Skin Care in Organ Transplant Patients Europe meeting report from Annual Meeting, Leiden, The Netherlands, 15-18 May 2014

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DOI: https://doi.org/10.1038/jid.2014.307

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Journal of Investigative Dermatology (2014) **134,** 2861–2863; doi:10.1038/jid.2014.307

The 14th Annual Meeting of ''Skin Care in Organ Transplant Patients Europe'' (SCOPE), a society formed by a group of European dermatologists interested in skin disease in organ transplant recipients (OTRs), was held in Leiden, The Netherlands, from 15 to 18 May 2014. The need for this interest group stems from the increasing numbers of OTRs and their increasing longevity, resulting in markedly increased numbers of squamous cell carcinoma of the skin (SCC) and other benign and malignant skin conditions. On the one hand, most experts believe OTRs to be a model group for SCC development where mechanisms such as chronic sun damage apply to the general population as well, making OTRs a proof-of-concept group with much accelerated cutaneous carcinogenesis. On the other hand, OTRs present with unique mechanisms such as non-immunologic effects of immunosuppressants and increased microbial, in particular viral counts, distinguishing OTR from the general population. Presentations at the SCOPE meeting thus reported findings from both OTR and the general population, as indicated below, to improve our understanding.

The epidemiology of basal cell carcinoma (BCC) in OTRs in Sweden was summarized by Britta Krynitz from the Karolinska Institute in Stockholm, Sweden. The nationwide database allows the study of expected and true incidence of BCC. Since 2004, BCC has systematically been registered on the basis of pathology reports. Histological grading into four types reflecting clinically aggressive behavior was used. A total of 7213 OTRs (63% kidney transplant recipients (KTR), 37% females) with a mean follow-up time of 6.4 years developed 1290 BCCs in total. A first cohort, who underwent transplantion between 2004 and 2011, included 4023 OTRs with 341 BCCs in 175 OTRs, whereas the second cohort, transplanted from 1994 to 2003, contained 3190 OTRs with 429 OTRs developing 949 BCCs. The standardized incidence ratios (SIR) for BCC were 6 (cohort 1) and 9 (cohort 2). OTR transplanted at a younger age (<45 years) showed an even higher SIR in the range of 10. The anatomical distribution was mainly to the head and neck followed by the trunk in both genders. In females, preponderance for the trunk in comparison with the general population was shown. Histological types were evenly split into nodular, superficial, and infiltrative BCC, similar to the general population. A history of melanoma and SCC before transplantation was associated with a fivefold and sevenfold increased risk for subsequent BCC, respectively. When comparing risk for BCC with the risk for SCC (SIR of 6 for BCC and an SIR of 100 for SCC), there was a 17-fold increased risk for SCC versus BCC in the OTRs analyzed.

Structured analyses of OTR cohorts are important for a better understanding of this special patient group. Alexandra Geusau, Allgemeines Krankenhaus, Vienna, Austria, reported on a monocentric cohort of 1130 patients with a median age of 56 years enrolled from 2000 to 2013. Heart transplant recipients (HTRs) made up 43%, liver transplant recipients 11%, lung transplant recipients (LTR) 17%, and KTRs 29%, with a median follow-up of 4.3 years. A total of 314 non-melanoma skin cancers (NMSC) occurred in 102 OTRs, translating into 10.1 NMSCs per 100 patient-years in HTR, 10.3 NMSCs per 100 patient-years for liver transplant, 20.3 NMSCs per 100 patient-years for lung transplant, and 16.2 NMSCs per 100 patient-years for KTRs. Gender, older age at transplantation, and lighter skin type were associated with increased SCC. Bacterial infections occurred in 16.1% of OTRs across all organs transplanted. *Candida* infection occurred in 9.2% and dermatophyte infection in 5.6% of OTRs, where KTRs suffered more *Candida* infections.

A retrospective cohort showing an increased incidence of skin cancer in comparison with other malignancies for HTR in the Czech Republic was reported by Zuzana Sečníková, Bulovka Hospital, Prague, Czech Republic. A total of 603 HTRs (81.8% males) were included. Dilated cardiomyopathy was the underlying condition before heart transplantation in half of the HTRs. Median time to diagnosis of NMSC was 10 years. A total of 119 cases of skin cancer with a median follow-up of 6.3 years were observed in 67 patients (61 males). SCC was most abundant, with 62 tumors (52%) arising. Skin

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The 14th Annual Meeting of SCOPE was held at the Leiden University Medical Center from 15 to 18 May 2014. The 15th Annual Meeting of SCOPE will be hosted in Vienna, Austria, by Alexandra Geusau, from 9 to 12 April 2015. Further information about SCOPE and its upcoming meetings is available at http://www.scopenetwork.org.

cancers made up half of all cancers occurring in this HTR cohort, where lung cancer, gastrointestinal, and post-transplant lymphoproliferative disorders were most frequent among the non-cutaneous cancers.

Risk factors in LTRs for skin cancer were reported by Chantal Bachmann, University Hospital, Zürich, Switzerland. A retrospective cohort analyzed risk factors in the first year after transplantation for SCC development in subsequent years. A total of 205 LTRs were included (female 51%, median age at transplantation 48 years). SCC occurred in a linear manner with 17% of LTRs at 5-year, 34% at 10-year, and 60% at 15-year follow-up affected by SCC. Cytomegalovirus (CMV) reactivation was associated with a 4.2-fold increased risk for SCC. Each instance of CMV reactivation doubled the risk for subsequent SCC. There was a dose–response relationship for every day of CMV replication and SCC incidence. Moxifloxacin use was associated with a 2.9-fold increased risk for SCC and showed a dose–response relationship for SCC incidence.

Clinical exposure to voriconazole is known to result in pronounced photosensitization and aggressive SCC formation with a short delay. The effect of voriconazole on keratinocyte viability *in vitro* was studied by Ahmad Jalili, Allgemeines Krankenhaus, Vienna, Austria. *In vitro*, adding all-*trans* retinoic acid and voriconazole to keratinocytes increased the absorbance of UVA and UVB. The viability and proliferation of keratinocytes and organotypic cultures were not affected by voriconazole, suggesting other mechanisms for the effect of voriconazole on the skin.

The efficacy of rapamycin in the prevention of future SCC was studied in a prospective study on renal transplant recipients switching from calcineurin inhibitors. The 2-year results published in NEJM 2012 showed a benefit of such a switch for low tumor load. Sylvie Euvrard, Hôpital Edouard Herriot, Lyon, France, now reported the 5-year follow-up of this study group. A total of 129 KTRs were enrolled at 61 years of median age with a mean duration of transplantation of 12 years. Eighty-three KTRs could be assessed at 5-year follow-up. In the case of 51 KTRs with a single SCC only at switch, SCC had recurred in 10% of rapamycin-treated KTR versus 44% of calcineurin-inhibitor–treated KTRs. For 32 KTRs with multiple SCCs at switch, SCC had recurred in 18% of patients in the rapamycin-treated KTR group versus 62% of calcineurin-inhibitor–treated KTRs. Renal function remained unchanged.

The impact of ethnicity and skin disease in OTRs is little explored and was analyzed at the transplantation center of Johns Hopkins University, Baltimore, USA. Liliane Borik showed that in over 5,000 transplant recipients at this center 33% were of non-Caucasian ethnicity. Within these non-Caucasian OTRs, the largest population of African Americans was further analyzed. NMSC occurred in 2.5% of African-American OTRs, whereas 41% suffered bacterial, 17% fungal, and 19% viral infections of the skin. Future algorithms for follow-up should consider ethnicity for differential recommendations and interventions.

Actinic keratosis (AK) in association with field cancerization (FC) as a risk for cutaneous SCC was the focus of a study from Manchester, UK, conducted by Wallingford, Lear, and Green. Charlotte Proby from Dundee University, UK, presented data gathered from questionnaires and skin exams in 452 kidney transplant recipients transplanted at a mean age of 52 years. In all 71% (323 of 452 patients) had no AK, and only one of them (0.3%) developed SCC over an 18-month prospective study compared with 7% (4/60) with discrete AK and 21% (15/70) with AK plus FC. The odds ratios found 20-fold increased risk when AK was present and 90-fold increased risk when FC with AK was present. Presence of AK with FC is thus a strong indicator for future SCC events and should be tackled with early intervention.

Charlotte Proby from Dundee, UK, reported genetic data from 20 cutaneous SCC, in which exome sequencing was performed. A high number of mutations, 10-fold higher than in any other solid cancers, was identified. TP53 and NOTCH gene mutations were the most abundant findings. Exome sequencing was validated in 102 SCCs using 454 deep sequencing of candidate genes. 454 sequencing identified NOTCH1 and/or NOTCH2 mutations in 82% of SCCs analyzed, making these mutations the most abundant in SCC. In a set of BRAF inhibitor–induced SCCs, six out of seven showed Notch1 mutations both in the tumor and in adjacent skin. Notch-mutated tumors showed no downstream activation of the Notch pathway, confirming that these were deleterious mutations.

Modern kinase inhibitors may show paradoxical increase of skin tumors. Vemurafenib inhibiting BRAFV600E induces keratoacanthoma-like SCC. Recent work of Catherine Harwood and colleagues, presented by Charlotte Proby, found that histological features consistent with HPV infection including koilocytosis could be identified in such SCCs (10 out of 12 biopsies). Forty-five skin tumors from seven such patients demonstrated low levels of p53 mutations contrasted by increased mutations in HRAS (15/45 SCC). Although HPV DNA could be detected in the majority (80%; 36/45) of these vemurafenib-associated skin lesions, only a minority (1/11 SCC, and 6/18 squamoproliferative lesions) contained viral loads indicative of active infection. Despite the presence of koilocytosis, the low viral copy number speaks against a substantial role for HPV in BRAF inhibitor–induced skin lesions.

Innate immunity may be fundamental in controlling cutaneous carcinogenesis in OTR, as adaptive immunity is subdued by immunosuppressants. Single nucleotide polymorphism analysis was reported by Piotr Dziunycz, University Hospital, Zürich, Switzerland, in 1119 OTR in a selected set of innate immunity genes. Although SCC development before transplantation showed no association, SCC development after transplantation was associated with polymorphisms in the IL1alpha and IL1beta genes with a hazard ratio of 2.81 and 5.02, respectively. On the basis of the findings in other solid cancers, the hypothesis was raised that inflammasome activation may contribute to SCC formation in OTR.

Prediction of an aggressive course in SCC for OTRs is difficult for lack of defined predicting histopathological

characteristics. Jean Kanitakis, Hôpital Eduard Herriot, Lyon, France, reported that among 1200 SCCs 34 primary, aggressive SCCs were diagnosed in 32 OTR, with later recurrences in 20 cases and metastasis in 14 cases. These were pathologically studied in comparison with 25 matched, but nonaggressive, SCCs of the same OTR group. An overall 62% of primary, aggressive SCC cases were localized on the head and neck. Clark level was associated with poor outcome.

Macrophages contribute to tumor formation in many cancers. Anne Marie Rhebergen, Yale University, New Haven, USA, summarized the analyses of tumor-associated macrophages in SCCs of OTRs. Lactic acid stimulation induces VEGF and Arginase-I expression in macrophages, resulting in M2 polarization with increased tumor growth in the mouse. Macrophage density in human SCCs was fourfold increased compared with BCCs and is observed early in carcinogenesis at the *in-situ* stage. Macrophage density was half in SCC *in situ* in OTRs compared with immunocompetent patients. Peritumoral macrophages showed an M2 polarization in immunocompetent patients but not in OTRs.

Tumor staging in SCC according to the American Joint Committee on Cancer (AJCC) confers little distinctive potential for the majority of tumors. Chrysalyne Schmults, Harvard University, Boston, USA, reported an alternative staging system, the Brigham and Women's Hospital (BWH) Staging System, which allows for appropriate upstaging of tumors with high risks of metastasis and death. Clinical diameter 2 cm or larger, depth beyond fat, poor differentiation, and perineural invasion of nerves of 0.1 mm diameter or more were set as the criteria for classification. Lack of risk factors resulted in 0.2% risk of local recurrence. Tumors with one risk factor (BWH T2a) had a 2% risk of nodal disease and 1% risk of SCC death. Tumors with multiple risk factors (BWH T2b/T3) had a 10-year risk of nodal metastasis of 20% and 10-year risk of SCC death of 8%. In all, fifty-two percent of immunosuppressed patients had multiple tumors compared with 22% in immunocompetent patients, whereas there were no differences in metastasis and SCC death.

Kaposi's sarcoma (KS) is an HHV-8-induced tumor of lymphatic endothelial cells with increased incidence in immunosuppression. Céleste Lebbé, Hôpital St Louis, Paris, France, summarized 89 KTRs affected by KS diagnosed at 18 months after transplantation on average. Complete remission was reached in 27% and progression was observed in 8% following reduction of immunosuppression and switch to mTOR inhibitors. Systemic treatment with liposomal doxorubicin, bleomycin, and taxol resulted in side effects in 30–42% of patients. Risk factors for relapse were previous relapse and use of mTOR inhibitors. Patient survival was 86% at 5 years and 71% at 10 years. There were no deaths due to KS, but 19% of deaths were related to treatment-associated adverse events.

HPV associates with SCC in OTR, but the exact mechanisms are still unclear. Roel Genders, Leiden University Medical Center, Leiden, The Netherlands, reported on the correlation of human beta papillomavirus serology and subsequent SCC risk. A total of 445 patients were examined with 1880 sera spanning the time from 1 year before until 1 year after transplantation with a clinical follow-up of up to 22 years. OTRs with skin cancer were seroreactive in 88% of cases compared with 71% of seropositive patients naive for skin cancer. The hazard ratio was 2.95 for keratinocyte carcinomas overall. After adjustment for age, sex, and organ transplanted, the hazard ratio was 3.2 for either SCC or BCC formation when seroreactivity was present around the transplantation.

Polyomaviruses have recently been recognized in Merkel cell carcinoma and other skin diseases with varying degrees of causal correlation. Expanding the body of knowledge, Mariet Feltkamp, Leiden University Medical Center, Leiden, The Netherlands, addressed polyomavirus seropositivity in 799 sera of immunocompetent Australians across all ages by Luminex analysis. Seroprevalences in the cohort studied were 68% for Merkel Cell polyoma virus, 81% for Trichodysplasia spinulosa–associated polyomavirus, 76% for human polyomavirus (HPyV)-6, 66% for HPyV-7, 24% for HPyV-9, and almost 100% for BK polyoma virus. Analyzing a cohort of 101 Dutch KTRs, seroconversion after transplantation was particularly seen for HPyV-9. Viral DNA could be detected in plasma, indicating active HPyV-9 replication in these patients.