

The Place of Skin Cancer Screening in Heart Transplant Recipient Follow-Up Protocols: A Case Series

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Abstract

Objectives

For solid organ transplant recipients the risk of skin cancer is markedly increased due to immunosuppression. Many studies propose an annual, or more frequent, skin screening program by a dermatologist. As the number of transplant recipients increases and survival times improve, the need for screening and rapid response (as required) access is increasing.

Design

In a quality control study we retrospectively examined the medical records of patients participating in an annual screening program between 1997 and 2012. A total of 69 medical records were studied and we here describe the program and present the findings.

Results

We found malignant melanoma in 3 cases. Cutaneous squamous cell carcinoma occurred in 16 patients and basal cell carcinoma in 12 patients. The most frequent skin lesions were actinic keratoses, reported in 20 patients.

Conclusions

Incidence rates for all diagnoses were elevated compared to the general population. Awareness of the increased risk for skin malignancies is of importance to those involved in the care of solid organ transplant recipients. Routines for early discovery of skin tumors are needed both in the form of screening, which can also establish risk group status and give preventive education, and as rapid response access for skin lesion diagnosis and treatment.

Keywords

Cutaneous squamous cell carcinoma; Heart transplant; Screening; Skin cancer.

Introduction

Increasing survival in solid organ transplants recipients has made the long-term complications more evident. Medication after heart transplant (HTx) consists of lifelong immunosuppression to prevent rejection. An increased incidence of skin cancer, with cutaneous squamous cell carcinoma (cSCC) being the most common, is one of the prominent side effects of immunosuppressive treatment. [1] Level of immunosuppressive therapy, age at transplant, male sex, presence of precancerous skin conditions, degree of sun exposure and skin type according to Fitzpatrick scale are predictors of skin cancer in HTx-patients. [2-4] In the Swedish general population the incidence of cSCC is 60.2/100.000 for men and 32.3/100.000/year for women and increasing. For basal cell carcinoma (BCC), the incidence is approximately 430/100.000/year. [5] In regions with high sun exposure, such as Australia, there is a 20 year post transplant risk for skin cancer of 70% and in an American study the incidence increased 4-30-fold. [3,6] In a Swedish study (lower degree of sun exposure), the estimated risk of cSCC compared to the normal population was increased 198-fold in heart- and lung transplant recipients and the risk of cSCC increased with time after transplant. The occurrence of the first cSCC is associated with risk for further cSCC. [4,7,8] Median time between first and second, second, third and fourth cancers are 24, 14.7 and 8.4 months, respectively. [4] In transplanted patients the cSCC is reported to be more aggressive, giving frequent local recurrence, metastasizing more often and correlating to the presence of extra cutaneous malignancies. [8,9] The rate of death due specifically to cSCC is not known but mortality is reported to be increased 50-150 fold. [4,9,10] Actinic Keratoses (AK) is a premalignant lesion reported to be associated with higher probability of cSCC. [11] The prevalence for AK in a group of heart transplant recipients was 18%. Other studies suggest, and the International society for heart and lung transplantation (ISHLT) guideline recommend, that frequent skin examinations and preventive information on reduced sun exposure may reduce the risk of mortality and morbidity due to skin cancer [3,7, 8,12-17].

The aim of this case series report was to review the results of an annual dermatological examination as a part of a screening program for skin cancer in HTx- recipients, describe the annual screening program and to discuss aspects of healthcare delivery for HTx patients in particular and the increasing group of solid organ recipients in general.

Method

For HTx recipients in the southeast healthcare region, Sweden, there has been a screening program for skin cancer since 1997. The screening program, which include an annual examination by a dermatologist are coordinated by the transplant team and scheduled during the regular heart transplant annual control visit. This in collaboration with the other departments involved, coordinated by the transplant team. The patients receive written and oral information regarding the increased risk for skin cancer prior to HTx. If a suspicious malignant skin lesion or other lesions was found appropriate assessment and treatment were undertaken if necessary. The examination findings, clinical and histological diagnosis and treatment were documented in the patient's medical records. The data presented in this study became available as part of internal quality control.

Statistical analyses were performed in Microsoft Excel. Differences were calculated using the two tailed Student's *t*-test and a *P* level of <0.05 was considered significant.

Results

In Sweden the transplantation- surgery is located in two centers. The pre-operative assessment and follow- up are performed at the University hospitals. In the southeast healthcare region, The Cardiology clinic at the University Hospital of Linköping provides this care.

A retrospective analysis of the medical records of HTx patients from the southeast healthcare region transplanted since the start of cardiac transplantation in 1986 was performed as a part of internal quality control. Records from a total of 93 patients transplanted between 1986- 2011 were studied. 5 patients deceased within 30 days post- transplant, 13 deceased before the introduction of the screening program and 6 patients were excluded due to missing data / medical record not being found. This resulted in the inclusion of 69 patients in the study. Of these, 26 patients died between 1997- 2012, but have contributed with years in the screening program review. Most patients was in Fitzpatrick scale I-III, one being at scale IV and one at scale VI. There was no patient with a previous history of skin malignancy. The total number of annual examinations in the material was 590, where men contributed with 383 (64%). There was no significant difference between the genders in age at transplant or time with transplant. We found no death due to skin malignancy in the material. The demographics of the material is presented in (Table 1) in two subgroups based on malignant or pre-malignant findings, or not at skin examination.

For the population with skin lesions, the mean time in the screening program were 10.5 years and for the group without skin lesion 6.3 years.

Malignant melanoma was found in 3 patients, one presenting with 2 lesions while the others representing with one lesion each. These tumours occurred early post- transplant, 1, 3 and 4 years respectively. These malignancies were all excised successfully and no local recurrence or metastatic disease was observed during follow up period.

Cutaneous SCC, the most common carcinoma in HTx patients, was diagnosed in 16 of the 69 patients. The total number of cSCCs found was 29, mostly found in sun exposed areas such as head, shoulders and neck. Six patients had more than one tumour, with the highest number being 5 tumours. There were no local recurrences or metastases after treatment (excision or cryotherapy) within the study period. The mean time elapsed after HTx for the patients with cSCC was 10.1 years until first diagnosis, however, the earliest tumour found occurred 4 years post transplant. These findings give an incidence rate of approximately 0.05 tumours /follow up year for men and 0.04 tumours/ follow up year for women. The incidence of cSCC in the general population expressed in the same way is 0.0006 tumour /year for men and 0,0003 tumour/ year for women. Thus in the HTx group, there was an 83-fold increased risk for cSCC for men and 133-fold increased risk for women, compared to the general population.

The usually benign tumour, BCC, was found in 12 patients. They presented with a total of 20 lesions and the mean time elapsed after HTx until first diagnoses were 9. 5 years. These findings give an incidence rate, for the group, of 0.03 BCC / follow up year. The incidence in the general population expressed in the same way is 0.004/ year. The rate of BCC in this group is thus 7.5 times higher than, and the SCC/BCC ratio in this study is 1.45:1 compared to a ratio of 1:4 in general population, in concordance with other studies. [1]

AK was found in 20 patients with a total number of 64 lesions. 6 of these patients presented with only one lesion while the others had between 2 and 8 lesions. The first AK occurred in mean 8.3 years after transplantation with the earliest lesion one year after transplant. These lesions were diagnosed clinically and treated with cryotherapy.

During the years of annual dermatological examinations, multiple benign lesions, for example verruca and eczema, have been diagnosed and treated. In addition to the examinations resulting in a diagnosis mentioned above, a total of 81 examinations ended up with a treatment or histological diagnosis (cryotherapy; 28, excision; 18, PAD; 35). 116 examinations had a finding at the screening but no treatment or further investigation was needed. For the total group a total of 91 PAD or excision were performed.

The mean concentration of Cyclosporine A (CYA), in the HTx-patients in this study has been decreasing from approximately 200ng/mL in 1996 to 100ng/mL in 2012. This due to more tailored immune suppressive treatment.

There was no difference in CYA- concentration between the two groups.

A summary of the findings is presented in (Table 2).

Table 1: Demographics

	With Skin lesion	Without Skin lesion	Total
	Mean (±SD) (n= 32)	Mean (±SD) (n= 37)	Mean (±SD) (n= 69)
Age at transplant (years)	47.6 (9.2)	45.5 (10.3)	47.5 (9.1)
Female (%)	41	22	30
Caucasian	32	35	67
Asian	0	1	1
Afro- European	0	1	1
Previous skin malignancy	0	0	0
Etiology of Heart Failure			
DCM	15	19	34
IHD	14	11	25
GUCH		3	3
Others	3	4	7
Known Smoker		4	4
Years with transplant	16.6 (7.2)	7.5 (3.3)	10.4 (4.6)

Table 1: The different group demographics in gender, age at transplant, ethnicity, previous smokers, previous skin malignancy, time with transplant and etiology of heart failure. Others; include myocarditis, sarcoidoses, arrhythmogenic right ventricle disease, aortic valve insufficiency, hypertrophic cardiomyopathy.

DCM: Dilated Cardiomyopathy, IHD: Ischemic Heart Disease, GUCH: Grown up Congenital Heart Disease, SD: Standard Deviation

Table 2: Results at a glance

Patients contributing with years in the screening program	69
Annual examinations in screening program	590
Number of PAD, excisions	91
Visits with dermatological diagnosis without treatment	116
Patients with MM	3 (4%)
Patients with cSCC	16 (23%)
Patients with BCC	12 (17%)
Patients with AK	20 (28%)

Table 2: MM: Malignant Melanoma, cSCC: Cutaneous Squamous Cell Carcinoma. BCC: Basal Cell Carcinoma. AK: Aktinic Keratoses

Discussion

Our findings that 1 of 4.3 HTx-recipients develop cSCC correlates well to the largest study to date on the solid organ transplant patients in Sweden which estimated an incidence of 1 in 4.5. [7] This study is performed in a small centre with a small sample size and it's generalisability is therefore difficult to determine.

To maintain a multidisciplinary collaboration it is important with coordination with the regular HTx annual control visit. Patients visiting a dermatologist may take the opportunity to discuss cosmetic issues which should be avoided to maintain high compliance for malignancy screening. For larger centers or centers starting a screening program, newer information techniques, such as patient online- booking, e-mail reminders and SMS might be a possible solution to increase the attendance to the annual follow up.

No patient in our study deceased from cutaneous malignancy and this screening program may have an impact on the total median survival rate of 16 years. In the international registry by ISHLT the mortality due to skin cancer is not individually reported. It seems, however, reasonable to assume that morbidity and mortality due to skin cancer in HTx patients are increased. In a UK study the cumulative mortality risk was 148-fold compared to the general population and 7 of 26 patients with more than 10 skin cancers died from metastatic disease. [4] Whether the absence of death due to skin cancer in our material is the result of small sample size or the screening (leading to early detection, treatment and thus improved survival) cannot be concluded with certainty. A general truth about skin cancer management is however that early detection improves survival, prompting us to suggest that the screening process may have played a role.

It is known that in the general population cSCC incidence is increasing. The transplant population will, at the time of transplant, conform with the general population in this regard. Thus patients undergoing transplant at the present time and indeed for the foreseeable future can be expected to have a higher inherent risk for cSCC than the population in our study and in previous studies. However, management of immunosuppression improves with time and might compensate for "era" effects of increased inherent risk in HTx patients. Evidence of improved management is seen in patients transplanted the last decade, for which ISHLT report a 4% absolute risk reduction in incidence for skin cancer within 7 years. [18] It is also seen in our material where the mean concentration of CYA is decreasing and a more tailored immunosuppressive treatment is used. How this balance (between increased inherent risk at transplant and more optimal immunosuppression) will work out in the future is difficult to predict.

The relatively high incidence of malignant melanoma in our study has not generally been seen in previous studies and may be a haphazard result of a screening examination.

It has been suggested that solid organ transplant patients can be classified (categorized) in regard to the risk for skin cancer prior to transplantation and thereafter allotted to screening programs of varying intensity. [4,15] Factors influencing risk classification are the same as the risk factors mentioned in the introduction with the addition of presence of actinic keratosis. The question that arises is whether all transplanted patients should be offered an annual dermatological screening visit as part of their yearly transplantation follow-up at their regional transplantation centre. Whilst most of screening visits in the early years after transplantation, as seen in our and other studies, will not result in detection of a malignancy, we consider that the overall 83-130 fold increased risk for cSCC that is seen in this group compared to the general population must be taken in to consideration. We consider that early screening

visits with negative outcome (failure to detect skin cancer) still fulfill an important role in patient training in regard to early detection and secondary prevention by changing the attitudes towards sun exposure and sun protection. If annual examinations are not applicable, recent studies show that a screening program of varying surveillance rate can lead to optimized use of resources. Patients considered at high risk for skin cancer need dermatological examination more frequently. For patients developing their first skin cancer, an intensive screening period is initiated. [4] Such screening is best provided by a skin cancer resource close to the patient's home. A period of freedom from skin cancer can lead to reduced screening frequency. This type of individual screening might be preferable but all times reliable rapid response access for dermatological assessment and treatment of new suspicious lesions can be performed by annual examinations. Our screening program is now a well working clinical routine and may indicate that an annual examination is an adequate way to minimize the morbidity and mortality for patients after solid organ transplantation.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. The project was supported by the county of Östergötland, Sweden.

Conflict of interest

None.

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