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Case Report

NONMELANOMA SKIN CANCER IN A HEART TRANSPLANT PATIENT: A CASE REPORT AND REVIEW OF THE LITERATURE

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SUMMARY – Nonmelanoma skin cancers (NMSC) are the most common malignancies in solid organ transplant recipients. The most common types of skin cancer in these patients are squamous cell carcinoma (SCC), followed by basal cell carcinoma. In immunosuppressed patients, specifically patients after solid organ transplantation, these carcinomas tend to be more aggressive and have a much higher incidence of metastasizing compared to general population. We present a case of a patient who developed numerous SCCs after successful heart transplantation. SCCs which occurred in our patient were mostly treated surgically. However, the lesion on the scalp relapsed after it had been treated surgically three times and therefore superficial x-ray radiation therapy was administered due to its localization and extensive size. In the next year, five more new SCCs occurred throughout the patient's body and all of them were removed surgically. Soon afterwards, the patient died from adenocarcinoma of the colon which rapidly progressed and metastasized.

Key words: *Skin cancer; Heart transplantation; Immunosuppressants; Radiotherapy*

Introduction

Nonmelanoma skin cancers (NMSC) are the most common malignancies in organ transplant recipients[1-6], and they present a variety of challenges for physicians. Organ transplant patients regularly undertake long-term immunosuppressive therapy, which has been implicated as a risk factor for malignancy, with the highest risk of developing squamous cell carcinoma (SCC), followed by basal cell carcinoma (BCC)[7-15]. These malignancies in immunosuppressed patients, specifically in organ-transplant recipients, tend to be much more aggressive and lethal than in the general population, with around 8% higher risk of metastases[16-21]. It has also been determined that patients who already have one SCC are under a much higher risk of developing another SCC[22-27]. We present a case of a heart-transplant recipient who developed several SCCs and was treated surgically and by radiation therapy as a second-line treatment because of relapses that occurred after surgical removal.

Case Report

A 71-year-old Caucasian male was admitted to our Department of Dermato-oncology with a crusty, scaly lesion which was located throughout the vertex and midscalp of the patient's head, with the exception of the site where skin graft had been previously in-

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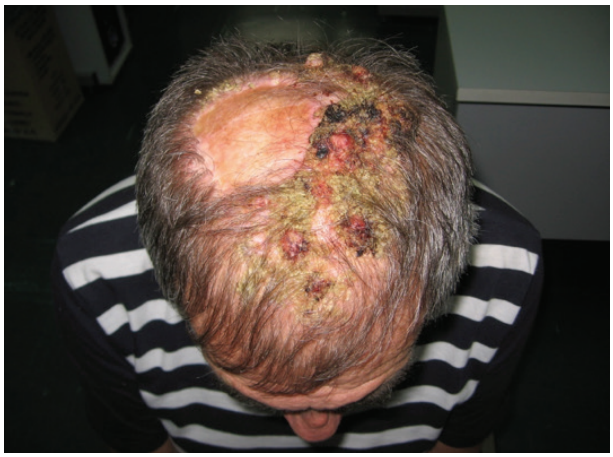

Fig. 1. Histopathologic analysis of biopsies obtained from three different locations confirmed the diagnosis of squamous cell carcinoma.

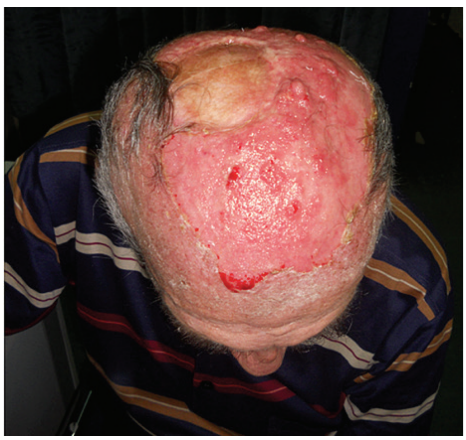

Fig. 2. The affected area four weeks of radiotherapy completion.

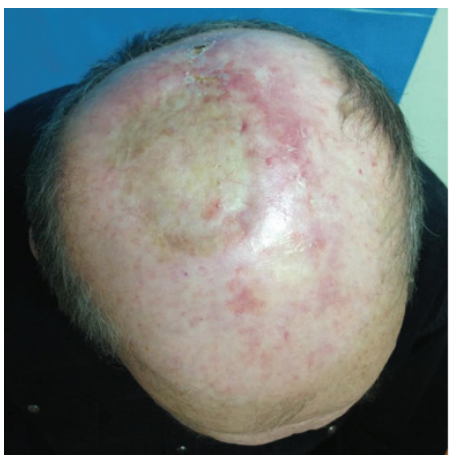

Fig. 3. The primary affected area at six-month follow up.

serted. Before presenting to our clinic, the patient had already undergone 3 surgical removals of SCC on his scalp during the course of three years. According to the surgeon in charge, surgical removal of the new lesion was no longer possible because of its size and localization, so radiotherapy was suggested as the treatment of choice. In 2001, 11 years prior to his dermatologic examination at our unit and 7 years prior to his first diagnosis of SCC, the patient had undergone heart transplantation. Because of that, he had been taking continuous immunosuppressive therapy with cyclosporine 2x150 mg, prednisone 10 mg (discontinued 1 year after transplantation) and Imuran (azathioprine) 2x10 mg daily. The patient stated he did not have any knowledge of other cutaneous malignancies in his family. Biopsies were obtained from three different locations on the lesion (Fig. 1) and histopathologic analysis confirmed the diagnosis of SCC. According to the National Comprehensive Cancer Network (NCCN) 2000 guidelines[28], which were current at the time, this lesion was specified as a high-risk SCC because of its size (>20 mm) and location (scalp). According to the new NCCN 2020 guidelines[29], this lesion would nowadays also be classified as a high-risk lesion because of the same criteria (size and location). The whole area affected by SCC was successfully treated by superficial x-ray therapy (SXRT) with a total dose of 60 Gy, which was applied in 12 fractions of 5 Gy, during the period of 6-7 weeks. One month after the treatment had been completed, we observed the expected, satisfactory epithelialization of the affected area (Fig. 2). At six-month follow up (Fig. 3) and eight-month follow up after initial diagnosis of SCC, the primary lesion healed adequately while a new nodular lesion was found in the right angle of the lower lip. Three months after surgical treatment of the new lesion, which was also histologically confirmed as SCC, a similar lesion occurred in the left side of the lower lip. In the next year, three more new SCCs occurred throughout the patient's body and all of them were removed surgically. Soon afterwards, the patient was diagnosed with adenocarcinoma of the colon which rapidly progressed and metastasized. The illness ended with lethal outcome around 4 years after the initial diagnosis.

Discussion

The occurrence of malignancies following solid organ transplantation was first observed after the onset

of renal transplantation in the late 1960s[30-32]. More recently, with the progress of heart transplantation, a similar phenomenon has been noticed[31]. A study conducted at Mayo Clinic in 2009 showed that the cumulative incidence rate of any skin cancer was 46.4% at 15 years after heart transplantation[33], and other studies indicated that malignancies accounted for 10% of deaths following cardiac transplantation[34]. The most common types of skin cancer in these patients are SCC and BCC. Although in general population most of these carcinomas are often curable and rarely fatal if treated on time, they can cause significant harm through local destruction. Moreover, if left untreated, a small subset of these carcinomas can metastasize and induce significant morbidity and mortality[35]. However, in immunosuppressed patients, specifically patients after solid organ transplantation, these carcinomas have around 8% higher incidence of metastasizing compared to general population[16-18].

The most common immunosuppressants prescribed for solid organ transplant recipients are calcineurin inhibitors (cyclosporine, tacrolimus), mycophenolic acids (mycophenolate mofetil, mycophenolate sodium), azathioprine, sirolimus, prednisone, basiliximab and anti-thymocyte globulin. In the majority of adult heart-transplant patients, triple therapy primarily with tacrolimus or cyclosporine, mycophenolate mofetil and prednisone is initiated. Prednisone is usually discontinued one year after cardiac transplantation[36]. At the time of our patient's heart transplantation, in 2001, azathioprine was the drug of choice instead of mycophenolate mofetil, which was usually prescribed in combination with cyclosporine or tacrolimus and prednisone[37]. Chronic immunosuppression and induction therapy can lead to decreased immune-mediated tumor surveillance and development of malignant tumors. Kaposi sarcoma (associated with human herpes simplex virus 8) and cutaneous anaplastic large-cell lymphoma (ALCL) usually occur early after transplantation, while other tumors such as NMSC, Merkel cell carcinoma, malignant melanoma or adnexal tumors manifest later in time[7,38,39]. Rarely, cutaneous T-cell lymphoma (*Mycosis fungoides*) and multiple atypical fibroxanthomas can occur[40-42]. The incidence of most of these tumors, including NMSC, increases in time after transplantation, with patients having a 6.7% higher risk of developing NMSC at 10 years and 20.4% higher risk at 20 years after organ transplantation[43]. Out of all skin malignancies, SCC contributes most to the increasing morbidity of skin diseases after organ transplantation[44-46]. Studies indicate that the overall incidence of SCC after organ transplantation is about 250 times higher and of BCC 10 times higher when compared with the general population[47], and that 20% to 75% of solid organ transplant recipients are affected by at least 1 SCC within 20 years, along with the increase of SCC over time[48,49]. Patients after heart transplantation also are at a higher risk of developing skin cancer in comparison to renal, liver and pancreas transplantation patients[50-52]. The cause of this phenomenon is still not clear, but older age of patients who undergo cardiac transplantation and more profound immunosuppression might have an impact[53,54]. Interestingly, studies indicate that liver-transplant patients have been shown to be more prone to developing BCC rather than SCC, in comparison to other solid-organ recipients who have a much higher incidence of SCC[16]. However, heart-transplant patients tend to develop BCC sooner than other solid-organ recipients[55].

The reason for the higher incidence of SCC in most organ transplant recipients may be mainly because the immune system has a different role in progression of BCC[56]. Recent evidence suggests that calcineurin inhibitors and p53 pathways have been particularly associated with development of SCC. Further clinical trials have shown that calcineurin inhibitors interfere with p53 signaling and nucleotide excision repair. In the studies, switching from calcineurin inhibitors to mammalian Target of Rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, led to significant reduction in the risk of developing new skin cancer[57-67].

The pathophysiologic process of skin cancer development in organ transplant patients can be explained mainly through two different mechanisms. First, some of the agents used in transplantation may be directly carcinogenic and second, long-term immunosuppression can disrupt the immune response to precancerous mutations, therefore UV-A and UV-B are major risk factors[68,69]. UV-B radiation-induced damage in SCC can be explained through mutations in some tumor suppressor genes such as p53[70], while UV-A has a role in DNA mutagenesis through creating local reactive oxidative stress and is particularly carcinogenic among immunosuppressed patients receiving azathioprine[71,72]. Regarding the choice of immunotherapy, the use of mycophenolate mofetil is associated with a significantly lower risk of developing malignancy, spe-

cifically SCC, compared to azathioprine[44,73-77]. Other than prolonged UV exposure, the most important predisposing factors for developing NMSC in organ transplant recipients include patients with Fitzpatrick skin type I-III, increasing age at the time of transplantation, male sex, cumulative sun exposure, duration and choice of immunosuppression regimen, verrucous papilloma, history of SCC or lymphoma before transplantation, as well as patients with previous keratotic lesions[8,33,78-85]. Some oncogenic viruses (in particular, human papillomavirus), genetic factors of the host, chronic ulcers, burn scars and various syndromes, such as xeroderma pigmentosum, albinism, epidermodysplasia verruciformis also have significant impact in the development of SCC[86-88]. In psoriatic patients, treatment with PUVA and the combination of psoralen and UVA rays also increases the incidence of SCC[89]. Therefore, the most effective prevention measures include sun protection practices, regulation of immunosuppressive therapy, and regular skin examination.

Management strategies for NMSC in organ transplant recipients should focus on educating post-transplant patients, regular full-skin examination, aggressive treatment of established malignancies, and prophylactic measures to reduce the risk of additional photodamage and malignant transformation[90-93]. Some studies claim that administration of acitretin can reduce the incidence of skin malignancies in heart-transplant patients[94]. All solid organ transplant recipients should have an initial dermatologic consultation followed by annual examination by transplantation physicians until the lesions occur, while patients at a high risk of skin cancer may benefit from yearly screening by a dermatologist[22,95-97].

Treatment of these lesions requires a multidisciplinary approach. Therapy modalities include conservative, ablative and surgical methods, and the goal of treatment is to remove the tumor completely while preserving the function and cosmetic appearance of the affected region. First-line therapy in patients diagnosed with NMSC, including SCC, is complete surgical removal of the lesion with margin control, such as in Mohs micrographic technique[21,35]. The recommended margins for excision range from 4-6 mm for low-risk SCC to 10-15 mm for high-risk lesions[98]. Radiation therapy is indicated in adjuvant setting, when the tumor is inoperable, cannot be removed in its entirety, or if the patient is over age 60[99]. Radiation therapy of NMSC includes SXRT, external beam radiation therapy, and brachytherapy[100]. In our patient, after three surgical removals of SCC on the scalp, second-line treatment for the new lesion on the scalp was radiation therapy, while other new lesions at different locations were treated surgically. Since a large portion of the scalp was affected (Fig. 1), the patient was not eligible for surgery and the radiation therapy of choice for our patient's lesion was SXRT, which is appropriate for elderly patients, as well as for the lesions that are difficult to reconstruct surgically[100]. According to NCCN guidelines for SCC[28,29], it is recommended that SCCs larger than 2 cm be treated with a total dose of 70 Gy during the course of 6-7 weeks, or with a total dose of 45-55 Gy during the course of 3-4 weeks. This type of administration of SXRT by fractionizing the total dose of received radiation not only reduces the risk of side effects such as fibrosis, necrosis or telangiectasia, but also provides improved aesthetic results.

Since the majority of cutaneous SCC most often metastasize through regional lymph nodes, in such aggressive tumors sentinel lymph node biopsy is indicated during the surgery. In the case of a positive sentinel lymph node, radiation therapy and radical lymph node dissection are indicated. Chemotherapy is typically reserved for patients with metastatic or locally advanced disease that cannot be treated with surgical and/or radiation therapies[35].

Conclusion

Patients after solid organ transplantation are at a much higher risk of developing NMSC, most often SCC. Cardiac transplant patients have a much higher incidence of developing skin malignancy in comparison to other solid organ recipients because of more profound immunosuppression, therefore revision of the immunosuppressive regimen is important in the management of high-risk patients. The management of these lesions requires a multidisciplinary approach. Surgery is the most often first-line therapy for SCC, but radiation therapy and chemotherapy can also be administered in some cases. In our patient, radiation therapy was administered because, after three surgical removals, SCC relapsed and spread throughout the scalp. Appropriate interventions also include sun protection practices such as sunscreen with high sun protection factor, mechanical protection with covers and clothing, skin cancer education, regulation of immunosuppressive therapy, and regular skin examination.

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Sažetak

NEMELANOMSKI KARCINOMI KOŽE U BOLESNIKA NAKON TRANSPLANTACIJE SRCA: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Nemelanomski karcinomi kože najčešći su zloćudni tumori kod primatelja solidnih organa. Najčešći tipovi karcinoma kože u ovih bolesnika su planocelularni karcinom, zatim bazocelularni karcinom. U imunosuprimiranih bolesnika, osobito u bolesnika nakon transplantacije organa, ovi karcinomi imaju tendenciju biti agresivniji i mnogo češće metastaziraju u usporedbi s istim karcinomima u općoj populaciji. Prikazujemo slučaj bolesnika koji je razvio brojne planocelularne karcinome nakon uspješne transplantacije srca. Planocelularni karcinomi kod našeg bolesnika liječeni su uglavnom kirurški. Međutim, lezija na tjemenu je recidivirala nakon što je tri puta kirurški liječena pa je stoga primijenjena terapija zračenjem zbog lokalizacije i ekstenzivne veličine lezije. Iduće godine bolesnik je razvio pet novih planocelularnih karcinoma i svi su uklonjeni kirurški. Ubrzo nakon toga bolesnik je preminuo od agresivnog adenokarcinoma debelog crijeva.

Ključne riječi: *Rak kože; Transplantacija srca; Imunosupresivi; Radioterapija*