Another subentity of CSMH is characterized by a circumscribed annular patch with multiple follicular papules. Unlike classical CSMH, there is no hyperpigmentation and the hair pattern changes are less prominent (4).

There have also been reports of patients with multiple CSMH (5).

Diffuse CSMH has been described as part of the Michelin-tyre-baby syndrome (6). This syndrome is characterized by a combination of anomalies, such as ringed skin creases, cleft palate, epicanthal folds, hyperteleorism, malformed ears and developmental delay (6).

On the basis of these criteria, we propose a clinical classification of CSMH of the skin.

1. Type 1: classical localized CSMH
2. Type 2: patchy follicular variant
3. Type 3: multiple CSMH
4. Type 4: diffuse CSMH

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Risk Factors for Skin Cancer in a Group of Renal Transplant Recipients

Sir,

Studies in northern Europe and Australia have detected a high incidence of skin cancer in renal transplant recipients (RTRs). Hartevelt et al. (1) found a cumulative incidence of skin cancer, ranging from 10% to 40%, at 10 and 20 years after transplantation. Bouwes Bavinck et al. (2), in a cohort of Australian patients, reported a higher incidence (from 45% to 70% at 10 and 20 years after transplantation), related to the more intense sun exposure at those latitudes. Only few reports have been published about RTRs from southern Europe and Italy. From 1990 to 1997 we enrolled a consecutive series of RTRs in a dermatological screening program, followed up by the Second Division of Surgery and Kidney Transplantation Centre of the Ospedale Civile Maggiore, Verona, Italy. All patients gave their informed consent before medical examination.

We examined 423 RTR subjects (290 males and 133 females), treated with 3 different immunosuppressive regimens: prednisolone+azathioprine (PA) (71 patients), prednisolone+azathioprine+cyclosporin (PAC) (191 patients), prednisolone+cyclosporin (PC) (161 patients). An accurate dermatological anamnesis was collected. Clinical records were available for all the patients. For each patient we recorded the following data: age, sex, stature, weight, date of the transplantation and of the visit, type and maintenance posology of the immunosuppressive drugs. The whole skin surface and mucous membranes were examined by a dermatologist. Any lesion suspected to be a skin cancer was excised and its histology examined. For estimates of potential prognostic factors, only variables available at the time of the transplant were considered: we took as an end point the diagnosis of cancer. Cox's proportional-hazards regression model (3),

performing backward stepping of variables with pre-assigned p values equal to 0.05 that controlled the stepping removal, and Kaplan and Meir survival curves were carried out.

The mean age of the RTRs at the visit was 46.2 years (SD 11.2, age range 19–68 years) and mean age at transplantation was 38.9 years (SD 11.7 age range 12–65 years), with no difference between males and females. Mean follow-up time was 7.6 years (SD 5.38, range 0–26 years): the PA group had a longer follow-up time (14.0 years) (SD 6.0) than the PAC group (6.6 years) (SD 3.9) and the PC group (5.9 years) (SD 4.7).

A total of 43 patients were excluded: 30 died of various accidents unrelated to the graft function and 13 rejected the graft (Table I).

A skin cancer was detected in 21/423 patients (5%) (BCC 10; Bowen 2; Keratoacanthomas 3; SCC 6). Cumulative incidence of the first cancer at 5, 10, 15 and 20 years of follow-up was 0.8%, 5.2%, 11.2% and 15.3%, respectively. The incidence of cancer was not significantly different in the 3

Table I. *Patients excluded from the study*

Immunosuppressive therapy	Death	Rejection	Total
PA	9	5	14
PAC	7	4	11
PC	14	4	18
Total	30	13	43

PA = prednisolone+azathioprine.
PAC = prednisolone+azathioprine+cyclosporin.
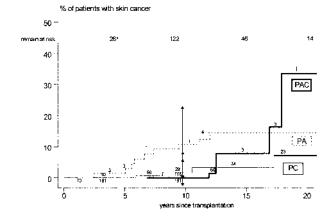PC = prednisolone+cyclosporin.

Fig. 1. Cumulative incidence of skin cancer in the 3 groups of renal transplant recipients. Kaplan and Meier survival analysis. (The numbers near the curves are the censored values). Log-rank test $\chi^2 = 0.55$ $p = 0.75$. PA = prednisolone + azathioprine. PAC = prednisolone + azathioprine + cyclosporin. PC = prednisolone + cyclosporin.

treatment groups (Fig. 1) even if the PA group had a longer follow-up time. Risk factor analysis is reported in Table II: only age at transplantation was found to be statistically significant (Hazard ratio 5.6; $p < 0.0001$). Due to the low number of cancers detected in our study population, we could not investigate other possible risk factors, such as skin type (according to Fitzpatrick), HLA antigens, or sun-exposure during work or leisure. Many well-known risk factors for non-melanoma skin cancer in RTRs are: drug-induced immunosuppression, the degree of sun exposure before and after the transplantation, some HLA antigens (HLA B27, HLA DR homozygosity, HLA B mismatch), skin infection with oncogenic HPV types. It is obvious that iatrogenic immunosuppression is an important risk factor; conflicting reports exist about whether there might be a higher risk for patients treated with azathioprine than patients who are given cyclosporin. Azathioprine (4) and its metabolites are mutagenic and they may be detected in the urine; also these metabolites are toxic to Langerhans' cells. Cyclosporin is not mutagenic, but has a higher immunosuppressive activity than azathioprine (5). Penn (6), among cyclosporin-treated patients, detected a double prevalence of lymphomas, and for Kaposi's sarcoma, an earlier onset (20 vs. 60 months) and

a four times higher risk. He described a higher prevalence of non-melanoma skin cancer among azathioprine-treated patients than among cyclosporin-treated patients (40% vs. 25%). Hiesse et al. (7) diagnosed 44 epitheliomas after a 20-year follow-up of 1600 RTRs: 28 cases were in the cyclosporin-treated group and only 16 cases were in the azathioprine-treated group, even though this group had double the time of follow-up. Bouwes Bavinck et al. (2) and Sheil (8) did not found any statistically significant relationship among the type of the immunosuppressive therapy (azathioprine alone, azathioprine + cyclosporin, cyclosporin alone) and skin cancer. Also, maintenance posology of immunosuppressive drugs, cumulative drug dosages and the number of acute rejection treatments seemed to have no effect. The only risk factors were age at transplantation (>45 years) and the length of follow-up time.

In our study population we found no statistically significant relationship between skin cancer and the type of immunosuppressive therapy even though the PA group had a longer follow-up time (14.0 years, SD 6.0 years). In the 3 groups of patients, cancer incidence increased with follow-up time. According to current literature and to our clinical experience, we conclude that skin cancer in RTRs seems not to be strictly related to the type of the immunosuppressive drugs, but mainly to the prolonged immunosuppression. This chronic immunodeficit allows the accumulation of the damages induced by other risk factors, such as UV rays and HPV. Further studies, on larger cohorts of patients will give us a better knowledge of pathogenetic mechanisms and of other possible risk factors.

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Table II. *Risk factors for skin cancer in renal transplant recipients. Cox proportional hazards regression model*

	Hazard ratio	95% C.I.	p
Age at transplantation (<45 years vs. >45 years)	5.6	2.5–15.3	0.0001
Sex (males vs. females)	1.05	0.43–2.59	0.9105
Episodes of rejection requiring adjunctive immunosuppressive therapy* (any number of rejections vs. no rejections)	0.51	0.18–1.47	0.1950

* Bolus of prednisolone i.v.