SCOPE meeting report Oslo June 10 - 12 2010

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This year marked the tenth annual meeting of SCOPE, an interest group of dermatologists for skin care in organ transplant recipients in Europe. The need for this interest group stems from the increasing numbers of organ transplant recipients and their increasing longevity which results in dramatically increased numbers of squamous cell carcinoma of the skin (SCC) and other benign and malignant skin conditions (Hofbauer *et al.*, 2010). SCOPE meetings have evolved to link a tightly-knit community of clinical dermatologists with basic researchers and in some instances also industry representatives. In a three day format, 60 participants from Europe and the US attended workshops followed by presentations in four separate sessions spanning from clinical observations and case series to clinical studies and translational research results at the Rijkshospitalet in Oslo from June 10 to 12 2010.

SCC PAIN workshop

The first workshop addressed the subject of clinically painful skin lesions. Most dermatologists following organ transplant recipients (OTR) feel that tenderness of a skin lesion is indicative for the presence of invasive squamous cell carcinoma of the skin (SCC), Irma Wisgerhof (Leiden University Medical Center) introduced. To validate this clinical impression, a clinical multicenter study, the PAIN study, was conceived at the Leiden Medical University Center in conjunction with Zürich University Hospital in 2009. With a simple design, at least one hundred consecutive lesions in OTR which were clinically suspicious and scheduled for diagnostic biopsy were assessed for spontaneous tenderness and tenderness on touch in each center. These findings were matched to the subsequent biopsies.

Additional centers in the UK, Netherlands, USA, Poland, Czech Republic, Turkey, Austria and Italy have now joined the SCOPE PAIN data collection process. Currently, up to 500 lesions have been assessed. An interim analysis of several hundred clinical lesions for tenderness showed a sensitivity of 40-70% and a specificity of 75-88% for the diagnosis of SCC in such lesions. Tenderness only lags some percentage points behind the clinical judgment of a dermatologist for such lesions. Inconsistencies between clinical and histopathological diagnosis were mainly keratoacanthoma, Bowen’s disease, basal cell carcinoma and viral

acanthopapilloma. Tenderness, hyperkeratoses, central horn plugs and ulceration seem predictive for the diagnosis of SCC, while bleeding as a symptom may not help in the diagnosis of SCC. The discussion focused on the classification of SCC and the distinction of keratoacanthoma (KA) from SCC, where most participants felt KA to be a variant of SCC, not a separate entity. Data collection will be concluded in March 2011 to allow final analyses to be presented at next year's SCOPE meeting.

OTR Kaposi Sarcoma workshop

The second workshop led by Céleste Lebbé (Hôpital St. Louis Paris) focused on Kaposi sarcoma (KS). A high prevalence of KS is typically observed in OTR and parallels the general seroprevalence for HHV8 in the respective countries. KS prevalence for OTR is at 0.4% in France to 2.3% in Italy. Risk factors for KS are age and African origin. Switching immunosuppression from calcineurin inhibitors (CNI) to mammalian target of rapamycin inhibitors (mTOR inhibitors) has emerged as beneficial in itself for many cases of KS in OTR. Chemotherapy with taxane and liposomal doxorubicin has shown efficacy against KS (Frances *et al.*, 2009).

Céleste Lebbé, Stefano Piaserico and Myrto Trakatelli coordinate the recently conceived SCOPE study on KS in OTR. Retrospectively, HHV8 status and other infections as well as cancer history (skin and other organs) and further parameters will be collected for OTR affected by KS in all participating centers. Details of the ongoing data collection (histological slide review, genotyping, ethical committee requirements) were discussed. A total of 70 KS cases will be sufficient for stratified analysis. Data collection will conclude by the end of 2010. A first interim analysis will be presented at the SCOPE meeting 2011.

SESSION 1: CLINICAL

The first session was opened by Jan Nico Bouwes Bavinck (Leiden University Medical Center) depicting the evolving SCOPE effort reflected by a steady increase in numbers of attendees and participating countries over the years since inception of SCOPE. Catherine Harwood (Barts and the London School of Medicine) and Charlotte Proby (Ninewells Hospital, University of Dundee) presented their study of skin cancer in an ethnically diverse renal transplant (RTR) population in the UK and its implications for skin surveillance. Over 1000 RTR have been followed up for almost 10000 patient years with 10%, 24%, 54% and 73% of cumulative SCC incidence at 5, 10, 20 and 30 years of transplantation. Risk factors for SCC were older age, Caucasian ethnicity and male gender. Two thirds of RTR affected by SCC suffered multiple tumors resulting

in a considerable tumor burden. 74% of all RTR who had suffered a first SCC developed another SCC in the next five years. In the African and Afro Caribbean RTR, however, KS was the most prevalent skin neoplasm with secondary complications such as lymphedema. A differentiated schedule for dermatological follow-up was suggested based on individual risk factors which was controversially discussed by the audience. In summary, the increasing numbers of OTR necessitate prospective studies analyzing cost effectiveness of prevention and therapy of skin cancer in OTR.

Baso-squamous cell carcinomas (BSCC) in OTR were addressed by Fanny Mougel (Hôpital Edouard Herriot, Lyon) as tumors defined by epithelial and basaloid components with HEA positivity. From 3520 OTR in Lyon, 24 cases of BSCC could be identified. A group of 12 BSCC was available for further study. Most were located in the head and neck area. BSCC patients were characterized by a high number of other skin neoplasms, while BSCC did not lead to metastasis in this cohort. HEA staining was recommended for the histopathological diagnosis of BSCC.

Skin conditions after renal transplantation in childhood in Norway were presented by Jan Sitek (Rijkshospitalet, Oslo). Living donors make up an exceptionally high 84% of renal transplants in this group. 178 pediatric RTR were identified and 70 were included into further work-up. The regime was based half on dual, half on triple immunosuppression in this RTR cohort. Pronounced hypertrichosis affected 20%, while 7% reported pronounced gingival hyperplasia. Striae were seen in 7% of RTR still under 18 years of age at observation and in 20% above 18 years. Sebaceous gland hyperplasia was seen only in RTR above 18 years. In RTR below 18 years at follow-up, no skin cancer was observed. In RTR adult at follow-up, BCC and melanoma were found in low numbers.

Jean Kanitakis (Hôpital Edouard Herriot, Lyon) presented cases of composite tissue allografts (hands and face). In conjunction with the main graft, a sentinel skin graft in a second location allowed serial biopsies for dermatopathological surveillance. Skin biopsies were studied for the diagnosis of acute and chronic rejection and the changes are graded according to the specific pathological Banff score. C4d deposits were not identified in biopsies, suggesting that rejection is not antibody-mediated, but rather driven by cellular activation. Progressive expression of neurofilaments tracks the sprouting of nerves into the composite allografts (Kanitakis *et al.*, 2000). Langerhans cells populating the epidermis remain of donor origin and renew locally (Kanitakis *et al.*, 2010).

The impact of skin cancer awareness on prophylactic behavior among renal transplant recipients was discussed by Beata Imko-Walczuk (Pomeranian Center, Gdansk). 182 RTR from 2 polish centers were surveyed. 60% recalled being informed about skin cancer and photoprotection. One third of these received advice before transplantation. Only one tenth was aware of the relationship of sun exposure and long-term skin cancer formation under immunosuppression. Half of all RTR never used sun screens. Depending on the level of knowledge, different behavioral patterns for photoprotection were observed. Prevention should thus be reinforced (Graczyk *et al.*, 2009).

SESSION 2: GENETIC RISK FACTORS AND VIRAL ONCOGENESIS

Genes regulating melanogenesis were introduced by Per Helsing (Rikshospitalet, Oslo) as risk factors for squamous cell carcinoma in RTR in Norway (Helsing *et al.*, 2008). Melanocortin receptor type I (MC1R) polymorphisms have been identified as risk factors for non-melanoma skin cancer. An association with BCC and melanoma is known for ASIP and TYR variations. Norwegian RTR were selected for a case control study. 80 RTR with SCC and 130 RTR without SCC were included. Skin phototype, hair and eye color did not differ, but viral warts were differently prevalent. 2 or more MC1R variants implied an odds ratio of above 4 for SCC independent of skin phototype. The specific p.Arg151Cys variant was associated with SCC. ASIP and TYR variants showed no association in this cohort. Genotyping may therefore inform about individual skin cancer risk in OTR.

Giant warts in a patient with autoimmune hepatitis and Hodgkin's disease were reported by Helena Gonzales (Dermatology Department, Gothenburg Hospital). Topical treatments had been exhausted to no avail. Acitretin at up to 0.5mg/kg bodyweight showed a dramatic reduction, albeit not complete clearance, of his lesion extent.

Human papilloma viruses (HPV) and cutaneous SCC were reviewed by Ingo Nindl (German Cancer Research Center, Heidelberg) (Kohler *et al.*, 2009). His group analyzed warts from OTR and immunocompetent patients. Increased prevalence and number of multiple infections of beta-/gamma-HPV types were shown in OTR. Up to 40% of warts were negative for wart-associated HPV. The resulting search led to the discovery of 10 new HPV types. HPV117 may play an active role in cutaneous wart formation and potentially skin carcinogenesis.

Frank Roesl (German Cancer Research Center, Heidelberg) expanded on Mastomys coucha as a natural

rodent model to study papillomavirus-mediated skin carcinogenesis. MnPV seems ubiquitous and not limited to the spontaneously developing skin tumors. The rolling circle amplification technique identified McPV2 as a new virus in mouse skin tumors. Humoral immune responses were looked at in a case control and a prospective study. MnPV showed increased seroreactivity in relation to tumor formation, while McPV2 seroreactivity showed no relationship. Based on this mouse model, virus-like particles may hold promise as vaccine for prevention of SCC in OTR (Koehl *et al.*, 2008; Nindl and Roesl, 2008).

Nikol Mladkova (Barts and the London School of Medicine and Dentistry, London) shed light on the role of Merkel cell polyomavirus (MCPyV) in non-melanoma skin cancer. Merkel cell carcinoma is a rare and aggressive neoplasm in the general population and seems increased 10- to 40-fold in OTR. The copy number of MCPyV according to the literature is lower in non-melanoma skin cancer than in MCC. In this study, 5 out of 8 MCC were positive for MCPyV and in accompanying NMSC, 15% were MCPyV positive. In the non-MCC patients, about 40% to 50% of non-melanoma skin cancers and warts were positive for MCPyV. Further studies will inform about functionality (Weissenborn *et al.*, 2005).

Trichodysplasia spinulosa is a rare condition in immunocompromised and leukemia patients with viral involvement. Mariet Feltkamp (Leiden University Medical Center) reported such a case in a heart transplant recipient which resolved on topical cidofovir bid within 3 months. The work up identified a new cutaneous human polyomavirus, tentatively named trichodysplasia spinulosa-associated polyomavirus (TSPyV). Collaboration to gather the preciously few clinical cases will be needed in the further clarification of the role of TSPyV (van der Meijden *et al.*, 2010).

HHV8 transmission and related morbidity in OTR were discussed by Céleste Lebbé (Hôpital St. Louis, Paris) (Frances *et al.*, 2009). In France, HHV seroprevalence historically is at about 1% in donors. This recent study screened donors within one week after organ donation, while OTR were screened within a week after donor status was determined. Prospective follow-up was performed for two years. Prevalence in donors was between 4 to 12%. 454 OTR seronegative for HHV8 and having received an organ from a HHV8 positive donor showed a seroconversion about 9 months following transplantation. The probability of seroconversion seems to be at 30%. Seroreversion and reconversion were commonly observed. HHV8 viremia was rare. Routine HHV8 screening may not be cost-effective.

MECHANISMS IN SKIN CARCINOGENESIS

Genome-wide SNP and expression profiling of cutaneous squamous cell carcinogenesis was presented by

Nikol Mladkova. 60 SCC with matching PBMC showed most commonly aberrations were on chromosome 3p and 9q. Laser capture microdissection allowed select analysis of tumor cells. The expression profile correlated with histological subtype, but not with immune status, viral status or gender. Genetic alterations in the progression to AK were observed in comparison to non-sun-exposed and sun-exposed skin. Jak-STAT and PPAR signaling pathways were activated in AK versus sun-exposed skin, while MAPK, ERB, and TGF-beta pathways were involved in AK progression to SCC (Gulati *et al.*, 2010).

Frank de Gruijl (Leiden University Medical Center) as keynote speaker led through the effects of immunosuppressants on UV carcinogenesis at early and late stages (de Gruijl *et al.*, 2010). Rapamycin inhibits angiogenesis and reduces skin tumors in mice independent of p53. Hairless mice under continued UV exposure were used to study initiation and promotion of neoplasms. TL12 fluorescent lamps used with 0.5 MED daily induce skin tumors within several months. Rapamycin inhibits tumor growth, while VEGF expression was down regulated, but does not delay the onset. p53 mutational spectra changed under rapamycin between small and large tumors. Mutant foci of p53 were less under rapamycin and more on cyclosporine A (CsA). CsA led to longer tumor latency on continued UV exposure. Larger tumors occur earlier when UV is given at the CsA trough serum levels, while a period of daily UV followed by CsA did not influence tumor formation.

Günther Hofbauer (Zürich University Hospital) summarized data recently published by Xunwei Wu and Gian-Paolo Dotto where ATF3 was identified as a AP-1 family member specifically induced by calcineurin inhibition such as through CsA. The upregulation of ATF3 down regulated p53 on the mRNA level, preventing senescence and thus promoting SCC formation (Wu *et al.*, 2010).

The Tumorapa Study is an open prospective randomized controlled study switching OTR affected by SCC from calcineurin inhibitors to rapamycin (Hofbauer *et al.*, 2010). Sylvie Euvrard, the Tumorapa study coordinator, reported interim analysis data. The study population has a balanced allocation to either maintenance of CNI or switch to rapamycin. At one year, in the rapamycin group 2.86% were affected with a new SCC (28% in the CNI group). 12.5% of patients on rapamycin had developed another SCC at 2 years follow-up, while maintenance of CNI was associated with 43.75% of patients affected by another SCC. Final analysis will show if the assumed differences can be confirmed.

miRNA expression in SCC was reported on by Piotr Dziunycz (Zürich University Hospital). The study detected upregulation of miR21 and miR184 with a decrease in miR203 in SCC compared to normal human epidermis. CsA or diclofenac had no impact on the expression of these miRs, UVA and UVB had a differential effect on the expression of miR, suggesting different roles for UV in miR regulation (Dziunycz *et*

al., 2010).

Per Arne Andresen (Rikshospitalet, Oslo) presented aspects of constitutive gene variants for TP53 (Helsing *et al.*, 2008) and IL10 and their potential as predictive markers in assessing risk of SCC in RTR. TP53 variants of codon 72 showed Arg/Pro to associate with an odds ratio of 0.37 for SCC. Larger studies will help to verify associations with viral involvement.

INFECTIONS AND MISCELLANEOUS:

Karin Jahn (Medical University of Vienna) reported the case of a liver transplant recipient presenting with erosions on the scalp. Extensive work-up revealed autoimmune bullous disease compatible with cicatricial pemphigoid of the Brunsting-Perry type in spite of systemic immunosuppression. Remission was achieved by increased systemic steroids and topical steroid application.

Candida isolates from organ transplant recipients were examined by Alexandra Geusau (Medical University of Vienna) for their in vitro susceptibility to newer antifungals (Antoniewicz *et al.*, 2009). Mucosal Candida infection is increased at transplantation and dose-dependent on oral prednisone. Over 220 OTR were compared to 217 controls. Candida glabrata was less well inhibited by fluconazole or posaconazole than by itraconazole or voriconazole. In general, Candida albicans seem easily controlled in vitro, while Candida glabrata, C. parapsilosis and C. krusei had higher rates of resistance. There was no difference between transplant patients and immunocompetent individuals.

Superficial fungal infections in 223 consecutive Polish RTR were studied by Beata Imko-Walczuk. Almost two thirds of all RTR had at least one fungal agent identified compared to one quarter only in the control group. Oral Candida colonization was most frequent with 40% of all cases. Foot nails were the second most affected site with Trichophyton mentagrophytes most prevalent (Predota *et al.*, 2009).

Clinical and dermatoscopic follow-up of acquired melanocytic nevi in organ transplant recipients was reported by Deniz Seçkin (Başkent University, Ankara). 15 OTR and 14 controls were followed for at least 9 months. 5 nevi removed in OTR (compound 3, dysplastic 2). Total number and the clinical features and dermatoscopic scores of nevi did not change over the observation period. In this pilot study, no impact for immunosuppression was noticed.

Subsequent squamous- and basal-cell carcinomas in kidney-transplant recipients after the first skin cancer were put in the spotlight by Irma Wisgerhof (Wisgerhof *et al.*, 2010). Follow up for 1906 patients showed a median of 11 years until the first NMSC occurred. Mainly, SCC was followed by SCC and BCC by BCC. Azathioprine increased the risk of SCC following SCC 2.5-fold. For BCC, living organ donation seemed a 2.5

fold risk elevation.

Charlotte Proby (Dundee) summarized PTPRD deletions in association with metastatic cutaneous squamous cell carcinoma (Lambert *et al.*, 2010). Well differentiated SCC had a distinct fingerprint genetically. A microdeletion at 9p23-24, encoding for PTPRD, was inversely correlated with differentiation and statistically associated with metastasis. Heterozygous missense mutations of PTPRD are common (37%), but promoter methylation was not found in cutaneous SCC. Further studies will shed more light on PTPRD as putative tumor suppressor gene.

The 11th SCOPE meeting will be hosted in Dundee, Scotland, UK by Charlotte Proby. We expect contributions from many European countries and our American colleagues from ITSCC (www.itscc.org). The 11th SCOPE meeting will take place from June 16 to June 18. Further information about SCOPE and its upcoming meeting including registration is available at www.scopenetwork.org.

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Figure 1

Attendants of the 10th annual SCOPE meeting gather on the steps of the Rijkshospitalet in Oslo Norway, the venue of this year's meeting.