SUBSEQUENT MIXED AND BASAL CELL CARCINOMAS IN A PATIENT AFTER KIDNEY TRANSPLANT – CASE REPORT

Virgil Pătrașcu¹, Elena Larisa Oprea², Andreea-Oana Enache¹
¹Dermatology Department, University of Medicine and Pharmacy of Craiova, Romania
²Dermatology Department, Emergency Clinical County Hospital, Craiova, Romania

Corresponding author:
Virgil Pătrașcu, Professor, MD, PhD
University of Medicine and Pharmacy from Craiova,
Petru Rareș Street, No2 4, 200345, Craiova, Romania
Phone: 004-0724273676
E-mail: vm.patrascu@gmail.com

Abstract

Non-melanoma skin cancer is generally caused by a combination of environmental, genetic and phenotypic factors. The risk of developing skin cancers increases under circumstances of reduced immune response. We present the case of a 62-year-old patient, urban area, known with kidney transplant, with immunosuppressive therapy since 2009, at which the first basal cell carcinoma occurred four years after the initiation of therapy. Over the next two years, she developed two more tumors and several actinic keratoses on the face. Based on the clinical and histopathological examination, we established the diagnosis of solid and ulcerated basal cell carcinoma of the nasal pyramid and mixed carcinoma (basal cell carcinoma and well differentiated squamous cell carcinoma) for the tumor localized in the right zygomatic region. Considering the patient’s immune status, we recommend quarterly surveillance due to the increased risk of relapse and the risk of developing new skin cancers.

Introduction

Patients with renal transplantation, undergoing immunosuppressive treatment over the course of their lifetime, represent the most important group of long-term surviving patients who have provided important information about the increasing risk of cancer. The cumulative risk of developing tumors, including skin cancers (basal cell carcinoma and squamous cell carcinoma), lymphomas and Kaposi’s sarcoma, is 14% in the first 10 years after transplantation and increases to 40% after 20 years, compared with 6% among the general population (1, 2).

Skin cancers are predominantly located on sun exposed areas. These cancers are more aggressive and have an increased metastatic potential in transplant patients.

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The risk factors for the development of skin cancer are: Ultraviolet (UV) radiation; Fitzpatrick phototypes I and II; smoking; infections (e.g., HPV, especially 5 and 8 serotypes, HIV infection); immunosuppressants (depending on the type and dose of the medication).

Immunosuppressive agents can mediate the appearance of skin cancers by three possible mechanisms: immune system reduction, direct carcinogenic effect, increased susceptibility to other carcinogenetic agents (3).

The initiation of carcinogenesis results from genetic mutations induced by UV in the DNA of human keratinocytes. In addition, UV-induced spe-
cific changes are found in p53 tumor suppressor gene. Thus, UV acts as both an initiator and a promoter of this process (4).

The most common classes of immunosuppressive drugs currently used in transplanted patients are: corticosteroids, calcineurin inhibitors, mTOR inhibitors, IMDH inhibitors and biological agents. Some studies suggest that Rapamycin inhibits the tumor growth. In addition, Rapamycin has been shown to inhibit several UV-induced mechanisms involved in skin carcinogenesis. Preliminary clinical studies reported a lower incidence of skin malignancy in transplant patients treated with this immunosuppressive agent compared to Cyclosporine (5).

Our case seems to contradict this data because the patient, although treated with Rapamune (Rapamycin), has developed several skin cancers.

Case report

A 62-year-old female patient, from urban area, presented with two tumors located in the right zygomatic region and the nasal pyramid (Fig. 1), and four hyperkeratotic plaques in the left temporal and zygomatic area (Fig. 2). The current lesions appeared two years before presentation (2015). The patient was diagnosed with basal cell carcinoma in 2013, which was excised.

The patient is known with congenital polycystic liver and kidney disease, renal insufficiency since 2001, for which she was treated with hemodialysis within 2005 and 2009. She had also history of chronic hepatitis C and ischemic stroke (2004), and in 2009 a kidney transplant was performed. From 2009 until presentation, she received therapy with immunosuppressive agents after renal transplant.

Initially, the patient followed systemic treatment with Cellcept (eight months) and Sandimmune (two years). After eight months she developed an allergic reaction, and the Cellcept was replaced with Myfortic (720 mg). The patient followed this treatment for 14 months, then Sandimmun was replaced with Prograf (two years). The current therapeutic regimen is Sirolimus 1 mg/day (1-0-0), 180 mg Myfortic 3 mg/day (1-1-1), and Prednisone 5 mg/day (0-1-0).

The clinical examination revealed a patient with a good general state of health, with asymmetric fa- cies (post-stroke), post-operative atrophic scar (left lumbar region) (Fig. 3), thickened, opaque toenails with subungual hyperkeratosis, right hemifacial hypotonia.

The results of laboratory examinations were within normal limits.

We performed excisional biopsy of the tumors located at the nasal pyramid and the right zygomatic region, followed by curettage and electrocautery of the base. The same treatment was applied for the keratotic plaques.

The result of the histological examination showed solid and ulcerated basal cell carcinoma (Fig. 4), for the tumor located at the nasal pyramid level and mixed carcinoma (basal cell carcinoma and well differentiated squamous cell carcinoma – Fig. 5) for the tumor located in the right zygomatic region.

The evolution after treatment was favorable.
Discussion

Solid organ transplantation and subsequent graft survival have increased worldwide because immunosuppression prevents or delay the graft rejection. However, side effects such as skin infections and neoplasms affect the majority of transplant patients (6).

Approximately 50% of transplant patients will have at least one episode of skin cancer in their lifetime. Out of these, 60-80% will develop new neoplastic lesions of the skin. The risk of SCC and BCC is 65-250 times and 10-16 times respectively higher than in the general population (3). In addition to SSC and BCC, the risk of developing melanoma, Kaposi’s sarcoma and Merkel cell carcinoma is also increased (7).

To determine the incidence of non-melanoma skin cancer in transplant recipients a study on a group of 288 kidney transplant patients was conducted (2004-2013, Portugal). The median age at transplantation was 47 years, with male gender predominance and the median transplant duration was 3.67 years. 131 non-melanoma skin cancers developed, including 69 SCC and 62 BCC (8).

Risk factors associated with the development of skin cancer in transplant patients include: past medical history of cancer (cutaneous or not), psoriasis, age at transplant (> 50 years), systemic biological therapy, use of phototherapy, personal history of extensive UV exposure and Fitzpatrick skin type I and II. Furthermore, higher levels of immunosuppressive drugs lead to an increased risk of non-melanoma skin cancer. The role of immunosuppressive therapy in solid organ transplantation is to maintain a balance between the graft and the immune response of the receptor. Among immunosuppressants, older agents such as azathioprine and cyclosporine may increase the risk of developing skin cancers, in contrast to newer agents such as sirolimus. The later interferes with the p53 protein signal and repair of DNA, elements which are particularly involved in the appearance of SCC (9, 10). However, not all studies support this hypothesis. Between 2000 and 2010, a study on 3539 transplant patients was conducted in the Kaiser Permanent Center of Northern California, to assess the risk of skin cancer in relation to sirolimus exposure. The study found that, out of 488 patients who were exposed to sirolimus, 47 developed an incident SCC, concluding that Sirolimus was not associated with a decrease in the risk of SCC in transplant patients (11). Sirolimus is indicated for the prophylaxis of organ rejection in adult patients receiving a renal transplant at low to moderate immunological risk. This drug inhibits T cell activation by blocking calcium dependent and calcium independent intracellular signal transduction. Sirolimus inhibits the activation of the mammalian target of rapamycin (mTOR), a kinase which plays a major role in cell cycle progression. The inhibition of mTOR, blocks some specific signal transduction pathways. The final step is inhibition of lymphocyte activation, which generates immunosuppression. In animals, Sirolimus has a direct effect on T- and B-cell activation, suppressing immune-mediated reactions (12).

Oral treatment with azathioprine, commonly used in post-transplant immunosuppressive regimens, results in the incorporation of 6-thioguanine (6-TG) into DNA. Cells exhibit defective repair mechanisms are resistance to 6-TG destruction. Azathioprine exposure confers a survival advantage on defective cells, which are hypermutable and may therefore contribute to the occurrence of non-melanoma skin cancers (13).

Due to iatrogenic immunosuppression, transplant patients are exposed to bacterial, viral and fungal infections. To prevent the occurrence of invasive fungal infections (commonly encountered in transplant patients) such as Aspergillus infection, patients can benefit from preventive treatment with Voriconazole, an independent risk factor for SSC. Some authors consider that the risk of SCC increases by approximately 73%, being directly related to the cumulative total dose. The mechanism is unclear, but studies suggest that this drug acts at DNA level and decreases the ability of DNA repair. Some studies suggest that there is a molecule (Voriconazole N-oxide) in the tegument of patients using Voriconazole that increases the absorption of UV radiation, resulting in DNA changes in keratinocyte through free oxygen radicals (3, 14).

In order to determine keratinocyte gene modification in people with skin cancer, a study based on the analysis of 35 tumors, 16 SCC and 19 BCC was performed. Immunohistochemical expression of p53 tumor suppressor gene protein was studied using the monoclonal antibody DO-7, directed against the mutant forms of this gene. Cell proliferation and apoptosis were also evaluated.
by Immunohistochemical analysis of Ki-67 nuclear antigen. The mean value of Ki-67 positive cells was comparable in both tumor groups, with an average of 40.6% in BCC and 34.6% in SCC. In the specialized literature, there are few data about the prognostic value of the Ki-67 marker and the relationship between a positive rate of Ki-67 and prognosis remains unclear. Bouzubar et al. claim that tumors which stain over 20% with Ki-67 are at high risk of relapse (15), while Wintzer et al. reported a more severe prognosis in patients with tumors having values of Ki67 >16% (16).

Another gene frequently involved in SCC development is p16 Ink4a. This oncogene occurs through mutations in the CDKN2A gene, located on the short arm of chromosome 9.

After investigating 61 cases of SCC, the presence of p16 oncoprotein was observed in 43 (70.5%) cases, the p53 marker was identified in 53 (86.8%) cases, and Ki67 in 54 (88.5%) cases (17).

Human leukocyte antigen (HLA) may play a role in the development of skin cancers. DR1, B27, DR7 and A11 have been associated with an increased risk of skin cancer. The way this process takes place is still unclear, but the donor-recipient exchange seems the most important, influencing the degree of immunosuppression needed to initiate this mechanism (3). In 1985, Myskowski et al. conducted what may be the first work attempting to associate some specific HLA antigens with skin cancers. They found the increased presence of HLA DR1 in patients with multiple SCC compared to healthy subjects (18). More recent studies sustain that HLA-DR15 is more often detected in patients with skin cancers, as compared with controls. There was also a positive correlation between the presence of HLA-B18 and cutaneous SCC. The antigen was more frequent in the population with kidney transplant and SCC, compared with the group without skin cancer (19).

In the pathogenesis of skin cancers UV radiation (UVA, UVB and UVC) are frequently involved. The photocarcinogenic effect of UVB appears to be through decreased immune surveillance (20, 21). UVB inhibits the antigen-presenting cell function, with secondary release of immunosuppressive cytokines. These will cause cellular DNA-damage by generating pyrimidine dimers in keratinocytes, thus acting as an important molecular trigger for UV-mediated immunosuppression. Also, the UV radiation causes mutations in tumor suppressor genes (e.g., p53), causing the impossibility of nuclear reshuffling, with subsequent initiation of carcinogenesis (22). Exposure to high doses of UV radiation can induce not only a local but also a systemic immunosuppression. This thing can be attributed to the generation of IL-10 under the action of solar radiation, induction of CD4 and CD25 lymphocytes and activation of AP-1 and NF-KB, which in turn, induce the secretion of IL-4 and IL-10 (3).

Skin cancer most often develops on areas of sun-exposed skin, and can be diagnosed early with various therapeutic methods, with good oncological, functional and aesthetic results. However, the key is to prevent its occurrence, especially in transplant patients, where the degree of immunosuppression limits certain treatments.

Chemoprevention strategies are focused on reducing and delaying the development of skin cancer in these patients, systemic retinoids being widely used by most authors. The role of systemic retinoids in skin cancer chemoprevention was first established in patients with Xeroderma pigmentosum. The mechanism by which retinoids have a chemopreventive effect for skin cancer is not well understood.

Several mechanisms may be involved, including: immunomodulation, induction of apoptosis, effects on cell cycle control, decarboxylation inhibition, inhibition of cellular proliferation and keratinization, promotion of cell differentiation (23). In vivo studies in murine models of skin carcinogenesis, revealed that retinoids target the B-Raf/Mek/Erk signaling pathway. Thus, it was speculated that retinoids play an antioxidant role, protecting against sunburns. They may act against the human papillomavirus (HPV), some genotypes having well-known carcinogenic potential (24). Preliminary studies on the use of retinoids in preventing skin cancer in high-risk patients and organ transplant recipients have produced discordant results. However, recent studies showed encouraging results. These data indicate the reduction of skin dysplasia (in high-risk transplant recipients) and >50% reduction of BCC incidence in high-risk patients using Imiquimod. Other antioxidants such as selenium, vitamins A, C, E and zinc have been proposed for cancer chemoprevention (25).

There are also studies examining the effects of difluoromethylornithine, polyphenol antioxidants and cyclooxygenase inhibitors in the chemoprevention of skin cancer in organ transplant patients.

Conclusions

Skin cancers are more common in organ transplant recipients than in the general population, especially SCC, which is more aggressive.

Patients with kidney transplants require close dermatological monitoring because of the iatrogenic immunosuppression, responsible for the increased susceptibility to infections and skin cancers.

In addition to photoprotection (the use of protective clothing and sunscreens with high SPF), a new method called chemoprevention is promoted. Potential agents included are the retinoids, di-
fluoromethylnornithine, polyphenolic antioxidants and cyclooxygenase inhibitors.

Conclusion

An extensive lietature search showed that only a small number of drug-induced Sweet’s syndrome cases occurred. Thus, we reported this case of drug related Sweet’s syndrome to help clinicians re- cognize this syndrome.

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Patient consent obtained.
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Bibliography

7. Susan O’Gorman, MD and Gillian Murphy, MD. An extensive literature search showed that only a small number of drug-induced Sweet’s syndrome cases occurred. Thus, we reported this case of drug related Sweet’s syndrome to help clinicians recognize this syndrome.