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ORIGINAL ARTICLE

# Skin disorders in patients transplanted in childhood

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## Summary

Only few data are available on skin disorders in pediatric organ transplant recipients. In order to describe the whole range of dermatological diseases in a population of pediatric organ transplant recipients, we studied a group of 217 consecutive organ transplant recipients (168 kidney, 29 heart, 19 liver, one lung) aged <18 years at transplantation followed at a single center. A total of 193 patients showed at least one skin disorder; 149 had more than one skin disease. The most common skin infections were warts (24.4%), pityriasis versicolor (20.7%), folliculitis (12.9%), intertrigo (6.5%); the most common drug side effects were hypertrichosis (69.6%), steroid acne (39.6%), gingival hyperplasia (29%) and severe xerosis (20.7%). Two patients (0.9%) developed non-melanoma skin cancer. Our study summarizes the main skin complications in patients transplanted in childhood and underlines the necessity of regular dermatologic surveillance of these patients.

## Introduction

Solid organ transplantation is now currently and increasingly performed for the treatment of various acute and chronic diseases. Along with organ transplantation, immunosuppression is commonly established using combination drug regimens to prevent graft rejection. Corticosteroids, azathioprine, cyclosporine A, tacrolimus, rapamycin and mycophenolate mofetil are commonly used immunosuppressive drugs. Polyclonal antilymphocyte or monoclonal anti-CD3 antibodies are less frequently employed. Long-term use of immunosuppressive drugs creates a state in which immune surveillance is impaired and has been shown to be associated with increased incidence of infection and malignancy [1–4].

Although there are several studies on skin diseases in adult organ transplant recipients, only few data are available on skin disorders in pediatric organ transplant recipients [5–7]. As the field of transplantation is expanding, the number of children who received organ transplants is rapidly growing. The aim of this study was to assess skin and mucosal diseases in large series of children after kidney, heart, liver and lung transplantation.

## Patients and methods

The study group included 217 patients (mean age at last examination 19.9 ± 8.3 years) aged <18 years at the time of transplantation (mean age at transplantation 10.8 ± 5.4 years): 46 (21.2%) patients had received their graft before the age of 6 years, 53 (24.4%) patients from 6 to 12 years, and 118 (54.4%) after the age of 12 years.

The group comprised of 131 boys and 86 girls (166 kidney, 28 heart, 19 liver, two kidney and liver, one kidney and heart, one lung recipients). The follow-up period ranged from 1 month to 28 years (mean follow-up 6.6 ± 5.7 years); 52 (24%) patients had a post-transplant follow-up longer than 10 years. The patients attended the clinic every 6 months and the entire skin was thoroughly examined. The skin conditions have been counted once per patient. A standard questionnaire and examination sheet were completed for each patient and included baseline demographic features, cause of organ failure before transplantation, date of transplantation and current immunosuppressive therapy regimen.

**Table 1.** Immunosuppressive regimens commonly used.

| Immunosuppressive regimen | Patients [*n* (%)] |
|---|---|
| CsA-Aza-Pdn | 109 (50.2) |
| CsA-Pdn | 39 (18) |
| FK-Pdn | 35 (16.1) |
| Other combinations (including CsA, Aza, FK, MM and Pdn) | 34 (15.6) |

CsA, Cyclosporine A; Aza, azathioprine; Pdn, prednisone; FK, tacrolimus (FK-506); MM, mycophenolate mofetil.

### Immunosuppressive regimen

Most patients (109, 50.2%) were treated with a triple therapy regimen consisting of a combination of cyclosporine A, azathioprine, prednisone (Table 1). Other combined immunosuppressive regimens frequently used are shown in Table 1.

Postoperatively, 56 (25.8%) patients received antilymphocyte globulin or antithymocyte globulin or both for 3–5 days.

### Statistical analysis

Statistical analyses were performed by SPSS software package (version 10.01, Chicago, 1999). Results are expressed as mean ± SD, unless otherwise specified. A comparison of mean values was made by Student's *t*-test. The ordinal data were analyzed using the Pearson's chi-squared test and, in situation with low cell count, Fisher's exact test. A logistic regression model was applied to evaluate the influence of individual factors on the prevalence of skin conditions. The explanatory variables included in the logistic regression model were the following: sex, age at transplantation, type of organ transplanted, length of follow-up (five groups: up to 2 years, 3–4 years, 5–6 years, 7–8 years and 9–10 years). The risk of skin diseases with time after transplantation was evaluated by Kaplan–Meier survival analysis. Outcomes of interest in the analysis included the time from transplantation to the first diagnosis of skin diseases, the date of patient's death, the date of loss to follow-up or the end of the study period.

## Results

### Frequency and distribution of skin diseases

A total of 193 patients (88.9%) showed at least one infectious, iatrogenic or neoplastic skin disorder related to the immunosuppressive drugs; 149 (68.6%) presented more than one skin disease. The cumulative incidence of infectious and drug induced side effects is shown in Figs 1 and 2.

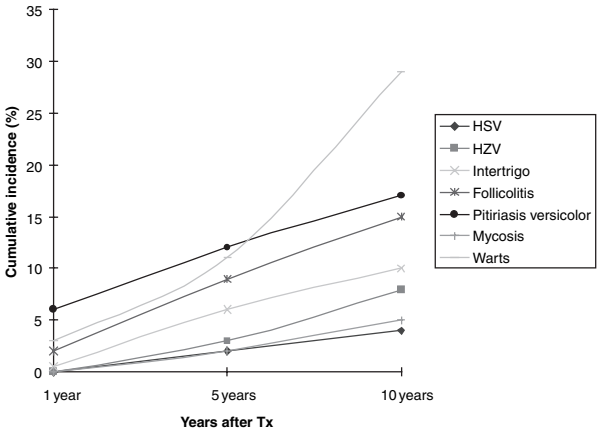


**Figure 1** Cumulative incidence of infections with time after transplantation.

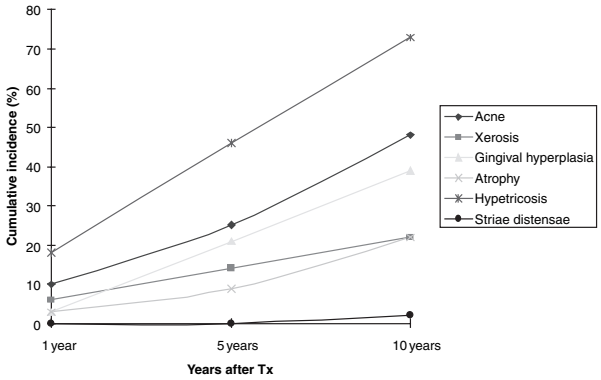


**Figure 2** Cumulative incidence of drug-induced side effects with time after transplantation.

The frequency of skin disease according to different age at transplantation is shown in Table 2.

### Infectious diseases

Infections were present in 56.2% of our pediatric transplant recipients, and 16.1% had multiple concurrent infections at the time of examination. A significant correlation was found between the risk of overall infectious processes and the type of organ transplanted (66.7% in heart, 26.3% in liver and 57.7% in kidney transplant recipients; odds ratio 5.5, 1 and 3.7, respectively; $P = 0.01$).

The frequency of infections with respect to the gender and the organ transplanted is given in Table 3.

Warts were the most frequent skin infection occurring in 24.4% of patients. They were localized mainly on hands or feet (58.4% of affected children; Fig. 3). The patients were treated with usual treatments (mainly cryo-

**Table 2.** Frequency of skin diseases according to different age at transplantation.

| Disease | Patients [*n* (%)] | Mean age at Tx (years) | Interval between Tx and onset of disease (years) | <6 years (%) (*n* = 46) | OR | 6–12 years (%) (*n* = 53) | OR | >12 years (%) (*n* = 118) | OR | *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Infections | | | | | | | | | | |
| Warts | 53 (24.4) | 12.3 | 3.2 ± 1.2 | 15.2 | | 24.5 | | 28 | | 0.23 |
| Pityriasis versicolor | 45 (20.7) | 13.6 | 0.8 ± 0.4 | 6.5 | 1 | 15.1 | 2.5 | 28.8 | 5.8 | 0.003 |
| Folliculitis | 28 (12.9) | 13.5 | 1.5 ± 1.2 | 4.3 | 1 | 7.5 | 1.7 | 18.6 | 5 | 0.02 |
| Intertrigo | 14 (6.5) | 11.4 | 1.8 ± 1.2 | 6.5 | | 3.8 | | 7.6 | | 0.63 |
| Herpes zoster virus | 10 (4.6) | 11.7 | 3 ± 2.3 | 4.3 | | 3.8 | | 5.1 | | 0.92 |
| Mycosis* | 6 (2.8) | 9.6 | 3.2 ± 1.8 | 4.3 | | 1.9 | | 2.5 | | 0.74 |
| Herpes simplex virus | 4 (1.8) | 11.2 | 1.9 ± 1.5 | 2.2 | | 1.9 | | 1.7 | | 0.97 |
| Onicomycosis | 2 (0.9) | 13 | 3.6 ± 1.9 | 0 | | 1.9 | | 0.8 | | 0.61 |
| Impetigo | 2 (0.9) | 13 | 1.9 ± 0.9 | 0 | | 0 | | 1.7 | | 0.42 |
| Drug side effects | | | | | | | | | | |
| Hyperthricosis | 151 (69.9) | 11 | 0.8 ± 0.7 | 65.2 | | 73.6 | | 69.5 | | |
| Acne | 86 (39.6) | 13 | 1 ± 0.9 | 17.4 | 1 | 30.2 | 2 | 52.5 | 5.2 | <0.0001 |
| Gingival hyperplasia | 63 (29) | 10.8 | 2 ± 1.5 | 21.7 | | 34 | | 29.7 | | 0.39 |
| Severe xerosis | 45 (20.7) | 9.9 | 1.1 ± 1 | 23.9 | | 22.6 | | 18.6 | | 0.70 |
| Skin atrophy | 34 (15.7) | 11.6 | 3 ± 1.2 | 8.7 | | 18.9 | | 16.9 | | 0.32 |
| Striae distensae | 2 (0.9) | 12.5 | 2.7 ± 0.7 | 0 | | 1.9 | | 0.8 | | 0.61 |
| Other conditions† | | | | | | | | | | |

Tx, transplantation.

*Tinea corporis, tinea pedis.

†skin fragility (17 patients), sebaceous hyperplasia (12), telangiectases (nine), seborrhoeic dermatitis (three), molluscum contagiosum (two), alopecia (two), follicular hyperkeratosis (two), purpura (two), pseudoacanthosis nigricans (two), dyshidrosis (two), angioma (two), perioral dermatitis (one), ichthyosis-like condition (one), disseminated xanthoma (one), benign genital epidermal neoplasia (one), condyloma (one), vaginitis (one), oral ulcers (one).

therapy), but without satisfactory results. Males were more often affected than females (28.2% vs. 18.6%; $P = 0.1$). The cumulative incidence of warts rose slightly during the first 5 years, from 3% after 1 year to 10% after 5 years. After this time period, the cumulative incidence increased steeply, reaching 30% 10 years after transplantation (Fig. 1).

Pityriasis versicolor occurred in 20.7% of patients, with clinically typical lesions in usual locations (trunk). In some of these patients, skin lesions appeared prominent, extensive and rapidly relapsing. The frequency of pityriasis versicolor increased with age at transplantation (odds ratio 2.5 for patients aged 6–12 years and 5.8 for patients more than 12 years of age compared with children under 6 years of age at transplantation; Table 2). No significant difference was found between males and females (21.4% vs. 19.8%).

Folliculitis was observed in 12.9% of patients. The back was the site most frequently affected. A significant relationship was found between the prevalence of folliculitis and the type of organ transplanted (heart 30%, kidney 11.3%, liver 0%; age at transplantation and length of follow-up adjusted *P*-value <0.01), but no correlation was found with gender (Table 3). We found a significant increase of prevalence of folliculitis in recipients aged more than 12 years at transplantation, with a fivefold higher risk compared with patients under 6 years old ($P = 0.02$). Topical antibacterial treatment was performed and gave successful results.

**Table 3.** Frequency (%) of infections with regard to gender and organ transplanted.

| Infection | Gender | | Organ transplanted | | |
|---|---|---|---|---|---|
| | Male | Female | Heart | Kidney | Liver |
| Warts | 28.2 | 18.6 | 35.7 | 27 | 14.3 |
| Herpes zoster virus | 4.6 | 4.7 | 6.7 | 4.8 | 0 |
| Herpes simplex virus | 3.1 | 0 | 3.3 | 1.2 | 5.3 |
| Intertrigo | 8.4 | 3.5 | 6.7 | 6.5 | 5.3 |
| Follicolitis* | 13.7 | 1.6 | **30** | **11.3** | **0** |
| Pityriasis versicolor | 21.4 | 19.8 | 10 | 24.4 | 5.3 |
| Mycosis | 2.3 | 3.5 | 6.7 | 2.4 | 0 |

***P* < 0.01** (adjusted for age at transplantation and length of follow-up).

Intertrigo occurred in 6.5% of patients (axillary folds, groin, navel, retroauricular areas); we found no significant association with type of organ transplanted, gender or age at transplantation.

Varicella-zoster infection was observed in 4.6% of patients of which two developed varicella and eight herpes zoster. Herpes zoster developed in lower limbs and trunk.

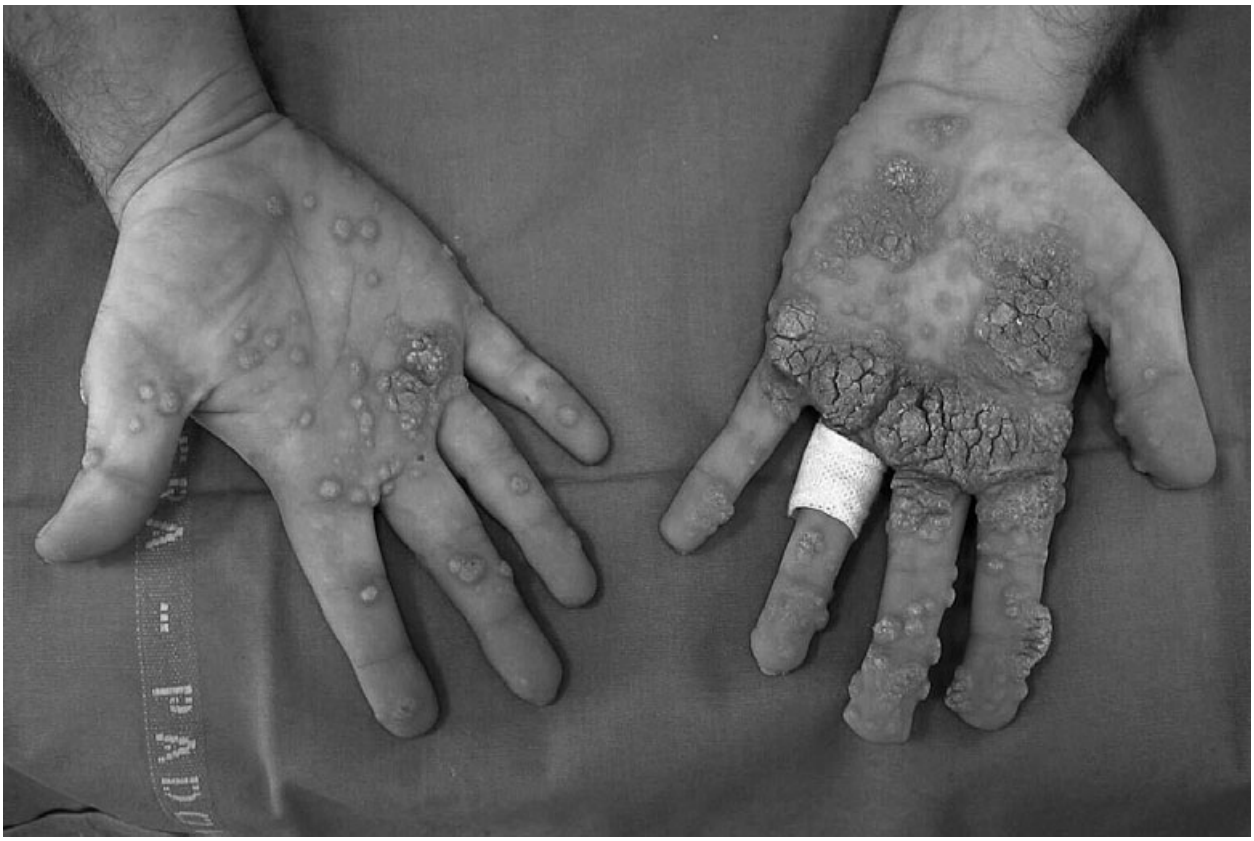

**Figure 3** Warts in a 17-year-old boy.

Patients were treated successfully with systemic acyclovir. No patients suffered from post-herpetic neuralgia.

Other infections which occurred with lower frequency are listed in Table 2.

### Side effects of immunosuppressive drugs

Nearly all patients developed mild to severe side effects related to steroids or cyclosporine A. The most common side effects were hypertrichosis and acne (Table 2). The frequency of drug side effects according to gender and organ transplanted is given in Table 4.

**Table 4.** Frequency (%) of drug side effects with regard to gender and organ transplanted.

| | Gender | | Organ transplanted | | |
|---|---|---|---|---|---|
| Drug side effects | Male | Female | heart | kidney | liver |
| Hypertrichosis* | 66.4 | 74.4 | **80** | **70.8** | **42.1** |
| Acne* | **46.6** | **29.1** | 33.3 | 42.3 | 26.3 |
| Skin atrophy | 14.5 | 17.4 | 16.7 | 16.7 | 5.3 |
| Gingival hyperplasia | 26.7 | 32.6 | 40 | 28.6 | 15.8 |
| Severe xerosis** | **14.5** | **30.2** | 33.3 | 18.5 | 21.1 |
| Striae distensae | 0.8 | 1.2 | 0 | 1.2 | 0 |

*$P = 0.01$ and **$P = 0.005$ (adjusted for age at transplantation and length of follow-up).

Hypertrichosis was observed in 69.6% of all patients, with a mean interval between transplantation and onset lower than 1 year (Fig. 4). Hypertrichosis tended to become less prominent as the post-transplantation interval lengthened. We found a higher frequency of hypertrichosis in heart and kidney recipients compared with liver recipients (Table 4). No difference was found according to gender and age at transplantation (Tables 2 and 4).

Acne was observed in 39.6% of all patients and appeared soon after transplantation (mean interval $1 \pm 0.7$ year). Most patients affected showed a monomorphic eruption of micro-papulopustular lesions mainly located on the face. We found development of acne to be associated with a higher age at transplantation (odds ratio 2 for patients aged 6–12 years and 5.2 for patients aged >12 years; $P < 0.0001$). Males were more affected than females (46.6% vs. 29.1%; age at transplantation and length of follow-up adjusted $P$-value $= 0.01$; Table 4). No statistically significant difference was found among recipients of different organs (Table 4).

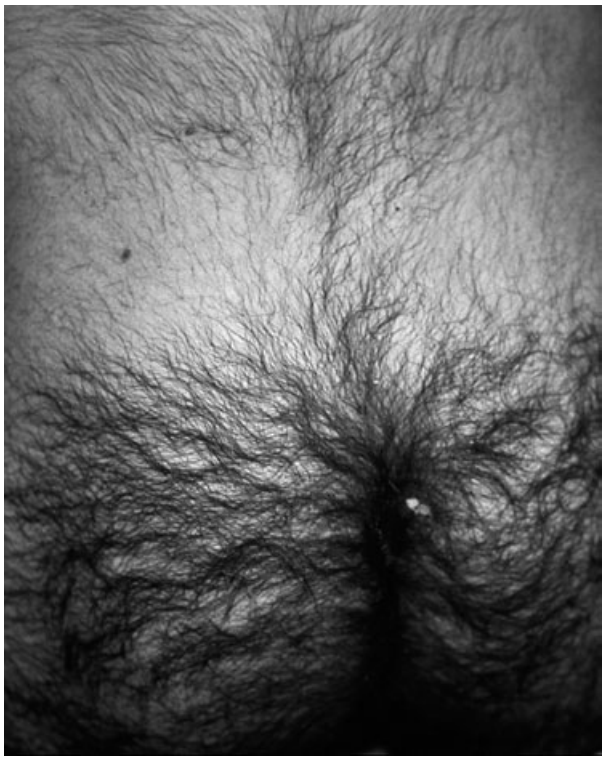

**Figure 4** Hypertrichosis in a 14-year-old boy.

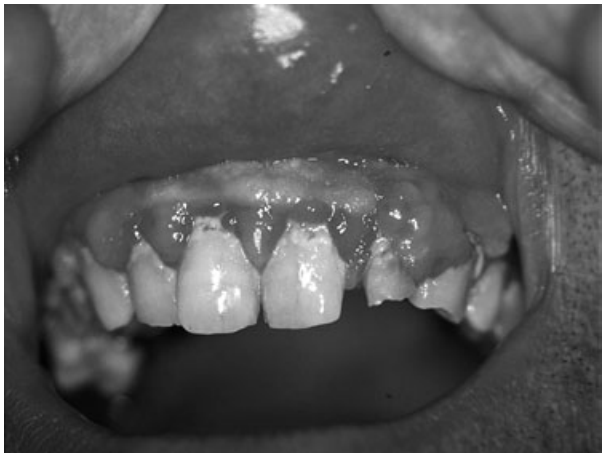

**Figure 5** Gingival hyperplasia in a 16-year-old boy.

Gingival hyperplasia was observed in 29% of patients (Fig. 5). Surgical treatment was required in some patients. No difference was found with regard to gender, organ transplanted and age at transplantation (Tables 2 and 4).

Severe xerosis was present in 20.7% of patients; itching was sometimes severe, but was relieved by the use of emollients. No statistically significant difference was found with regard to different organ transplanted and age at transplantation (Tables 2 and 4). We found a statistically significant difference between males and females (14.5% vs. 30.2%; age at transplantation and length of follow-up adjusted $P$-value $= 0.005$).

Pronounced skin atrophy was observed in 15.7% of patients. No difference was found with regard to gender, organ transplanted and age at transplantation (as shown in Tables 2 and 4).

Other less frequent drug-related conditions are detailed in Table 2.

### Precancerous and cancerous lesions

Two patients developed dysplastic nevi on the trunk at 5 and 7 years after transplantation. Two patients developed actinic keratosis on the face at 10 and 23 years after transplantation (Table 5). The same patients who showed actinic keratosis developed also non-melanoma skin cancer (Table 5).

## Discussion

Several studies have described cutaneous lesions in solid organ transplant patients, but few have been focused on skin disorders in pediatric recipients [5–7].

In our study, the most frequent cutaneous disorders were side effects of the drugs which were not related to the immunosuppressive action of the agent used.

Hypertrichosis occurred in about 70% of patients, developing very early in the post-transplant period (i.e. <1 year), but becoming much less evident with time. This might be related to the higher cyclosporine A load in the first months after transplantation, load which is subsequently tapered down to the maintenance level. Heart recipients, who underwent higher maintenance dosages of cyclosporine A, had a higher frequency of hypertrichosis compared with kidney and liver patients.

Cyclosporine A was also responsible for the high incidence of gingival hyperplasia (29% of patients), which in some subjects was so pronounced to require repeated surgical intervention.

Steroid acne is different from usual acne, in that it presents with a monomorphic eruption of papulopustular lesions, without comedones. We found an increased frequency of acne in postpubertal recipients which is consistent with a possible steroid-induced facilitation of the sebaceous gland response to androgens.

As regard to cutaneous manifestations possibly related to the immunosuppressive activity of the drugs used, some kind of skin infection was present in more than half of the population studied, warts being the most common. Infections were significantly associated with the type of

**Table 5.** Precancerous lesions and skin cancer in pediatric organ transplanted patients.

| Patients | Age at Tx (years) | Organ Tx | Precancerous lesions | Site | Time after Tx | Skin cancer | Site | Time after Tx | Current therapy |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 18 | Heart | Actinic keratosis | Helix | 10 years | SCC | Lower lip | 5 years | CsA, Aza |
| 2 | 13 | Kidney | Actinic keratosis | Forehead | 23 years | SCC | Left hand | 11 years | CsA, Aza, Pdn |
| | | | | | | BCC | Temporal region | 24 years | CsA, Pdn |
| 3 | 18 | Kidney | Dysplastic nevus | Trunk | 7 years | – | – | – | CsA, Pdn |
| 4 | 14 | Kidney | Dysplastic nevus | Trunk | 5 years | – | – | – | CsA, Pdn, MM |

Tx, transplantation; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; CsA, Cyclosporine A; Aza, azathioprine; Pdn, prednisone; MM, mycophenolate mofetil.

organ transplanted, being more frequent in heart and kidney transplant recipients. As a matter of fact, heart recipients undergo the highest immunosuppressive load and liver recipients the lowest.

Warts represented the most common infective disease. Generally, once warts had developed, the patient never became free of them. Risk of developing warts increased with time after transplantation, reaching a cumulative incidence of 30% after 10 years, and was higher in heart transplant patients.

Pityriasis versicolor surprisingly occurred in more than 20% of our pediatric patients, with a much higher frequency and a more aggressive clinical course than that usually seen in our population of patients transplanted in adulthood. Pityriasis versicolor was more common in postpubertal patients.

Two patients (0.9%) developed dysplastic nevi at 19 and 25 years of age. This early development of dysplastic nevi in young patients, underlines the risk of developing melanoma for transplanted children, as previously suggested by other authors [5, 8].

Moreover, two patients (0.9%) developed squamous cell carcinoma. A heightened risk of developing squamous cell carcinoma is well known in adult transplant recipients [1–4]. This risk is relatively low in children, probably because of both the lower amount of pretransplant sunlight exposure and the more accurate prevention of sunlight exposure in these patients after the transplantation if compared with adult patients. However, this risk is likely to increase with longer follow-up, when patients who received transplants during childhood, will have been maintained on immunosuppressive therapy for several decades. Regular dermatologic surveillance of these patients is thus advised for the remainder of their lives.

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