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Trends in Kaposi's Sarcoma Morbidity: A Retrospective Cohort Study of Heart and Lung Transplant Recipients

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Data on post-transplant Kaposi's sarcoma in heart and lung transplant recipients are sparse. This study examined the incidence of biopsy-proven post-transplant Kaposi's sarcoma in thoracic organ recipients over a period of 20 years. As mammalian target of rapamycin inhibitors were introduced in 2006 as optional maintenance immunosuppressive therapy, the overall results were analysed and stratified into 2 groups: 1996 to 2005 and 2006 to 2016. A total of 867 transplant recipients met the study criteria. Post-transplant Kaposi's sarcoma was diagnosed in 7 (0.81%) patients. Five cases (0.19% of transplant recipients) were recorded in 1996 to 2005 and 2 (0.03% of transplant recipients) in 2006 to 2016 ($p = 0.04$). Multivariable logistic regression analyses identified the following as risk factors: period of transplantation (odds ratio (OR) 4.844, 95% confidence interval (95% CI) 1.156–20.291), age at transplantation (OR 1.066, 95% CI 0.992–1.145), and North African origin (OR 7.282, 95% CI 12.55–42.254). This study found a decreased incidence of post-transplant Kaposi's sarcoma over the last 20 years, mainly attributed to the change in immunosuppressive therapy.

SIGNIFICANCE

Post-transplant Kaposi's sarcoma was a common cancer in heart and lung transplant recipients; however, recent data on the epidemiology of the disease are sparse. The present study of 867 heart and lung transplant recipients demonstrates a trend of a decrease in the incidence of the disease over the last 20 years. This change can be attributed mainly to the amount and quality of immunotherapy. Other associated risk factors were: early period of transplantation, older age at transplantation, and North African origin. Hence, immunosuppressive therapy with mammalian target of rapamycin inhibitors is warranted in this population, especially those who meet the high-risk criteria.

Four distinct epidemiological forms of KS have been described, all related to infection with HHV-8 (1, 4–6). Iatrogenic or post-transplant Kaposi's sarcoma (PT-KS) is similar to AIDS-related KS in terms of clinical manifestations and tendency for regression on reduction of immunosuppression. KS was the most common tumour found after solid organ transplantation in areas where HHV-8 is endemic, and most cases occurred in individuals of Mediterranean, Jewish, Arabic, Caribbean, or African descent (7, 8).

The introduction of highly effective immunosuppressive therapy in the 1980s reduced the incidence of acute organ rejection in transplant recipients. At the same time, however, it increased the risk of infections and cancer (9). An early study from the 1990s showed that solid organ transplant recipients had an 84-fold increased risk of KS compared with the general population (10). The disease regressed with the cessation, reduction, or modification of the immunosuppressive therapy in most patients (11).

In recent studies, there has been a decrease in the incidence of KS among solid organ transplant recipients (12), owing mainly to the reduction in immunosuppression and the introduction of mechanistic target of mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus (12, 13). mTOR inhibitors interfere with interleukin-2-mediated signal transduction by blocking cytokines that induce T- and B-cell activation, conferring them with anti-proliferative, anti-angiogenic, and potentially anti-viral qualities (14). A study of kidney transplant recipients found that mTOR inhibitors not only exerted an anti-rejection effect on organ allografts, they also prevented the progression of KS (13). However, data

Kaposi's sarcoma (KS) was first described in 1872 by the dermatologist Moritz Kaposi as an unusual skin tumour localized to the lower extremities, affecting elderly Mediterranean or Ashkenazi Jewish men (1). The disease remained obscure until the early 1980s when reports began to emerge of unusually aggressive cases of KS and other opportunistic infections associated with immunosuppression in homosexual men (2). Epidemiological studies suggested a link between the increased appearance of KS and a transmissible agent, heralding the discovery of acquired immune deficiency syndrome (AIDS) and the human immunodeficiency virus (HIV). In 1994, researchers identified a novel gamma herpesvirus in biopsies from patients with AIDS, which was subsequently named human herpesvirus 8 (HHV-8) or KS-associated herpesvirus (3).

on PT-KS in the rapidly growing population of heart and lung transplant recipients remain sparse.

The aims of the present study were to examine the incidence of KS in heart and lung transplant recipients in Israel over the past 20 years; to investigate possible factors associated with morbidity trends; and to characterize the biological behaviour of the disease.

MATERIALS AND METHODS

Study participants and setting methods

A retrospective cohort study design was used. The centralized manual and electronic medical record databases of Rabin Medical Center were reviewed for all patients attending its specialized dermatology clinic for organ transplant recipients between 1 January 1996 and 31 December 2016. Patients with a biopsy-proven diagnosis of KS were identified.

Rabin Medical Center, a major tertiary hospital in central Israel, has the largest transplantation unit and follow-up centre for solid organ transplant recipients, accounting for 50% of all heart and 100% of lung transplants in the country.

Demographic and clinical data were collected, and a dataset was established as follows: whole cohort (patient date of birth, sex, and birth place, type of transplanted organ, and date of transplantation); patients with KS (date of KS diagnosis in months after transplantation, induction and maintenance therapies, lesion distribution, extra-cutaneous manifestations, treatment, and outcome). Patients aged ≤18 years were excluded from the study, as were patients who were diagnosed with KS before transplantation or were HIV-positive and patients with an undetermined histological diagnosis or insufficient demographic or clinical information.

In Israel, mTOR inhibitors were introduced in 2006 as optional maintenance immunosuppressive therapy for heart and lung transplant recipients. Therefore, for the purpose of the current study, the incidence of PT-KS and the clinical, epidemiological, and demographic characteristics of the transplant recipients were analysed overall and between 2 time-periods: 1996 to 2005 and 2006 to 2016. There was no change in the induction regimens used for lung and heart transplants during the 20 years of the study.

In addition, to examine the morbidity trends of KS, all cases of biopsy-proven KS recorded in the Israel National Cancer Registry for the same time-period were identified.

The main outcome measures of the study were the incidence of KS in the study population and associated risk factors. In addition, the biologic characteristics of KS in heart and lung transplant recipients were evaluated.

In order to assess the trend of classical KS in the general population of Israel in the corresponding period the study data were derived from the Israel National Cancer Registry (INCR).

Statistical analysis

Continuous variables are presented as means and standard deviations, and categorical variables as numbers and percentages. Continuous variables were analysed by independent-samples t-tests, and categorical variables, by Wald χ^2 and Fisher's tests. The impact of PT-KS status on 20-year survival within the heart and lung transplant population was examined by time-to-event variables using Kaplan–Meier survival analysis. Univariate and multivariable logistic regression analyses were used to identify the association between outcome (KS) and each of the explanatory (independent) variables and to detect potential confounders. Analyses were adjusted for clinically relevant factors previously reported in the literature to be associated with transplant status and PT-KS, including sex, type of transplanted organ, age at transplan-

tation, and period of transplantation. Adjusted multivariable binary logistic regression analysis was used to examine the odds ratios (OR) and 95% confidence intervals (95% CI) of transplantation status for the development of PT-KS. The crude incidence rates of KS were compared between post-transplant patients and the general population. The age-adjusted PT-KS incidence rate was calculated separately for the 2 time-periods. Two-sided p-values <0.05 were considered statistically significant. Data analysis was performed with SAS Enterprise 9.4 software (SAS Institute Inc., Cary, NC, USA).

The study protocol was conducted in accordance with the provisions of the Declaration of Helsinki and approved by the local Institutional Ethics Committee (approval number 0482-13-RMC).

RESULTS

The study identified 867 patients who underwent heart ($n=225$, 25.9%) or lung ($n=642$, 74.1%) transplantation between 1996 and 2016. The majority of recipients were men ($n=578$, 66.6%). Mean age at transplantation was 54.7 ± 13.8 years. Evaluation of countries of origin yielded 475 patients (54.8%) born in Israel, 171 (19.7%) in Europe/America, 121 (14%) in North Africa, and 97 (11.2%) in Asia; data were missing for 3 patients.

PT-KS was diagnosed in 7 patients (0.8%): 3 of the 225 heart transplant recipients (1.3%) and 4 of the 642 lung transplant recipients (0.6%). They included 6 men (85.7%) and 1 woman; mean age 62.3 ± 4.7 years at transplantation (compared with 54.7 ± 13.8 years for the transplant recipients without PT-KS), and 63.7 ± 5.1 years of age at the diagnosis of KS (range 58–70 years). The median time from transplantation to diagnosis of KS was 6.8 months. Five patients (71.4%) were born in North-Africa and one each (14.3%) were born in Israel and Europe/America.

Division by time revealed that 268 of the heart and lung transplants (30.9%) were performed from 1996 to 2005, before mTOR inhibitors treatment was introduced, and 599 (69.1%) were performed from 2006 to 2016. PT-KS was reported in 5 patients in the first period (71.4%; 0.19% of transplants) and 2 in the second period (28.6%; 0.03% of transplants); this difference was statistically significant ($p=0.032$). The corresponding mean age at transplantation of these subgroups was 52.7 ± 14 and 55.7 ± 13.6 years ($p=0.56$), and at diagnosis of PT-KS, 63.8 ± 5.4 and 63.5 ± 6.4 years ($p=0.6$). **Table I** shows the PT-KS incidence rates by type of transplant, overall and by study period. The difference between the periods for both heart and lung transplants was statistically significant ($p=0.02$).

Table II shows the demographic and clinical data of the patients with PT-KS, separately for heart and lung transplant recipients in the first period, and for lung transplant recipients in the second period. On univariate analysis to identify possible predictive factors of the occurrence of PT-KS, findings were significant for period of transplantation ($p=0.032$), age at transplantation ($p=0.011$), and country of origin ($p=0.004$), but not sex or transplanted organ. The odds ratio of acquiring PT-

Table I. Incidence rates of post-transplant Kaposi's sarcoma (KS) among heart and lung transplant recipients

Factors	Cases *n*	Incidence rate/100,000	Age-adjusted incidence rate/100,000	*p*-value
KS among both lung and heart transplant recipients				
Overall	7	807.4	548.6	
1996–2005	5	1,865.7	1,318.8	0.02*
2006–2016	2	333.9	269.9	
KS among lung transplant recipients				
Overall	4	623.1	431.3	
Female	1	408.2	231.1	0.59
Male	3	755.7	572.2	
1996–2005	2	1,351.4	844.6	0.2
2006–2016	2	404.9	326.8	
KS among heart transplant recipients				
Overall	3	1,333.3	919.6	
Female	0	0	0	0.39
Male	3	1,657.5	1,153.8	
1996–2005	3	2,500	1,965.1	0.1
2006–2016	0	0	0	

*p < 0.05.

KS was higher by 4.9 in the first period than the second period (*p* = 0.036), and the risk increased by 6% for each year of age (borderline significance).

Table III shows the results of the univariate and multivariable logistic regression analyses, controlling for transplantation period, age at transplantation, and birth place.

According to the Israel National Cancer Registry, 3,205 patients were diagnosed with KS between 1990 and 2014, of whom 2,219 (69.2%) were men. Countries of origin were divided as follows: Africa 899 patients (28.1%), Asia 554 (17.3%), Europe/America 1,305 (40.7%), and Israel 302 (9.4%). The median age at diagnosis was 74 years, with a mean of 71.8 years, which was approximately 8 years older than the mean age at diagnosis of the patients with PT-KS in the present study (*p* = 0.016). The earliest case was diagnosed at age 17 years and the latest at age 103 years. **Fig. 1** is a graphic representation of the incidence of KS in the general population in Israel from 1990 to 2014.

Table III. Odds ratio analysis for period of transplantation, age at transplantation, and birth place

Effect	Point estimate	95% CI	
Period: 1996–2005 vs 2006–2016	4.844	1.156	20.291
Age at transplantation	1.066	0.992	1.145
Birth place: Africa vs Israel	7.282	1.255	42.254
Birth place: Asia vs Israel	0.726	0.032	16.398
Birth place: Europe/Americas vs Israel	1.607	0.178	14.484

95% CI: 95% confidential interval.

DISCUSSION

The epidemiology of PT-KS is particularly interesting, given the well-established link between KS and immunosuppression (6), and the high immunosuppressive regimen thoracic organ transplant recipients receive relative to liver and kidney transplant recipients. Furthermore, as the prevalence of HHV-8 is fairly high in the Israeli population (15), we would expect thoracic transplant recipients in Israel to have a particularly high PT-KS rate. However, there were only 7 cases of PT-KS among 867 patients over the 20-year period (0.81%). Moreover, in another study from Rabin Medical Center on PT-KS in kidney and liver transplant recipients from 1990 to 2014, Sorin et al. (unpublished data) found higher rates of PT-KS; 23 cases in 2006 patients (1.1%). Surprisingly, it was previously observed that PT-KS was more common in kidney recipients, with a much smaller incidence in recipients of other solid organs, i.e. mainly hearts and livers (6). To date, no satisfactory mechanistic explanation for this phenomenon has been found.

Data in the literature on PT-KS among thoracic organ transplant is extremely scarce. **Table IV** summarizes the incidence rates in earlier studies (16–18).

Univariate and multivariable logistic regression analyses identified the transplantation period as 1 of the 3 major risk factors for PT-KS. Specifically, the odds of acquiring KS were higher by 4.9 in patients operated in 1996 to 2005 than in patients operated in 2006 to 2016. As the major difference between these periods was the

Table II. Clinical and demographic parameters of the cohort of transplant recipients with post-transplant Kaposi's sarcoma

Patient	Age at diagnosis, years/sex	Place of birth	Induction	Maintenance	Months after transplant	Lesion distribution	Extra-cutaneous	Treatment and outcome
A. Heart transplant recipients between 1996 and 2005								
1	60/M	Africa – Algeria	ATG	CsA+AZA	1	Lower limb	None	Partial regression with radiation
2	71/M	Africa	ATG	CsA	3	Rt lower leg	None	None
3	61/M	Europe/America – Former USSR	ATG	Tac+MMF	5	Lt lower leg & inner thigh	None	Partial regression with radiation
B. Lung transplant recipients between 1996 and 2005								
1	68/M	Africa – Morocco	AZA+methyl-prednisolone	AZA+CsA+ prednisone	96	Lower limb	None	Regression following switch from Tac to sirolimus
2	59/M	Africa – Tunisia	AZA+methyl-prednisolone	AZA+CsA+ prednisone	23	Lower & upper limb	None	Partial regression with radiotherapy
C. Lung transplant recipients between 2006 and 2016								
1	59/M	Israel	MMF+methyl-prednisolone	MMF+Tac	9	None	Lymph nodes	Succumbed shortly after switching from Tac to Sirolimus
2	68/F	Africa – Tunisia	MMF+methyl-prednisolone	MMF+Tac	7	Lt lower leg	None	Full regression with everolimus

ATG: anti-thymocyte globulin; AZA: azathioprine; CsA: cyclosporine A; Lt: left; MMF: mycophenolate mofetil; Rt: right; Tac: tacrolimus.
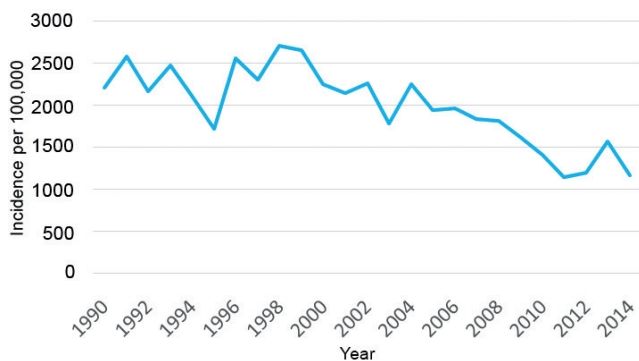
Fig. 1. Incidence of Kaposi's sarcoma in the general population in Israel 1990–2014.

inclusion of mTOR inhibitors in the postoperative immunosuppression regimen of heart transplant recipients, we attribute the lowered risk of KS in the second period at least partly to this factor.

The effect of the regimen change is supported by comparing the incidence rate between the heart and lung transplant recipients. In the second period, after mTOR inhibitors were introduced, there were no new cases of PT-KS among the heart transplant recipients.

There were also changes in the treatment of lung transplant recipients over the study period, but they occurred gradually and not systematically. In particular, azathioprine, a purine analogue and anti-metabolite, and cyclosporine A, an inhibitor of T cell activation (19), are both associated with a high risk of skin cancer (20, 21), and were eventually replaced by more advanced agents, such as mycophenolate mofetil and tacrolimus. The significant reduction in the incidence of PT-KS in the lung transplant recipients in the second period is in line with the current "less is better" approach to immunosuppression (i.e. dosage reduction and more individualized immunosuppressive treatment). However, no specific induction or maintenance medications were significantly associated with KS risk (18, 22).

Induction therapies in heart transplants included antithymocyte globulin, has similar adverse effects on the T-cell population to azathioprine and methylprednisolone (23). However, as the same induction regimen was used consistently throughout the study period, it may be presumed that it did not contribute to morbidity trends.

Information on the current status of KS in the general population of Israel is coordinated by the Israel Natio-

nal Cancer Registry. There is a 2-year delay between submission of the reports and their presentation in the registry; therefore, the data were analysed only up to 2014. KS rates in the general population include cases of PT-KS, but as those numbers are relatively very low, we assume that their impact is negligible. Fig. 1 shows that the incidence of KS remained relatively stable from 1990 to 1998 and then, as reported in a recent study (17), declined steadily and significantly. In the present study in the same period, the number of PT-KS decreased sharply, from 5 in the first period (0.19% of transplants) to 2 in the second period (0.03% of transplants) ($p=0.032$). Although the current study compared PT-KS incidence between 2 distinct periods, we assume that the change over time, as in the general population, was gradual. We hypothesize that the subtle decline in classic KS rates in the general population had only a minor influence on background incidence, suggesting that the change in the amount and quality of immunosuppressive therapy had a greater impact.

Two other risk factors were identified on multivariable logistic regression analyses. There was a borderline association between the development of KS and age at transplantation, with the PT-KS risk increasing by 6% for each year of age. Classic KS is typically seen in older men. The risk of PT-KS has been found to be highest in the first year after transplantation, and then decreases considerably as time passes (18). In addition, the highest rates of PT-KS were found among transplant recipients who were born in North Africa (71.4%), although they constituted only a small percentage of the transplant recipient population (13.96%). Accordingly, a previous study of classic KS in the Israeli population reported variations in incidence by geographical origin, with the highest rates in countries surrounding the Mediterranean Sea, such as Algeria, Tunisia, and Morocco (24). It is important to note, that a proportion of our transplant recipients who were born in Israel were descendants of families who migrated from epidemiologically significant geographical regions.

Similar to classic KS, most of the current patients with PT-KS cases were men (1) and most of the lesions were found in the lower extremities (25). However, a few lesions were also found in unusual areas, such as the upper extremities and lymph nodes. The mean age at diagnosis for PT-KS was significantly lower than the mean age at diagnosis of classic KS in the general population ($p=0.016$). These findings suggest that the biological behaviour of PT-KS is similar to classic KS, with the exception of younger age at diagnosis, which is probably explained by the immunosuppression.

Strengths and limitations of the study

The current study population is highly representative of the transplant population in Israel, where all lung

Table IV. Comparison of post-transplant Kaposi's sarcoma incidence rates from earlier studies

Author	Year	Origin	Heart transplants n (%)	Lung transplants n (%)
Previous studies				
Zahger, et al. (16)	1993	Israel	18 (11)	
Piselli, et al. (17)	1970–2006	Italy	1,447 (0.05)	244 (0.08)
Present study	1996–2006	Israel	120 (0.25)	148 (0.14)
	2006–2016	Israel	105 (0)	494 (0.04)
	1996–2016	Israel	225 (0.07)	642 (0.03)

transplantations and approximately 50% of all heart transplantations are performed at Rabin Medical Center. All these patients regularly visit a transplant physician, and all attend our specialized dermatology clinic. Biopsy studies are performed even if the initial diagnosis of KS was made elsewhere. By including only biopsy-proven cases, we eliminated patients who may have been misdiagnosed on the basis of clinical appearance alone. To our knowledge, no patient suspected of having KS at our clinic has refused to undergo a biopsy. Owing to the prognosis of the heart and lung transplantations, there was little likelihood of a lost-to-follow-up bias.

The current study was limited by the retrospective design. A prospective study in a larger sample is needed to confirm the results. As the patient data were retrieved from medical records, the clinical assessments may not be consistent among patients.

Unlike other non-melanoma skin cancers, KS appears shortly after transplantation. Nevertheless, the current study may have missed a minority of patients in the latency period after transplantation, in which the disease eventually developed.

Conclusion

The population of heart and lung transplant recipients has hardly been investigated in terms of the development and characteristics of PT-KS. The current comprehensive retrospective evaluation suggests a trend of decreased incidence of PT-KS over the last 20 years, at least partly attributable to the change and reduction in immunosuppressive therapy. This finding is a reflection of the trend of decreased incidence in classic KS in the general population of Israel. Risk factors associated with the disease were early period of transplantation, older age at transplantation, and North African origin. The clinical appearance and behaviour of PT-KS is similar to classic KS, except for an earlier age of onset.

The results of this study suggest that immunosuppressive therapy should be personalized and optimized, and that maintenance therapy with mTOR inhibitors may be warranted in heart and lung transplant recipients, especially those who meet the high risk criteria for KS found here. Further studies of the morbidity trends, risk factors, and clinical manifestations of PT-KS will contribute to the development of preventive and therapeutic measures.

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