short review

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Skin tumours in organ transplant recipients—implications for the plastic surgeon

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Summary Squamous cell carcinoma of the skin (SCC) and basal cell carcinoma (BCC) are common entities, often with a benign course. Tumour biology, however, is different in immunosuppressed individuals, such as organ transplant recipients (OTR). As immunosuppression-sparing protocols have not yet been successfully introduced to the clinics, nonmelanoma skin cancers (NMSCs) will continue to affect a majority of OTR, leading to significant morbidity and mortality. Interdisciplinary treatment including the transplant physician, dermatologist and the plastic surgeon is warranted for optimal patient management. This review focuses on special tumour characteristics and therapeutic requirements among OTR. Recommendations for local treatment and oncoplastic surgery are discussed.

Keywords Nonmelanoma skin cancer · Squamous cell skin cancer · Basal cell cancer · Immunosuppression · Oncoplastic surgery

Immunosuppression and NMSC development

Nonmelanoma skin cancer (NMSC) is known for its high prevalence in fair-skinned individuals, and correlates with cumulative ultraviolet light (UV) exposure [1]. In immunocompetent persons, 1 of 4 NMNCs are basal cell carcinomas (BCC). This ratio, however, is reversed in the transplant population, with squamous cell carcinomas (SCC) representing the majority. According to the literature, the risk for immunocompromised patients to develop SCC is increased 50- to 200-fold [2, 3].

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Apart from the increased incidence, tumour biology clearly differs from the non-transplanted population. Immunosuppression has been shown to decrease outcomes of NMSCs in large meta-analysis [4] and prospective clinical trials [5]. OTR have a 30–52-times higher mortality compared with the general population [6].

Generally, immunosuppressive dose and time of exposure seem to be important contributing factors. Liver transplant recipients, which require the lowest trough levels to prevent rejection, also carry the lowest risk for posttransplant NMSCs [7].

One immunosuppressive drug which is clearly linked to SCC development is azathioprine, known for its direct contribution to UV-induced DNA damage [8]. The influence of other immunosuppressive drugs, such as calcineurin inhibitors, seem to be rather indirect: The immunocompromised host can eliminate DNA changes, mostly UV-induced, less efficiently. This is supported by the fact that 20–30% of all precancerous lesions progress to invasive SCCs in OTR, which is twice as much compared to non-transplanted patients [9].

Preventive measures

As UV-exposure remains the conditio sine qua non for the development of NMSC even among OTR, patient education in terms of sun protection is an important cornerstone [10]. Regular dermatologic visits, and pro-active bioptic mapping of suspicious lesions, is warranted.

The favourable effects of mTOR (mammalian target of rapamycin) inhibitors on various types of cancer have been previously described. Also for SCCs, the mTOR inhibitors have shown decreased incidence in de novo tumorigenesis, slowed progression or even regression of precancerous lesions [11]. A limited im-

munosuppressive potency, and specific side effects, however, preclude a more widespread use of mTOR inhibitors instead of CNIs (calcineurin inhibitors).

Apart from the modification of immunosuppression, chemoprevention is currently assessed: Nicotinamide is a cofactor for ATP (adenosine triphosphate) production, and enhances DNA repair. In a randomized controlled trial, patients with a history of at least two NMSCs in the previous 5 years were included. Both the incidence of BCCs and SCCs decreased by 20 and 30%, respectively, during a period of 12 months [12]. Nicotinamide was recently shown to decrease the number of actinic keratoses in a study collective of OTR [13].

Surgical approach

Organ transplant recipients often have extensive areas of actinic keratoses or even invasive SCCs. For the treatment of larger sun-exposed areas, a "field therapy" with bioptic mapping, topical therapy, and surgical excision with clear margins is recommended.

The plastic surgeon often becomes involved in the setting of a high-risk tumour. This includes SCCs of poor histologic differentiation, large size, deep invasion, or certain anatomic locations: SCCs which are located near the parotid gland have been described to be especially at risk for metastasis to the draining lymph nodes [14]. Tumours of the ear drain to the parotid lymphatic nodes and are thus considered of high risk for lymph node metastasis. SCCs on the scalp often involve hair follicles, and are at great risk for local recurrence. Other high-risk areas include the lower lip and the dorsum of the hand.

Perineural involvement is a hallmark of aggressively growing SCC not only in immunocompromised patients. Perineural invasion has been described especially for mid-facial NMSCs. This histologic feature may be present in neurologically asymptomatic patients. As highlighted by two case series, this phenomenon may be responsible for tumour recurrence at different anatomical sites, previously referred to as "skip lesions" [15, 16].

Guidelines for surgical margins in high-risk patients are inconsistent [17]. Most dermatologic societies recommend surgical margins of at least 4 mm in the periphery [18], ranging up to 13–15 mm [19] for morphoeic lesions. Recommendations for deep margins are not provided by all societies, however, the necessity of obtaining a three-dimensional histologic analysis is consistently stated [17]. According to the NCCN (National Cancer Care Network) guideline, however, a static excision margin cannot be stated for transplant patients in general, but has to be modified according to other risk variables, such as tumour location, size and histologic features [18]. For tumours with deep tissue invasion, screening for nodal metastasis is recommended. Via CT or MRI, invasion of deep structures is ruled out.

Sentinel-node biopsy may be indicated for high-risk SCCs, to detect subclinical lymph node metastasis. This could further implicate lymph node dissection, or adjuvant radiotherapy [20]. The latter is often recommended in high-risk settings, however, information from prospective clinical trials is lacking [18].

Reconstruction of surgical defects

In high-risk patients such as transplant recipients, any reconstruction should only be attempted upon histologic confirmation of clear surgical margins. For an optimal functional and aesthetic coverage, the size and the location of the defect have to be considered.

Wound healing by secondary intention is the easiest option, and may lead to a very favourable outcome in certain facial areas, such as the nasal ala or the medial canthus [21]. For larger defects in many facial areas, either full thickness skin grafts or local flaps are considered. In patients with large field involvement, any coverage methods that lead to tissue rearrangement (i.e. local flaps) should be applied with caution in order not to blur further histologic analysis of the surroundings [14].

After solid organ transplantation, wound healing complications have been described more frequently. However, most of the cases have been reported after the initial transplant surgery [22]. As NMSCs appear increasingly at later timepoints after transplantation, the contribution of immunosuppression to impaired wound healing cannot be clearly stated. General risk factors for wound healing deficiencies include the use of corticosteroids and mTOR inhibitors.

Metastatic disease

SCCs that have spread to regional lymph nodes have a poor prognosis in immunocompromised patients. Lymph node dissection is recommended for patients with proven metastatic disease [23]. In any case, these patients must be discussed and managed by an interdisciplinary team. Any decrease, alteration or discontinuation of immunosuppression must be weighed against the risk of transplant rejection [18]. The mTOR inhibitors have shown not only to decrease the incidence of de novo NMSCs, but also to support regression of existing premalignant skin lesions [11].

Systemic therapy with retinoids is recommended for patients who develop 5–10 SCCs per year, and can be seen as additional therapy to surgical excision of malignant lesions [2].

Conclusions

NMSCs have an increased incidence and altered tumour biology in OTR. Sun protection, regular dermatologic screening and pro-active bioptic mapping are recommended. Among dermatologic societies, the recommendations for surgical margins vary, but

clearly exceed the recommendations for low-risk lesions. Obtaining tumour-free margins not only in the horizontal plane, but also towards the underlying tissue, is important. Any type of surgical reconstruction may only be performed after complete resection. Changes to the immunosuppressive management of OTR with NMSCs, such as a switch to mTOR inhibitors, are best managed by an interdisciplinary tumour conference.

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