Risk of Malignancy in Post Renal Transplant Patient with Long Term Immunosuppression

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Abstract—*Organ transplantation and its techniques have encountered a great deal of improvement and development in last 50 years after the first renal transplant which took place in 1950 in United States of America on Ruth tucker a 44 years women. Organ transplant have become safer and lesser risky due to several advancements in the surgical and medicinal fields. Renal transplant is one of the major organ transplant which accounts for around 12,000 transplants all over the world. Immunosuppression, just like any other transplant is a major part of renal transplant which includes the use of medicinal regime like Tacrolimus, Cyclosporine and Rapamycin which is a must for the graft recipient. But the immunosuppressive medication have shown a number of tormenting effects on patients health which can lead to severe consequences like cancer, cardiovascular diseases, bone related disorders and infections.*

1. INTRODUCTION

Organ or graft transplantation is a well accepted method for the treatment of end stage organ failure. With the discovery and advancement of immunosuppressive drugs the risk of rejection is reduced and the life expectancy of the transplant recipients has increased. But the long time outcome of immunosuppressants is proving to be fatal for the patients due to the malignancies like cancer, cardiovascular disorders and bone diseases. These malignancies limit the success of the transplant [1]. Renal transplant is one the most common transplant today in India and abroad. There are over 200 dedicated approved kidney transplant centers in India. Since 1990 there have been 18686 transplants in India alone [2]. It's a major concern that even after a successful transplant the patient is under the risk of developing dreadful medical conditions. These malignancies can occur due to various mechanisms which are initiated as the direct effect of the immunosuppressant drug or because of the other factors that comes into the play because of the immunocompromised condition. [3]

2. CANCER

All De novo malignancy in renal transplant recipients is 3-4 times higher than normal population [4-7]. It's also higher than the patients who are on dialysis and on transplant waiting list [5]. A number of studies support the fact that cancer will soon overtake cardiovascular disease as the primary cause of death post transplant [9, 10]. An analysis by the Australia and New Zealand transplant registry demonstrate that cancer has already overrun cardiovascular diseases as the major reason for death post transplantation [8]. Elevation in the cases of cancer can be because of a number of facts that directly or indirectly contributes to the process of oncogenesis lie changing trends of use of immunosuppressive drugs6. Initially a number of registries showed the incidences of cancer post transplantation for example Israel Penn International Transplant Tumor registry, Australian and New Zealand Transplant Registry [7, 9, 11].

The main type of cancers in renal transplant patients were post transplant lymphoproliferative disorders (PTLD), lymphomas, cancer of skin, lips, vulva, perineum, insitu carcinoma and renal carcinomas. PTLD showed its presence in extra nodal sites like brain. 13077 renal transplants were performed in Australia and New Zealand during 1980-2003 which revealed that renal transplant recipients were three times more likely to develop cancer than the general population [8].

With increase in duration of immunosuppression and high dose, the incidences of cancer also increases which links the development of cancer to the suggestion that cancer develops due the immunosuppressed state rather than because of any specific immunosuppressive agent [2]. Still there are a number of evidences that relate immunosuppressive drugs to carcinogenesis as some immunosuppressant shows carcinogenic properties. Corticosteroids, calcineurin inhibitors i.e. cyclosporine and Tacrolimus, anti metabolite azathriopine, inosine monophosphate dehydrogenase inhibitor mycophenolate mofetil and Mtor inhibitor sirolimus and everolimus are the main immunosuppressive agents used in renal transplant these days. Amongst all, corticosteroids are the most common components in the medication used post transplant due to which it's difficult to assess their contribution in malignancies [5]. According to Danish cancer registry and North Jutland Prescription Database amongst 59043 individuals who were observed for over 8 years, prescribed with corticosteroids, the risk of basal cell and

squamous cell carcinoma of the skin increased relative to the expected values [8].

The calcineurin inhibitors Tacrolimus and cyclosporine have also been associated with malignant developments in renal transplant recipients [9-12]. In an analysis of 30 clinical trials to determine oncological effect of Tacrolimus and cyclosporine, no difference in the incidence of malignancy was seen in the first year [13].

Azathriopine has also been associated with post transplant malignancies because of its inability to repair DNA damage and its property to evoke codon misread [14].

Cancer in renal transplant patients is treated using similar procedures which are used for non transplant patients i.e. surgery, radio therapeutic and chemotherapeutic treatments [2]. In case of Kaposi's sarcoma or PTLDs, reduction in application of immunosuppression is recommended. An mTOR inhibitor therapy can be used in the case of renal cell carcinoma due to its antineoplastic effects [15]. Similarly nucleoside inhibitors can be used to treat Epstein Barr virus aggressively. Malignancies like Monoclonal Lymphoproliferation require combinational therapies like chemotherapy along with CHOP or cyclophosphamide, doxorubicin, vincristine, and steroids. Anti CD-20 monoclonal antibody rituximab has also been added to the protocol.

3. CARDIOVASCULAR DISEASE

Cardiovascular disease is considered to be the most common cause of death post renal transplant.4 over the years the death rate haven't declined and the probability that epidemiological risk factors involved in coronary artery disease in general population are common with transplant recipients. And if there are any factors unique to transplant population than they seem to be contributing to the increase in coronary artery disease. A study conducted by Kasiske and colleagues on 403 renal recipients for a period of 4 years (1977-1986) revealed that the incidence of ischemic heart diseases in 15% renal patients was four times more than in general population [16]. Rationale for the elevated incidences of cardiovascular diseases is not fully understood but an insight is provided regarding relationship between renal transplant and cardiac diseases as a result of which renal disease is now considered as a cardiac risk factor. Factors which are unique to the uremic patients i.e. hyperparathyroidism, abnormal vascular calcification and imbalanced calcium, phosphorous metabolism might also play an important role as transplant patients are expose to uremic conditions for a considerable amount of time. Progressive graft dysfunction generally co-occur with proteinuria which can lead to hyperlipidemia which is a well known cardiac risk factor contributing to both transplant population and end stage renal diseases. Dialysis patients show abnormalities like low levels of HDL, normal total cholesterol level, hypertriglyceridemia. Contradictory to which, transplant recipients show hypertriglyceridemia, elevated LDL hypercholesterolemia, slightly increased HDL values, and elevated VLDL cholesterol [17].

Amongst the complications post transplantation, hyperlipidemia is one of the common problems which are also associated with immunosuppressive drugs such as corticosteroids and cyclosporine. In major studies post transplant hyperlipidemia is seen as an important risk factor for ischemic heart disease [18]. Therefore an appropriate cardiac evaluation is essential and it's reasonable to obtain coronary angiogram in type 1 diabetes patients over 45 years of age and for patients younger than 45 should be examined for other cardiac risk factors evaluated through the patient's clinical history [19].

4. BONE DISEASE

Osteoporosis is considered as an important health issue throughout the world which is characterized by loss in the bone mass and as a result of which, increase in the fracture risk. This could be because of primary reasons like age related bone loss or postmenopausal estrogen deficiency or because of secondary reasons like metabolic deregulation, use of corticosteroids in numerous therapies. Detrimental effect of corticosteroids can be direct or indirect. Direct effect causes inhibition of bone formation as a result of low osteoblast functioning whereas indirect effect is caused by reduction in the calcium absorption by the gut and an increase in the renal calcium excretion. Rapid bone loss is experienced in first 12-18 months of the corticosteroid therapy [20]. Corticosteroid therapy adds on to the age and the estrogen deficiency. It associates the female gender with a higher risk of fracture in the group of renal transplant patients [21]. Cyclosporine and Tacrolimus FK506 causes increased bone reabsorption which is greater than the counteracting process of bone formation which is represented by increase in the serum bone Gla protein concentrations [22]. Patients undergoing renal transplant generally exhibit renal osteodystrophy before the surgery. osteomalacia, hyperparathyroidism and a dynamic bone diseases fall under this category and contribute additively to bone diseases post transplant. Persistent hyperparathyroidism after transplant with serum calcium levels above 13mg/dl might lead to osteopenia with parathyroidectomy as the last resort.

Due to such detrimental effect of corticosteroids several studies are been conducted to limit the use of corticosteroids in the post transplant medication. Some of these methods involve basic therapies like estrogen replacement for postmenopausal women and calcium supplement for the general population. Use of calcitriol has shown decrease in the vertribral fracture but the dose is very limited due to its side effects o patients with hyperthyroidism and hypercalcemia [23]. Other more effective therapies include the use of cyclic etidronate which prevents corticosteroid induced bone loss22.on the other hand pamidronate has showm promising results in preventing lumbar spine and femoral neck bone

mass loss26. calcitonin, an anti reabsorptive drug has been used to treat corticosteroid induced osteoporosis [20].

Osteonecrosis is another complication which is correlated to methylprednisolone which is a type of synthetic glucosteroid [24]. Osteonecrosis is characterized by pain in the femoral head. A variety if surgical approaches are available for treatment [23].

5. INFECTION

Infection is one of the most important complications that a patient faces post transplant. With advancement in medication the infection incidences has dropped down to 15-44% from 70% [25]. This is because of advancement in surgical techniques, better immunosuppression, use of prophylactic antimicrobial drugs, effective therapies and more improved drugs.

Most common infection of all is the bacterial infections. It involves urinary tract infection, respiratory tract infection and infection in the intravenous lines. Incidence of urinary tract infection is more than 30% in the first three months after transplantation [26]. The clinical manifestation can be in the form of septicemia, pyelonephritis or asymptomatic bacteriuria. many health centres and research institutes promote the use of trimethoprimsulfamethoxazole as treatment against urinary tract infection and listeria, nocardia etc.

Community acquired infections such as common cold, diarrheal syndromes, sexually transmitted diseases, pneumococcal influenza can affect transplant recipient.

Opportunistic infections can take place at any time after first month when the effect of immunosuppressants is highest. There is a clear relationship between degree of immunosuppression and development of opportunistic infections [27]. Cytomegalo virus or CMV is one of the most common infections in the renal transplant patient population with an incidence of 34 to 55% [26]. The major impact of disease is seen in the first 1-4 months after transplant. Transmission of the disease generally takes place through blood transfusion through seropositive donor and through an infected organ. Primary infection generally occurs when a seropositive donor donates kidney to seronegetive recipients. this grou of patients are at the highest risk. Superinfection can occur when reactivation of donor virus takes place in seropositive recipient [28]. Valacyclovir has shown promising effectiveness in the prevention of CMV disease [29].

Most common clinical manifestation of CMV is leucopenia, fever, pneumonitis, gastrointestinal involvement like abdominal cramping, diarrhea, hepatitis etc. As CMV infection can cause high intensity immunosuppression of the host defence system, superinfection through other pathogens like pneumocystis,listeria etc should be considered [25].

Epstein-Barr virus plays a fundamental role in the development of lymphoproliferative disorders posttransplant. Acyclovir is used as prophylactic medication.

Varicella –Zoster virus or VZV can be a genesis for reactivation infection which can manifest in the form of zoster lesions in the dermatomal pattern. Primary disease can be severe with life threatening hepatitis,encephalitis, pneumonia, intravascular coagulation. Vesella Zoster immune globin administration in the early period of exposure can prevent the serious illness [25].

In renal transplant patients, the main reason of liver cancer is hepatitis b and hepatitis c virus. amongst the population of the renal transplant recipient 50% of the patients develop liver cancer in 10 years [36].

In the population of renal graft recipient the most common fungal infection is the Candida albican. Other fungal organisms who attack the immunocompromised recipients are aspergillus and Cryptococcus. Tuberculosis is a worldwide problem that patients face post renal transplant. This could arise due to primary infections or due to reactivation.

All transplant patients are given vaccination for hepatitis A, B pneumococcal disease, diphtheria, tetanus. These diseases have a potential to be way more serious in immunocompromised patients [32].

6. CONCLUSION

It's a given that none of the transplant therapies can be successful without a strict immunosuppressive regime. Immunosuppressants reduce the incidences of acute renal transplant rejection. It increases the life expectancy of the allograft recipients but post transplant malignancies have emerged as a reason for mortality in these population. It's very important that prospective clinical studies are done to evaluate the effect of immunosuppression on other aspects of the health and its fatal side effects.

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