ORIGINAL ARTICLE

Location of nonmelanoma skin cancers in patients after kidney transplantation

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KEY WORDS

basal cell carcinoma, location of cancer, kidney transplantation, nonmelanoma skin cancers, squamous cell carcinoma

ABSTRACT

INTRODUCTION Long-term use of immunosuppressant therapy makes kidney transplant recipients particularly susceptible to infections and skin cancers.

OBJECTIVES The aim of the study was to evaluate the type and location of nonmelanoma skin cancers (NMSCs) in patients after kidney transplantation.

PATIENTS AND METHODS The study included 486 patients (296 men and 190 women; mean age, 46.1 ±13.1 years) after deceased-donor kidney transplantation, most of whom received triple immunosuppressive therapy. Patients underwent skin examination. All suspicious lesions were thoroughly described in terms of their type, size, and location. Only patients with histologically confirmed malignancy were included in the study.

RESULTS Of all 486 patients, 25 were diagnosed with 53 NMSCs, including 39 basal cell carcinomas, 13 squamous cell carcinomas, and 1 case of Bowen's disease. The lesions were observed on the face (n = 34), upper limb (n = 8), neck (n = 6), and trunk (n = 5).

CONCLUSIONS Most NMSCs were located on the sun-exposed areas, emphasizing the effect of ultraviolet radiation on the pathogenesis of skin cancers. The presence of lesions on the skin that had not been exposed to the sun indicates that a physical examination of the entire skin is necessary.

INTRODUCTION Patients after kidney transplantation require long-term use of immunosuppressant agents, which makes them particularly vulnerable to the development of infectious complications.[1,2] Infectious skin lesions of viral, fungal, and bacterial etiology are an important clinical problem in immunosuppressed patients.[3-5] There are also numerous data indicating an increased incidence of skin cancers in this patient group.[6,7] The risk of developing cancer increases with the doses and duration of immunosuppressive treatment.[8-11] In addition to immunosuppressive therapy, the other risk factors for skin cancers include exposure to ultraviolet (UV) radiation, sunburn episodes in childhood, the presence of solar keratoses, the presence of neoplastic lesions before transplantation, male sex, and older age.[12-16]

The aim of the study was to evaluate the type and location of nonmelanoma skin cancers (NMSCs) in patients after kidney transplantation.

PATIENTS AND METHODS The study included 486 patients (296 men [60.9%] and 190 women [39.1%]; mean age, 46.1 ±13.1 years [range, 18–74 years]) after deceased-donor kidney transplantation. All patients attended an outpatient clinic for transplant patients at the University Hospital in Kraków, Poland. In the analyzed group, 480 patients received the first graft and 6 received the second.

The mean time from transplantation at the first visit was 54.7 ±48.8 months (median, 42.5; range, 0–298 months). Chronic glomerulonephritis was the most common cause of chronic kidney failure. Most patients (80.7%) were treated with hemodialysis before transplantation.

A combination of cyclosporine A (CyA) with mycophenolate mofetil (MMF) and steroids was the most common treatment regimen (207 patients, 42.5%); moreover, 102 patients (20.9%) remained on tacrolimus (TAC) + MMF and steroids, and 53 patients (10.9%) on

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Received: February 10, 2014.
Revision accepted: April 15, 2014.
Published online: April 15, 2014.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2014; 124 (5): 233-238
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TABLE 1 Location of nonmelanoma skin cancers in kidney transplant patients

Location	BCC, n (%)	SCC, n (%)	Total
face	23 (59.0)	11 (78.6)	34 (64.2)
neck	6 (15.4)	0	6 (11.3)
trunk	5 (12.8)	0	5 (9.4)
upper limb	5 (12.8)	3 (21.4)	8 (15.1)
total	39 (100)	14 (100)	53 (100)

Abbreviations: BCC – basal cell carcinoma, SCC – squamous cell carcinoma

TABLE 2 Location of nonmelanoma skin cancers on the face in kidney transplant patients

Location	BCC	SCC	Total
nose	8 (34.8)	1 (9.0)	9 (26.4)
temple	5 (21.8)	2 (18.2)	7 (20.6)
hecek	4 (17.4)	3 (27.3)	7 (20.6)
forehead	4 (17.4)	0	4 (11.8)
ear	1 (43.0)	3 (27.3)	4 (11.8)
eyelid	0	2 (18.2)	2 (5.9)
the area of the upper lip	1 (4.3)	0	1 (2.9)
total	23 (100)	11 (100)	34 (100)

Abbreviations: see TABLE 1

CyA + azathioprine (AZA) + steroids. The mean daily doses at 1 and 6 months after transplantation were 5 mg/kg body weight (b.w.) and 3.2 mg/kg b.w., respectively, for CyA; 0.2 mg/kg b.w. and 0.07 mg/kg b.w., respectively, for TAC; 30 mg/kg b.w. and 17 mg/kg b.w., respectively, for MMF; and 2 m/kg b.w. and 1.5 mg/kg b.w., respectively, for AZA. Acute rejection was observed in 85 patients (17.5%). Rejection was treated by methylprednisolone in 75 of the patients (88.2%) and by methylprednisolone in combination with muromonab-CD3 (Orthoclone OKT3) in 6 patients (7.1%) and in combination with antithymocyte globulin in 4 patients (4.7%). The type of immunosuppression was described in detail in previous papers.[3,4]

Before enrolment, all patients were informed about the aim and methods of the study and signed informed consent. The study was approved by the Bioethical Committee of the Jagiellonian University (No. KBET/100/B/2006).

All suspicious skin lesions detected during skin examination were thoroughly described in terms of their type, size, and site. Only patients with histologically confirmed malignancy were included in the study.

For nominal variables, the number of patients and the percentage of the corresponding group were reported. Continuous data were presented as mean ± standard deviation. Frequency tables were analyzed using the χ^2 test. Differences between the groups regarding age and time from transplantation were studied with the *t* test. The results were considered statistically significant at a *P* value of less than 0.05. Statistical analysis was performed with the Statistica 9.0 software (StatSoft).

RESULTS Of 486 patients, 25 (5.1%) were diagnosed with an NMSC, including 8 women (32%) and 17 men (68%). Eleven of those patients (44.0%) had single lesions, while 14 (56.0%) had multiple lesions. In 15 patients (60.0%), only basal cell carcinomas (BCCs) were found, in 7 patients (28.0%) only squamous cell carcinomas (SCCs), and 3 patients (12%) were diagnosed both with SCCs and BCCs. Overall, 53 NMSC lesions were found (TABLE 1), including 39 BCCs (73.6%) and 14 SCCs (26.4%) (including 1 case of Bowen's disease).

Lesions were most often observed on the face (n = 34, 64.2%), mainly the nose (9 of 34 lesions, 26.5%) (TABLE 2). Moreover, they were found on the upper limb (n = 8, 15.1%), neck (n = 6, 11.3%), and trunk (n = 5, 9.4%); no skin cancers were observed on the lower limb (TABLE 1). Most of the lesions (81.1%) were located on the sun-exposed areas ($P = 0.0002$ for BCCs and $P = 0.001$ for SCCs); in particular, 30 of 39 BCCs (76.9%) and 13 of 14 SCCs (92.9%).

There was no significant correlation between the skin phototype according to the Fitzpatrick skin type classification and the incidence of NMSC ($P = 0.2$). NMSCs were diagnosed in 4 patients (11.1%) with skin type I, 9 (4.97%) in those with skin type II, and 12 (5.71%) in those with skin type III.

NMSCs were more often diagnosed in patients treated with AZA (8.4% vs. 3.4%; $P = 0.019$) and less often in those treated with MMF (3.7% vs. 8.8%; $P = 0.022$). There was no association between the treatment with CyA ($P = 0.13$) or TAC ($P = 0.08$) and the presence of NMSC. Moreover, there were no differences between patients with single and multiple NMSC lesions in terms of

sex (P = 0.7), age (P = 0.5), time from transplantation (P = 0.2), skin type (P = 0.3), the history of sun burns (P = 0.5), or the intensity of sun exposure (P = 0.7). Furthermore, no associations were observed between the treatment with AZA (P = 0.3) or MMF (P = 0.08) and the presence of multiple lesions.

DISCUSSION The results of our study indicate that sun exposure is a particularly significant risk factor for the development of an NMSC in patients after kidney transplantation. Of all 53 NMSC lesions diagnosed in 25 of 486 patients with a transplanted kidney, 34 (64.2%) were located on the face, which is the most exposed area.

Numerous data indicate that NMSCs are among the most often diagnosed neoplastic lesions in transplant recipients.[7,8] Multiple cancer lesions and more aggressive clinical course are observed more often in patients with renal graft than in the general population.[17] As in immunocompetent subjects, there are many interacting factors involved in the development of NMSC, with sun exposure being the most crucial.[18,19]

The risk of developing skin cancers varies by a geographical region. Available data indicate that the highest rates of these cancers are observed in Australia, where after 5 years post-transplantation, skin cancers were found in 20%, after 10 years in 45%, and after 20 years in 75% of graft recipients. Even higher prevalence, of 52.2% at 10 years and 82.1% at 20 years, was observed in other studies.[20-24] In Poland, the incidence of NMSCs in graft recipients is lower, and Imko-Walczuk [25] reported that 2.5% of the patients are affected after 5 years, 7.8% after 10 years, and 16% after 20 years.

In a study on the Spanish population, Garcia Bernat et al.[10] observed 162 NMSCs in 73 of 289 patients (25.2%) over 72 months. They reported the predominance of BCCs, with a BCC-to-SCC ratio of 2.2:1. The occurrence of NMSCs increased with duration of immunosuppression and was 20.7% at 5 years, 37.35% at 10 years, and 53.08% at 15 years post-transplantation. An advanced age at the time of transplantation, bright skin, and occupational exposure to the sun have been associated with an increased risk of NMSCs. The association between UV light and the development of NMSCs is confirmed by the fact that lesions usually appear on sun-exposed parts of the body, and the incidence of these cancers is the highest in countries with high insolation.[19,20] Moreover, this association may be supported by the study of Penny et al.,[26] who demonstrated that the incidence of NMSCs is increased in patients with higher concentrations of 25(OH)D_3 resulting from increased exposure to sunlight.[26] Similar relationships were observed previously in the general population.[27]

In a study by Imko-Walczuk[25] on a population of patients after kidney transplantation from the area of Gdańsk in Poland, the location of skin cancers was similar to that observed in the general population, where 76% of SCCs and 72% of BCCs were related to the head and neck regions. As for other sites, 16% of BCCs and 5% of SCCs were observed on the trunk, while 19% of SCCs and 9% of BCCs were found on the upper and lower limbs, which is consistent with the findings of other authors.[17,28,29]

There are discrepancies in the literature concerning the relation of SCCs to BCCs in patients after kidney transplantation. Most of the publications reported a predominant percentage of patients with SCCs,[7,30] although there are also a number of publications showing a higher percentage of BCCs than that of SCCs, as observed in the general population.[10,25]

BCC is the most common skin cancer in the general population. Both in the general population and kidney transplant patients, most of the lesions were located on the face, above the line connecting the corner of the mouth with the lower part of the nose.[16,31] In patients undergoing immunosuppressive therapy, the lesions are more common (20%–25%) in the areas not exposed to sunlight. In addition, in patients after transplantation, BCC occurs about 15 years earlier than in the general population, in which it affects mainly people aged more than 60 years.[19] Light skin phototype, the presence of BCC prior to transplantation, and older age at surgery are risk factors for BCC.[10,19,20,22]

Depending on the morphological characteristics, the following clinical types of BCC are distinguished: nodular, dye, ulcerative, sclerodermа-like, cystic, and superficial widespread. A nodular BCC is the most common type of cancer diagnosed in the general population. It is characterized by a pearly or waxy color and the presence of teleangiectasias on the surface. An ulcerative BCC is particularly common within the nasolabial folds and in the corner of the eye and ear areas. Ulceration is surrounded by a pearly border, which allows to distinguish this type of cancer from ulcers of different etiology. Infiltration and destruction of the surrounding tissues, including the bone and cartilage, may frequently occur. A dye BCC is rare in Caucasians. This bluish or black lesion is predominantly nodular with a raised margin. In the differential diagnosis, a malignant melanoma should be excluded.[16,31]

The clinical picture of a scleroderma-like BCC comprises an atrophic scar with few telangiectasias. These lesions are mainly located on the face and never undergo ulceration. Similarity to the scar or outbreaks of scleroderma often causes diagnostic problems.[31] A cystic BCC is usually located on the eyelid and has a shiny pearly surface covered with small teleangiectasies. Owing to strong resemblance to the cysts of the sweat glands, a histopathological study is needed if the lesion does not resolve spontaneously. A superficial widespread BCC is most commonly found on the trunk. A typical change involves focal, erythematosus scabby patches, which locally become slowly enlarged and which resemble

psoriasis and eczematous focus in clinical picture. The presence of a characteristic roller on the periphery facilitates a proper diagnosis. Some authors claimed that it represents the most common type of BCC observed in transplant patients.[16,31]

SCC is a skin tumor derived from the squamous epithelium. It has much higher malignancy than BCC and most often develops from precancerous lesions in the areas exposed to UV radiation. Of note, in patients after transplantation, SCC is growing much faster than BCC, has a tendency to increase, and in 8% to 12% of the cases, it can invade regional lymph nodes.[15]

SCC is usually found on the skin and at the border of the skin and mucous membranes (usually the lower lip). The latter site is associated with a much higher risk of metastases to the lymph nodes. There are 2 clinical types of SCC: ulcerative (characterized by deeply penetrating ulcers with raised and infiltrated edges) and verrucous (characterized by less infiltration towards the bottom of a hypertrophic lesion).[15]

In summary, similarly to the general population, NMSC lesions in our study group were located primarily on the skin exposed to UV radiation.[7] According to some authors, it is the most frequent location of skin cancers in patients after transplantation.[9,22,25,32] In our study, lesions were most often observed on the face, which is in line with other studies.[19,25,33] These results along with a higher incidence of skin cancers observed in Australia and New Zealand compared with countries with moderate sun exposure[14,22,25,34] confirm the role of UV radiation in the pathogenesis of skin cancers. The fact that skin cancers in patients after transplantation are primarily located on the skin exposed to the sun underlines an important role of UV radiation in the pathogenesis of these lesions.[11,15,35] To minimize the adverse effects of UV radiation, it is necessary to implement antitumor prevention in all patients undergoing immunosuppressive therapy. The use of protective creams and clothing as well as avoidance of excessive exposure to sunlight are crucial. The results of the previous studies indicate that it is necessary to systematically educate patients on sun protection.[36-40] Only comprehensive preventive strategies can lower an extremely high risk of increased morbidity and mortality in patients on renal replacement therapy.[25,41,42]

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ARTYKUŁ ORYGINALNY

Lokalizacja nieczerniakowych raków skóry u chorych po przeszczepieniu nerki

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SŁOWA KLUCZOWE

lokalizacja nowotworu, nieczerniakowe raki skóry, przeszczepienie nerki, rak kolczysto-komórkowy, rak podstawnokomórkowy

STRESZCZENIE

WPROWADZENIE Chorzy po przeszczepieniu nerki z uwagi na konieczność długotrwałego stosowania leków immunosupresyjnych są szczególnie narażeni na rozwój powikłań infekcyjnych oraz nowotworów skóry.
CELE Celem pracy była ocena typu i lokalizacji nieczerniakowych raków skóry (*nonmelanoma skin cancers* – NMSCs) u pacjentów po przeszczepieniu nerki.
PACJENCI I METODY Badaniami objęto 486 chorych (296 mężczyzn i 190 kobiet, średni wiek, 46,1 ± 13,1 lat) po przeszczepieniu nerki od dawców zmarłych, pozostających w większości w trakcie trójlekowej terapii immunosupresyjnej. Chorzy zostali poddani badaniu dermatologicznemu. Wszystkie wykryte zmiany podejrzane o proces nowotworowy zostały szczegółowo opisane, określono ich rodzaj, wielkość oraz lokalizację. Do badania włączono tylko tych pacjentów, u których złośliwość nowotworów została potwierdzona badaniem histopatologicznym.
WYNIKI W badanej grupie 486 chorych u 25 stwierdzono 53 ogniska NMSC, w tym 39 raków podstawnokomórkowych, 13 raków kolczystokomórkowych i jedno ognisko choroby Bowena. Zmiany te były zlokalizowane na twarzy (n = 34), na kończynie górnej (n = 8), na szyi (n = 6) i na tułowiu (n = 5).
WNIOSKI Większość rozpoznanych NMSCs była zlokalizowana na odsłoniętej skórze, co może potwierdzać wpływ promieniowania UV na rozwój tych zmian. Fakt wykrycia zmian na zasłoniętej skórze wskazuje na konieczność oceny całej skóry podczas badania fizykalnego.

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Praca wpłynęła: 10.02.2014.
Przyjęta do druku: 15.04.2014.
Publikacja online: 15.04.2014.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2014; 124 (5): 233-238
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