Study of Causes of Renal Allograft Dysfunction: A Clinico-Pathological Analysis

Thesis

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By

Bossy Abdullatief Hemaia
M.B.B.Ch.
Cairo University

Supervised by

Professor Dawlat Belal
Professor of Internal Medicine
Faculty of Medicine,
Cairo University

Professor Salwa Ibrahim
Professor of Internal Medicine
Faculty of Medicine,
Cairo University

Professor Sawsan Fadda
Professor of Pathology
Faculty of Medicine,
Cairo University

Faculty of Medicine

Cairo University

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Abstract

Background and Objectives:

Kidney transplantation is currently the treatment of choice for end-stage renal disease (ESRD). It should be strongly considered for all patients with ESRD with no contraindication to this operation.

Renal allograft dysfunction has many etiologies. The greatest considerations are rejection, nephrotoxicity of calcineurin inhibitors, and recurrence of native kidney disease. This retrospective study aimed to review the causes of renal allograft dysfunction histologically and the possible associated factors.

Methods:

It was carried out on renal transplant recipients in King Fahd unit from January 2003 to January 2010 (147). The mean age was 28.18±12.24 years. As regard gender: 110 male and 37 female patients. Nearly 27% experienced at least one episode of renal allograft dysfunction.

Results:

Results revealed that the most frequent pathology encountered was acute active rejection (46.7%) while interstitial fibrosis with borderline rejection was the least frequent (5%). The results showed that increased donor's age was proven to be an important factor. The type of pathology encountered was different according to the age of donors e.g chronic CsA effect and interstitial fibrosis occurred more in older donors (39±9.3, 45.3±6.3 respectively) than other types of pathological diagnosis. The time of allograft biopsy just after renal allograft dysfunction was significantly correlated with the type of pathology. As regard graft survival, 125 grafts (85%) survived for 48 months postoperatively and 22 grafts (15%) were lost.

The main causes of graft loss were death of recipients with a functioning graft (68.1%).

Conclusions:

Keywords: Renal transplantation, Causes of rejection, Kidney biopsy, Renal Allograft dysfunction .

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Bossy Abdullatief Hemaia

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List of Abbreviations

AV	Acute vascular rejection
ANCA	Anti neutrophilic cytoplasmic antibody
ATN	Acute tubular necrosis
ACR	Acute cellular rejection
AHR	Acute humoral rejection
ALG	Anti lymphocytic immunoglobulin
ATG	Anti thymocyte immunoglobulin
CIN	Calcinurine inhibitors
CMV	Cytomeglovirus
CDC	Complement-dependent lymphocytotoxicity
CV	Chronic vascular rejection
CAR	Chronic allograft rejection
CAN	Chronic allograft nephropathy
DDT	Dithiothreitol
DM	Diabetes Mellitus
EBV	Ebstein barr virus
EM	Electronmicroscope
ESRD	End stage renal disease
FKBP	Fujimycin binding protein
GN	Glomerulonephritis
GI	Gastro intestinal
GBM	Glomerular basement membrane
HLA	Humal leucocytic antigen
HUS	Heamolyic ureamic syndrome
HAR	Hyper acute rejection
HTN	Hypertension
ID	Identical
IL-2	Interleukin-2
IMPDH	Inosine monophosphate dehydrogenize enzyme
MMF	Mycophenolate mofetil
mTOR	Mammalian target of Rapamycin

NFAT	Nuclear factor of activated T-cells
PPD	Purified protein derivative
PTC	Peritubular capillaries
PVN	Polyoma virus nephropathy
PRA	Panel reactive antibody
PTLD	Post transplant lymphoproliferative disorder
RPR	Rapid plasma reagent
SCR	Subclinical rejection
TMA	Thrombotic microangiopathy
TA	Transplanted arteriopathy

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Introduction

Renal transplantation is the standard of care for patients with end-stage renal disease ***(U.S. Renal Data System, USRDS 2007 - Danovitch, GM, 2010)*** and must be discussed with patients with advancing chronic kidney disease (CKD). Recent improvements in kidney transplantation have been driven largely by lower acute rejection rates and better long-term graft survival attributed to immunosuppressive agents ***(Yang, 2006)***. New strategies have emerged to minimize the side effects of immunosuppression therapy and the risks of infection, malignancy, chronic allograft dysfunction, and cardiovascular disease ***(Cole,* et al., *2008 - Vanrenterghem,* et al., 2008 - *Matas,* et al., 2008).** The preparation of CKD patients for renal transplantation should start from the time of its recognition and should occur in parallel with efforts to prevent and delay its progression ***(Danovitch, GM, 2010).*** The improved life expectancy and quality-of-life benefits of transplantation over dialysis therapy have attracted an increasing number of patients to the transplantation option; ideally, patients are evaluated for and undergo transplantation before the initiation of dialysis treatment ***(Danovitch, GM, 2010).***

Renal transplantation is a successful therapy for end-stage renal failure. With the increase in patients entering the waiting lists and the lack of similar increase in donor availability, the long-term success of transplantation is a pressing clinical need. This will help to reduce the number of patients entering the waiting list due to the failure of a first transplant. New immunosuppressive drugs have been very successful in improving short-term allograft survival and there is emerging data on some improvement in long-term survival ***(Hernandez-Fuentes, M.P. and Lechler, R.I, 2005).***

Nonetheless, late deterioration of allografts remains an important problem, particularly in view of the increasing demand for transplants. Kidney and heart allografts currently fail at a rate of **5** % each year post-transplantation ***(Hernandez-Fuentes, M.P. and Lechler, R.I, 2005).***

The most common complication of renal transplantation is allograft dysfunction, which in some cases leads to graft loss. Although there is a wide intercenter variability, data from the United States indicate that overall one-year unadjusted survival of a renal allograft is approximately **89** % for a deceased donor kidney and approximately **95** % for a living donor kidney ***(Kadambi PV, and Brennan DC, 2011).***

A number of risk factors have been identified for lower one-year deceased donor renal allograft survival. These include prior sensitization with more than **50** % panel reactivity, the presence of delayed graft function (defined as the requirement for dialysis during the first week after transplantation), the number and severity of rejection episodes, second or third transplant, donor age less than five or greater than 60 years, greater degrees of HLA mismatching, and allograft dysfunction at discharge (plasma creatinine concentration above 2 mg/dL) ***(Kadambi PV, and Brennan DC, 2011).***

The causes of renal allograft dysfunction vary with the time after transplantation. These periods are usually classified as ***immediate*** (zero to one week postsurgery), ***early*** (1 to 12 weeks postsurgery), ***late acute*** (after three months), and ***late chronic*** (years). Renal failure persisting after transplantation is called delayed graft function (***DGF***). The principal underlying causes of kidney allograft dysfunction immediately after transplantation include post-ischemic acute tubular necrosis (ATN), volume depletion, thrombosis of the renal artery or vein, and post-renal causes ***(Irish***

WD, et al., 2003 - Schnuelle P, et al., 2009). Among patients with initial graft function who then develop renal insufficiency (1 to 12 weeks post-transplantation), the major causes in this setting are calcineurin inhibitor toxicity, acute allograft rejection, urinary obstruction, infection, hypovolemia, and recurrent disease. Acute allograft dysfunction that develops more than three months after transplantation is most commonly due to calcineurin inhibitor toxicity, acute allograft rejection, urinary obstruction, volume depletion, recurrent disease, and de novo renal disease. Slowly progressive renal disease that occurs over a period of years after renal transplantation (often associated with persistent proteinuria) most commonly results from chronic allograft nephropathy, calcineurin inhibitor nephrotoxicity, hypertensive nephrosclerosis, viral infections, and recurrent or de novo renal disease ***(Nickeleit V, et al., 2000 - Chadban S, 2001- EBPG Expert Group on Renal Transplantation, 2002 - Kadambi PV, and Brennan DC, 2011).***

The causes of renal allograft loss have changed with the introduction of new immunosuppressive agents. In the pioneer era of transplantation most renal allografts were lost during the first year after transplantation due to acute rejection episodes. Nowadays, chronic allograft nephropathy became the leading cause of graft loss. CAN and patient death with allograft function are the 2 major causes of renal allograft loss after the first year, accounting for **80** % or more of cases ***(Kreis HA, and Ponticelli C., 2001).*** According to current estimates from the United Network for Organ Sharing (UNOS), the half-lives for renal allografts performed in 1995 and 1996 from living and cadaveric donors are 15.3 and 10.4 years, respectively ***(Yang, 2006).*** Consequently, much attention has been focused on better understanding the causes of CAN and patient death with a functioning allograft in an attempt to