality. Prevention of post-transplant infections may be targeted at reducing exposures, balancing immunosuppression, infection prophylaxis and patient behaviour modification.

Conclusion

The unfortunate course of this patient involving multiple comorbidities and disabilities remains a clinical conundrum. A guarded long term prognosis and post-transplant psychosocial rehabilitation raises ethical issues in such transplant cases where a

downhill course is seen despite astute efforts by the healthcare fraternity. The recent rise of immunocompromised populace especially in developing countries may require special managed care facilities where rapid diagnosis, treatment, and control of polymicrobial infections may be targeted. With the menace of drug resistant infections looming large, such a case requires quarantine, containment and long term follow up.

Conflicts of Interest: None

References

1. Patel R, Paya CV. Infections in solid organ transplant recipients. *Clin Micro Rev* 1997; 10 (1):86-124. www.ncbi.nlm.nih.gov/pubmed/8993860.
2. Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. *Clin Infect Dis* 1998; 27(5):1266-77. www.ncbi.nlm.nih.gov/pubmed/9827281.
3. Humar A. Reactivation of viruses in solid organ transplant patients receiving cytomegalovirus prophylaxis. *Transplantation* 2006; 27;82(2 Suppl):S9-S14. <http://www.medscape.com/medline/abstract/16858271>
4. Khan ID, Sahni AK. Bacterial infections and emerging resistance in renal transplant recipients. *Bangladesh J Med Sci* 2015; 14 (1): 14-21. <http://www.banglajol.info/index.php/BJMS/article/view/16306>
5. Khan ID, Sahni AK, Bharadwaj R, Lall M, Jindal AK, Sashindran VK. Emerging organisms in a tertiary healthcare set up. *Med J Armed Forces India* 2014; 70 (2): 120-8. www.ncbi.nlm.nih.gov/pubmed/24843199
6. Khan ID, Lall M, Sen S, Ninawe SM, Chandola P. Multiresistant elizabethkingia meningoseptica infections in tertiary care. *Med J Armed Forces India* 2014. <http://dx.doi.org/10.1016/j.mjafi.2014.02.002>
7. Sweny P. Infection in solid organ transplant recipients. *Curr Opin Infect Dis* 1989; 2:572-7.
8. Lodoen MB, Lanier LL. Viral modulation of NK cell immunity. *Nat Rev Microbiol* 2005; 3:59-69. www.ncbi.nlm.nih.gov/pubmed/15608700
9. Dummer JS, Ho M: Infections in solid organ transplant recipients. In: Mandell GL, Bennett JE, Dolin R, Eds. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Disease*, 6th ed. Philadelphia: Churchill Livingstone; 2005; 3501-10.
10. Davis CL. Post-transplant infections. Transplantation as treatment of end stage renal disease. In: Schrier RW, Henrich WL, Bennet WM, Eds. *Atlas of diseases of the kidney*. Philadelphia, Current Medicine, 1999; pp. 10.1-10.40.
11. Romero FA, Razonable RR. Infections in liver transplant recipients. *World J Hepatol* 2011; 3(4): 83-92. www.ncbi.nlm.nih.gov/pubmed/21603030
12. Kindt TJ, Osborne BA, Goldsby R, Eds. *Transplant immunology*. In: Kuby Immunology, 6th edn. Freeman WH & Company, 2006; 357-492.