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Abstract: Organ transplant recipients (OTR) are at a significantly increased risk for developing a wide variety of skin cancers, particularly epithelial skin cancer, Merkel cell carcinoma and Kaposi's sarcoma. Melanoma, skin adnexal neoplasm and cutaneous lymphomas are also more common in OTR and may differ in their clinicopathologic presentation from tumors in immunocompetent patients. The accuracy of clinical diagnosis of suspected premalignant and malignant skin lesions in OTR is modest. Therefore, histopathological diagnosis is an essential element for the diagnostic workup of skin cancers and, in addition, provides important information on prognosis. Squamous cell carcinoma and intraepithelial neoplasias (actinic keratosis, squamous cell carcinoma in situ or Bowen's disease) are the most common forms of skin cancer in OTR. The risk of Merkel cell carcinoma and Kaposi's sarcoma is dramatically increased in OTR. Merkel cell carcinoma shows a highly aggressive course. Kaposi's sarcoma tends to spread to extracutaneous sites. Primary cutaneous lymphomas developing after organ transplantation are rare. The spectrum of cutaneous B cell lymphomas in OTR, in particular, differs significantly from that of the general population, with a predominance of Epstein-Barr virus-driven posttransplant lymphoproliferative disorder. This review discusses the clinical and histopathological aspects of skin cancers in OTR, the impact of dermatopathological analysis on prognosis and the understanding of the pathogenesis of these neoplasms.

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Skin Cancer in Organ Transplant Recipients

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Key Words

Skin cancers · Immunosuppression · Organ transplantation

Abstract

Organ transplant recipients (OTR) are at a significantly increased risk for developing a wide variety of skin cancers, particularly epithelial skin cancer, Merkel cell carcinoma and Kaposi's sarcoma. Melanoma, skin adnexal neoplasm and cutaneous lymphomas are also more common in OTR and may differ in their clinicopathologic presentation from tumors in immunocompetent patients. The accuracy of clinical diagnosis of suspected premalignant and malignant skin lesions in OTR is modest. Therefore, histopathological diagnosis is an essential element for the diagnostic workup of skin cancers and, in addition, provides important information on prognosis. Squamous cell carcinoma and intraepithelial neoplasias (actinic keratosis, squamous cell carcinoma in situ or Bowen's disease) are the most common forms of skin cancer in OTR. The risk of Merkel cell carcinoma and Kaposi's sarcoma is dramatically increased in OTR. Merkel cell carcinoma shows a highly aggressive course. Kaposi's sarcoma tends to spread to extracutaneous sites. Primary cutaneous lymphomas developing after organ transplantation are rare. The spectrum of cutaneous B cell lymphomas in OTR, in particular, differs significantly from that of the general population, with a predominance of Epstein-Barr virus-driven posttrans-

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Introduction

Organ transplantation recipients (OTR) receive immunosuppressive treatment to maintain adequate graft function. Apart from this beneficial and intended effect, the immunosuppression and consecutively decreased immunosurveillance, however, carry the risk for the development of a wide variety of cancers including epithelial skin cancer, Merkel cell carcinoma (MCC) and Kaposi's sarcoma (KS). The spectrum of skin cancers in OTR and their prevalence depends on the grafted organ, the intensity and composition as well as the duration of the immunosuppressive therapy, UV light exposure, genetic factors and immunological control of oncogenic viruses which are involved in the pathogenesis of skin neoplasias. Skin tumors represent a major part of transplantation-related morbidity and mortality. Among the epithelial skin cancers, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) account for more than 90% of all skin

cancers in OTR (for review see [1]). Primary cutaneous lymphomas appearing in OTR are rare and differ significantly from posttransplant lymphoproliferative disorder (PTLD) at other extranodal sites. In an organ-specific manner, there is a preponderance of T cell-derived, Epstein-Barr virus-negative lymphoproliferations. The less frequent primary cutaneous B cell-derived PTLD is usually monomorphic with a blastic morphology and an aggressive biological behavior.

As the accuracy of clinical diagnosis of suspected premalignant and malignant skin lesions in OTR is limited, the histopathological diagnosis is essential for the diagnostic workup of skin cancers [2]. In this review, we discuss the pathogenetic aspects and the clinicopathological features of the most common skin cancers and lymphomas in OTR.

Epithelial Skin Neoplasms

SCC and Its Precursors

Cutaneous SCC is the most common skin cancer in OTR and occurs 65–250 times more frequently than in the general population [3]. Within 20 years of transplantation, 20–75% of OTR are affected by at least one SCC. The high incidence of SCC results in an SCC to BCC ratio of 5:1 in OTR. This ratio differs from the one in the general population, in which BCC is more prevalent than SCC (ratio SCC to BCC = 1:4) [1]. Men are at a higher risk for SCC [3, 4]. UV-light-exposed body regions are the predilection sites for SCC, its precursors actinic/solar keratosis (AK) and SCC in situ.

AK presents with erythematous and often hyperkeratotic skin lesions. Field cancerization with multiple AK within one anatomic region is a common finding [5]. AK is characterized by disarranged stratification of the lower part of the epidermis and dysplastic keratinocytes which may extend into the upper parts of the hair follicle epithelium. Acantholysis and hyperparakeratosis, often alternating with orthokeratosis, as well as increased melanin deposition are common findings. In Bowen's disease (BD), the epidermis shows full-thickness atypia with enlarged and sometimes multinucleated keratinocytes with prominent nuclear pleomorphism and atypical mitoses. BD often occurs multifocally in OTR and also arises in body areas protected from UV light such as the trunk or in the anogenital area. A rather dense inflammatory infiltrate composed of lymphocytes, histiocytes and plasma cells is common in AK and BD. Early recognition and treatment of precancerous lesions are



Fig. 1. SCC: hyperkeratotic plaque on the lower lip in a renal transplant recipient.

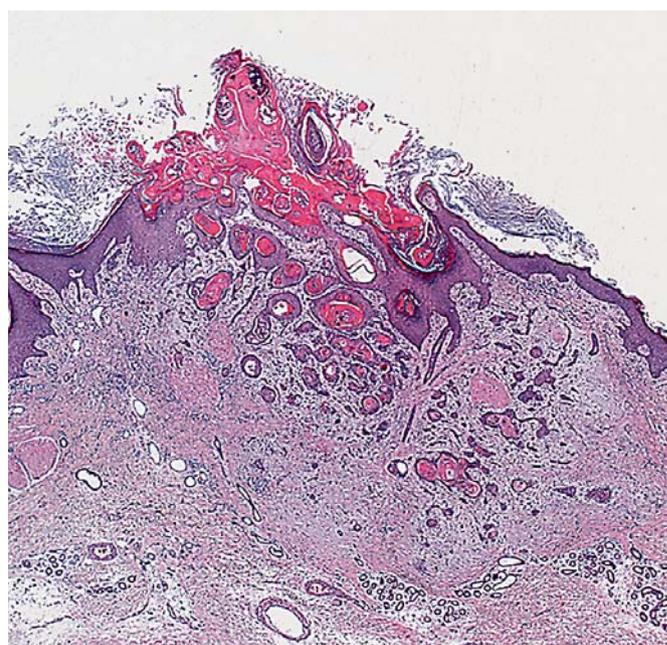


Fig. 2. SCC: proliferation of epithelial cells with squamous differentiation. Note hyperkeratosis. HE. Original magnification $\times 2.5$.

recommended to prevent the development of invasive tumors [6].

SCC manifests with a hyperkeratotic or ulcerated plaque or nodule (fig. 1). Histologically, it shows invasive growth of epithelial tumor cells arising from the epidermis (fig. 2). Ulceration is common. The neoplastic cells show squamous differentiation with variable degrees of keratinization, mitoses and prominent nuclear pleomorphism, particularly at the invasion front and in poorly differentiated SCC. Differentiation (grading) of SCC in OTR does not differ from SCC in the general population



Fig. 3. Nodular BCC with marked telangiectasias on the right temple.

[4]. SCC in OTR presents more often with spindle cell morphology found in 20% of the lesions, and acantholysis [4, 7]. Expression of cytokeratins (especially CK 5/6), p63 and CAM5.2 is particularly helpful for proving the epithelial origin of spindle cell SCC. Perineural growth appears not to be more frequent in OTR, but it indicates more extensive growth and a higher risk of recurrence [4, 8, 9]. The peritumoral inflammatory infiltrate is significantly less intense in OTR [4]. Verrucous SCC represents a highly differentiated form of SCC, which more commonly arises in the anogenital area and oral mucosa. Histologically, it shows blunt-ended epithelial proliferations with bulbous downgrowths. As the malignant nature of this SCC variant may be readily overlooked in small and superficial biopsies, its diagnosis often requires large biopsies as well as the clinicopathological correlation. Prognostic markers in SCC of an increased recurrence rate and/or poor prognosis due to subsequent metastasis include localization (the ear, lip, scalp and temple are primary sites), tumor thickness (>4 mm), tumor size (>2 cm), Clark level IV, poor differentiation, spindle cell morphology, ulceration, acantholytic changes, single cell invasion, perineural growth and bone invasion [10, 11].

The pathogenesis of SCC is multifactorial, involving human papillomaviruses, UV-light-induced genetic changes and altered tumor microenvironment. Remarkably, immunosuppressive drugs, such as azathioprine, and UV light radiation act synergistically mutagenic [12, 13]. Infection with beta human papillomaviruses is associated with an increased risk of SCC, and susceptibility to UV light and SCC is stronger in beta human papillomavirus-seropositive patients [14]. Genetic alterations of the tumor suppressor gene p53 have been found in premalignant and malignant skin lesions of renal transplant recipients (RTR)

[15]. A subset of SCC harbors mutations of H-RAS, but not K-RAS or N-RAS, and alterations of CDKN2A [16]. Loss of heterozygosity can be observed in SCC of OTR as well as in the general population [17]. MicroRNA-21 and microRNA-184 are upregulated in SCC of OTR and their expression is increased by UVA light [18]. The tumor microenvironment is characterized by a reduced number of CD123+ plasmacytoid dendritic cells and FOXP3+ T cells in the peritumoral inflammatory infiltrate; this is associated with progression of SCC in OTR [8].

Surgical excision including Mohs surgery is the first-line therapy of SCC [6, 19]. A reduction of immunosuppressive drugs should be considered in patients with several SCC or multifocal BD and those with metastatic SCC [6]. Conversion from calcineurin inhibitors to the mTOR inhibitor sirolimus reduces the thickness and vascularization of SCC in OTR and should be considered in early SCC development, in particular [20, 21].

Basal Cell Carcinoma

BCC is the second most frequent cancer in OTR [1, 3] with a 10- to 16-fold increased risk among OTR compared to the general population. In a retrospective study, BCC was found in 14.5% of RTR and manifests with a delay of 5–11 years after the transplant [22]. UV-light-exposed body regions, particularly the head and neck, are predilection sites. There are numerous clinical and histological variants of BCC [23], but the clinical and histological features of BCC in OTR do not differ significantly from those in immunocompetent individuals. Nodular BCC is the most common form seen in OTR (fig. 3). It presents clinically as a nodular lesion, often undergoing ulceration, and histologically as variably sized nodular proliferations of basaloid epithelial cells displaying a characteristic palisading arrangement of nuclei at the periphery. Cystic foci, adnexal differentiation and pigmentation may be present. The tumor islands are separated from the surrounding tumor stroma by characteristic, often mucin-containing clefts, which are visible in vivo by reflectance confocal microscopy and therefore do not represent a retraction artifact, as previously believed. The superficial variant of BCC more commonly develops on the trunk or the limbs, is slightly infiltrated, erythematous or partially pigmented and may grow up to several centimeters in diameter. The aggregates of basaloid tumor cells bud from the interfollicular epidermis and appear to be multifocal but, in fact, represent a superficial reticulated network of tumor strands. Tumor growth in superficial BCC remains restricted to the upper dermis with a tumor depth less than 0.5 mm. Progression into nodular

or morpheiform BCC, however, can take place. A prominent tumor stroma and an inflammatory infiltrate are almost invariably present in superficial BCC, although the infiltrate is reported to be less pronounced in BCC of OTR than in the general population [10]. The morpheiform variant of BCC manifests as a depressed, often hypopigmented, scar-like lesion. The histology is characterized by an ill-defined proliferation of small strands of basaloid tumor cells embedded in a dense, sclerotic stroma. Perineural growth is not uncommon. Basosquamous (cell) carcinoma is considered a variant of BCC with focal squamous differentiation. In OTR, it is a rare tumor with an incidence of 0.3% and develops with a long delay of up to 13 years after the organ transplant [24].

Surgical excision is the first-line therapy for nodular and morpheiform BCC. Micrographically controlled excision or Mohs surgery is indicated for lesions in specific body regions (the nose and eye) to limit surgical defects, for recurrent BCC and for tumors with perineural growth. For superficial BCC, treatment with photodynamic therapy, cryosurgery or laser surgery, imiquimod and topical 5-fluorouracil are alternatives to surgical excision. The prognosis of BCC does not seem to be worse in OTR compared to in the general population [22, 25]. Recurrence after surgical excision has been observed in 10% of RTR [22]. Metastasizing BCC is exceedingly rare. Therefore, BCCs in RTR do not require treatment different from that for other patient groups. Pathogenetically, genetic alterations in the sonic hedgehog pathway involving patched homologue 1 (PTCH1), a tumor suppressor gene, and a G-protein-coupled receptor (SMOH) play an important role [23]. Thus, inhibition of the hedgehog pathways represents a promising therapeutic approach and has been employed especially for advanced BCC.

Adnexal Skin Neoplasms

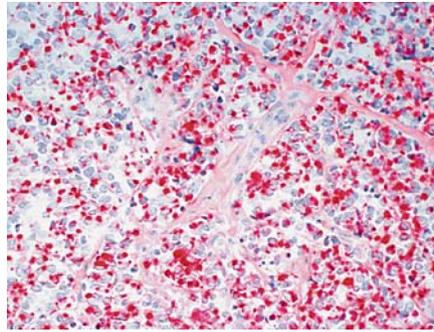
Adnexal skin neoplasms comprise benign or malignant epithelial tumors with differentiation towards hair follicle epithelium (trichogenic), eccrine or apocrine sweat glands or sebaceous glands. OTR are at increased risk for cutaneous adnexal neoplasms which affect 3% of OTR [4]. Most OTR with adnexal skin neoplasms (71%) also suffer from other nonmelanoma skin cancers. Benign tumors include pilomatricoma, tumor of the follicular infundibulum, sebaceous adenoma and eccrine poroma. Malignant adnexal tumors, particularly sebaceous carcinoma, seem to be more common in OTR than in the general population. Fourteen percent of RTR had multiple adnexal tumors with the head and neck being the predilection site (74%) [4].

Merkel Cell Carcinoma

MCC (a synonym for primary cutaneous neuroendocrine carcinoma) is a rare but highly aggressive neoplasm with a poor prognosis. The relative risk of OTR developing MCC is 0.13 per 100 person-years and is 5- to 10-fold more than in the general population [26]. Risk factors are exposure to UV light, age, chronic lymphocytic leukemia and immunosuppression. MCC shows a male preponderance and affects OTR mostly in their fifth decade, with a latency of 7.6 years after the organ transplant (range 5–286 months) [27]. Predilection sites are UV-light-exposed skin regions, particularly the head and neck. Usually, MCC presents as a solitary, rapidly growing, red-to-bluish dome-shaped nodule, which may ulcerate. In one third of the patients, MCC is clinically misinterpreted as cysts. Histologically, nodular or diffuse infiltrates of small- to medium-sized basaloid-appearing or blast-like cells with hyperchromatic nuclei, focal necrosis and mitoses are found. The trabecular growth pattern with ribbons of tumor cells is rarer. Occasionally, focal squamous differentiation can be observed. Small-cell type and vascular invasion are considered as histological markers of poor prognosis. At the periphery of the tumor, dissection of collagen bundles by strands of tumor cells or scattered single tumor cells with small hyperchromatic nuclei may be misinterpreted as peritumoral lymphocytic infiltrate. Tumor cells in MCC may display pagetoid spread into the overlying epidermis which has to be distinguished by immunohistochemistry from malignant melanoma, Paget's disease, SCC in situ with pagetoid growth and sebaceous carcinoma [28]. Occasionally, MCC contains a dense intra- and peritumoral lymphocytic infiltrate which may mimic lymphoma or pseudolymphoma and obscure tumor cells [29]. Collisions of MCC and SCC in situ, invasive SCC or BCC have been reported [30]. Tumor cells in MCC express pancytokeratin (in 100% of cases) and cytokeratin 20 (CK20; in 65–93%) with a characteristic perinuclear dot-like pattern (fig. 4), CAM5.2 (in 100%) and EMA (in 100%). The tumor cells express the neuroendocrine markers synaptophysin (67–75%) and chromogranin (75%) as well as CD56 (N-CAM). A recent study showed that p63 expression represents a strong risk factor for shortened survival, but this finding has yet to be confirmed by studies on larger cohorts [31].

The clonal integration of Merkel cell polyomavirus (MCPyV) DNA into tumor cell DNA indicates that this polyomavirus contributes to tumor development. MCPyV is present in the majority (60–90%) of MCC cases. The presence of MCPyV DNA, however, is not re-

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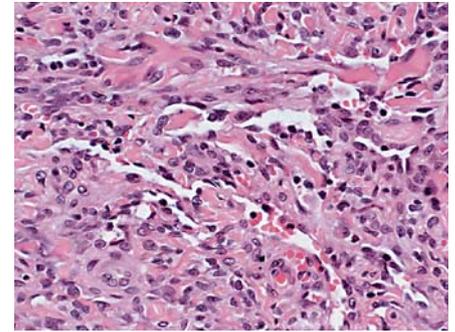


Fig. 4. Characteristic perinuclear dot-like pattern of cytokeratin 20 (red; immunohistochemistry). Original magnification $\times 200$.

Fig. 5. KS (patch stage) with irregularly shaped and thin-walled vessels dissecting dermal collagen bundle. HE. Original magnification $\times 200$.

stricted to MCC; viral DNA has also been found in other benign and malignant neoplasms such as nonmelanoma skin cancers, seborrheic keratoses and common warts [32], and may be carried to these lesions via blood-borne inflammatory CD14⁺ CD16⁻ monocytes serving as a reservoir for MCPyV [33]. In comparison, detection of the large T antigen of MCPyV by immunohistochemistry is a useful adjunctive marker for the diagnosis of MCC [34]. MCC metastasizes in 68% of the patients [35]. Sentinel lymph node biopsy has therefore been recommended for MCC. Prognosis is generally poor with a 5-year-survival rate of less than 50%. Treatment includes local wide excision, radiotherapy and multiagent chemotherapy for metastatic disease.

Kaposi's Sarcoma

KS accounts for 5.7% of all cancers in OTR. Its incidence is 400- to 500-fold more than in the nontransplant population [36]. KS often occurs sooner after organ transplantation than nonmelanoma skin cancers, with an average delay after surgery that ranges from 2 months to 18 years (mean 13 months) [36, 37]. The male to female ratio is 1:2–3 in immunocompromised patients and hereby differs from the ratio in classic KS (17:1). Three clinical and histological stages (patch – plaque – tumor) can be distinguished.

The early skin lesions (patch stage) are characterized by a proliferation of dilated, irregularly shaped and thin-walled vessels lined by a single layer of flattened endothelial cells lacking significant atypia (fig. 5). These vessels dissociate dermal collagen bundles and surround preexisting blood vessels and skin appendages, a phenomenon termed promontory sign. Extravasated erythrocytes and hemosiderin deposits are present. The intra- and peritumoral inflammatory infiltrate consists of plasma cell,

lymphocytes and macrophages. Progressive lymphangioma and targetoid hemosiderotic hemangioma have to be differentiated from early KS. In addition, the findings in early or patch-stage KS are subtle and may be misdiagnosed as inflammatory dermatosis. In the plaque and nodular stages, a proliferation of spindle-shaped cells predominates with slit-like vessels sometimes filled by erythrocytes. Cytological atypia of tumor cells is relatively subtle, in contrast to angiosarcoma. Clinical and histological variants of KS include the micronodular form, presenting with tiny red papules clinically resembling capillary hemangioma, and hyperkeratotic (verrucous), keloidal, molluscoid, pyogenic granuloma-like and intravascular KS [38, 39]. The tumor cells express endothelial markers (CD31, CD34 and von Willebrand factor/factor VIII), podoplanin and PROX-1. *Human herpesvirus 8* (HHV-8) is the etiologic agent of KS. Immunohistochemical detection of HHV-8 is a crucial diagnostic tool with a high sensitivity and specificity [40]. HHV-8 induces a reprogramming of CD34⁺ blood endothelial cells to express a lymphatic phenotype [podoplanin (PROX-1)]. Viral proteins of HHV-8 such as vIL-6 or v-cyclin result in deregulation of the cell cycle, inhibition of apoptosis of tumor cells and suppression of antitumoral host immune response. The virus is usually acquired months to years before the occurrence of KS. HHV-8 can be transmitted by horizontal and vertical transmission via sexual contact, blood or body fluids. In OTR, KS usually develops following HHV-8 reactivation, although transmission from the graft is not uncommon. In contrast to the classic form of KS, which runs a slowly progressive and indolent course, the 5-year survival rate of KS in OTR is 69% [41]. Mucocutaneous lesions of KS are found in more than 75% of OTR with 25–50% of the patients developing visceral lesions during the course of the disease [36]. Treatment of KS in OTR comprises a reduction of immunosuppressive drugs, which leads to complete re-

mission in 25–30% of patients but carries the risk for rejection of the transplanted organ, switching the immunosuppressive medication to an mTOR inhibitor, surgical excision, radiotherapy, intralesional bleomycin injection, liposomal anthracyclines and interferon alpha. Clinical tumor regression after topical treatment with imiquimod does not necessarily indicate complete tumor regression as, histologically, tumor persistence has been identified [42].

Cutaneous Melanoma

The risk for cutaneous melanoma (CM) is only slightly increased, but CM shows a significant mortality [1, 43, 44]. It accounts for approximately 6% of skin cancers in OTR and mostly affects young patients (mean age 36 years) with a male preponderance. It develops after a median posttransplant delay of 4–5 years [1, 43, 45, 46]. Risk factors for CM in OTR include intermittent exposure to UV light (and sunburns), inability to tan, multiple and dysplastic nevi as well as a family history of CM. The clinical presentation does not differ from that in immunocompetent individuals [46]. Histologically, CM is characterized by asymmetrical architecture, cellular atypia of melanocytes arranged as single units or in confluent nests, intraepidermal pagetoid spread of atypical melanocytes and a lack of maturation of the intradermal component of the neoplasm. Early forms of acral lentiginous and mucosal CM show only subtle findings with a few atypical melanocytes in the junctional area. Lentigo melanoma in situ (so-called lentigo maligna) is prone to being misinterpreted as dysplastic nevus, particularly in incisional biopsies. Therefore, melanocytic lesions with dysplastic features occurring in UV-light-exposed skin should be completely excised.

The desmoplastic variant of CM (DM) typically arises from lentigo maligna, manifests with a diffuse proliferation of spindle-cell tumor cells and may completely lack pigmentation. Staining for S-100 protein and p75 are the most sensitive markers for DM, whereas other melanocytic markers are often absent. Prognostic criteria in CM are tumor thickness (TD; Breslow index), mitotic index (in MM with a TD <1 mm), and ulceration. In a series of OTR reported in 1996, MM showed a TD >0.76 mm or greater than Clark's level III in 69% of patients [45]. In a recent study, however, the TD was <1 mm in the majority of cases [44], which may be as a result of closer screening of OTR for skin cancers. CM with Breslow thickness <2 mm in OTR has a similar

prognosis to tumors in the general population, whereas MM with Breslow thickness >2 mm exhibits a worse prognosis than CM in immunocompetent individuals [47]. Sentinel lymph node biopsy is recommended for cases with a TD of between 1 and 4 mm and/or stage pT1b (AJCC classification, 2010) with a mitotic index of >1 mitosis per mm². Interestingly, melanocytic tumors from OTR have been found to have a lower frequency of BRAFV600E mutations than similar lesions from immunocompetent individuals (45.4 vs. 63.5%, $p < 0.05$) [48]. A reduction of immunosuppressive treatment is recommended for OTR with CM [19]. In patients with CM prior to organ transplantation, there seems not to be a higher risk for recurrence or metastasis.

Cutaneous Lymphomas

PTLD represent lymphoid proliferations developing as a consequence of immunosuppression in a recipient of a solid organ, bone marrow or stem cell allograft. PTLD affects 1–5% of solid OTR, but primary cutaneous lymphomas in OTR appear to be rare and so far only a few cases have been reported. They develop 5–8 years after organ transplantation [1, 49]. According to the WHO classification (2008; 4th edition), PTLD is classified as early lesions, polymorphic, monomorphic PTLD and classic Hodgkin lymphoma-type PTLD [50]. In contrast to nodal and other extranodal lymphomas in OTR, 70% of primary cutaneous lymphomas in OTR are of T cell origin, whereas only 30% are cutaneous B cell lymphomas [Seckin, submitted]. Mycosis fungoides and cutaneous CD30+ lymphoproliferative disorders (CD30+ LPD) appear to be the most common forms of primary cutaneous lymphomas of T cell origin. MF presents with erythematous and slightly scaling patches and plaques mostly on the trunk. Histologically, the disease is characterized by an epidermotropic infiltrate of atypical small to medium-sized lymphocytes. Similar to other patients with MF, the disease in OTR appears to progress slowly. Cutaneous CD30+ LPD manifest with nodular, often ulcerated lesions. In contrast to CD30+ LPD in the general population, spontaneous regression of tumoral lesions is not observed in OTR. Histologically, dense infiltrates of large pleomorphic and anaplastic lymphoid cells are seen [51]. By definition, more than 75% of tumor cells express CD30 in addition to T cell markers (CD2, CD4 and CD8). CD30+ LPD run an aggressive course in OTR, which is in contrast to the excellent prognosis of cutaneous CD30+ LPD in the general population. Staging examinations are

essential to distinguish the primary cutaneous from the systemic form of CD30+ LPD. The epidemiology and composition of cutaneous B cell lymphomas in OTR differ significantly from those in immunocompetent patients. In OTR, B cell lymphomas are often monomorphic and of large-cell morphology (centroblastic, immunoblastic and plasmablastic) [49]. The vast majority are associated with Epstein-Barr virus as shown by the presence of Epstein-Barr virus RNA transcripts (EBER) by in situ hybridization.

Conclusions

OTR are at a significantly increased risk for developing a wide variety of skin cancers. As atypical clinical manifestations are not infrequent and the accuracy of clinical diagnosis is limited, histopathology plays a crucial role in the diagnostic workup of skin cancer in OTR and may also provide important prognostic data.

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