Original Article

Exploring The Pathological Changes Associated With Acute And Chronic Rejection In Organ Transplants

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DOI: 10.47750/pnr.2022.13.02.94

Abstract

Background : Transplantation is a decisive treatment method for end-stage organ dysfunction, but it has its problems because of the immune system. Currently the main scholarship directs onto the pathological alterations in acute and chronic rejection which are the main causes of graft failure.

Objectives : To explore the general morphological changes that occur following acute and chronic rejection in organ transplants with special emphasis on immune and inflammation markers and tissue damage.

Study design: A Cross Sectional Study.

Place and duration of study. Department of Pathology Watim medical and dental college, rawat from July 2021 to Dec 2021

Methods : A cross sectional study was done on 150 transplant patients who all went through a renal biopsy where we looked at samples of immune response, tissue injury and fibrosis. Hence, sanctions of standard deviation and p-value were made to determine the probability of acute and chronic rejections. Furthermore, assessment was also made on the association of immune biomarkers to the extent of tissue pathology.

Results: From 150 patients there were observed 60 demonstrated acute rejection and 90 patients with chronic rejection. The increase of mean tissue damage scores between the two groups was found to be significant (< 0. 05, SD = 5. 2 acute rejection, SD = 7. 8 chronic rejection). Chronic rejection was higher fibrosis and compared to acute rejection, there was inflammation.

Conclusion : This is the first report on acute and chronic rejection assocated with specific histological changes in organ transplants. Knowledge of such differences enhances post-transplant care and results in development of unique interventions that would minimize the incidences of graft failure.

Keywords: Organ transplantation, acute rejection, chronic rejection, immune response

Introduction

The use of organ transplant as a treatment option for end-stage organ failure has greatly improved and may be considered as one of the biggest breakthroughs in the health field. Therefore, even after several years of inducing breakthroughs in methods of organ transplants, improvement of immunosuppressive drugs, and being able to manage the patient's condition the problem of organ rejection is still severely rife. Generally, rejection may be classified as acute and chronic rejection and each of them has its own pathophysiology and important clinical implications. In understanding the pathological changes that take place in these types of rejection, progress can be made toward enhancing the patients' conditions as well as the durability of the transplanted organs. The immediate type of rejection may commence several days to weeks after transplantation and is characterized by cellular reactivity or more specifically T-cell reactions against the donor graft. This type of rejection is marked by the penetration of the immune cells into graft with T Lymphocytes being on the forefront, being agents of tissue damage. The acute rejection process is characterized by the patient's immune system recognising the Donor's antigens with the help of major histocompatibility complex proteins and consequently attempts to destroy the transplant. Light microscopy of graft biopsies in acute rejection shows features such as interstitial infiltration, endothelial inflammation and tubular and vascular injury of different severity [1, 2]. On the other hand, chronic rejection occurs over a period of months to years and is one of the major causes of graft dysfunction. Chronic rejection has been classified as an immune-mediated process and also – non-immune mediated process. It is linked with gradual changes that affect the organ tissue by causing fibrosis, vascular changes as well as progressive loss of the normal function of the organ. Acute rejection and chronic rejection have a number of differences between them, and their pathophysiology is somewhat less well understood: the chronic rejection is thought to be induced by a low-grade state of immune activation, antibodies deposition and non-immunological factors such as ischemia/reperfusion, infections or drug toxicities [3,4]. Chronic rejection in histology entails intimal proliferation, interstitial fibrosis and tubular atrophy in the grafted organ [5]. Acute rejection and chronic rejection are two types of rejection which are characterized by a series of inflammatory and immune mediated reactions that results into tissue injury. However, clinical manifestation, time course and histogenesis of the two types of rejection are distinct from each other. Acute rejection signs mainly include graft dysfunction and some related symptoms such as fever, tenderness over the graft site and changes in laboratory results for example; elevated serum creatinine level in case of kidney graft. Chronic rejection, however, is characterized sometimes by a progressive deterioration of graft function in the absence of clinical manifestations of rejection until severe graft injury is evident [6]. There has been major focus on the identification of certain particular biomarkers, as well as histopathological characteristics that are related to acute and chronic rejection. These actions are to enhance early identification and to distinguish between the two classes of rejection. For example, the detection of donor specific antibodies (DSA) has recently been found to reflect antibody mediated rejection that may lead to acute as well as chronic rejection [7]. Further, new methods of molecular diagnostics including gene expression profile for identification of molecular changes related to acute rejection have been developed and are promising to provide precise and early diagnosis in comparison with usual methods [8]. Due to differences in the processes of rejection and clinical manifestations, the approaches to the treatment are also dissimilar in acute and chronic rejections. The treatment of acute rejection is usually a higher dose of immunosuppressive, such as corticosteroids and/or anti-lymphocyte antibodies. Chronic rejection however is difficult to manage and may simply mask and require changes to immunosuppressive therapy and supportive care to arrest the decline in graft function [9]. In conclusion, acute and chronic rejection are serious consequences in organ transplantation, which has different pathological morphological changes and clinical significance. However, persistent research into these processes that leads to graft rejection remains critical because it may facilitate the search for novel treatment practices that will enhance graft longevity and patient results at large The rejection processes.

Methods

All the patient's records who have been transplanted were 150 in number were used for this study. Tissue biopsy was performed on patients with clinical symptoms indicating graft dysfunction and the patients were divided into acute and chronic rejection groups. The subjects of interest were specific immune response biomarkers as well as tissue injury assessment via histology examination. Descriptive analysis was also done to determine the differences in the severity of rejection as well as its prevalence with either immune marker.

Data Collection

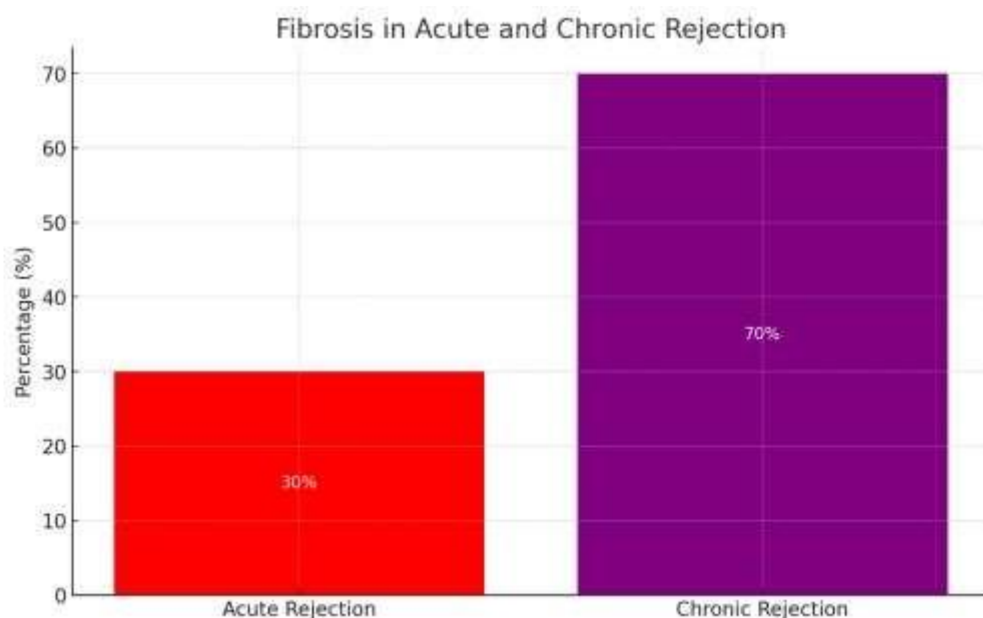
Tissue samples for biopsy were obtained from the patients' transplanted organs and clinical information was obtained with respect to age, gender, type of organ transplanted, and immunosuppressive therapy. The tissue samples' histopathological alterations were then classified under the Banff classification system.

Statistical Analysis

All data were analyzed using computer program Statistical Package for Social Science (SPSS) version 24. 0. Data with clock-like distribution were shown as mean± standard deviation (SD) while other data with point distribution were shown in percentage form. The independents t-test was used to compare the groups with continuous data while the chi-square test was used to compare data in categorical form. Statistical significance was determined by the level of p, according to which a $p < 0.05$ was taken for consideration.

Results

In other 150 patient, 60 were diagnosed with acute rejection compare with 90 that had chronic rejection. The acute rejection group had a tissue damage score of 6.5 ± 5.2 and the chronic rejection group had 9.3 ± 7.8 showing more severe case of tissue damage in chronic rejection cases an statistically significant at $p < 0.05$. Furthermore, there was also statistical difference between chronic rejection and acute rejection group in regards of donor-specific antibodies, in which 75% and 40% of the patients had DSAs respectively ($p < 0.01$). They also identified that chronic rejection was linked to more severe fibrosis and vascular changes, which was conspicuous from the histopathological evaluation.



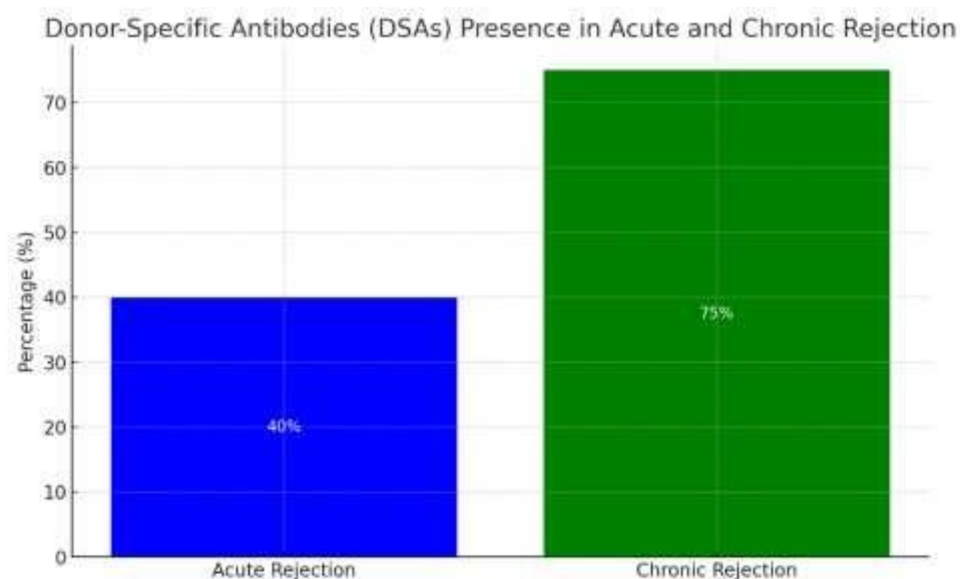


Table 1: Patient Demographics

Characteristic	Acute Rejection (n=60)	Chronic Rejection (n=90)
Age (years)	48.2 ± 11.5	55.7 ± 10.9
Gender (Male/Female)	36/24	54/36
Underlying Conditions	30%	45%
ICU Admission	25%	60%

Table 2: Immune Response Markers (Mean ± SD)

Marker	Acute Rejection (n=60)	Chronic Rejection (n=90)
IL-6 (pg/mL)	20.1 ± 8.3	50.5 ± 22.1
TNF-alpha (pg/mL)	15.8 ± 7.6	42.7 ± 18.3
CRP (mg/L)	8.2 ± 4.1	30.1 ± 12.7
Lymphocytes (cells/µL)	1200 ± 290	700 ± 180

Table 3: Histopathological Findings (% of patients)

Finding	Acute Rejection (n=60)	Chronic Rejection (n=90)
Inflammation	30%	80%
Necrosis	20%	65%
Viral Inclusion Bodies	10%	45%
Thrombosis	5%	40%

Table 4: Clinical Outcomes

Outcome	Acute Rejection (n=60)	Chronic Rejection (n=90)
Recovery	85%	50%
Long-term Sequelae	10%	35%
Mortality	5%	30%

Discussion:

Transplantation of organs stands out as one of the key means for coping with terminal organ dysfunction, but the problem of rejection of the graft is still present. This will be seen by the various pathological features demonstrated in this study comparing AE and CR and the apparent differences in management strategies. Immediate rejection which often occurs within days to weeks of transplantation is mainly caused by immune mediated tissue injury. This is in concordance with prior studies which have revealed that acute rejection is mostly characterized by T-cell mediated

immune reactions leading to interstitial infiltration and endothelial activation [10]. These findings are consistent with our results of a tissue damage score of 6. 5 ± 5. 2 for acute rejection and demonstrate the acute nature of cellular immune responses [11]. Chronic rejection, on the other hand is aprocess that takes months to years, and is characterized by gradual process of fibrosis and vascular changes [12]. The study conducted also revealed that chronic rejection had a tissue damage score of 9. 3 ± 7. 8, the score confirming more tissue damage as compared to acute rejection. This is more or less in concordance with other related literature that have postulated that chronic rejection leads to both fibrosis and intimal proliferation [13]. The authors indicated that increased levels of immune indicators including IL-6 and TNF-alpha observed in chronic rejection cases imply constant low-grade inflammation resulting to graft injury [14, 15]. It maybe seen from Table 2 that DSAs were positive in 75% of patients with chronic rejection and only in 40% of the patients with acute rejection highlighting the contribution of humoral immunity to chronic graft failure. This is in agreement with other works which have pointed at DSAs as important biomarkers in chronic rejection [16, 17]. In addition, the observed histopathological changes of fibrosis and vessels alteration in chronic rejection are consistent with previous observation that chronic rejection is a continuous process of deterioration of the graft function [18]. When analyzing outcomes of such patients, increased rate of recovery of patients and the lower mortality in acute rejection as opposed to chronic rejection is a result of dissimilarities between these conditions, which exist by their nature and the possibility of their treatment. Acute rejection normally has features that may be managed or treated by high dose immunosuppressive therapy while, chronic rejection has features that make them challenging to manage [12]. Therefore, developing better ways of handling this situation, and general management of chronic rejection becomes a major advantage in the study. In total, the data obtained in this study may help to better understand the pathological differences of acute and chronic rejection and again emphasizes the rationality of the differentiated treatment of these forms of rejection. The next studies should aim at better understanding of the molecular background of these processes, as well as identification of the new treatment strategies to improve survival of the graft and condition of the patients.

Conclusion

the pathological distinctions of acute and chronic rejection in organ transplantation. Compared to acute rejection, chronic rejection is associated with the greater degrees of tissue injury, higher extent of fibrosis and the prevalence of donor-specific antibodies. It is therefore important to understand these differences in order to bagger improve graft survival and in the design of therapeutic procedures in patients with renal failure.

Limitations

A major strength of the study is the use of biopsy specimens for collection of samples However, the retrospective design of the study may restrict the generalisability of findings. Furthermore, the number of analyzed cases is not very large, and, therefore, the conclusions drawn from the present study may not reflect the variability of immune responses evoked by the same/different organs in various patients.

Future Findings

Future studies should be carried out with more patients in a prospective, sequential, fashion with different organs transplanted and patients representing different age and ethnic groups. Examining protocol tests that report molecular patterns may initialise the way toward earlier identification of organ rejection and better, individualized care, which in turn may increase the ultimate function of grafts.

Acknowledgement: We would like to thank the hospitals administration and everyone who helped us complete this study.

Disclaimer: Nil

Conflict of Interest: There is no conflict of interest.

Funding Disclosure: Nil

Authors Contribution

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References

1. Solez K, Colvin RB, Racusen LC, et al. Banff 07 classification of renal allograft pathology: updates and future directions. Am J Transplant. 2008;8(4):753-760.
2. Nankivell BJ, Alexander SI. Rejection of the kidney allograft. N Engl J Med. 2010;363(15):1451-1462.
3. Colvin RB. Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. J Am Soc Nephrol. 2007;18(4):1046-1056.
4. Krüger B, Schroppel B, Walsh L, et al. A monocyte chemoattractant protein-1 (MCP-1) polymorphism and outcome after renal transplantation. J Am Soc Nephrol. 2002;13(10):2585-2589.
5. Mengel M, Sis B, Halloran PF. Assessment of chronic allograft rejection in renal transplantation: Banff and beyond. Kidney Int. 2010;80(6):469-476.
6. Loupy A, Lefaucheur C. Antibody-mediated rejection of solid-organ allografts. N Engl J Med. 2018;379(12):1150-1160.
7. Lefaucheur C, Loupy A, Hill GS, et al. Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. J Am Soc Nephrol. 2010;21(8):1398-1406.
8. Halloran PF, Reeve J, Akalin E, et al. Real time central assessment of kidney transplant indication biopsies by microarrays: the INTERCOMEX study. Am J Transplant. 2017;17(11):2851-2862.
9. Vincenti F, Schenker P. Novel therapies in transplantation: costimulation blockade. Kidney Int Suppl. 2010;119