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Original Article

Malignancy in Egyptian living-donor kidney transplant recipients

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Abstract

Background/Aims: A markedly increased incidence of malignancy among transplant recipients is well recognized. However, the incidence and pattern of post-transplantation malignancies show some discrepancy in different reports. The aim of this work was to study malignant complications in our kidney transplant patients
Patients & methods: Out of 1200 live donor kidney transplantations performed in our center, 50 patients experienced 52 clinically evident malignancies (4.3%).
Results: The recipient mean age at the time of cancer diagnosis was 36.6±8.6 years, and 36 were males. They developed malignancy at a mean interval of 112±53 months post transplantation, and the range of follow up after diagnosis was 67-207 months. Forty patients (80%) received cyclosporine (CsA) as one of the immunosuppressive drugs. The main de novo malignancies were 24 Kaposi's sarcomas, 5 lymphomas, 5 breast cancers, 4 bladder cancers. The patients with malignancy had a significantly higher incidence of both acute rejection episodes during the first year after transplantation and the cumulative dose of steroids after 12 month. Tailored reduction of immunosuppressive drugs was initially tried in all patients. However, some patients still needed further specific treatment. Response to treatment was more favorable in Kaposi's sarcoma. Twenty six patients died, out of them 13 had functioning grafts.
Conclusion: We conclude that Kaposi's sarcoma is the most prevalent post transplant malignancy in our locality and it carries the most favorable prognosis. Early diagnosis, modification of immunosuppression may help to control post-transplantation malignancy. Post-transplant malignancy may affect the graft and patient survival.

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Key words: Kidney; malignancy; transplantation

Introduction

Renal allograft recipients have a well documented increased incidence of malignant neoplasia than the general population. Moreover, the distribution of cancer types is different and there is some discrepancy in different post-transplantation malignancy reports [1,2]. Penn presented data on 7668 types of malignancy that occurred in 7192 organ transplant recipients [3]. The predominant tumors are skin/lip carcinomas, lymphoma, Kaposi's sarcoma, renal carcinomas, hepatobiliary tumors, and soft tissue/visceral sarcomas. If malignancies of skin are excluded, a cancer incidence of 400% in transplant recipients is usual.
Data from several large renal transplant series show an overall incidence of cancer ranging from 4 to 18% with an average of 6% [3,4]. Immunosuppression is known to favor the development of various types of
tumors. The other possible risk factors include chronic antigenic stimulation, activation of oncogenic viruses, uremia, interval after transplantation, racial and genetic susceptibility. We report here on the characteristics of malignancies diagnosed among 1200 live donor kidney transplant recipients performed in Mansoura Urology and Nephrology Center, Egypt.

Material and methods

From March 1976 to October 1999, 1200 live donor kidney transplants were performed in the Urology & Nephrology Center, Mansoura University, Egypt. Recipients suspected to have malignancy were evaluated regarding the type of malignancy by thorough clinical, laboratory, radiological, endoscopic and histopathological modalities.
Cancer patients data were collected in terms of sex, age, post-transplantation duration, immunosuppressive protocols, graft function and outcome, frequency of

rejection episodes, chronic allograft nephropathy, cumulative steroid dose and schistosomal infection. Patients with malignancy were compared with non malignant kidney transplant recipients among 1200 cases who served as a control group.

Statistical analysis

Statistical analysis was carried out using SPSS package. For univariate analysis, student t-test and Chi square test were used. Multivariate analysis was carried out using COX logistic regression. Differences were compared using log rank test. P value < 0.05 was considered significant. Kaplan-Meier tests were used to evaluate differences in graft and patient survival.

Results

Out of 1200 patients who received live donor kidney transplants in our center during the last 23 years, 52 malignancies were diagnosed in 50 patients with an overall prevalence of (4.3%). These malignancies developed in 39 males and 11 females. The mean age of patients at the time of diagnosis of their malignant tumors was 36.6±8.6 (range 18-53) years. The mean latency period between transplantation and the diagnosis of these malignant tumors was 72.7±58.2 months for solid tumors and 37.7±23.5 months for Kaposi's sarcoma. Diagnosis of malignancy was documented in 40 out of 764 kidney transplant recipients receiving cyclosporine (5.2%) while 9 out of 340 patients receiving azathioprine (2.6%) developed cancer. In the last two years, tacrolimus (FK 506) and mycophenolate mofetil (MMF) were introduced as rescue immunosuppressive therapy. Two patients out of 96 (2.1 %) on tacrolimus and one patient out of 174 patients on MMF (0.6%) have documented to develop cancer.
Table 1, shows that Kaposi's sarcoma was the commonest type of malignancy being diagnosed in 49% of total malignancies and 1.9% of all transplant recipients.

Table 1. Distribution of malignancy among kidney transplant recipients

	No.	*% of total malignancy (n= 52)*	*% of total transplants (n= 1200)*
Kaposi's sarcoma	24	46.2	2.0
Lymphoma	5	9.6	0.4
Cancer breast	5	9.6	0.4
Cancer bladder	4	7.7	0.3
Cancer head of pancreas	2	3.8	0.2
Cancer lip	2	3.8	0.2
Thyroid carcinoma	2	3.8	0.2
Hepatoma	2	3.8	0.2
Cancer colon	1	1.9	0.08
Cancer prostate	1	1.9	0.08
Bronchogenic carcinoma	1	1.9	0.08
Malignant fibrous histiocytoma	1	1.9	0.08
Recurrent nasopharyngeal carcinoma	1	1.9	0.08
Cancer larynx	1	1.9	0.08

Kaposi's sarcoma

Out of 24 cases of Kaposi's sarcoma, two patients had another malignancy, carcinoma of the bladder in one and cancer breast in the other patient. Lesions of Kaposi's sarcoma were cutaneous in 20, visceral and cutaneous in 3, and visceral in 1 case. The cutaneous lesions were multiple, mainly involving the lower limbs and genitalia. Histopathological examination showed multiple thin walled capillaries, lined plump endothelial cells, and between these capillaries fusiform cells running in different directions; the degree of mitosis among these fusiform cells was not marked. The case with isolated visceral lesion presented with intestinal mass complicated by intussusception, whereas in the cases with mixed cutaneous and visceral involvement, lesions affected the oropharynx and cervical lymph nodes.
The first line of treatment adopted for these patients was tailored reduction of immunosuppression by gradual decrease of azathioprine dose till regression of the tumor was observed. If there was no satisfactory response gradual reduction of the cyclosporine dose was utilized to achieve the lower acceptable trough level (50- 75ng/ml). In refractory tumors, the steroid dose was reduced to 2.5 to 5mg/day. Other lines of treatment include intralesional injection of bleomycin sulfate and superficial irradiation which were used for residual skin lesions, while vincristine was given intravenously in two cases with mixed visceral and cutaneous lesions. Surgical excision with a safety margin was performed for the case with intestinal Kaposi's sarcoma.
Following these therapeutic modalities, complete regression was achieved in 10 cases (4 have good graft function, 4 with moderately functioning grafts and 2 died with graft function due cardiovascular causes), 14 cases show partial response on modulation of immunosuppressive therapy and lost their grafts later on and returned back to hemodialysis.

Lymphoma

Diagnosis of lymphoma was made in 5 cases; two with non Hodgkin lymphoma of the gastric lymph nodes, one presented with retroperitoneal mass, one involved the brain, while the last presented with an intestinal mass. Four patients were on cyclosporine and the other two were receiving steroids and azathioprine.

In addition to tailored reduction of immunosuppressive drugs, surgical treatment as well as chemotherapy was also adopted. However, the response to treatment was poor; one is still living on dialysis and 5 patients died eventually, four of them had good functioning grafts.

Breast cancer

Diagnosis of cancer breast was confirmed in 5 cases, four females and one second transplant male (duct carcinoma of left breast).The four female patients were on cyclosporine and the male patient was on steroids, tacrolimus, and mycophenolate mofetil. Three female patients responded well to radical mastectomy, radiotherapy, and estrogen therapy, as well as reduction of immunosuppressive drugs. At present they still have good graft function. The other two cases were considered for palliative chemotherapy and hormonal therapy due to evidence of wide spread metastasis at the time of diagnosis.

Cancer of the bladder

Carcinoma of the urinary bladder developed in 4 adult males, 8 - 16 years after transplantation. In all of them a history of urinary schistosomiasis and its treatment was documented. Hematuria was the presenting symptom and the diagnosis was established by cystoscopy and bladder biopsy. Modification of immunosuppressive therapy was adopted in all patients. One of these patients developed carcinoma in situ and was treated by intravesical chemotherapy. Three patients had muscle-invasive bladder tumors and required cystectomy and orthotopic bladder substitution. Unfortunately, within 2 years of the cystectomy, they all died from distant metastasis. The patient with carcinoma in situ died while on hemodialysis due to massive gastrointestinal hemorrhage.

Cancer head of pancreas

There were two cases diagnosed to have cancer head of pancreas 9 and 15 years post transplantation. The first case was on triple therapy (steroid, cyclosporine and azathioprine and the other received conventional immunosuppressive therapy. They presented with epigastric pain and jaundice. Reduction of immunosuppressive drugs as well as surgical removal of the mass was the mode of treatment adopted for both patients. One patient died with functioning graft due to hepatic metastasis and the other is still living with a moderately functioning graft.

Cancer thyroid

Diagnosis of cancer thyroid was documented in 2 cases 6 years after transplantation. They presented with palpable solitary nodules. Histopathological examination confirmed the diagnosis of papillary carcinoma of the thyroid. Immunosuppression was mediated by steroid and tacrolimus in one and azathioprine and steroids in the other. As usual, reduction of immunosuppression was adopted in addition to total thyroidectomy and postoperative radiotherapy. Following this treatment, one patient is still living with moderately functioning graft and the other patient died due to cardiovascular causes.

Basal cell carcinoma of the Lip

This carcinoma was diagnosed in two males 9 months and 6 years, respectively, after transplantation. Both cases were receiving cyclosporine in addition to steroids and azathioprine. Surgical excision with safety margin in addition to tailoring of immunosuppression led to long-lasting control.

Hepatoma

It was diagnosed in two male patients, 4 and 6 years after transplantation, while they were on triple immunosuppression. They had a history of intestinal schistosomal infection but laboratory investigations revealed absence of hepatitis Band C viral infection. They presented with jaundice and tender liver. Ultrasound demonstrated space occupying lesions in the liver, and CT guided biopsy confirmed the
diagnosis of hepatocellular carcinoma grade H. Rapid deterioration of general condition despite complete withdrawal of immunosuppression was noticed, and both patients died from severe septicemia and consumption coagulopathy.

Other malignancies

Carcinoma of the larynx was diagnosed in one male patient while on conventional immunosuppression 5 years post-transplantation. Modulation of immunosuppressive drugs, surgical excision and radiotherapy were tried but the response was poor and the patient died from metastasis one year later with good graft function.
Cancer prostate was diagnosed in one patient 54 years old 6 years after transplantation. He was on triple immunosuppression and the main presentation was Hematuria. Good response was obtained after total prostatectomy and modification of immunosuppression by withholding azathioprine.
Bronchogenic carcinoma was diagnosed in 55 year old male patient 4 years post transplantation. He gave a history of heavy smoking for more than 10 years. The main presentation was hemoptysis and recurrent chest infection. In spite of withdrawal of immunosuppression and radiotherapy, the patient died while on hemodialysis from wide spread metastasis.
Malignant fibrous histiocytoma was diagnosed in one case. The patient presented 2 years following transplantation with motor deficits involving the upper limbs, associated with epileptic fits. CT scan showed brain-space occupying lesions as well as osteolytic lesions in the skull and terminal phalanges. Histopathological examination of the biopsy taken from terminal phalanges confirmed the diagnosis. Reduction of immunosuppression beside irradiation to the lesion was tried with an unsatisfactory response which necessitated withholding immunosuppression. Dialysis

was instituted for 3 months, but the patient died from cardiovascular causes.

Cancer colon was documented in a 50 years old male patient while on triple immunosuppression, 8 years after transplantation. The etiology of his renal failure was gouty nephropathy. He presented with abnormal bowel habits. Right hemicolectomy was carried out in addition to withdrawal of azathioprine. This patient showed a good response to this modality of treatment, but two years later he died from myocardial infarction with a good graft function.

Recurrent nasopharyngeal carcinoma

This tumor recurred 1 year post transplantation and 10 years after cure of the primary tumor in a 30 year old male patient who was on triple immunosuppression. The patient did not give a history of his primary tumor. Recurrence was in the form of a mass eroding the upper cervical vertebra. Deep irradiation to the lesion in addition to immunosuppression modulation had no response, and the patient died with a functioning graft from metastasis.

The overall results of patient and graft outcome of the recipients who developed malignancy are summarized in table 2.

Table 2. Patients and graft outcome in kidney transplant recipients with malignancy

	Good	*Moderate*	*Lost*	*Total*
Living	9	11	4	24
Dead	7	5	14	26
Total	16	16	18	50

Table 3 shows univariate analysis of some risk factors for development of malignancy in kidney transplants. Univariate analysis revealed that recipient age, pre-transplant hypertension, serum creatinine at the time of diagnosis, HLA-A,B-DR mismatches, chronic rejection are independent risk factors for developing cancer after transplantation. However, the clinical grade was the only independent risk factor according to multivariate analysis.

Table 3. Univariate analysis of graft survival in kidney transplant recipients with malignancy

	P
Recipient Age	***0.002***
Recipient sex	0.5
Donor age	0.4
Donor sex	0.1
Consanguinity	0.6
Blood group	0.3
Blood transfusion	0.3
No. of blood transfusions	0.7
Schistosomiasis	0.7
Original kidney disease	0.8
HLA (class I)	0.2
HLA-DR (class II)	0.7
HLA (class I + II) Mismatch	0.05
Pretransplant hypertension	***0.05***
No. of transplant received	0.6
Worm ischemia time	0.8
Time of diuresis	0.7
No. of renal arteries	0.2
1ry immunosuppression	0.3
Total dose steroids (3 months)	0.7
No. of acute rejections	0.3
Mean S. creatinine at time of diagnosis	***0.01***
Urological complications	0.6
Post transplant hypertension	0.1
Chronic rejection	***0.04***
Medical infection post transplant	0.1
Diabetes mellitus post transplant	0.2
Clinical grading	***0.001***
Serum creatinine interval at last follow up	***0.04***

Table 4 gives comparison between patients with malignancy (n=50) and their control group (n=1150). The malignancy group showed a significantly higher serum creatinine level along with a higher I-year cumulative steroid dose. This means that a greater degree of immunosuppression prevailed in the malignant group.

Moreover, 6.7% of the malignancy group experienced no rejection episodes during the first year after transplantation, in comparison to 39% in the control group. Two or more rejection episodes were diagnosed in 93.3% of the malignant group and only 61 % of the control group during the same period. These findings support the hypothesis that severe depression of immunity may suppress the ability to discover and destroy malignant cells induced by various carcinogens. Chronic antigenic stimulation by the foreign antigens of transplanted organs may overcome the partially depressed immune system and lead to malignancy.

Table 4. Comparative analysis of transplant patients with malignancy and control group

	Malignancy (n=50)	*Control* (n=1150)	*P value*
Recipient age (ys)			
M ± SD	36.6±8.6	29.7±10.2	0.008
Range	18-53	5-62	
Donor age (ys)			
M ± SD	33.6±8.9	35.3±10.1	0.24
Range	21-56	21-65	
Recipient sex (M/F)	39/11	853/297	0.7
Pre transplant dialysis duration (months)	8.3±4.8	12.9±8.9	0.1
Pre transplant blood transfusion			
No	11	393	
Third party	38	711	*0.03*
Donor specific	1	6	
Inapplicable	-	39.	
Pre transplant hypertension (Yes/No) consanguinity	22/28	685/465	*0.01*
Parents	11	299	
Siblings	28	560	0.3
Off springs	7	82	
Unrelated	4	208	
Haplotype mismatches			
Identical	2	86	0.5
One mismatch	34	660	
Two mismatch	4	104	
Retransplant	1	42	0.7
Primary Immunosuppression			
Azathioprine + steroid	9	331	
CsA+steroid	16	161	0.1
Triple	24	603	
Frequency of acute rejection			
No	3	474	
One	30	528	*0.02*
Two or more	17	147	
Mean cumulative steroid dose at 1 year(gm)	14.7±7	10.2+6.7	*0.04*
Serum creatinine interval at last follow up			
< 2 mg%	23	739	
2-4mg%	12	131	*0.008*
> 4mg%	2	57	
Chronic rejection (Yes/NO)	22/28	329/764	*0.02*

Figures 1,2 show the actuarial graft and patient survival, respectively, in kidney transplant recipients with malignant (n= 50) and non malignant group (n= 1150).

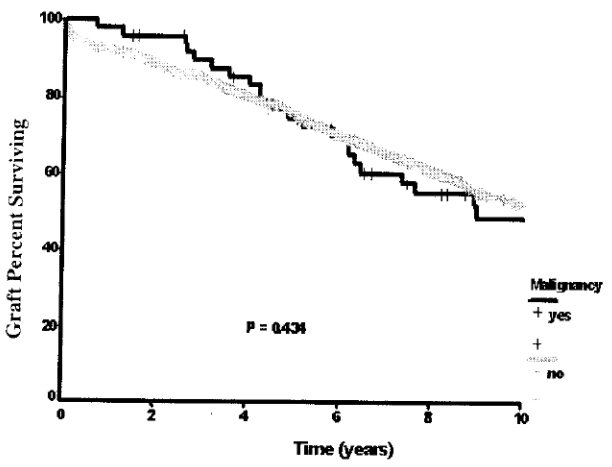

Fig. 1. Graft survival in both groups

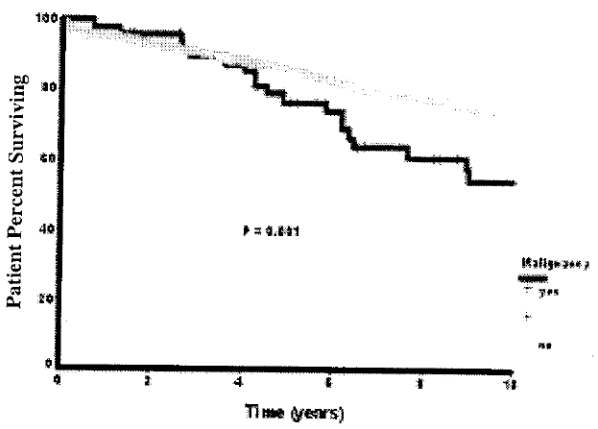

Fig. 2. Patient survival in both groups

Discussion

Recent reports concerning the risk of developing de novo malignancy after kidney transplantation have

increased. However, most of these reports consisted of a heterogeneous population who were subjected to different therapeutic regimens; multiple ethnic and geographical backgrounds [4,5,6,12,13,14].

This is a report on the incidence of malignancies among 1200 Egyptian live donor kidney transplant recipients followed up in our center. Cumulative incidence, clinical presentation, types of malignancies encountered, therapeutic approaches and overall response to treatment modalities are presented.

The overall incidence of malignancy in our kidney transplant population was 3.9%, with a mean latency period between diagnosis and transplantation of 112±53 months. This incidence was only 1.6% at 5 years rising to 3%, and 3.7% at 10 and 20 years, respectively. The overall incidence is lower than what had been reported reported by Penn [7], Schmidt et al. [6], and Yang et al [9], but agree with that of Vogt et al [2] who reported an accumulated data on 7668 types of malignancy that occurred in 7192 organ transplant recipients of different ethnic groups and geographic distribution, giving the average cancer incidence of 6% (range 4%, to 18%). Our lower incidence could be explained by the fact that our patients had a lower mean age at transplantation (29.5±7.6 year) and received live-donor grafts with no induction therapy and lower maintenance immunosuppression than in cadaveric donor transplants.

Our data showed that the overall interval between transplantation and development of malignancy was 78 months for solid tumors and 37 months for Kaposi's sarcoma. Malignancies tended to occur earlier in CsA-treated (62.5±47.6 months) than after azathioprine treated (112.6±35.2 months) (P= < 0.05), this is in agreement with many other reports [17,18,20].

Interestingly, the distribution of different cancer types among our Egyptian kidney transplant recipients was different from that of the nontransplant population and also from those series reported in other centers [4,5,7,9,10,11]. Our data demonstrated that Kaposi's sarcoma (KS) represented nearly one half of malignancies that developed in our posttransplant population.

Kaposi's sarcoma (KS) has been reported to occur with exceptionally higher incidence among Arabs, Jewish or Mediterranean transplant patients [4,18,19]. The magnitude of the increased risk of Kaposi's sarcoma due to transplantation was evaluated in several studies. It ranged from 25 to 400 folds according to ethnic and geographic backgrounds [20]. The tumor is a multicentric vascular neoplasm of

mesenchymal cell in origin and presents in two forms, non visceral lesions (70%) confined to skin or oropharyngeal mucosa and visceral disease (30%) mainly involving the gastrointestinal tract, lungs and lymph nodes. The outcome of patients with non-visceral KS is much better than those with visceral disease [20]. In our series, 10 out of 20 patients with cutaneous KS responded more favorably to therapeutic modalities, while the four patients either with visceral lesions or combined visceral and cutaneous KS showed an unsatisfactory response; all of them died while on dialysis (4-12 months) following the diagnosis.

The incidence of skin and lip cancer other than Kaposi's sarcoma was reported to be 36.9% in malignancies in many reports [7,11], while this was found only in 3.8% in our series, which unexpectedly comprises a very low incidence despite the fact that our patients are exposed to copious sunshine and moreover, they received azathioprine which is metabolized to 6 mercaptopurine and methyl nitro-thio-imidozole, proposed to have strong photo-oxidative activities in the presence of DV light. The incidence of Kaposi's sarcoma and rarity of other skin cancers in our transplant population could be postulated to be due to racial and/or genetic background.

Post transplantation lymphoproliferative disorders (PTLD) is one of the most frequent tumors among graft recipients, comprising 15-25%, compared with 5% in the general population [15]. This may be as a consequence of introduction of CsA in the early 1980 and the very potent new immunosuppressants such as monoclonal antibodies, MMF and FK506 [15]. It is generally accepted that Epstein Barr virus (EBV) infection or reactivation by anti- T lymphocyte regimens may play a role in the pathogenesis of PTLD [17]. In our series, the incidence of PTLD was low (11.5%). Our six patients with PTLD had non Hodgkin's lymphoma with no evidence of previous EBV infection. The low incidence of PTLD in our series may be explained by low immunosuppression regimens used in our live-donor transplant recipients.

Carcinoma of the urinary bladder is the most common solid tumor in men in Egypt and squamous tumor represented the majority of cases as a result of endemic bilharzial cystitis [19]. In our series, bladder cancer developed in 4 male patients, a high incidence which is nearly 4-times that reported in the Cincinnati Tumor Registry (7.7% versus 2.2%, respectively) and 20 times more than that reported by Sheil [22]. A high incidence was also reported by Buzzeo and associates, who calculated that renal transplant recipients have a relative rişk of 3.3 of developing bladder cancer, compared with a similar cohort of the normal population [23]. In addition, Thon et al stated a 15% incidence of transitional cell carcinoma of the renal pelvis, ureter and bladder among 65 patients who had a kidney transplant as a result of analgesic nephropathy [24].

Although carcinoma of the bilharzial bladder is often diagnosed in an advanced stage, the diagnosis was made early in our cases (T 1 s- T2 NoMo) due to the strict follow up regimen adopted for these patients. Cyclosporine was not found to increase the risk of bladder cancer, as 3 out of four patients with cancer bladder were under azathioprine and prednisolone. So, it seems that immunosuppression alone dose not increase the risk of urinary tract cancer after transplantation. However, Schmidt et al [25] found an increased incidence of cancer of the urinary system only in the cyclosporine treated group.

Several reports in the literature suggested that the prevalence of renal cell carcinoma is high in the native kidneys in both hemodialysis and kidney transplant patients [25,26]. Contrary to these reports we could not find any cases with renal carcinoma in our series. This may be explained by the relatively short duration of pre-transplant dialysis in kidney recipients with consequent low incidence of acquired cystic disease in these patients.

Carcinoma of the breast which is commonly encountered in the general population, are not seen more frequently in renal transplant patients [27,28]. However, one report suggested higher incidence of de novo breast carcinoma among transplant populations [27], and higher rate of recurrence in other report [29]. In our report, breast carcinoma was documented in 5 cases (9.6%), four of them were females. Two females were not married, and have a family history of breast carcinoma. Early diagnosis of breast carcinoma in these females had impact on their favorable outcome. Conversely, breast carcinoma in males is known to be advanced at the time of diagnosis with less favorable outcome, which was the case in our patient.

Two patients (4.2%) developed multiple malignancies, one with bladder cancer and the other with breast carcinoma, in addition to cutaneous Kaposi's sarcoma in both. The overall outcome of these patients was worse than others with single tumor. This may be attributed to aggressive reduction of immunosuppression in these patients. Penn [30], and Gutierrez et al [31], described high incidence of multiple tumor in their series 42% and 28%, respectively.

Providing variable therapeutic modalities to our patients, a favorable response was achieved in more than 40% of cases. Good response was mainly encountered in cutaneous Kaposi's sarcoma and female breast carcinoma. The mainstay of treatment of post-transplant Kaposi's sarcoma is reduction or discontinuation of immunosuppressive therapy, and beside this retailoring of the immunosuppression, we found that local injection of bleomycin sulphate and superficial irradiation for any residual lesions is very helpful to avoid over reduction of immunosuppressive medication which may increase the risk of chronic rejection and eventually graft loss.

Unfortunately surgical excision and/or discontinuation of immunosuppressive drugs was not followed by favorable response in most cases with lymphoma or carcinoma of the bladder, but was effective in cases of female breast carcinoma ,cancer prostate and lip carcinoma. Penn [30] reported disappointing results with epithelial neoplasms, but achieved complete remission in 29% of cases with non-Hodgkin's lymphoma, mainly after surgical excision, reduction of immunosuppression, and in some cases with adjuvant chemotherapy and radiotherapy.

In conclusion, malignancy is a growing problem for kidney transplant recipients. With the use of more potent immunosuppressive drugs, and the increasing duration after transplantation, malignancies will be an important cause of patient mortality with functioning graft. The higher incidence rate of these malignancies in transplant recipients requires high standards of preventive measures. Any suspicious lesion that may occur in the course of follow up of transplant patients must be examined thoroughly. Modification of immunosuppressive drugs may help to control post transplant malignancy, especially in cases with Kaposi's sarcoma.

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