

Dermatological Complications of Immunosuppression in Kidney and Heart Transplant Recipients

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Organ transplant recipients may develop a number of dermatological complications, including malignant and premalignant skin disease, related to the long-term immunosuppressive drug treatment. With only one centre performing organ transplantation in Norway and with the availability of a well-functioning national cancer registry, various aspects of transplantation-related dermatological complications were studied.

Risk estimations of skin cancer in the complete Norwegian cohort of kidney and heart transplant recipients (n=2,561) were studied by the use of standardized incidence ratios and multivariable Cox regression. Transplant recipients had an increased risk for cutaneous squamous cell carcinoma (65-fold), malignant melanoma (three-fold), and Kaposi's sarcoma (84-fold), and for lip squamous cell carcinoma (20-fold), compared to the general population. After adjustment for age and organ (kidney or heart), transplant recipients on cyclosporine, azathioprine, and prednisolone had a significantly, 4.2 (95% confidence interval [CI] 2.1-8.5) times, higher risk of cutaneous squamous cell carcinoma relative to the historical



Petter Jensen Gjersvik defended his doctoral thesis at the new Rikshospitalet in Oslo on June 15th, 2000. From left: Professor Olle Larkö, Sahlgrenska University Hospital, Göteborg (1st Opponent), Dr Gjersvik, Professor Christian Hall, University of Oslo Medical School (Dean and Chairman), Dr Tove Eeg Larsen, Ullevål University Hospital, Oslo (3rd Opponent), and Dr Dagfinn Albrechtsen, Rikshospitalet, Oslo (2nd Opponent).

group of transplant recipients on azathioprine and prednisolone. After adjustment for age and type of immunosuppressive regimen, heart transplant recipients had a 2.1 (CI 0.96-4.6) times higher risk than kidney transplant recipients. Number of transplantations, use of additional anti-rejection therapy (ATG and/or OKT3), recipient HLA-A11, -B27, and -DR7, donor/recipient mismatch for HLA-B, and recipient homozygosity for HLA-DR were not found to be risk factors. The results indicate that the risk of post-transplant cutaneous squamous cell carcinoma is related to the degree of immunosuppression caused by long-term immunosuppressive therapy.

By the use of polymerase chain reaction DNA-sequences of the recently discovered human herpes virus 8 (Kaposi's sarcoma-associated her-

pes virus) were detected in 11 of 14 biopsy specimens from cutaneous Kaposi's sarcoma, including immunosuppressive therapy-related type (3 of 3), HIV-related type (4 of 5), and classical type (4 of 6). The results support the hypothesis of a pathological role for human herpes virus 8 in all types of Kaposi's sarcoma.

Twenty-seven keratoacanthomas and 29 cutaneous squamous cell carcinomas were examined for the expression of the cell surface carbohydrate sialyl-Tn, the expression of which is correlated with poor prognosis in several human adenocarcinomas, and of the Ki67 epitope, a marker for cell proliferation. By immunohistochemistry, basaloid tumour cells at the periphery of tumour nests and keratinized, differentiated tumour cells showed some degree of sialyl-Tn

expression more often in keratoacanthomas than in squamous cell carcinomas (59% vs 10%; $p < 0.001$; and 89% vs 31%; $p < 0.001$). By immunohistochemical examination of parallel sections and by double immunofluorescence, sialyl-Tn antigen expression was primarily seen in cells that did not express Ki67, although some overlap was present. Keratoacanthomas from transplant recipients did not differ in sialyl-Tn expression compared to those from non-immunosuppressed patients. The results indicate that sialyl-Tn expression is not directly related to cell proliferation, but rather to cellular features of post-mitotic cells, and that sialyl-Tn is not associated with malignant phenotype.

All Norwegian heart transplant recipients with more than one year's survival ($n=140$) were investigated for dermatological disorders. Patients alive at the end of 1993 ($n=122$) were examined clinically, and the medical records for all patients were reviewed. Malignant skin tumours (i.e. basal cell carcinoma, squamous cell carcinoma and malignant melanoma), premalignant skin tumours (i.e. carcinoma in situ and solar keratosis), and/or keratoacanthoma were found in 34 patients (24.3%), of which 18 patients

(12.9%) had malignant skin tumours. Ratio of number of transplant recipients with squamous cell carcinoma and number of transplant recipients with basal cell carcinoma were lower than in most studies among kidney transplant recipients, possibly due to differences in degree of immunosuppression and/or sun exposure. Other frequent dermatological diagnoses included hypertrichosis (86.9%), steroid-induced skin features (59.8%), common warts (42.6%), and seborrheic skin disorders (20.5%).

Eleven patients with organ transplants immunosuppressed with cyclosporine and with culture-proven dermatophyte toe nail infection, were given 250 mg/day terbinafine orally for 12 weeks. No changes in cyclosporine dosage were made. A small, but statistically significant decrease in mean specific cyclosporine blood through levels were found at 4, 8 and 12 weeks. Terbinafine is a safe therapeutic option in cyclosporine-treated patients with dermatophyte nail infection, but cyclosporine levels should be monitored during treatment.

The studies document the need for close dermatological surveillance of organ transplant recipients. An

evaluation of long-term side effects of immunosuppressive drugs, including skin cancer, should be taken into account when new and more powerful immunosuppressive drugs or drug combinations are introduced.

List of original publication

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Petter Jensen Gjersvik (born 1952) graduated from the University of Oslo Medical School (cand.med.) in 1979, and has served in various clinical and research positions at the Department of Dermatology, Rikshospitalet, Oslo from 1982. He is an Assistant Editor of *The Journal of the Norwegian Medical Association* from 1998, and has worked part time in private practice from 1991. He was member of the Central Board of the Norwegian Medical Association in 1994-97.