Basic and clinical features of cutaneous squamous cell carcinoma in organ transplant recipients

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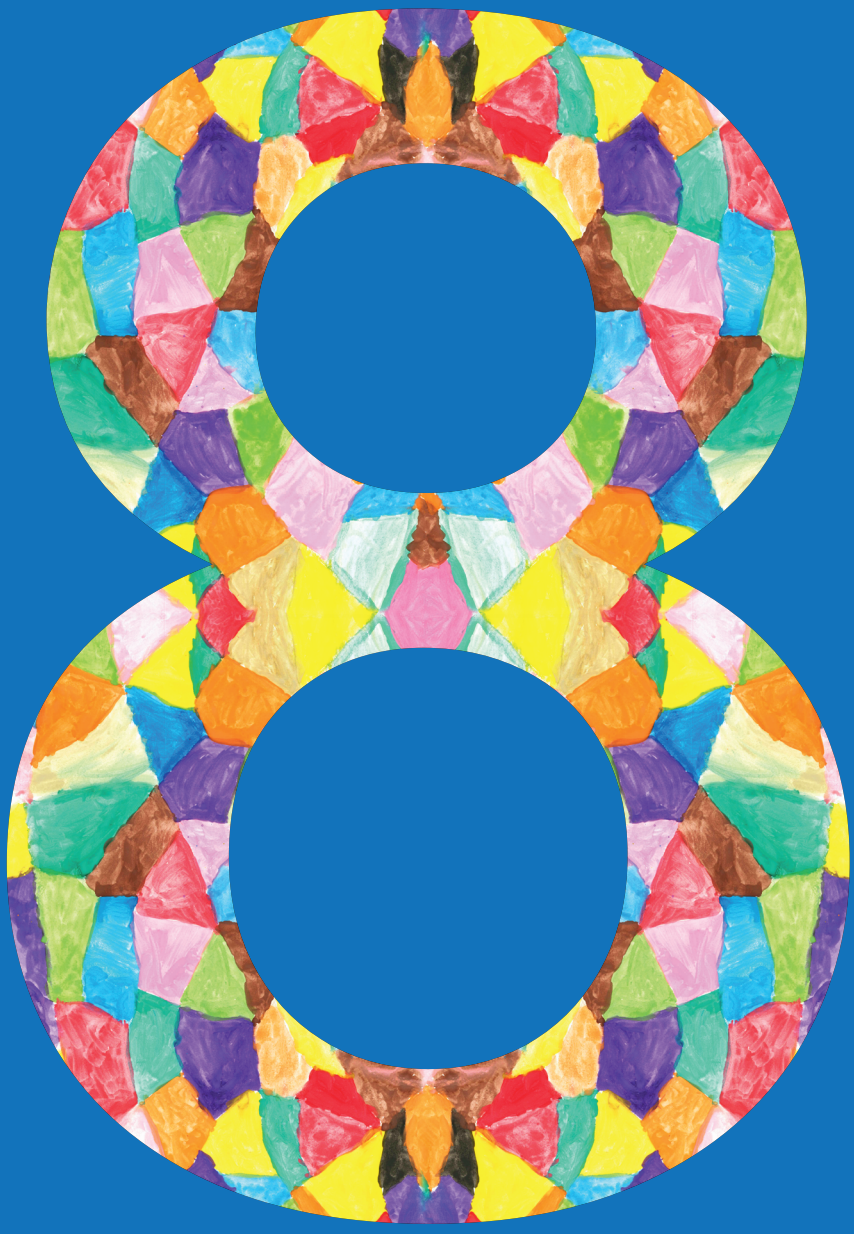

CHAPTER 8

Summary and discussion

Introduction

The risk of cutaneous squamous cell carcinoma (cSCC) is highly increased in organ transplant recipients (OTR) and these tumors carry a major health burden for these patients. This thesis dealt with several aspects of cSCC in OTR. The chapters 2 and 3 review the role of HPV in cSCC and study HPV as a prognostic factor in the aetiology of cSCC. Subsequently, diagnostic factors were studied. In chapter 4 we intended to identify p16 as a possible histopathological marker for cSCC and in chapter 5 we studied the clinical implication of pain as a symptom to differentiate cSCC from other keratinocyte lesions. In chapter 6 we reviewed the literature on metastasis risk in immunocompetent versus OTR population. We studied in chapter 7 in our own population the risk for metastasis, and subsequently risk factors, of cSCC in OTR compared to immunocompetent patients.

The role of HPV

Most studies investigating HPV seroresponses in association with keratinocyte carcinoma (KC) development concerned cross-sectional and case-control studies in the immunocompetent and OTR population with conflicting results.[1-10]

Case-control studies have the disadvantage that a temporal relationship between the exposure and outcome cannot be established. Cohort studies are better equipped for this type of investigation and, therefore, we designed a cohort study with a prolonged follow-up period up to 22 years. HPV serology before and just after the organ transplantation was determined and the OTR were followed until the development of a first KC or by the death of the patient or the end of the follow-up period. The hazard ratio (HR) to develop KC in OTR who were tested Beta-PV seropositive around the time of transplantation compared with Beta-PV-seronegative OTR was 2.9 (95% confidence interval (CI) 1.3–6.4). The HR for cSCC was 2.9 (95% CI 0.99–8.5) and for basal cell carcinoma (BCC) it was 3.1 (95% CI 1.2–8.0). These data were largely confirmed in a recent study which prospectively evaluated the association of Beta-PV in eyebrow hair and seroresponses with KC in OTR.[11] The presence of 5 or more different Beta-PV types in eyebrow hair was associated with a HR of 1.7 (95% CI 1.1- 2.6). No significant association was seen between serum antibodies and cSCC, but a trend of a positive association could be observed. This study did not show an association between Beta-PV and BCC.[11]

A similar association between Beta-PV and cSCC has been established in

immunocompetent individuals. A recently published systematic review included 14 studies with a total of 3112 adult immunocompetent study participants with cSCC and 6020 controls to clarify this association and to evaluate Beta-PV-HPV involvement in cSCC development.[12] The overall association between Beta-PV and cSCC was significant with an adjusted pooled OR of 1.42 (95% CI 1.18-1.72). Subgroup analysis in studies using only serology for HPV detection showed a significant association between Beta-PV with an increased risk of cSCC development with a pooled OR of 1.4 (95% CI 1.2-1.8).
Animal studies also support the role of Beta-PV in the development of cSCC. An elegant study with HPV positive and negative Mastomys coucha (a multimammate rodent that functions as a model which reflects the human situation in many aspects) showed that after UV-exposure the papillomavirus positive animals developed cSCC much more rapidly than the papillomavirus negative animals.[13]

Diagnostic factors

cSCC can be difficult to diagnose in some cases , both clinically and histopathologically. Especially the differentiation from other keratinocyte lesions can be challenging. Since OTR develop numerous types of keratinocyte lesions and the malignant lesions need to be identified as early as possible a search for new diagnostic cSCC markers is useful.

The role of p16 immunostaining

We investigated p16 immunohistochemical staining patterns in order to differentiate between different types of keratinocyte neoplasia; actinic keratosis (AK), Bowen' s disease (BD) , cSCC and benign keratotic lesions in OTR. We found a gradual increase in P16 immunostaining patterns from AK grade 1 to cSCC, as also described in a previous study.[14] The most prominent staining pattern, throughout the whole epidermis, was seen in BD. Furthermore, BD did not follow the gradual staining pattern as observed in AK and cSCC. This might support the opinion that BD could be regarded as a separate entity, instead of part of the classical spectrum of keratinocyte dysplasia from AK to BD to cSCC.[15] It is known that BD does not have to be preceded by an AK and it has clinically different features compared to AK and cSCC.[16-20] However, this is highly speculative and further scientific evidence is needed to confirm this hypothesis.[21] Unfortunately, we did not find distinct patterns of p16 immunostaining that could be used in differentiating cSCC from AK or BD.

Pain as a diagnostic factor

We have found that pain is a powerful warning signal for cSCC in OTR. Especially in patients with numerous skin lesions, pain can be helpful in differentiating cSCC from benign keratinocyte lesions.

Pain is shown to be associated with the degree of inflammation, presence of neutrophils and eosinophils in the inflammatory infiltrate, ulceration, perineural invasion, depth of invasion, and largest diameter length of skin lesion.[22] In collaboration with the University hospital of Zurich, we have found that in OTR, Prostaglandin E2, Tumor Necrosis Factor α, and Pro-opiomelanocortin are potential mediators of pain in cSCC.[23] These mediators are involved in the inflammation process and pain sensation of the skin. The results suggest a role of these mediators in the local tumor microenvironment in mediating pain in cSCC. In clinical practice, pain is a helpful indicator in differentiating cSCC from benign keratinocyte lesions in OTR. However, the exact microenvironment of cytokines involved in pain by cSCC has to be elucidated in more detail.

Metastasis of cSCC in OTR

Incidence

We systematically reviewed the literature and also studied the incidence of cSCC metastases in OTR and the immunocompetent population in our own institute. Our systematic review in chapter 6 showed a higher overall risk of cSCC metastasis in OTR compared to the immunocompetent population. Metastasis risks per single cSCC were substantially lower in both groups. The pooled metastasis risk estimate for OTR was respectively 7.3% (95% CI 6.2-8.4) for cSCC on total body, and 11.0% (95% CI 7.7-14.8) for cSCC of the head and neck area. For the immunocompetent population reported risk estimate analysis showed a pooled metastatic risk of 3.1% (95% CI 2.8-3.4) in total body cSCC and of 8.5% (95% CI 7.3-9.8) in cSCC of the head and neck area. Pooled risk estimate per single cSCC in OTR was 1.3% (95% CI 1.0-1.7) in total body cSCC and 4.0% (95% CI 2.7-5.5) in cSCC of the head and neck area.

In the immunocompetent population these pooled risk estimates were respectively 2.4% (95% CI 2.1-2.6) and 6.7% (95% CI 5.7-7.8). A very recent national population-based study in England which was not included in our systematic review identified a cumulative metastasis incidence of cSCC of 1.1% in women and 2.4% in men with a primary cSCC and immunosuppressed patients carried a twofold higher risk for metastasis.[24]

The metastasis risk of cSCC in our institution over a 10 year period in a cohort of 134 OTR and 459 immunocompetent patients was reported in chapter 7. In all, 23 patients (3.9%; 95% CI 2.6-5.8) developed a metastasis from a cSCC diagnosed in the study period, eight (6.0%; 95% CI 3.1-11.3) in OTR and 15 (3.3%; 95% CI 2.0-5.3) in immunocompetent patients. The metastasis incidence rate ratio for OTR was 1.6 (95% CI 0.67–3.81). Patients with multiple tumors, and especially OTR in our specialized clinic, may be under frequent and strict surveillance, so that new tumors will be detected at an earlier stage. This could partly explain the relatively low number of metastases that we found in our own institution.

General risk factors

Current tumor features that are considered as high risk are increased tumor size, recurrent tumor, poor differentiation grade, perineural, lymphatic, or vascular involvement and depth >6 mm or invasion beyond subcutaneous fat.[25] A case series showed that aggressive cSCC in OTR have a median depth of 6.2mm and local recurrence was present in 45% of cases. Also perineural invasion (39%), poor differentiation (41%) and location in the head and neck area (79%) were present in those cSCC.[26] In the OTR who were studied in our own institution, head and neck location, older age at transplantation and older age at diagnosis of first cSCC were associated with metastasis (Chapter 7). Most of the cSCC that metastasized were still smaller than 2 cm. In the immunocompetent patients in our institution tumor size and tumor depth were associated with metastasis (Chapter 7).

Immunosuppression as a risk factor

Results regarding immunosuppression as a risk factor are contradictory. Immunocompromised status has been considered as a high risk host factor by some studies,[25] but another study that investigated the risk of nodal metastasis in head and neck cSCC, did not find immunosuppression to be a significant factor for the development of LN metastasis.[27] A recent systematic review and meta-analysis (17248 patients with 23421 cSCC) found immunosuppression to be a significant risk factor and tumor depth was associated with the highest risk of local recurrence and metastasis of cSCC.[28] Immunosuppressed patients have demonstrated in one report a higher risk of local recurrence and regional recurrence compared to immunocompetent patients (10.5%).[29] In immunosuppressed patients with cSCC of the head and neck, these cSCC more frequently present with high-risk pathologic

features and inferior outcomes.[30] Immunosuppression is also correlated with decreased disease-specific survival, either by metastasis or because of tumor growth by local infiltration.[31-34]

Future perspectives

Because the incidence of KC is still rising, it is evident that prevention and early detection is of upmost importance in the management of these cancers. Vaccination against papillomavirus was effective in preventing cSCC in the Mastomys coucha.[35] Prophylactic vaccination potentially can also be helpful in preventing the development of cSCC in OTR,[36] but so far no studies were performed in humans to investigate this possibility.

Also the challenge in daily practice is to identify cSCC, especially high-risk cSCC, and to detect a metastasis as early as possible. There is currently no role for p16 immunostaining to be used routinely in the diagnosis of KC. Studying possible markers, which can clearly differentiate between benign, pre-malignant and malignant keratinocyte lesions, can be helpful in the future to make adequate decision for the best treatment. In clinical practice, pain is a helpful indicator in differentiating cSCC from benign lesions. However, the exact microenvironment of cytokines involved in pain by cSCC has to be elucidated in more detail. Early detection and treatment of cSCC prevents it to grow deeper and therefore lowers the risk for metastasis. Early intervention for metastases can confer to a survival advantage and radiologic imaging in patients with high-risk cSCC may influence management.[37] Ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are currently the most frequently used methods for the detection of metastasis. Today there is no consensus in the use of radiologic imaging in the management of cSCC as to which of these methods should be used at what time points and how frequently.[37,38] Sentinel lymph node biopsy can be used as an adjuvant method in detecting metastasis. However it has to be established which patients benefit the most from this procedure, especially in high risk populations like OTR. [39]

The most commonly used tool to identify high-risk cSCC is the T stage of the TNM (tumor, nodes, metastasis) classification. However, current staging systems (7th and 8th edition of the AJCC staging system, the staging system used by Breuninger et al and the Brigham and Women's Hospital (BWH) staging system) poorly to moderately distinguish between patients who developed metastasis and those who did not.[40] A

new evidence-based risk stratification system into low, intermediate, and high risk cSCC has been proposed recently, to better allow risk stratification of cSCC based on tumor characteristics and other risk factors, including immunosuppression.[41]
Due to the ongoing insight in risk factors for cSCC, evidence based guidelines for the care of cSCC will be periodically updated with the most recent published data. The improvements in staging systems leads to more precise risk stratification and identification of aggressive cSCC, allowing for an accurate framework for management based on these risk levels.[42-44] Overall, due to higher risk of immunosuppression, it is most important to keep in mind that close and regular inspection of the skin with adequate and rapid diagnosis and treatment of cSCC is important to prevent metastasis in OTR.[45]

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