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Cutaneous Complications in Heart Transplant Recipients in Norway 1983–1993

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All Norwegian heart transplant recipients with more than one year's survival (n = 140) were investigated for dermatological disorders. Observation time after transplantation was 1–10 years (mean 5.0 years). Patients alive at the end of 1993 (n = 122) were examined clinically, and medical records for all patients were reviewed. The histopathological diagnoses of excised skin specimens were reevaluated. Malignant skin tumours (i.e. basal cell carcinoma, squamous cell carcinoma and malignant melanoma) and/or premalignant skin tumours (i.e. morbus Bowen (carcinoma in situ), solar keratosis and keratoacanthoma) were found in 34 patients (24.3%), of which 18 patients (12.9%) had malignant skin tumours. Seventeen lesions diagnosed as keratoacanthoma and two lesions diagnosed as morbus Bowen had primarily been diagnosed as squamous cell carcinoma. Five patients (3.6%) had multiple keratoacanthomas. Other frequent dermatological diagnoses included hypertrichosis (86.9%), steroid-induced skin features (59.8%), common warts (42.6%) and seborrheic skin disorders (20.5%). This study demonstrates the importance of dermatological surveillance in the follow-up of heart transplant recipients. ***Key words: immunosuppression; cyclosporine; skin cancer; keratoacanthoma.***

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Kidney transplant recipients run a greater risk of developing various dermatological disorders, including malignant and premalignant skin lesions (1–9). Heart transplant recipients are assumed to have similar long-term cutaneous complications, but there are to our knowledge only two survey reports on skin disease following heart transplantation (10, 11), both with a short follow-up time and both from areas with high levels of solar UV radiation, known to be an important etiological factor of skin cancer (9, 12, 13). We therefore decided to investigate the occurrence of skin disease among heart transplant recipients in Norway. The aim of this study was to describe the whole range of dermatological disease in this group of patients.

MATERIAL AND METHODS

Patients

At Rikshospitalet Heart Transplantation Unit, University of Oslo, Norway, 162 patients received a cardiac transplant from 1983 through 1992. Transplant recipients who died within 1 year after surgery (n = 31) were excluded, and 9 Norwegians who had been transplanted abroad were included, making the total number of patients in the study 140.

The female/male ratio was 27/113, and the mean age was 47.7 years (range 2–63) at the time of transplantation. The mean observation time from transplantation to death (n = 18) or end of follow-up was 5.0 years (range 1–10 years). All patients, except one of Pakistani origin, were Caucasian. One patient had a malignant skin lesion (basal cell carcinoma) diagnosed before transplantation.

Immunosuppressive maintenance therapy consisted of cyclosporine A (serum levels adjusted to 150–200 ng/ml), azathioprine (2 mg/kg/day) and prednisolone (0.1 mg/kg/day). Exceptions were 5 patients without azathioprine and 2 patients without long-term steroid therapy. No cytolytic induction therapy was used. Episodes of rejection were treated with 1 g methylprednisolone i.v. for 3 days. Moderate to severe rejections were additionally treated with rabbit antithymocyte globulin (55 patients) and/or muromonab-CD3 (Orthoclone OKT3; 4 patients).

Clinical data and examinations

Data regarding skin lesions were extracted from medical records for all 140 patients. Clinical examinations of the 122 patients alive at the end of 1993 were carried out by one dermatologist (PJ). Skin biopsies or excision specimens for histopathology, skin/nail scrapings for fungal culture and specimens for bacterial or viral culture were performed when appropriate.

Histopathological examinations

Skin biopsies and excision specimens were examined/reexamined by one pathologist (OPFC). The histopathological diagnoses of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), malignant melanoma, morbus Bowen (carcinoma in situ), solar keratosis and keratoacanthoma (KA) were established in accordance with accepted criteria (14).

KA may be difficult to differentiate from SCC and other skin tumours (14, 15). Therefore, special emphasis was put on the criteria of KA: 1) clinical information on rapid initial growth, 2) typical clinical appearance of a firm, hemispheric, symmetric, skin-coloured or erythematous papule or nodule with a central, often umbilicated, keratinous core, and 3) the following histopathological findings: symmetric architecture with keratin-filled invagination of epidermis developing into a keratin-filled core, epidermal shoulder or lip, epidermal strands extending into dermis, glossy appearance of keratinocytes, infiltration not extending to the deeper layer of dermis (14, 15).

RESULTS

Skin tumours

Thirty-four patients (24.3%) had malignant and/or premalignant skin lesions, including KA (Table I). Among the 68 patients with ≥5 years observation time, the corresponding number was 26 (38.2%).

A total of 27 malignant skin lesions were diagnosed in 18 of the 140 patients (12.9%), 13 BCCs, 12 SCCs, and 2 malignant melanomas (Table I). Among the 68 patients with ≥5 years observation time, the corresponding number was 16 (23.5%). None of the patients died of malignant skin tumour, and no metastatic lesions were diagnosed. All but one SCC and all but three BCCs were located on sun-exposed skin areas (face, neck or dorsum of hands).

Twenty-eight patients had lesions diagnosed as morbus Bow-

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Table I. *Malignant and premalignant skin lesions in 140 Norwegian heart transplant recipients*

	No.(%) of patients	No.of lesions
Skin cancer	18 (12.9)	27
– Basal cell carcinoma	10 (7.1)	13
– Squamous cell carcinoma	9 (6.4)	12
– Malignant melanoma	1 (0.7)	2
Morbus Bowen (carcinoma in situ)	13 (9.3)	25
Solar keratosis	18 (12.9)	*
Keratoacanthoma	8 (5.7)	44
In total	34 (24.3)	96*

*Number of solar keratoses was not recorded

en (number of lesions = 25; 2 lesions had primarily been diagnosed as SCC) and/or solar keratosis (Table I). Morbus Bowen, being an intraepithelial carcinoma in situ, and solar keratosis are regarded as premalignant lesions (14). Twelve of these patients also had one or more BCCs and/or SCCs. No cases of Kaposi's sarcoma or cutaneous lymphoma were diagnosed.

Eight patients had 44 KAs (Table I), of which 18 occurred in one patient. For 29 of these lesions the original histopathological diagnosis was other than KA: SCC (n = 17), verrucous squamous cell hyperplasia with atypia (n = 8), BCC (n = 1), morbus Bowen (n = 1), solar keratosis (n = 1) and verruca vulgaris (n = 1). Five of the patients with KA, all with multiple KAs, were found to have SCC and/or BCC as well.

Skin infections

Among the 122 patients who were clinically examined by a dermatologist in this study, 52 patients (42.6%) had common warts. Six patients had more than 20 lesions each. No correlation between the occurrence of skin cancer and common warts was evident.

Other viral and fungal infections included herpes simplex (n = 10), herpes zoster (n = 9), varicella (n = 2), condyloma accuminata (n = 3), dermatophyte onychomycosis (n = 9), pityriasis versicolor (n = 5) and candidiasis (n = 3). Bacterial infections were limited to a few cases of folliculitis and impetigo with little clinical significance.

Other skin disorders

Hypertrichosis was reported by 106 patients (86.9%) and xerodermia (dry skin) by 32 (26.2%). Steroid-induced skin features, such as teleangiectasias, cutaneous atrophy, purpura, erythrosis interfollicularis colli, and/or striae, were seen in 73 patients (59.8%). In 25 patients (20.5%) seborrheic skin disease was diagnosed, such as acne or acneiform lesions (n = 13), rosacea (n = 7), seborrheic dermatitis (n = 1), and sebaceous gland hyperplasia (n = 4).

Eight patients had psoriasis, 3 of whom had typical psoriatic lesions at the time of dermatological examination. Three of the 8 patients had noticed a marked reduction in disease activity during the time of cyclosporine therapy. Other dermatological diagnoses included seborrheic keratosis, dermatofibroma, atheroma, mucoid cyst, keloid, dysplastic naevi, hyperhidrosis, pruritus, non-specific dermatitis and keratosis pilaris.

DISCUSSION

The problem of dermatological disease in immunocompromised patients is increasing, because of the increasing number and observation time of organ transplant recipients (16). To our knowledge, this is the first report on long-term cutaneous complications in heart transplant recipients. It reveals that skin disorders, including malignant and premalignant skin tumours, are frequent in heart transplant recipients on immunosuppressive maintenance drug therapy with cyclosporine, azathioprine and prednisolone in an area with relatively low levels of solar UV radiation. This is in accordance with similar studies among renal transplant recipients (1–9).

The main concern regarding long-term cutaneous complications in organ transplant recipients is the high incidence of malignant lesions (16–19). In most studies the occurrence of skin cancer is reported as period prevalence, calculated as the ratio between the number of transplant recipients with skin cancer and the total number of transplant recipients (1–7, 19). In our cohort of heart transplant recipients, this period prevalence was found to be 12.9%. In studies of renal transplant recipients this proportion varies from 4.0–15.0% (1–7, 19). This variation may be explained by variable mean observation time after transplantation, different diagnostic criteria for skin tumours, different races and skin types of patients, different geographical locations with dissimilar UV exposure, variations in immunosuppressive regimens and other factors. One important characteristic of our group of patients is that all received cyclosporine, in contrast to groups of renal transplant recipients (1–7, 19).

A more accurate measure of the increased occurrence of skin cancer in transplant recipients is the standardized incidence ratio, calculated as the ratio between the observed number of cases in the transplanted population and the expected number of cases estimated on the basis of age-, calendar period- and gender-specific rates obtained from a cancer registry. This has previously been done in studies among renal transplant recipients, showing a marked increase in the occurrence of SCC and BCC (1, 4).

In the present study, 9 patients with SCC were found. Based on age- and gender-specific rates calculated from the registration of SCC in The Cancer Registry of Norway, the expected number of patients with SCC in this study should be <1, showing a marked increase in the incidence of SCC also in heart transplant recipients. Similar rates for BCC (as well as non-malignant skin diseases) are not available. For malignant melanoma, the scope of the study is too small for evaluation of incidence.

Since KA typically regresses spontaneously, KA can be regarded as a benign tumour despite the fact that it may have malignant histological features (14, 15). In most studies of renal transplant recipients KA is not included among skin cancers (1–8). Nevertheless, there are reports on KAs with an SCC-like malignant course (15, 20). So far, immunohistochemical and other methods have failed to distinguish KA from SCC (15, 20, 21). Many authors therefore regard KAs and SCCs as a spec-

trum of the same disease, with KA as a type of regressing SCC (15, 20, 21), and recommend that lesions diagnosed as KA be treated as potential aggressive tumours (15, 20). The diagnosis of KA and its relationship to SCC remains a challenge, especially in the increasingly large group of organ transplant recipients, and needs to be studied further.

The mechanisms of the increased occurrence of skin cancer in organ transplant recipients are uncertain but are probably related to decreased immune competence in tumour surveillance during pharmacological immunosuppression (16).

Solar exposure has been found to be an important etiological factor of skin cancer (9, 12, 13). In our study nearly all SCCs and BCCs were located in skin areas most heavily exposed to sunlight, supporting this view. A correlation between light skin type and skin cancer was not evident in our study, but the number of patients was relatively small. An effort was made to identify our patients' sun habits, and many patients were unaware of, or had neglected advice on, the need for UV protection.

Oncogenic subtypes of human papillomavirus (HPV) have been reported in SCCs of renal transplant recipients (22, 23), suggesting a role for certain HPV subtypes in their etiology. However, the results and interpretations of such studies are conflicting (24, 25). An association between the occurrence of common warts and SCCs has been suggested in other studies (9, 26), but was not evident in this study.

Common warts were very common, as in renal transplant recipients (2, 3, 8, 9). Although not life-threatening, a large number of verrucae, and/or verrucae localized to fingers or feet, may cause problems in daily activities. Theoretically, a similarly increased prevalence of dermatomycosis would be expected, but there is no study to confirm this (16).

Almost all patients had some degree of hypertrichosis, and some a pronounced degree. For many female patients this was a significant problem. Hypertrichosis is caused by cyclosporine (27). The significance and cause of dry skin is unclear (27).

Steroid-induced skin changes were almost universal, and in many cases pronounced. The development or worsening of seborrheic skin disorders seen in many of our patients must be assumed to be a result of systemic steroid therapy. From a dermatological viewpoint the immunosuppressive regimen should preferably be without steroid maintenance therapy.

Some patients with preexisting psoriasis reported a decrease in psoriasis activity, which was to be expected due to the known antipsoriatic effect of cyclosporine (28).

In conclusion, heart transplant recipients have a high frequency of skin disorders, including malignant and premalignant skin lesions. Patients, physicians and nurses should be aware of the importance of preventive measures and early diagnosis of skin disease in these patients. Patients with suspected skin lesions should have easy access to a dermatologist, and patients with diagnosed premalignant skin lesions, KA and/or skin cancer should be examined regularly by a dermatologist.

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