Int Urol Nephrol (2009) 41:679–685
DOI 10.1007/s11255-008-9483-z

NEPHROLOGY - ORIGINAL PAPER

Kaposi's sarcoma following living donor kidney transplantation: review of 7,939 recipients

Behzad Einollahi · Mahboob Lessan-Pezeshki · Mohammad Hossein Nourbala · Naser Simforoosh · Vahid Pourfarziani · Eghlim Nemati · Mohsen Nafar · Abbas Basiri · Fatemeh Pour-Reza-Gholi · Ahmad Firoozan · Mohammad Hassan Ghadiani · Khadijeh Makhdoomi · Ali Ghafari · Pedram Ahmadpour · Farshid Oliaei · Mohammad Reza Ardalan · Atieh Makhlogh · Hamid Reza Samimagham · Jalal Azmandian

Received: 9 July 2008 / Accepted: 22 September 2008 / Published online: 14 November 2008

Abstract
Introduction Kaposi's sarcoma (KS) is one of the most common tumors to occur in kidney recipients, especially in the Middle East countries. Limited data with adequate sample size exist about the development of KS in living kidney recipients.
Methods Therefore, we made a plan for a multicenter study, accounting for up to 36% ($n = 7{,}939$) of all kidney transplantation in Iran, to determine the incidence of KS after kidney transplantation between 1984 and 2007.
Results Fifty-five (0.69%) recipients who developed KS after kidney transplantation were retrospectively evaluated with a median follow-up of 24 (1–180) months. KS occurred more often in older age when compared to patients without KS (49 ± 12 vs. 38 ± 15 years, $P = 0.000$). KS was frequently found during the first 2 years after transplantation (72.7%). Skin involvement was universal. Furthermore, overall mortality rate was 18%, and it was higher in patients with visceral involvement compared to those with mucocutaneous lesions ($P = 0.01$). However, KS had no adverse affect on patient and graft survival rates compared to those without KS. Forty-four patients with limited mucocutaneous disease and four with visceral disease responded to withdrawal or reduction of immunosuppression with or without other treatment modalities. Renal function was preserved when

B. Einollahi (✉) · M. H. Nourbala · V. Pourfarziani · E. Nemati · M. H. Ghadiani
Nephrology Research Center, Baqiyatallah University of Medical Sciences, Mollasadra St. Vanak Sq., Tehran, Iran
e-mail: behzad.einollahi@gmail.com; einollahi@bmsu.ac.ir; einollahib@yahoo.com

M. Lessan-Pezeshki
Nephrology Department, Tehran University of Medical Sciences, Tehran, Iran

N. Simforoosh · M. Nafar · A. Basiri · F. Pour-Reza-Gholi · A. Firoozan · P. Ahmadpour
Kidney Transplant Department, Shahid Beheshti University of Medical Sciences, Tehran, Iran

K. Makhdoomi · A. Ghafari
Nephrology Department, Urmia University of Medical Sciences, Urmia, Iran

F. Oliaei
Nephrology Department, Babol University of Medical Sciences, Babol, Iran

M. R. Ardalan
Nephrology Department, Tabriz University of Medical Sciences, Tabriz, Iran

A. Makhlogh
Nephrology Department, Sari University of Medical Sciences, Sari, Iran

H. R. Samimagham
Nephrology Department, Hormozgan University of Medical Sciences, Hormozgan, Iran

J. Azmandian
Nephrology Department, Kerman University of Medical Sciences, Kerman, Iran

immunosuppression was reduced instead of withdrawn in patients with and without visceral involvement ($P = 0.001$ and 0.008, respectively).
Conclusion The high incidence of KS in this large population studied, as compared to that reported in other transplant patient groups, suggests that genetic predisposition may play a pathogenetic role.

Keywords Kaposi's sarcoma · Kidney transplantation · Tumor · Iran

Introduction

Skin cancers are the most common malignancies among kidney transplant patients who receive immunosuppressive agents. Kaposi's sarcoma (KS) is one of the most common tumors to occur in kidney recipients, especially in the countries of the Middle East. Its prevalence in comparison with other cancers is also relatively higher in Iran (>35%) [1]. A literature review showed that the most common post-transplantation malignancy is of skin origin, predominating with squamous cell carcinoma (SCC) [2, 3]. Penn reported higher incidence of KS in certain racial groups, such as Arabs, Italians, Jews, Greeks, and blacks [4]. The prevalence of KS following kidney transplantation varies significantly in different geographic areas [5], supporting the theory of ethnic or environmental factors in its pathogenesis.

Although Iran has the largest reported experience of kidney transplantation among the Middle East countries [6], there are limited data available on cancers in living kidney recipients. There have also been no reports on the incidence of malignancy from the transplant registry in Iran. It is difficult to accurately determine the incidence of most tumors and to compare their rates of occurrence with those in the general population using data from single-center studies [7–10]. Although information on cancers after renal transplants remains limited, some studies have suggested a pattern of tumor development different from that in Western countries; Kaposi's sarcoma is the most common malignancy following kidney transplantation in Iran [7, 9]. Thus, we made a plan for a larger and multicenter study with adequate sample size to determine the incidence of KS development in Iranian renal transplant recipients. In the current study, we collected data from eight kidney transplant centers, accounting for up to 36% of all kidney transplantation in Iran between 1984 and 2007, to detect the incidence and to determine the impact of demographic factors, immunosuppression, treatment options, and outcome of KS after kidney transplantation.

Materials and methods

We conducted a retrospective analysis to identify all cases of Kaposi's sarcoma complicating kidney transplantation at eight centers. A total of 7,939 patients (36.8% female and 63.2% male) who received a kidney between October 1984 and February 2007 was surveyed for the development of KS. Because virtually all the patients who received a kidney allograft at our centers were observed as outpatients within 12 months of transplantation and at least every 2–3 months thereafter, we believe that the observed incidence of Kaposi's sarcoma was not underestimated. The median follow-up period since KS diagnosis was 24 (1–180) months. Figure 1 shows the year of onset of disease.

The time between kidney transplantation and KS onset was defined as the period between the graft and the first signs of Kaposi's sarcoma. All KS specimens were confirmed by histologic examination. Formalin-

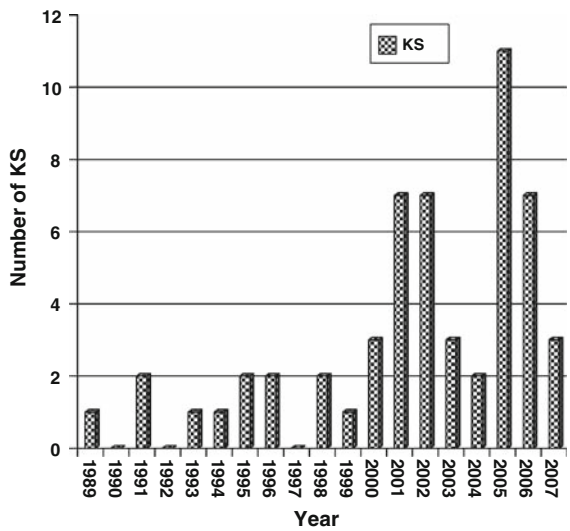

Fig. 1 Onset year of Kaposi's sarcoma

fixed and paraffin-embedded tissue sections were processed and stained with hematoxylin and eosin (H & E), periodic acid Schiff, and trichrome by routine clinical methods.

The variables studied were patient age, gender, donor source, immunosuppressive regimen before and after diagnosis of KS, post-transplant latency period, simultaneous neoplastic or infectious problems, cytomegalovirus (CMV) serology, treatment received, progression of KS in individual patients, serum creatinine level at the time of diagnosis and follow-up visits, rejection episodes, the clinical presentation of KS, follow-up, and outcome.

All KS cases were seropositive for CMV. Pretransplantation CMV serologic status was documented in their donors (100%), of whom 8% were seronegative and 92% were seropositive at transplantation. Pretransplantation hepatitis C serologic status was documented in all patients. All the tested patients were seronegative at transplantation. None of the patients was HIV-positive.

At KS diagnosis, immunosuppressive regimens consisted of various combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil (MMF), and anti-thymocyte/lymphocyte globulin (ATG/ALG). Before 2000, patients received dual maintenance immunosuppression with prednisone and azathioprine or triple therapy with cyclosporine, prednisone, and azathioprine. After 2000, the majority of patients received cyclosporine, prednisone, and MMF as well. Rejection episodes not responding to steroid pulse therapy were treated with ATG/ALG in the majority. ATG/ALG was used for induction in highly sensitized patients, those receiving kidneys from deceased donors, patients with poorly matching living donors, and patients with the second or more transplants. None of the patients received OKT3. Of the 55 recipients who developed KS, 9 received ATG/ALG. All patients who had taken ATG/ALG received prophylactic antiviral therapy, ganciclovir, for a minimum of 1 month after transplantation.

A rather uniform approach to the management of tumor was used. On diagnosis of the KS, the first step in the majority of patients was promptly to reduce or withdraw cyclosporine and to reduce azathioprine/MMF. In the case of progression of the lesions, azathioprine/MMF was also stopped. Changing cyclosporine to sirolimus in association with the reduction or withdrawal of other immunosuppressives was successfully done in three recipients. Besides surgical excisions of the lesions, chemotherapy and/or radiotherapy was performed according to the clinical picture. Outcome was assessed by response to therapy, remission duration, and survival. Thirty-four patients had a complete remission, and 15 had a partial remission of lesions that responded to chemotherapy or radiotherapy. The six patients with generalized KS died in spite of the above-mentioned therapeutic interventions.

Statistics

Data were analyzed using the Statistical Packages for Social Sciences (SPSS) version 13.0 for Windows. Categorical data and continuous variables were reviewed using relative frequency and mean values $\pm$ standard deviation, respectively. Continuous data of the two groups, with or with no KS, were compared by Student's *t*-test and non-parametric data by Mann–Whitney *U* test. Categorical data were analyzed using the chi-square or Fisher's exact test. The Spearman's rank correlation coefficient was used to evaluate the strength of association between two continuous variables. KS-free patient and graft survival rates were defined as the time from diagnosis of the KS to death and graft loss, respectively. We also compared overall patient and graft survival rates of recipients who had KS with 3,014 kidney transplants of two centers who had no patients with KS. Overall survival was calculated using the Kaplan–Meier method, and comparisons were made with log-rank analysis. Statistical significance was defined as a probability value less than 0.05.

Results

Fifty-five (0.69%) recipients who developed KS after kidney transplantation were retrospectively evaluated with a median follow-up of 24 (1–180) months, representing 34% of all post-transplant malignancies (55 out of 162 cases). In addition, one patient had post-transplant proliferative disorders (PTLD), and another had renal cell carcinoma as well. The demographic characteristics of the patients who had

Table 1 Characteristics of kidney transplant recipients with Kaposi's sarcoma

Characteristic	Value
Recipient age at the time of diagnosis, years	
Mean ± SD (range), median	50 ± 11 (21–71), 52
Recipient gender (male/female), *n*	33/22
Time from transplantation to diagnosis, months	
Mean ± SD (range), median	27 ± 33 (2–143), 12
Mean follow-up after diagnosis, months	
Mean ± SD (range), median	34 ± 35 (1–180), 24
Donor source, *n*	
Living unrelated/living related/deceased	46/8/1
Episodes of acute rejection	4
Treatment modalities, *n*	
Withdrawal of IS/reduction of IS/change to sirolimus/ chemotherapy/radiotherapy/ surgical excision of the lesions/died before treatment	19/30/3/11/4/5/2
Response to treatment, *n*	
Yes/no	48/7
Renal allograft outcome, *n*	
Good/lost	46/9
Patient outcome, *n* (%)	
6-month mortality/overall mortality	6 (11%)/10 (18%)
KS-free survival, Kaplan–Meier (%)	
Patient survival (1 and 5 years)	89, 66
Graft survival (1 and 5 years)	83, 55
Distribution of lesions, *n*	
Cutaneous or mucocutaneous/ visceral	48/7

SD Standard deviation, *n* number

KS are summarized in Table 1. Furthermore, the incidences of other skin cancers were lower than KS: SCC 17 (0.21%), BCC 9 (0.11%), and melanoma 2 (0.02%). Male recipients had more tumors than female recipients; the male-to-female ratio in the affected patients was 1.5:1, although this difference was not statistically significant between the KS and non-KS groups ($P = 0.6$).

The donor source in only one case was deceased; the majority of patients received living donor kidneys, 8 from living related donors (LRD) and 46 from living unrelated donors (LURD). There were no

Table 2 Statistical data analysis in kidney recipients with and without Kaposi's sarcoma

	KS group ($n = 55$)	Non-KS group ($n = 7{,}884$)	*P* value
Age in years at transplantation, years			
Mean ± SD	48 ± 12	37 ± 15	0.000
Gender (male/female), *n*	33/22	4,980/2904	0.6
Donor source (%)			
LRD/LURD/ deceased	14.6/83.6/ 1.8	9.7/87.9/2.4	0.4
MMF/AZA-based immunosuppressive regimen, *n*	33/22	5,222/2663	0.4
Age categories, *n*			
20–59 years	46	6,624	0.02
≥60 years	9	588	

KS Kaposi's sarcoma, *n* number, *SD* standard deviation, *LRD* living related donor, *LURD* living unrelated donor, *MMF* mycophenolate mofetil, *AZA* azathioprine

statistically significant differences among the two groups in terms of donor sources ($P = 0.4$) (Table 2). The higher occurrence of KS in renal transplant recipients reached statistical significance considering the age at transplantation; i.e., KS occurred more frequently in patients with older age when compared to recipients without KS (49 ± 12 vs. 38 ± 15 years, $P = 0.000$) (Table 2). The clinical presentation of KS was demonstrated more frequently in the first 2 years after transplantation (72.7%); this means that the time interval between transplantation and onset of KS was relatively early as compared to other tumors, with a median period of 12 months. Four of the treated patients experienced acute rejection after withdrawal of immunosuppressive treatment. Withdrawal of immunosuppression in patients with and without visceral involvement was associated with more graft loss when compared to reduction of immunosuppressive therapy ($P = 0.001$ and 0.008, respectively).

Skin involvement was universal, and the legs were affected twice as commonly as the arms (17 vs. 9). Furthermore, the overall mortality rate was higher in patients with visceral involvement compared to those who had mucocutaneous lesions ($P = 0.01$). The main cause of mortality was sepsis. Thirty-nine patients are alive with a functioning graft, and six are alive while on dialysis. Patient and graft survival rates from the time of KS onset had no significant

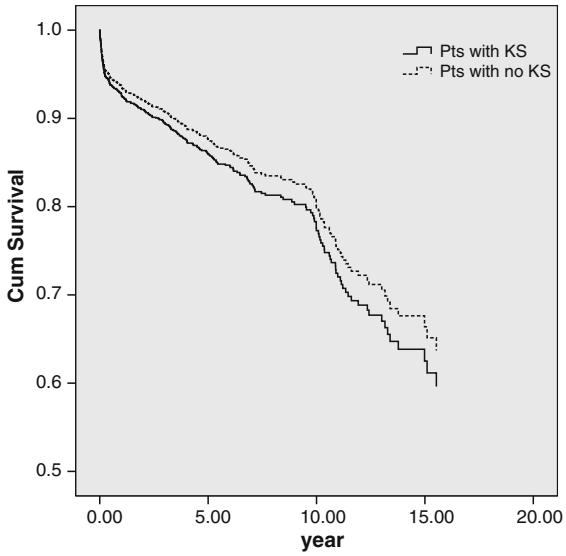

Fig. 2 Patient survival in recipients with and without KS. Pts, Patients; KS, Kaposi's sarcoma

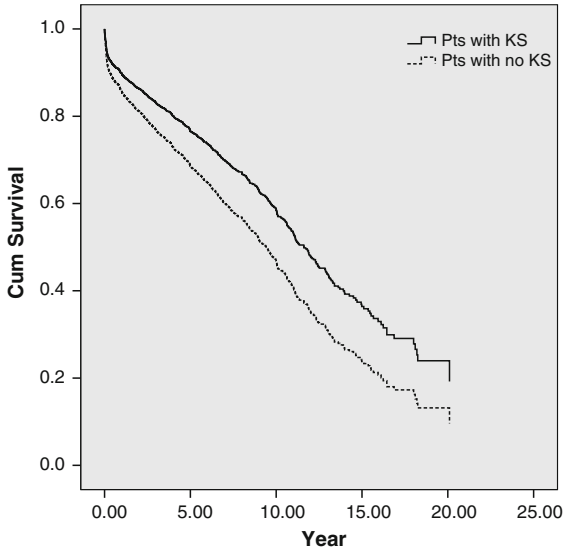

Fig. 3 Graft survival in recipients with and without KS. Pts, Patients; KS, Kaposi's sarcoma

differences in terms of the age, gender, and time presentation since transplantation in all recipients ($P = 0.8$, 0.5, and 0.9 and $P = 0.5$, 0.8, and 0.7, respectively). Figures 2 and 3 show no significant differences in patient and graft survival rates between recipients with and without KS ($P = 0.6$ and 0.1, respectively). CMV infection was found only in two patients who had KS. There was no relationship between developing KS and CMV serologic status before transplantation.

Twenty-nine patients were diagnosed with early onset (before the 1st year), 19 with late onset (1–5 years), and 7 with very late onset (>5 years). The relation between outcome and these groups was not significant.

Forty-four patients with limited skin and/or mucosal disease and four with visceral disease responded to withdrawal or reduction of immunosuppression with or without other treatment modalities. Renal function was preserved when immunosuppression was reduced instead of withdrawn in patients with and without visceral involvement ($P = 0.001$ and 0.008, respectively).

Discussion

The incidence of KS in kidney recipients has steadily increased following an enormous increase in the number of kidney transplantations during the recent decades, particularly of those of Mediterranean descent [11]. KS is most often seen in transplant recipients of Mediterranean, Jewish, Arabic, Caribbean, or African descent; the reported incidence ranges from 0.5% in most Western countries (including the United States) up to 5.3% in Saudi Arabia [11]. Since in our institution an assay for HHV8 serology was not available during the study, we could not examine the relationship between KS occurrence and HHV8 seropositivity reported from Saudi Arabia [12]. In comparison with other malignancies, KS was relatively more prevalent in our study (34% of all tumors). In the previous reports, KS was consistently the most common malignancy after kidney transplantation [1]. In developed countries, the risk of KS is increased [13], accounting for up to 10% of all post-transplant cancers [14, 15]. In the current study, KS was equally common in males and females once correction was made for the differential transplant rates. The male–female ratio of post-transplant KS reportedly ranges between 3:1 and 1.5:1 [16, 17]. In all other forms of KS, the disease is much more common in men [1]. Post-transplant KS, like the epidemic form, tends to occur in younger patients and is less strongly correlated with the onset of the disease than with the duration of immunosuppression [18]. KS after kidney transplantation usually appears

early (a mean interval of 13 months from surgery); its onset has been documented as late as 18 years afterwards, though [11]. Furthermore, the mean age of our patients at onset was 50 years, which was younger than that among patients with classic KS. On the other hand, the mean age of patients with KS was higher than those who had no disease. Ninety percent of transplant recipients with KS have cutaneous lesions, mucosal lesions, or both [11], like the current results. In the present study, visceral disease predominantly affected the lungs, followed by the gastrointestinal tract and lymph nodes, but extracutaneous involvement most commonly involved lymph nodes rather than the intestines and lungs in other reports [11]. In addition, like our results, the legs were affected twice as often as the arms [19]. In post-transplant KS, the course of skin disease was generally benign; mortality at 6 months after diagnosis was only observed in six cases.

Based on our policy, reduction of immunosuppression has remained the mainstay of treatment of post-transplant KS. In a report, patients were managed with the reduction of immunosuppression for a minimum of 1 month only before other forms of therapy were introduced [20]. In our study, reduction of immunosuppression in patients with limited disease resulted in remission in all cases; in addition, kidney allograft function remained preserved. This suggests that withdrawal of immunosuppression is unnecessary as the primary therapeutic choice in patients with the disease limited to the skin. Although KS usually regresses after cessation or reduction of immunosuppression, this manipulation in kidney transplants leads to the loss of the graft in approximately half of patients [21]. In our study, reduction or discontinuation of immunosuppressive agents following the diagnosis of KS caused complete remission of this cancer in most patients, which resulted in graft loss in seven (13%) cases. Therefore, withdrawal or reduction of immunosuppression seemed to be relatively safe for kidney allograft function. Furthermore, we have previously reported the same results [22]. In other reports, varying degrees of success have been achieved, but recipients with visceral KS universally have a poor prognosis [20]. Furthermore, the overall mortality rate was higher in our patients with visceral involvement compared to those who had mucocutaneous lesions ($P = 0.01$). We have suggested a management algorithm based on progressive reduction and eventual withdrawal of immunosuppressive drugs. However, the current recommendation for treatment of the visceral involvement is withdrawal of immunosuppression [23].

The incidence of KS has increased since the year 2000 (65% of all KS) when MMF was introduced to the majority of kidney transplant patients, and it is not clear whether the introduction of MMF contributes to the phenomenon. However, we found no correlation between KS and receiving MMF-based immunosuppression (Table 2).

Patients who received grafts from deceased donors consisted of a small number of all our recipients (2.4%); thus, this study deals with a multicenter nationwide experience with kidney recipients from living donors. Moreover, to the best of our knowledge, the current study shows the largest living donor kidney transplant population that assesses KS up until now.

Conclusion

The high incidence of KS in this large population studied, as compared to that reported in other transplant patient groups, suggests that genetic predisposition may play a pathogenetic role. However, immunosuppression is the leading factor in kidney transplant recipients. Reduction or withdrawal of immunosuppression caused complete remission in most patients with or without surgical intervention, chemotherapy, or radiotherapy.

References

1. Einollahi B (2007) Kaposi sarcoma after kidney transplantation. IJKD 1:2–11
2. Chiang YJ, Chen CH, Wu CT et al (2004) De Novo cancer occurrence after renal transplantation: a medical center experience in Taiwan. Transplant Proc 36:2150–2215. doi: 10.1016/j.transproceed.2004.08.013
3. Kasiske BL, Vazquez MA, Harmon WE et al (2000) Recommendation for the outpatient surveillance of renal transplant recipients. J Am Soc Nephrol 11:S1–S86
4. Penn I (1995) Sarcomas in organ allograft recipients. Transplantation 60:1485–1491
5. Frances C (1998) Kaposi's sarcoma after renal transplantation. Nephrol Dial Transplant 13:2768–2773. doi: 10.1093/ndt/13.11.2768

6. Einollahi B, Taheri S (2008) Renal transplantation practice in Iran and the Middle East: report from Iran and a review of the literature. Ann Transplant 13:5–14
7. Nafar M, Einollahi B, Hemati K, Poor Reza Gholi F, Firouzan A (2005) Development of malignancy following living donor kidney transplantation. Transplant Proc 37:3065–3067. doi:10.1016/j.transproceed.2005.08.011
8. Shahbazian H (2004) Kaposi sarcoma in kidney transplanted patients. Urol J 1:111–114
9. Einollahi B, Nourbala MH, Lessan-Pezeshki M et al (2001) Incidence of postrenal transplantation malignancies: a report of two centers in Tehran, Iran. Transplant Proc 33:2812–2813. doi:10.1016/S0041-1345(01)02199-6
10. Lessan-Pezeshki M, Einollahi B, Khatami MR, Mahdavi M (2001) Kidney transplantation and Kaposi's sarcoma: review of 2052 recipients. Transplant Proc 33:2818−2819. doi:10.1016/S0041-1345(01)02203-5
11. Euvrard S, Kanitakis J, Claudy A (2003) Skin cancers after organ transplantation. N Engl J Med 348:1681–1691. doi:10.1056/NEJMra022137
12. Qunibi WY, Barri Y, Alfurayh O, Almeshari K, Khan B, Taher S, Sheth K (1993) Kaposi's sarcoma in renal transplant recipients: a report on 26 cases from a single institution. Transplant Proc 25:1402–1405
13. Harwood AR, Osoba D, Hofstader SL et al (1979) Kaposi's sarcoma in recipients of renal transplants. Am J Med 67:759–765. doi:10.1016/0002-9343(79)90731-9
14. Penn I (1986) The occurrence of malignant tumors in immunosuppressed states. Prog Allergy 37:259–300
15. Montagnino G, Bencini PL, Tarantino A, Caputo R, Ponticelli C (1994) Clinical features and course of Kaposi's sarcoma in kidney transplant patients: report of 13 cases. Am J Nephrol 14:121–126
16. Qunibi W, Akhtar M, Sheth K et al (1988) Kaposi's sarcoma: the most common tumor after renal transplantation in Saudi Arabia. Am J Med 84:225–232. doi:10.1016/0002-9343(88)90418-4
17. Szende B, Toth A, Perner F, Nagy K, Takacs K (1997) Clinicopathologic aspects of 8 Kaposi's sarcomas among 1009 renal transplant patients. Gen Diagn Pathol 143:209–213
18. Penn I (1979) Kaposi's sarcoma in organ transplant recipients: report of 20 cases. Transplantation 27:8–11
19. Gotti E, Remuzzi G (1997) Post-transplant Kaposi's sarcoma. J Am Soc Nephrol 8:130–137
20. Shepherd FA, Maher E, Cardella C, Cole E, Greig P, Wade JA et al (1997) Treatment of Kaposi's sarcoma after solid organ transplantation. J Clin Oncol 15:2371–2377
21. Antman K, Chang Y (2000) Kaposi's sarcoma. N Engl J Med 342:1027–1038. doi:10.1056/NEJM200004063421407
22. Firoozan A, Hosseini Moghaddam SM, Einollahi B et al (2005) Outcome of Kaposi's sarcoma and graft following discontinuation of immunosuppressive drugs in renal transplant recipients. Transplant Proc 37:3061–3064. doi:10.1016/j.transproceed.2005.07.042
23. al-Sulaiman MH, al-Khader AA (1994) Kaposi's sarcoma in renal transplant recipients. Transplant Sci 4:46–60