

Risk of infectious diseases and cutaneous tumours in solid organ recipients: A meta-analysis of literature

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Abstract

AIM: To compare the risk of cutaneous infections and tumours in kidney transplant recipients with data recently published about this topic.

METHODS: In the present work, we evaluated the incidence of bacterial, fungal and viral cutaneous infectious diseases and the development of skin cancers in a cohort of 436 patients who underwent a renal transplantation. The median age at transplantation of our patients was 50 years and the median duration of the immunosuppression was of 7.2 years. Data obtained

from our cohort were compared with those obtained by a systematic review of the literature of the last 20 years about the same topic.

RESULTS: Infectious diseases were the most frequent dermatological disorders that were diagnosed after transplantation, affecting about the 16.5% of patients. Herpes virus reactivation occurs in about the 35% of patients and is more common within 6 mo from transplantation, whereas when the immunosuppression is reduced, skin infections are mainly represented by Human Papilloma Virus infections and localized mycosis, such as pityriasis versicolor and superficial candidiasis. Bacterial infections were relatively rare and occur mainly in the first months after transplantation. The cumulative risk to develop skin cancer enhance significantly over the time, as consequence of long-term immunosuppressive regimens. Endogenous and exogenous risk factors, as well as the schedule of immunosuppression can play a role and justify the different incidence of skin cancer in the various series.

CONCLUSION: Skin infections and cancer, commonly diagnosed in transplanted patients, impact on survival and life-quality, justifying the realization of follow-up programs for the early diagnosis and treatment.

Key words: Skin infectious disease; Cutaneous tumours; Transplantations; Risk; Solid organ recipients

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Core tip: Patients who underwent solid organ transplantation frequently suffer from skin infections and malignancies, due to the effects of long-term immunosuppressive therapy. Here, we compare our data about the risk to develop infectious disease and non-melanoma skin cancer in solid organ transplantation recipients, together with a meta-analysis of data recently reported

by literature about this topic.

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INTRODUCTION

It has been shown that patients receiving solid organ transplants have an increased risk of developing cutaneous infectious disease and skin tumours, as consequence of the long-term immunosuppressive treatment^[1-3]. Infective complications are an important cause of morbidity and mortality, and the introduction of potent immunosuppressive agents like tacrolimus or mycophenolate mophetil may result in an increased risk of bacteric, fungine or viral infections^[4]. The risk to develop skin cancer increase over the time and the various immunosuppressive regimens has different oncogenetic potential: the risk to develop a skin cancer is mainly related with azathioprine and cyclosporine^[5], whereas mammalian target of rapamycin inhibitors have been associated with a lower incidence of *de novo* skin cancer^[6]. However, the risk could also depend by other endogenous and exogenous conditions: history of sunburns and ultraviolet (UV) exposure, life habits, skin phototype, concomitant infections and specific genetic signatures can have a major impact in the onset and progression of these specific tumours^[6-8]. In particular, different oncogenic and non-oncogenic Human papilloma virus (HPV) strains are frequently isolated from both normal skin and cutaneous tumours in transplant recipients, but their carcinogenetic role should be definitively established.

In this study, we report data about infective skin diseases and cutaneous tumours in a group of 436 renal transplant recipients followed-up at our centre. We also provide an overview and meta-analysis of data published in the recent literature about this topic.

MATERIALS AND METHODS

Data about 436 renal transplant recipients with a dermatological follow-up at our centre were recorded. The 61.3% of these were males and the 38.7% females; median age at transplantation was 50 years and the median duration of immunosuppression was 7.2 years. For each patient, we evaluated the presence of any infectious dermatological disease and the development of skin cancers.

Moreover, a review of the English language literature of the last 20 years was performed using the MEDLINE database, using the key words “infectious skin diseases”, “cutaneous tumours” and “solid organ recipients”. We included only peer reviewed series with more than 50

cases; single case reports and series with less than 50 cases were excluded as well as articles published on journals without peer review system. No restrictions on the basis of ethnicity were applied.

Fifty-two papers were considered for the analysis.

Statistical analysis was performed with SPSS software (SPSS, Chicago, IL) and with Kaplan-Mayer curves.

RESULTS

Infective disease

Viral, bacterial and fungal diseases were frequently reported in almost all the solid organ recipients cohort published in literature. In our cases, infectious diseases were the most frequent dermatological disorders that were diagnosed after transplantation, affecting the 16.7% of patients.

Viral infections

Herpes simplex virus (HSV) infections are relatively frequent in organ transplant recipients. Infections with reactivated HSV occur with an incidence of up to 35% primarily in the first three weeks following transplantation^[9]. Marrow transplant patients are most at risk, but also solid organ transplant recipients show an higher incidence of HSV infections than immunocompetent people especially when preventive antiviral treatment was not performed^[10]. There are very different incidence rates of HSV infections in literature depending on the type of immunosuppressive treatment, the geographical area considered and the mean time from transplantation (Table 1). However, there are no remarkable differences when considering the type of organ transplanted. We found a prevalence of HSV recurrent infections (2.4%) similar to those reported by Bakr *et al*^[11] and Belloni-Fortina *et al*^[12].

Human herpesvirus 6 and 7 (HHV-6 and HHV-7), ubiquitous in humans, cause exanthema subitum in childhood and remain in a latent form in the body after primary infection. Two to three weeks following transplantation up to 30% of all transplant recipients have a reactivation of HHV-6 even if most infections remain asymptomatic^[13].

Primary or recurrent varicella zoster virus (VZV) infections can occur in 1%-30% of solid organ transplant recipients with a mean time of onset from transplantation of 9-23 mo and a peak after 6 mo^[14]. As it can be seen in Table 1 some authors report lower incidence rates of VZV infections probably because herpetic eruptions develop more commonly during the first year after transplantation^[15] and the mean time since transplantation was lower than 1 year^[11,12]. Cito megalo virus (CMV), another member of Herpesvirus, is found in 50%-75% of solid organ transplant recipients. CMV rarely causes cutaneous infections but can facilitate other opportunistic skin infections by modulating cell-mediated immunity^[14].

Viral warts and condiloma acuminata are clinical expression of HPV infection. Viral warts are frequent in long-term immunosuppressed patients with prevalence rates

Table 1 Incidence of viral infections in solid organ recipients *n* (%)

Ref.	No. of cases/ population	Age (yr)	M/F	Median follow- up time	Therapy	HSV infections	VZV infections	HPV infections
Greenberg <i>et al</i> ^[53]	68/Kidney	NA	NA	NA	NA	10 (14.7)	NA	NA
Hogewoning <i>et al</i> ^[15]	134/Kidney	32.6 ± 10.3	80/54	NA	NA	9 (6.7)	24 (17.9)	NA
Bakr <i>et al</i> ^[11]	302/Kidney	35.9 ± 11.3	216/86	0.25-23 yr	Miscellaneous	9 (3)	3 (1)	33 (10.9)
Savoia <i>et al</i> ^[65]	286/Kidney	NA	273/163	9.3 (0.1-39.8) yr	66.7% combination therapy (tacrolimus in 90%)	11 (2.5)	NA	45 (10.3)
Belloni-Fortina <i>et al</i> ^[12]	161/Liver	47.4 ± 11	116/45	NA	NA	3 (2)	3 (2)	30 (19)
Lima <i>et al</i> ^[22]	53/Kidney	44	28/25	52.5% of patients over 5 yr	44% prednisone 31% mycophenolate	3 (5.7)	4 (7.5)	14 (26.4)

For each literature study has been indicated number of included patients, type of solid organ transplantation, median age, sex, median follow-up time after solid organ transplantation, type of immunosuppressive treatment and the percentage of patients affected by herpes simplex virus (HSV), varicella zoster virus (VZV) and human papilloma virus (HPV) infections. NA: Data non available in the considered study; M: Male; F: Female.

-ranging from 35% and 85% 5 years after transplantation^[15,16]. We found a prevalence of 12.2% similar to those reported in different studies conducted on other kidney and liver transplant patients^[11,12].

Viral warts usually develop on sun-exposed areas, especially in fairer skin-type patients. They are usually multiple and display fewer tendencies for spontaneous regression than in immunocompetent individuals. Their extension may be so widespread to constitute general verrucosis. The types of human HPV found in organ transplant recipients may be different from that seen in the general population. In a study, nine of 10 HPV detected in organ transplant recipients were gamma-PV and one belonged to the genus beta-PV^[17]. Other authors report that the most frequent HPV types are HPV-5 and HPV-8, *i.e.*, the same types that can be easily found in epidermodysplasia verruciforme (EV)^[18].

Bacterial infections

In the first month by transplantation there is an high frequency of generally trivial nosocomial diseases. The frequent wound infections that can be seen in this period are increasingly been caused by antibiotic resistant strains [vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus Aureus* (MRSA)]^[11,19].

In immunosuppressed individuals *Staphylococcus aureus* infections manifest frequently as pyoderma. However, subcutaneous abscesses, erysipelas, and impetigo may develop in the long term^[14].

Interestingly a prospective study on 604 heart transplant patients report an high prevalence of infections in the first year from transplantation with a majority of bacterial infections^[20], probably as a consequence of higher dosage of immunosuppressive treatment in order to avoid acute rejections. However, when considering only skin infections, the prevalence was similar to those reported by Perera *et al*^[21] and Lima *et al*^[22]. When confronted to other reports (Table 2), bacterial infections were relatively rare in our experience and occurred only in 1.4% of the patients.

Necrotizing fasciitis (NF) is a devastating infectious disease with 0.04 cases per 1000 person-years in the

general population. The mortality rate is 25% to 30% and the most common pathogen in type II NF is *Streptococcus pyogenes*^[23]. The characteristics of NF in renal transplant patients are poorly understood due to the rarity of NF in this population. To date, there have only been described 12 cases^[24]. When comparing with NF in immunocompetent individuals, fungal etiology appears more common but, surprisingly, the overall mortality rate is lower (16.7% *vs* 25%-30%). Age and use of mycophenolate are associated with an increased risk of death^[24].

Nocardiosis is a rare opportunistic infection caused by aerobic Actinomycetes *Nocardia* and can be associated with severe complications in kidney transplant recipients. Studies showed, in the last 2 decades, that the incidence of *Nocardia* infection in kidney transplant recipients was approximately 0.4%-1.3%^[25]. To date, more than 70 cases of Nocardiosis in renal transplant recipients have been described. Nocardiosis appears after a mean time of 34.1 mo from transplantation and is more frequent in patients with a prior history of acute rejection and in treatment with cyclosporine. Lung, brain, skin, and subcutaneous tissue were the most frequently involved organs^[26]. The mortality rate varies between 16.67%^[26] and 25%^[27].

Although the incidence of tuberculosis in renal transplant recipients is 5 times higher than in the general population tuberculosis is still rare in organ transplant recipients with reported rates of 0.35%-15% depending on the geographical area considered^[19]. Among infected transplant recipients, 63% have a pulmonary involvement, 25% have systemic dissemination and 12% have an exclusively extrapulmonary involvement^[28].

Skin involvement is generally a sign of disseminated tuberculosis and imposes the research of a visceral involvement. Only 18 cases of cutaneous miliary tuberculosis in patients older than 15 have been described in literature from 1889 and 1991^[29-31].

Atypical mycobacterioses are rarer than *M. tuberculosis* infections and are seen in 0.16%-2.8% of solid organ transplant recipients^[32]. Among them, some sporadic cases of infections by *M. Abscessus* and *M. Marinum* are reported in literature^[33,34].

Table 2 Incidence of bacterial infections in solid organ recipients *n* (%)

Ref.	No. of cases/ population	Age (yr)	M/F	Median follow- up time	Therapy	Bacterial infections
Bakr <i>et al</i> ^[11]	302/Kidney	35.9 ± 11.3	216/86	0.25-23 yr	Miscellaneous	47 (16) Mainly folliculitis and impetigo
Hogewoning <i>et al</i> ^[15]	134/Kidney	32.6 ± 10.3	80/54	NA	NA	28 (20.9) Mainly folliculitis, ectyma and erysipelas (3)
Alangaden <i>et al</i> ^[66]	127/Liver	47 ± 12	79/62	NA	79% prednisone 72% tacrolimus 28% sirolimus	17 (13) Mainly wound infections and skin and soft tissue infections
Perera <i>et al</i> ^[21]	100/Liver	42.5	NA	5.5 (0.75-16) yr	35% cyclosporine, azathioprine and prednisone 48% prednisone and tacrolimus 17% tacrolimus	5 (5) Mainly folliculitis and 1 case of erythrasma
Sánchez-Lázaro <i>et al</i> ^[20]	604/Heart	51	506/98	First year after transplantation	NA	36 (5.9)
Savoia <i>et al</i> ^[65]	286/Kidney	NA	273/163	9.3 (0.1-39.8) yr	66.7% combination therapy comprising tacrolimus in 90%	6 (1.4) All cases of erysipelas
Lima <i>et al</i> ^[22]	53/Kidney	44	28/25	52.5% of patients over 5 yr	44% prednisone 31% mycophenolate	3 (5.7) 2 cases of furuncle and 1 cellulitis

For each literature study has been indicated number of included patients, type of solid organ transplantation, median age, sex, median follow-up time after solid organ transplantation, type of immunosuppressive treatment and the percentage of patients affected by bacterial infections; when available, type of bacterial infection has been specified. NA: Data non available in the considered study; M: Male; F: Female.

Table 3 Incidence of fungal infections in solid organ transplant recipients *n* (%)

Ref.	No. of cases/ population	Age (yr)	M/F	Median follow- up time	Therapy	<i>Candida spp</i>	<i>Malassezia furfur</i>	<i>Dermatophytes</i>
Virgili <i>et al</i> ^[36]	73/Kidney	22-68	44/29	0.25-26 yr	50.7% association of prednisone, cyclosporine and azathioprine	4 (5.4)	20 (27.4)	7 (9.6)
Güleç <i>et al</i> ^[37]	102/Kidney	31.9 ± 10.3	68/34	4.5 ± 4.55 yr	38.2% association of prednisone, mycophenolate and cyclosporine	31 (30.4)	37 (36.3)	10 (9.8)
Perera <i>et al</i> ^[21]	100/Liver	42.5	NA	5.5 (0.75-16) yr	48% association of prednisone and tacrolimus	19%	4%	11%
Lima <i>et al</i> ^[22]	53/Kidney	44	28/25	NA	83% prednisone 58.5% mycophenolate 50.9% cyclosporine	14 (22.6)	9 (17)	8 (15)

For each literature study has been indicated number of included patients, type of solid organ transplantation, median age, sex, median follow-up time after solid organ transplantation, type of immunosuppressive treatment and the percentage of patients affected by fungal infections. NA: Data non available in the considered study; M: Male; F: Female.

Fungal Infections

Among superficial fungal infection, candidiasis of the mouth and intertriginous skin areas is frequent in the early post-transplant time^[35], probably as a consequence of the higher dosage of immunosuppressant treatment in this period (Tables 3 and 4).

Pityriasis versicolor (PV) is such as frequent as superficial candidiasis. Some authors reported prevalence rates of this infection caused by *Malassezia furfur* higher than 30% in cohorts of renal transplant patients^[36,37]. Whereas, there are very few literature reports about the prevalence of PV in other solid organ transplant recipients. Perera *et al*^[21] report a prevalence ratio of PV of 4% in a group of liver transplant recipient. In our cohort, mycosis, mainly represented by onychomycosis, tinea cruris and genital candidiasis, were observed in the 1.8% of cases.

Deep fungal infections comprise two distinct group of conditions, the subcutaneous and systemic mycoses. Subcutaneous mycoses are caused by fungi that have been introduced directly into the skin through a penetrating injury^[36,38]. Systemic dissemination is rare in the immunocompetent patients but could be more frequent in immunosuppressed subjects. Sporotrichosis, mycetoma and chromoblastomycosis are the most frequent subcutaneous infections observed in this group of patients.

Systemic mycoses are fungal infections whose initial portal entry into the body is usually a deep site (*e.g.*, lung and gastrointestinal tract). Skin is usually affected as consequence of systemic dissemination but it may be the primary site in the immunocompromised patients that usually develop systemic candidiasis, aspergillosis, histoplasmosis and cryptococcosis^[39-42]. Incidence rates of

Table 4 Incidence of fungal infections in solid organ transplant recipients *n* (%)

Ref.	No. of cases/ population	Age (yr)	M/F	Median follow- up time	Therapy	Systemic infections	<i>Candida</i> spp	<i>Aspergillus</i> spp
Collins <i>et al</i> ^[45]	158/Liver	46	84/74	NA	Cyclosporine, azathioprine and prednisone	34 (21.5)	28 (17.7)	5 (3.2)
Briegel <i>et al</i> ^[44]	141/Liver	47 ± 12	79/62	NA	Prednisone, cyclosporine and azathioprine	25 (17.7)	10 (7)	11 (7.8)
Kanj <i>et al</i> ^[46]	73/Heart-Lung	NA	NA	NA	NA	37 (50.6)	19 (26)	18 (24.6)
Abbott <i>et al</i> ^[47]	33479/Kidney	43	20154/13325	NA	72.2% with cyclosporine, 65.2% with mycophenolate	595 (1.7)	445 (1.3)	80 (0.2)
Singh <i>et al</i> ^[39]	130/Liver	NA	NA	NA	tacrolimus	11 (14)	6 (5)	4 (3)
Alangaden <i>et al</i> ^[66]	127/Kidney	47.1 ± 12.5	76/51	NA	72% tacrolimus	5 (3.9)	5 (3.9)	NA
Pugliese <i>et al</i> ^[67]	278/Miscellaneous	NA	NA	5.5 ± 5.9 yr	Various	46 (16.5)	45 (16.2)	1 (0.3)
Tessari <i>et al</i> ^[43]	3293/Miscellaneous	NA	2384/909	NA	NA	22 (0.7)	NA	NA

For each literature study has been indicated number of included patients, type of solid organ transplantation, median age, sex, median follow-up time after solid organ transplantation, type of immunosuppressive treatment and the percentage of patients affected by systemic fungal infections. NA: Data non available in the considered study; M: Male; F: Female.

deep fungal infections in solid organ transplant recipients varies from 0.5% to 30%^[39,40]. These studies, however, do not clearly distinguish between primary deep skin mycoses and systemic infections. In an Italian series of 3293 consecutive organ transplant recipients with a mean follow-up time since transplantation of 2.5 ± 2 years, only 22 cases of deep mycoses were detected with a prevalence ratio of 0.7%. Six patients had subsequent systemic involvement and three died of systemic dissemination^[43]. In a US study conducted on 130 liver transplant patients the authors found 6 cases of systemic candidiasis and 4 of aspergillosis^[19]. Other older series conducted on liver transplant patients and exclusively based on detection of systemic mycosis found higher rates of *Candida* and *Aspergillus* infections^[44,45]. This higher incidence could probably derive by an higher use of cyclosporine and azathioprine as tacrolimus and sirolimus weren't still commonly used until the late 90 s.

When considering lung transplant recipients, invasive fungal infections occur in 15% to 35% of the patients with *Aspergillus* species accounting for nearly half of them^[46-48]. The reported prevalence of *Candida* infections is similar^[46].

On the other, hand kidney transplant patients seem to be less frequently affected by invasive fungal infections as reported in some United States series^[38,47]. This incidence could be affected by a lower dose of immunosuppressive treatment and a higher use of tacrolimus instead of cyclosporine and azathioprine when confronted with lung and liver transplant recipient.

Cutaneous tumours

Data about the risk to develop non-melanoma skin cancer (NMSC) and the clinical characteristics of the various published series are resumed in Table 5.

The percentage of NMSCs diagnosed after a solid organ transplantation varied from 25% to 35% in the larger series published by literature^[3,49,50]. The Basal cell carcinoma (BCC)/Squamous cell carcinoma (SCC) ratio was from 1:1.2 to 1:7^[3,49-51]. Fekets *et al*^[52] report a

significantly lower percentage of solid organ recipients affected by NMSC (9.5%), but in this study there is a bias due to the relatively short follow-up period.

The 23.5% of our patients developed a NMSCs in the post-transplant period, with a BCC/SCC ratio of 2.45:1. This percentage was similar to that reported in our previous work, conducted on smaller series^[53]. Fifty-four per cent of BCCs and 81% of SCCs develop on sun-exposed areas. Patients who developed skin cancers were preferentially males ($P = 0.0017$) and were characterized by a significantly higher age at transplantation ($P < 0.001$) and by a significantly longer duration of immunosuppressive regimen ($P < 0.0001$), according with data reported by others authors^[3,50,54]. Also elderly patients^[51] showed a higher risk to develop cutaneous tumours. In our experience, exogenous risk factors significantly linked to NMSC risk were outdoor job ($P = 0.0413$), as well as demonstrated in others series^[52,53], and incorrect use of sunscreen ($P = 0.0252$). We failed to demonstrate a significant association between lower phototypes and risk of NMSC, as demonstrated by several literature series^[3,50,51,53].

In the majority of published studies, cyclosporine and/or azathioprine-based immunosuppressive regimens showed a significant correlation with the risk of developing skin cancer^[3,49,51,52]. On the contrary, we could not identify a specific immunosuppressive drug as a distinctive factor for the development of NMSC.

DISCUSSION

Organ transplantation ensures a prolonged life expectancy and a better quality of life for patients affected by chronic renal, liver, lung or heart failure. However, long-term immunosuppressive therapy causes important inhibitory effects on immune defence mechanism, leading to frequent skin infections and malignancies that are an important cause of morbidity and mortality for solid organ transplant recipients^[1-3].

The schedule of immunosuppressive drugs influences

Table 5 Risk to develop non-melanoma skin cancer and clinical characteristics of the various published series

Ref.	No. of cases/ population	NMSC	BCC/SCC ratio	Median age at transplantation	Median follow- up time	Risk factors associated with NMSC
España <i>et al</i> ^[54]	92/Heart	15.2%	1:1.5	NA	NA	Immunosuppression UV exposure Skin type
Ong <i>et al</i> ^[68]	455/Heart Australia	31%	3:1	NA	NA	Caucasian origin Age at transplantation Duration of follow up Cyclosporin
Hiesse <i>et al</i> ^[5]	1710/Kidney France	7.5%-8.2%	NA	35.5 yr	9 yr	
Moloney <i>et al</i> ^[8]	1755/Kidney Ireland	27.7%	1:2	40 yr	5.35 yr	Age at transplantation Duration of immunosuppression Age at transplantation Male sex
Mackenzie <i>et al</i> ^[49]	384/Kidney New Zealand	25%	1:1.2	41.5 yr	5.3 yr (0.01-33.4)	Cyclosporine/Azathioprine Duration of immunosuppression
Sandoval <i>et al</i> ^[63]	91/Kidney Chile	16%	1:1-9	NA	7.3 yr (1 mo-29 yr)	
Fekecs <i>et al</i> ^[52]	116/Kidney, pancreas Hungary	9.5%	1:4	49.3 yr	NA	Painful sunburns Occupational UV exposure Cyclosporine

For each literature study has been indicated number of included patients, type of solid organ transplantation, median age at transplantation, median follow-up time after solid organ transplantation, percentage of patients affected by NMSC and BCC/SCC ratio. Risk factors significantly associated to the development of non-melanoma skin cancer in each study are indicated in the right column. NA: Data non available in the considered study; UV: Ultraviolet; NMSC: Non-melanoma skin cancer; BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma.

the type and the timing of skin disease. The main problems in the first months are usually represented by wound infections and HSV reactivations, whereas opportunistic infections and herpes zoster develop mainly within 6 months from transplantation. Thereafter, as immunosuppression is reduced, the most frequently observed skin infections are represented by mycoses and HPV infections^[55]. On the contrary, the risk to develop skin cancer increases over time: the cumulative incidence of skin cancers increases significantly with the duration of graft, increasing from 5% after 1 year to 43% after 10 years, as demonstrated in several European series^[51,52]. In the kidney recipients from our series the median time to onset of skin tumours was 9.9 years from the transplantation.

Moreover, tacrolimus and micophenolate mofetil are mainly related to the risk to develop skin infections, whereas the higher carcinogenic risk has been described for azathioprine and cyclosporine^[3,6,49,51]. The oncogenic power of cyclosporine in solid organ recipients was confirmed by a large retrospective study^[5] that demonstrated a risk of skin cancer significantly higher in the group of CyA-treated patients in comparison with the historical group of patients treated with azathioprine-steroids regimens. Moreover, it has recently been demonstrated that azathioprine induces chronic oxidative stress by forming reactive oxygen species (ROS) causing mutagenic damage of the DNA, that could lead to development of NMSC in organ transplantation recipients.

In literature^[55-57], the frequency of HPV infections in transplant recipient varies from 6% to 92%, depending on the type and the duration of the immunosuppressive protocol. We observed viral warts in 10.3% of patients from our series, a percentage superimposable to that

of 8.2% recently reported in another Italian study^[58], probably due to the similarity in the immunosuppressive treatment schedules. Despite some investigations demonstrated that persistent HPV infections can induce malignant transformation of squamous epithelial cells by inactivation of p53, and clinical and histological analyses show progression of viral warts *via* dysplastic lesions up to invasive squamous cell carcinomas, the pathogenic role of HPV in skin tumorigenesis is still in part unclear^[59]. With the use of PCR methods, a prevalence of HPV in 69%-88% of squamous cell carcinoma in transplant recipients was found, in particular high-risk HPV types like HPV-16 and epidermodysplasia verruciformis associated HPV types. The prevalence in organ transplant recipients is significantly higher in comparison to immunocompetent patients (about 50%)^[60]. On the other side, there were no significant differences of HPV prevalence in basal cell carcinoma between immunocompromised and immunocompetent individuals^[1].

Herpes zoster was diagnosed in 2.1% of our patients; this percentage is relatively lower in comparison with data reported by other authors^[55]. However, no significant differences from other series were found when data were stratified on the basis of different age groups. In fact, Herpes zoster affects essentially patients over 60 years, whereas median age of our population was 50 years. In transplanted patients, HSV and HVZ usually provoke limited infections but can also generate diffuse, hemorrhagic, ulcerated and widespread skin lesions more frequently than in immunocompetent individuals^[61]. Also visceral implication are not rare.

When confronted to other reports, bacterial infections were relatively rare in our experience. This could be

considered a consequence of an higher mean time from transplantation in our cohort, as it has been seen that bacterial infections develop more frequently in the first month from transplantation. Moreover we didn't consider folliculitis because they were all of minor entity and we believed that they were more associated to chronic use of steroid rather than to bacterial infections.

A wide variation (7%-75%) in the frequency of superficial fungal infections is reported in several studies; literature data suggest that cutaneous fungal infections in renal transplant recipients are more common in tropical and sub-tropical countries^[37]. However, different authors report similar prevalences of dermatophytosis in immunosuppressed and immunocompetent people. Probably that could derive by the necessity of the coexistence of an environmental exposure to pathogenic fungi together with the administration of immunosuppressive agents^[37]. Also in our experience, the incidence of superficial fungal infections was low, and only 3 cases of onychomycosis (1.1%) were identified. Systemic fungal infections occur in the 5%-20% of solid organ recipients, mainly caused by *Candida* or *Aspergillus*^[55].

The problem about increased risk of skin cancer in solid organ transplant recipients is well known in literature. In particular, it has been estimated a 10-fold increased risk for BCC and a 50-100-fold for SCC. In our experience, the percentage of patients who developed NMSC was 24.8%. This percentage and the BCC/SCC ratio were similar to those reported in recent studies conducted in Italy^[7,58] and Spain^[50,62] (22% and 25.2%, respectively), probably due to the similarity in skin phenotype, exogenous risk factors exposure and in the immunosuppressive treatment schedule^[49,63]. On the contrary, the prevalence of skin cancers in a group of Australian kidney transplant recipients was significantly higher (35%), supporting the importance of latitude and sun exposure on tumour development^[3]. Moreover, differences in the median age at transplantation in the various series could partially justify the variability in the percentage of patients that develop a NMSC. Higher age at transplantation is in fact a factor strictly related to the risk of skin cancer in the majority of published series^[3,49,50,64]. The length of follow-up could also represent a bias in the different series; the majority of the authors state in fact that the risk to develop cutaneous tumours increase over the time, as the consequence of the longer immunosuppression period^[8].

In conclusion, solid organ transplant recipients today have a prolonged life expectancy and a better quality of life. However, cutaneous infections and NMSCs can heavily impact on the quality of life and prognosis of these patients. For this reason it is necessary to perform periodical accurate dermatological controls in order to promptly identify any suspicious lesions. Individual follow-up programs should be realized on the basis of specific risk factor analysis, to optimize the cost-benefit ratio.

COMMENTS

Background

Cutaneous disorders are frequent in chronic renal failure. The majority of these dermatological disorders disappear after kidney transplantation; however, infectious diseases and cutaneous malignancies occur frequently in organ transplant recipients, mainly as a consequence of the long-term immunosuppressive treatment. Infectious skin diseases were frequently diagnosed after transplantation, affecting about the 16.5% of patients whereas dermatological screening identifies cutaneous tumours in about 35% of KTR patients. The relative risk of developing skin cancer is 20 to 40 fold increased, in comparison with the general population.

Research frontiers

Type and duration of the immunosuppressive treatment are currently considered as the major factors related to the development of infective and malignant skin lesions in patients receiving solid organ transplants. However other endogenous and exogenous risk factors can justify the different prevalence ratios reported in several literature studies.

Innovations and breakthroughs

Comparing data from the English language literature of the last 20 years with the results from our cohort of 436 kidney transplant recipients, the authors highlight the characteristics and risk factors for the different skin diseases occurring in transplant recipients.

Applications

Development of an integrated risk stratification protocol for skin diseases in transplant recipients with the aim of optimizing cost-benefit ratio of their treatment.

Peer review

The authors have performed a good study, the manuscript is interesting.

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