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Skin Lesions in Renal Transplant Patients after 10–23 Years of Immunosuppressive Therapy

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Ninety-eight patients with 10–23 years of uninterrupted immunosuppressive therapy due to renal transplants were investigated for signs of skin disease. Thirty-seven per cent had or had had premalignant or malignant skin lesions. This is significantly different from a control population ($p < 0.0001$). There was also a correlation between the length of the immunosuppressive therapy and the risk of acquiring squamous cell skin cancers ($p < 0.05$). Fifty-five per cent had common viral warts at the time of the present examination. The duration of immunosuppressive therapy also correlated with the presence of warts ($p < 0.01$). Seven patients had mycosis and four patients had seborrheic eczema. In one-third of the patients the skin appeared normal. ***Key words: Long-term immunosuppression; Skin cancer; Warts.***

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Organ transplant recipients with chronic immunosuppressive therapy run an increased risk of developing dysplastic (i.e. premalignant and malignant) skin lesions, which tend to be multiple and sometimes rather aggressive (1, 2). In addition to other risk factors such as old age and residence in high ultraviolet (UV) radiation areas, the incidence of these lesions is influenced by the length of immunosuppressive therapy (1–5). Also, benign skin lesions tend to cause morbidity and therapeutic problems in long-term organ transplant patients and increasingly so with time (5, 6, 7).

The aim of this study was to assess prospectively the magnitude of dermatological problems in a population of long term renal transplant patients treated at the Renal Transplant Unit in Gothenburg, Sweden.

PATIENTS AND METHODS

Renal transplant patients with at least 10 years of uninterrupted immunosuppressive therapy were selected for this study as they attended the Renal Transplant Unit for routine check-up examinations. Previously treated malignant and premalignant skin lesions were registered and the skin examined for benign, premalignant and malignant lesions by one dermatologist, who was also responsible for a previously collected control population used for statistical comparison (8).

Actinic keratosis and Bowen's disease were registered as premalignant lesions. Malignant lesions comprised invasive squamous cell carcinoma (SCC), basal cell carcinoma (BCC), malignant histiocytoma and sweat gland carcinoma. Lip cancer and cancer of the vulva were not included. The non-malignant lesions were: keratoacanthoma, common viral warts, dermatomycosis, rosacea and seborrheic eczema. Stigmata due to steroid medication were also noted.

Ninety-eight patients were included, 55 men and 43 women. The mean age was 50 years (range 18–76). The duration of continuous immunosuppressive therapy varied between 10 and 23 years and exceeded 15 years in 39 patients and 20 years in 12 patients. All patients had functioning renal allografts with good and stable renal function in all cases but 8, who had serum creatinine levels between 275 and 500 μmol/l. Seventy-one patients had retained their first renal grafts and 27 had been retransplanted 1–3 times, in 22 cases with the last transplantation more than 10 years ago. Five patients had recent retransplants (0.5–2 years).

Immunosuppressive therapy consisted of azathioprine and prednisolone, with the addition of cyclosporin in the five patients with recent retransplants. The azathioprine dose was 25–125 mg/day in 84% of the patients (mean 71.2 mg/day). Thirteen patients had 150–200 mg daily and one patient had been off azathioprine for 1.5 years. The prednisolone dose was 2.5–10 mg/day in 94% of the patients. Six patients had been off steroids for 14–22 years. Cyclosporin was administered to whole blood trough concentrations of 150–400 μg/l (Sandoz polyclonal RIA kit).

Statistics

The possible differences in the existence of various skin lesions between the transplant and the control populations were tested by means of the normal approximation test, which, with the number of observations in this study, corresponds to the Student's t-test. When the presence of skin lesions was measured cumulatively, the number of lesions was divided by age in order to obtain a comparable measure regardless of that factor. The correlation between the time of immunosuppressive therapy and the existence of skin lesions was investigated with Pearson's correlation coefficient. This is equivalent to a *t*-test for different treatment time in the groups with and without skin lesions.

Table I. *Dysplastic skin diagnoses in 98 long-term renal transplant patients, totally and by location (no. of patients).*

Location	Diagnosis				
	Actinic keratosis	Bowen's disease	Squamous cell carcinoma	Basal cell carcinoma	Other
All locations	28	9	7	16	2
– face	13	2	2	7	1[a]
– arm	3	1	–	3	–
– hand	13	4	2	2	–
– trunk	3	4	3	9	1[b]
– leg	2	1	1	3	–
– foot	–	–	–	–	–

[a] Malignant histiocytoma, [b] Sweat gland carcinoma

RESULTS

Dysplastic skin lesions

Thirty-six patients (37%) had malignant or premalignant skin lesions, either at the time of the present examination or previously during the post-transplant period. This is 3.5 times more than would be expected in the control population ($p < 0.0001$). There was a statistically significant correlation between the length of immunosuppressive therapy and the risk of acquiring SCC ($p < 0.05$). No such correlation was found for BCC. Fifteen patients had more than one premalignant/malignant diagnosis. Multiple lesions of the same type were frequently seen. There were two exceptional patients with several hundred lesions each over the years. One of these had mainly superficial BCCs on the trunk and also extensive actinic keratoses, later followed by recurring invasive SCCs on several locations. The other patient had hundreds of tiny lesions, mainly characterized as Bowen's disease and BCCs. Both patients have required numerous surgical and other procedures.

Lymph node metastases were seen in one case of squamous cell carcinoma of the upper eyelid, requiring enucleation of the eye, radical neck dissection and radiotherapy. He is free of recurrence more than 4 years afterwards.

The diagnoses and locations of malignant and premalignant skin lesions are reported in Table I. In cases of multiple lesions, one lesion of each kind per region is registered.

Benign skin lesions

Fifty-four patients (55%) had common viral warts at the time of the examination (Table II). Previous episodes of warts could not be accounted for. The length of immunosuppressive therapy correlated statistically with the presence of warts ($p < 0.01$). Some patients had solitary warts while most had multiple lesions, in the form of either multiple hand or foot warts or, in a few cases, a general verrucosis with hundreds of tiny warts over the entire body surface. In the latter case, the warts were often intermingled with other skin lesions such as actinic keratoses, benign skin papillomas and seborrheic verrucae.

Seven patients had hand or foot mycosis. Seborrheic eczema was seen in four patients. Three patients had rosacea as a more or less chronic problem. Keratoacanthomas were noted in eight patients (including previously removed lesions).

22% of the patients had, usually slight, sequelae of previous high dose steroid medication, either atrophic and often hyperpigmented skin or remnants after cushingoid striae. Common lesions were telangiectasias of the face. One-fifth of the patients complained of dry skin.

Table II. *Non-malignant skin lesions in 98 long-term renal transplant patients.*

	No of patients
Viral warts	54
Dermatomycosis	7
Seborrheic eczema	4
Rosacea	3
Keratoacanthomas	8
Corticosteroid atrophy	21
Dry skin	18
Normal skin	33

"Transplant hand"

There are two dermatological conditions often seen in long-term transplant patients, both affecting the dorsal aspects of the hand and forearm. One is the above-mentioned hyperpigmented, atrophic and parchment-like skin with frequent hematomas and ecchymoses after minor trauma and with delayed healing of bruises and wounds. This condition is due to the steroid medication.

The other condition, almost exclusively seen in transplant patients (and therefore here suggestedly called "transplant hand"), is a dry and somewhat scaly skin with increasing numbers of either verrucae planae or actinic keratoses, or both. These lesions are most prominent on the dorsum of the hand but tend also to involve the forearm. Besides having malignant potential, this condition may become so severe as to constitute a real cosmetic and social problem. One of our patients required excision of the dorsal skin of the hands and fingers followed by skin transplantation, with a satisfactory functional and cosmetic result.

DISCUSSION

We increasingly meet individuals with functioning renal allografts for more than one or even two decades, thus experiencing both the benefits and side effects of chronic immunosuppressive therapy. Balanced immunosuppression with azathioprine and prednisolone allows both good general health and maintained long-term graft function, but at the expense of occasional infectious, malignant and other complications. The organ system by far most frequently affected by immunosuppression-related side effects is the skin. In our population of renal transplant patients with chronic immunosuppression for 10–23 years, 37% had experienced malignant and pre-malignant skin lesions. 22% had sequelae of the steroid medication as such. Thirty-four per cent were considered to have normal skin.

Estimates of the risk of renal transplant patients' acquiring skin malignancy have ranged from 4 to 20 times the normal incidence, with lower figures for areas with low ambient UV-radiation and higher figures for sunny and dry parts of the world (1, 3, 4, 9, 10). The cumulative incidence increases rapidly with the duration of immunosuppression: in this series, 25% had had skin cancer after 10–23 years. In a high UV radiation area, 44% had skin cancer after 9 years (1). The one-year risk of acquiring skin cancer also increases with time: risk ratios exceeding 100 have been calculated for patients 8–9 years after transplantation (4). Solar radiation is the most important factor for the development of skin cancer and chronic medication with azathioprine and prednisolone has been calculated to exert an additive effect of the same order of magnitude as high age and outdoor occupation (3).

The immunosuppressive therapy seems to accelerate the development from actinic keratoses to infiltrating squamous cell carcinomas and also increase the tendency of these tumours to form metastases (1). In accordance with this, most investigators have found the increased skin cancer incidence almost exclusively to be due to SCC, resulting in an inverse ratio between this tumour and BCC compared to what is seen in the general population (1, 2, 6). This was not the case among our patients, however, where BCCs were also very frequent, with a more "normal" SCC/BCC ratio. The reason for this discrepancy is not clear. Variations in diagnostic criteria and validity of statistics might be one explanation. It can also be speculated, however, that the differences are due to the residence of our patient population at high latitudes with low ambient UV-radiation.

Most skin lesions, malignant and non-malignant, respond well to ordinary local treatments. Therapeutic problems arise when lesions tend to be multiple and rapidly recurring. In our experience, a reduction of the immunosuppressive therapy has greatly improved the situation in such cases. Another possible approach might be the use of retinoids, locally or systemically, to enhance the ability of the skin to resist malignant degeneration (11, 12, 13).

Seborrheic eczema has recently been associated with defective immunocompetence, especially as seen in Acquired Immuno Deficiency Syndrome and related conditions. The reason why this disease is not more frequently seen in renal transplant patients is probably that the immunosuppressive regimen used is not heavy enough to facilitate this disease.

Keratoacanthomas were not included in the statistical calculations as they are non-malignant by definition (14). However, the distinction between this entity and SCC is not clearly defined, and the diagnosis often has to be changed according to the clinical behaviour of the tumour. Keratoacanthomas should therefore be regarded as potentially aggressive (1).

Conventional immunosuppression with azathioprine and prednisolone has been abandoned by most transplant centres and replaced by cyclosporin, usually in various combinations with low doses of prednisolone and/or azathioprine and prednisolone. While these new regimens undoubtedly offer more effective and safer immunosuppression, it still remains to be seen whether this effectiveness will also result in changing incidences of malignant or infectious skin complications. Our present perspective of five to six years of observation is obviously not long enough to determine this, as both malignant and nonmalignant skin lesions tend to occur with increasing frequency with time of immunosuppression. Cyclosporin-treated patients seem to have skin problems similar to those seen with conventional immunosuppression (4, 5, 15). It is our general impression, however, that the skin of patients on cyclosporin-based regimens is in better condition. A tendency towards lower skin cancer incidences with cyclosporin regimens was also reported by the Cincinnati Transplant Tumor Registry, even when the problem of different follow-up times was considered (15).

The skin lesions described in this article may be regarded as easily detectable side effects of chronic immunosuppression and as such serve as an impetus to reconsider, i.e. reduce the dosage of, above all, azathioprine. A reluctance to do so is natural, due to the potential risk of endangering the integrity of a well-functioning graft by underimmunosuppression. Objective means of assessing the immunosuppression actually achieved in the individual patient are lacking but might, if available, be of help in this difficult decision.

In conclusion, long-term use of conventional immunosuppression with azathioprine and prednisolone is associated with high incidences of skin diseases. New, cyclosporin-based, regimens seem to have similar effects. Although usually harmless and easily containable by conventional methods, such lesions may occasionally present major problems. Skin disease is in fact the most frequent untoward effect registered in long-term transplant patients. Skin disease deserves continued monitoring by those caring for transplant patients, in the interest of the patients and for scientific assessment of the effects of new immunosuppressive regimens. Education of patients and medical staff for early detection and treatment of skin lesions is important, as are preventive measures, including avoidance of excessive exposure to UV-radiation and the use of sunscreens and also careful reduction of azathioprine dosages in long-term transplant patients.

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