Renal transplant related skin conditions

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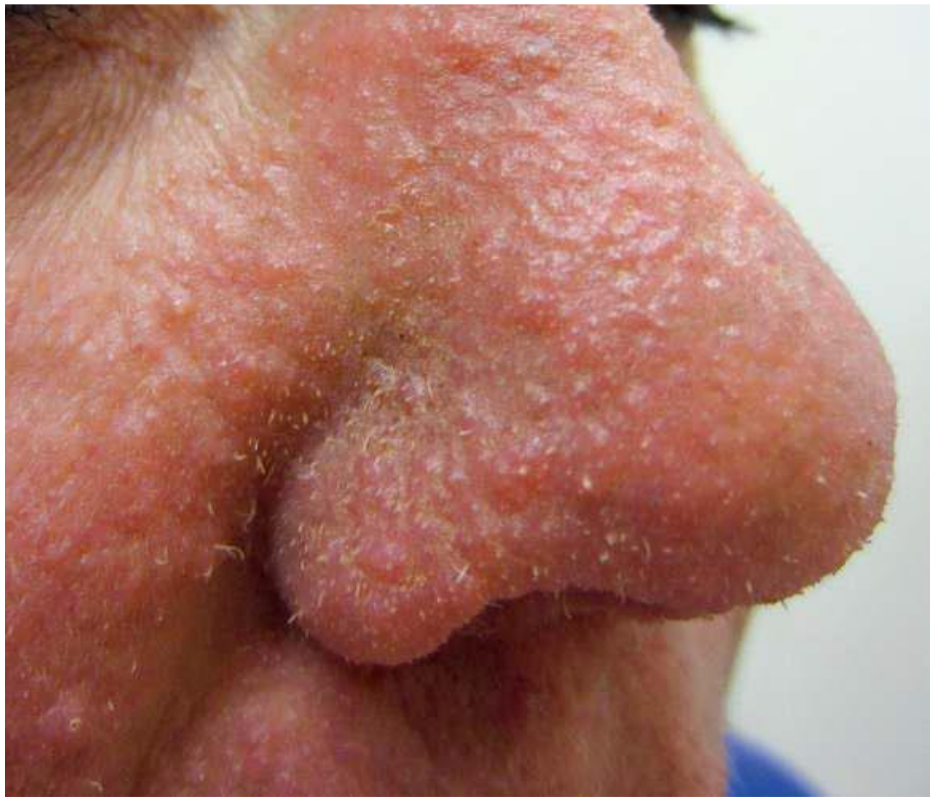
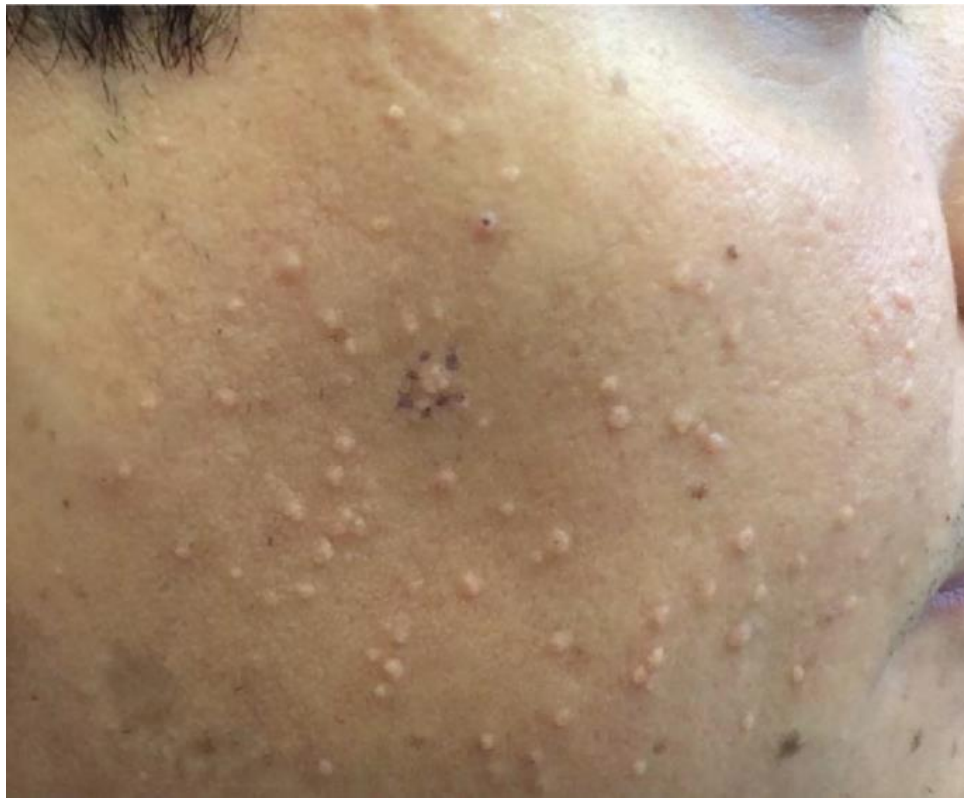
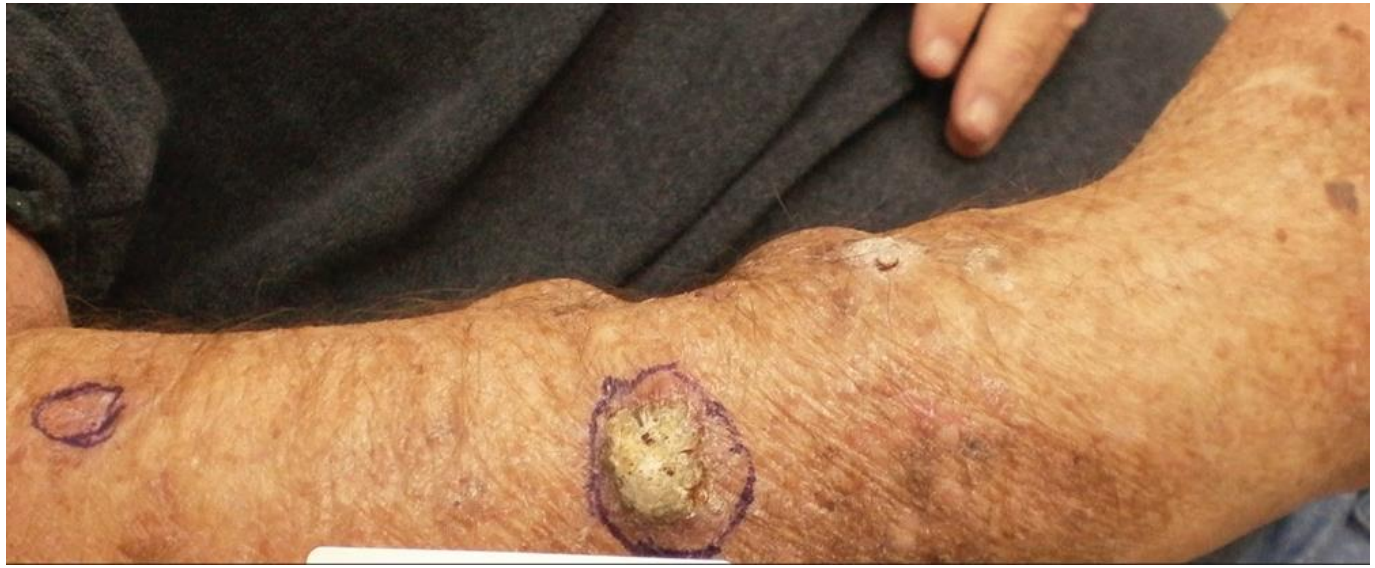


Viral associated trichodysplasia



Sebaceous hyperplasia



Squamous cell carcinoma

Outline

- Cutaneous malignancies
- Drug-induced side effects
- Infections

A 60 year old white male presents for kidney transplant follow-up, 21 years after a deceased donor transplant. Despite an early cellular rejection episode, he has maintained excellent allograft function (baseline creatinine 107 μmol/L) without humoral sensitization on a dual regimen of cyclosporine and azathioprine. He has a history of photodamage but no history of skin cancer or solid-organ malignancy. He has recently had a 1 cm tender keratotic nodule excised from his shin, confirmed histologically as invasive cutaneous squamous cell carcinoma (CSCC). The patient asks whether anything can be done to decrease his risk of cancer recurrence without putting their allograft at undue risk.

Bottomley MJ, Massey PR, Thuraisingham R, Doyle A, Rao S, Bibee KP, Bouwes Bavinck JN, Jambusaria-Pahlajani A, Harwood CA. Interventions after first post-transplant cutaneous squamous cell carcinoma: a proposed decision framework. Transplant International

Malignancies

- Susceptibility factors for NMSC
  - Older age
  - Male sex
  - Fair skin type
  - UV exposure
  - Duration of immunosuppression
  - HPV infection: HPV DNA is detected in 90 percent of SCC in renal-transplant patients
  - Voriconazole :photosensitive activity
- Incidence of NMSC : 12% with SCC as the most predominant tumor
  - the incidence of lip cancer is 50 times higher than in the general population
- The median time to first CSCC is typically many years after transplant, unless pre-transplant history of CSCC
- more aggressive phenotype, multifocal, higher metastatic, and recurrence rate
- Subgroup analysis per geographic location: 1.2% (95% CI: 0.4%–2%) in Middle East

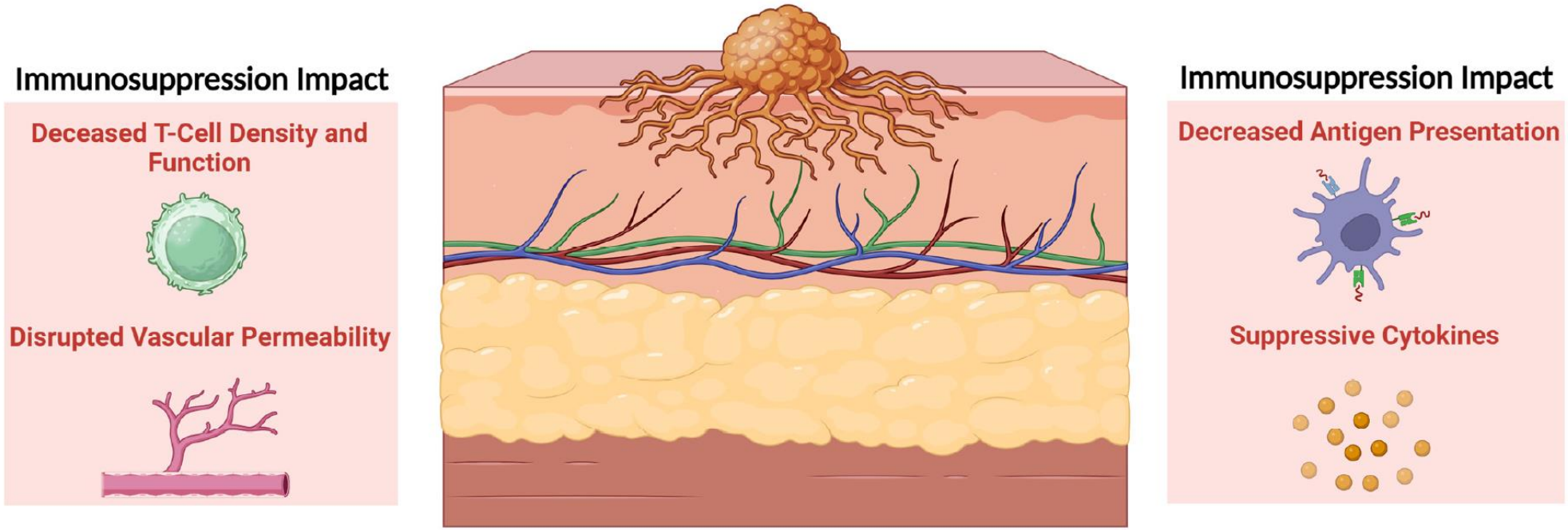
Matinfar M, Shahidi S, Feizi A. Incidence of nonmelanoma skin cancer in renal transplant recipients: A systematic review and meta-analysis. Journal of Research in Medical Sciences. 2018 Jan 1;23(1):14.

Table 1
Standard incidence ratio of post-renal transplant malignancies compared to general population.

Standard incidence ratio compared to general population	**Post-renal transplant malignancies**
>5	Non-melanomatous skin cancers, post-transplant lymphoproliferative disorder, renal cell carcinoma, lip, Kaposi sarcoma
2–5	Thyroid cancer, melanoma, multiple myeloma, leukemia
<2	Brain cancer, prostate cancer, lung cancer

Matinfar M, Shahidi S, Feizi A. Incidence of nonmelanoma skin cancer in renal transplant recipients: A systematic review and meta-analysis. Journal of Research in Medical Sciences. 2018 Jan 1;23(1):14.

CUTANEOUS SQUAMOUS CELL CARCINOMA AND IMMUNOSUPPRESSION

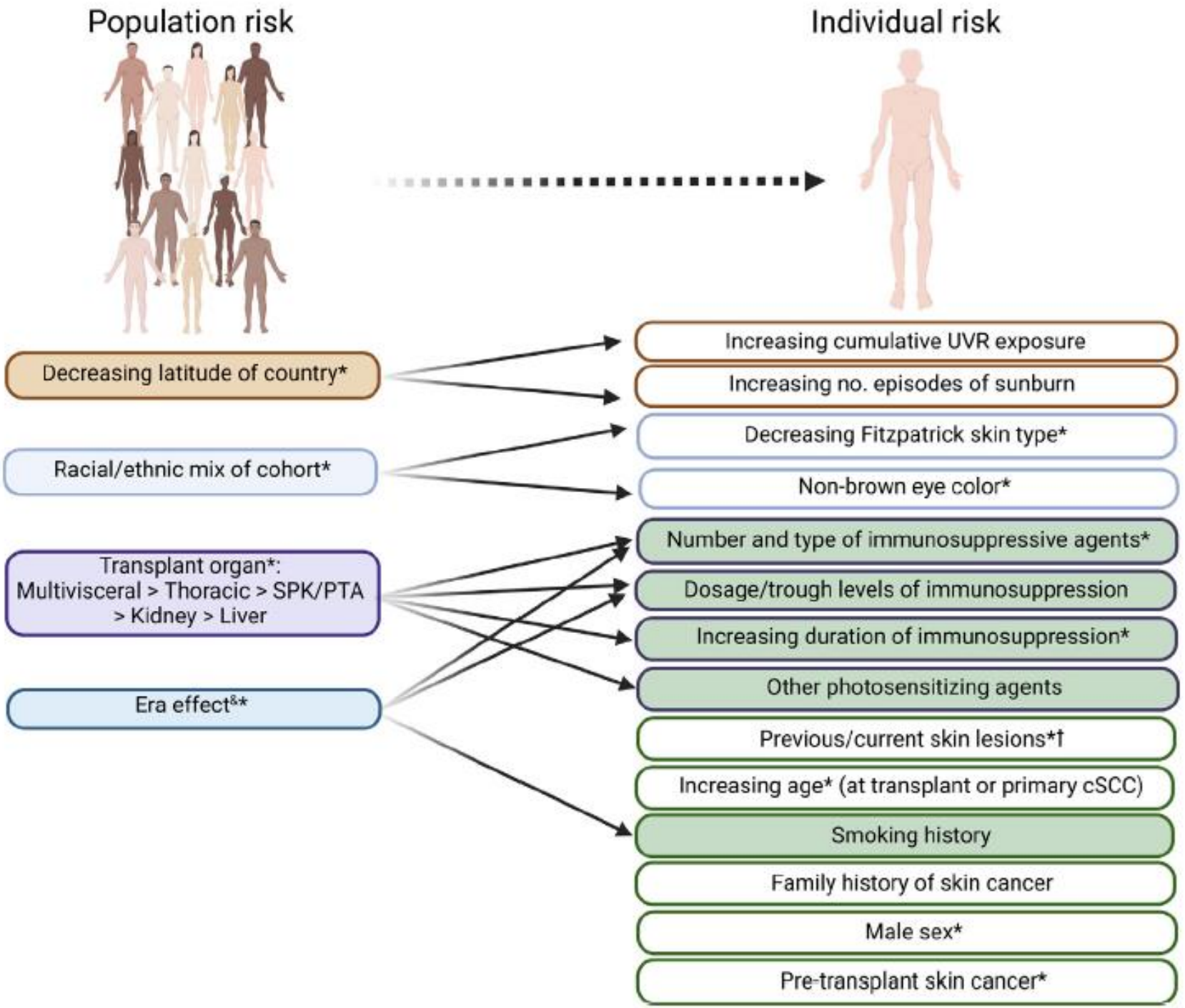


Immunosuppression and Immune Dysfunction Risk Factors for Cutaneous Squamous Cell Carcinoma Development

Khaddour K, Murakami N, Ruiz ES, Silk AW. Cutaneous squamous cell carcinoma in patients with solid-organ-transplant-associated immunosuppression. Cancers. 2024 Sep 4;16(17):3083.

Prevention stage	Definition	Example(s) relevant to post-transplant CSCC
Primordial and primary	Prevent disease onset in susceptible individuals (i.e., with one or more risk factors)	Education regarding UV exposure, promoting use of photoprotection (such as sunscreen)
Secondary	Identify patients with early disease and prevent progression	Skin cancer screening, topical or systemic chemoprevention (including management of premalignant lesions) or modulation of immunosuppression in patient with first CSCC to prevent further CSCC.
Tertiary	Decrease morbidity and mortality of individuals with advanced disease	Surgery or radiotherapy to locally advanced lesions to prevent metastatic spread; immunotherapy for treatment of metastatic lesions
Quaternary	Protect individuals from medical interventions that may cause more harm than good	Avoiding sensitization and rejection resulting from immunosuppression modulation

Staging of disease prevention differs in post-transplant skin cancer compared to other diseases, where progression does not solely represent growth and metastasis of a single malignancy, but also the development of further asynchronous primary lesions. Summarized from references (20, 21, 31).



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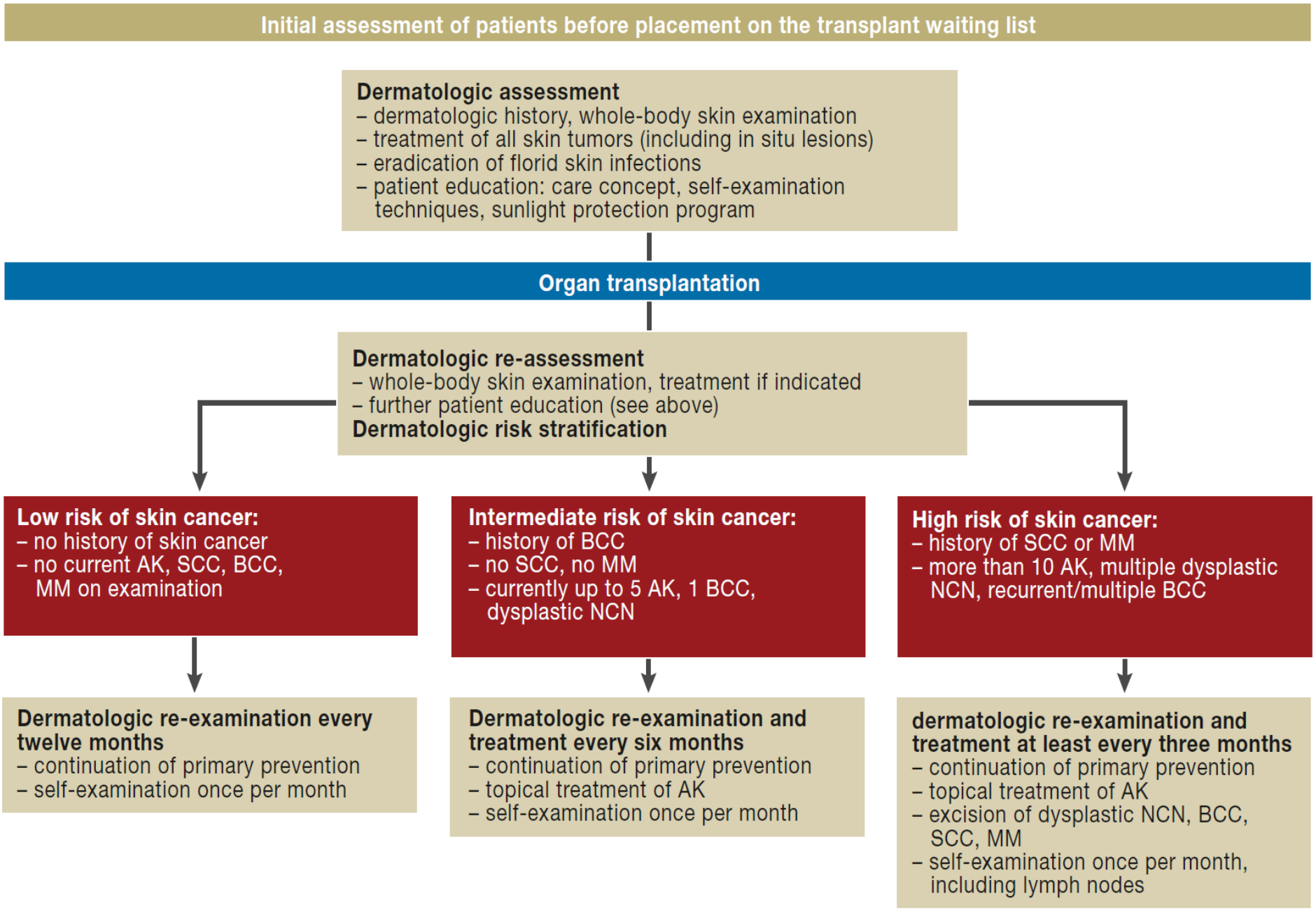
Prevention

- Limiting skin exposure
- Frequent dermatologic screening
- Early treatment of precancerous lesions
  - Discrete lesions: Destructive therapy
  - Confluent areas: topical 5-fluorouracil (5-FU)

Ulrich C, Arnold R, Frei U, Hetzer R, Neuhaus P, Stockfleth E. Skin changes following organ transplantation: an interdisciplinary challenge. Deutsches Ärzteblatt International. 2014 Mar 14;111(11):188.

FIGURE 2



Ulrich C, Arnold R, Frei U, Hetzer R, Neuhaus P, Stockfleth E. Skin changes following organ transplantation: an interdisciplinary challenge. Deutsches Ärzteblatt International. 2014 Mar 14;111(11):188.

TABLE 2

Dermato-oncologic criteria for patient evaluation before transplantation

Skin tumor	Transplantation possible without special concern	Dermatologic assessment recommended	Criterion of exclusion for transplantation	Interval to dermatologic reassessment after diagnosis of skin cancer (if transplantation was not possible at first)
Basal cell carcinoma				
primary	X			5 years
metastatic, in remission			X	not applicable
metastatic, not in remission			X	
Squamous cell carcinoma				
primary, low risk	X			
primary, high risk*[1]		X		3 years
metastatic, in remission			X	3–5 years
metastatic, not in remission			X	not applicable
Melanoma				
stage 0*[2] (in situ)	X			
stage I*[2]		X		2–3 years
stage II*[2]			X	3–5 years
stage III*[2]			X	not applicable
stage IV*[2]			X	not applicable
Merkel- cell carcinoma				
primary		X		2–3 years
metastatic, in remission			X	3–5 years
metastatic, not in remission			X	not applicable
Kaposi's sarcoma		X		3 years
Dermatofibrosarcoma protuberans	X			
Rare malignant skin tumors[3]		X		3 years

Ulrich C, Arnold R, Frei U, Hetzer R, Neuhaus P, Stockfleth E.
Skin changes following organ transplantation: an interdisciplinary challenge. Deutsches Ärzteblatt International.
2014 Mar 14;111(11):188.

Prevention

- Chemoprophylaxis
- **No significant changes in kidney allograft function or risk of allosensitization**
  - Retinoid
    - should be administered for many years
    - rebound NMSC development on cessation may occur
      - 3–4 months after drug cessation
    - Discontinuation rate due to side effects: 19%–39%
      - xerosis and alopecia

waiting until multiple/high-risk CSCC formation

  - Nicotinamide 500 mg twice daily
    - protection against photocarcinogenesis
    - 30% reduction in CSCC compared to placebo over 12 months
    - rebound effects

Acitretin

Published in final edited form as:
Dermatol Surg. 2021 January 01; 47(1): 125–126. doi:10.1097/DSS.0000000000002423.

Efficacy and Cost Analysis for Acitretin for Basal and Squamous Cell Carcinoma Prophylaxis in Renal Transplant Recipients

O. Badri[1], **C.D. Schmults**[1], **P.S. Karia**[1,2], **E.S. Ruiz**[1]

[1]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

During the mean 2.05-year pre-treatment period, 103 patients developed 37 BCCs and 232 SCCs. During the mean 1.38-year post-treatment period (range 0.5 to 3.17 years), there were 8 BCCs and 71 SCCs. This corresponded to a 73% reduction in BCC (mean: 0.10 per patient per year), 54% reduction in SCC (mean: 0.57 per patient per year), and 56% reduction in KC (mean: 0.68 per patient per year) (Table 2). There was no statistical difference in the reduction by tumor subtype ($p>0.05$). Nearly all patients experienced some mucocutaneous xerosis, 14 (14%) discontinued therapy, and 1 (1%) took a drug holiday.

Badri O, Schmults CD, Karia PS, Ruiz ES. Efficacy and cost analysis for acitretin for basal and squamous cell carcinoma prophylaxis in renal transplant recipients. Dermatologic Surgery. 2021 Jan 1;47(1):125-6.

Prevention

- Individualized selection and dosing of immunosuppressive drugs
  - mild reduction in immunosuppression
    - multiple skin cancers per year
    - individual high-risk skin cancers

Immunosuppressive drugs

- Azathioprine
  - 10% of Australian and US kidney transplant are on Aza
  - promotes UVA absorption by DNA
  - Directly induce skin tumors
  - Multiple SCCs as well as of warts
  - should be replaced by mycophenolic acid or mTOR inhibitors
- Calcineurin inhibitors
  - A trial of high- versus low-dose cyclosporine in organ transplant recipients resulted in a lower incidence of tumors in the low-dose group over 66 months of follow-up (19% vs. 32%, $p<0.034$)
  - Impairs UVR-induced DNA damage repair and apoptotic mechanisms and promotes tumor growth
  - combining cyclosporine with an mTOR inhibitor significantly lowers the incidence
  - Tacrolimus-based regimens seem to reduce the incidence of NMSC: controversial

Ulrich C, Arnold R, Frei U, Hetzer R, Neuhaus P, Stockfleth E. Skin changes following organ transplantation: an interdisciplinary challenge. Deutsches Ärzteblatt International. 2014 Mar 14;111(11):188.

Immunosuppressive drugs

- Mycophenolate Mofetil :less effect on photo-carcinogenesis than azathioprine and calcineurin inhibitors
  - Does not promote UVA sensitivity
  - may inhibit DNA repair
- mTOR inhibitors
  - Antiproliferative effect
  - Inhibitory effect on tumor angio –genesis
  - A 25%–40% reduction in further CSCC risk over 2-year in those converted to sirolimus
    - similar patient and graft survival
    - poorly tolerated
      - proteinuria, pneumonitis, oedema, impaired wound healing, teratogenicity and hyperlipidaemia
    - rebound effect
  - In patients with post-transplant squamous cell carcinoma, switching from a calcineurin inhibitor to sirolimus reduces the risk further
    - These benefits should be balanced against the increased risk of cardiovascular and infection-related mortality
      - higher intensity mTORi regimens
- Everolimus
  - comparable transplant outcomes: alongside low-dose calcineurin inhibition

Sirolimus

Use of sirolimus as an adjuvant therapy for kidney transplant recipients with high-risk cutaneous squamous cell carcinomas: a prospective non-randomized controlled study

The most noteworthy finding was a substantial decrease in the incidence density of moderately differentiated lesions (present in 83% of the patients in the sirolimus group) from the second year of sirolimus administration, compared to a significant increase in this parameter in the control group over time. This

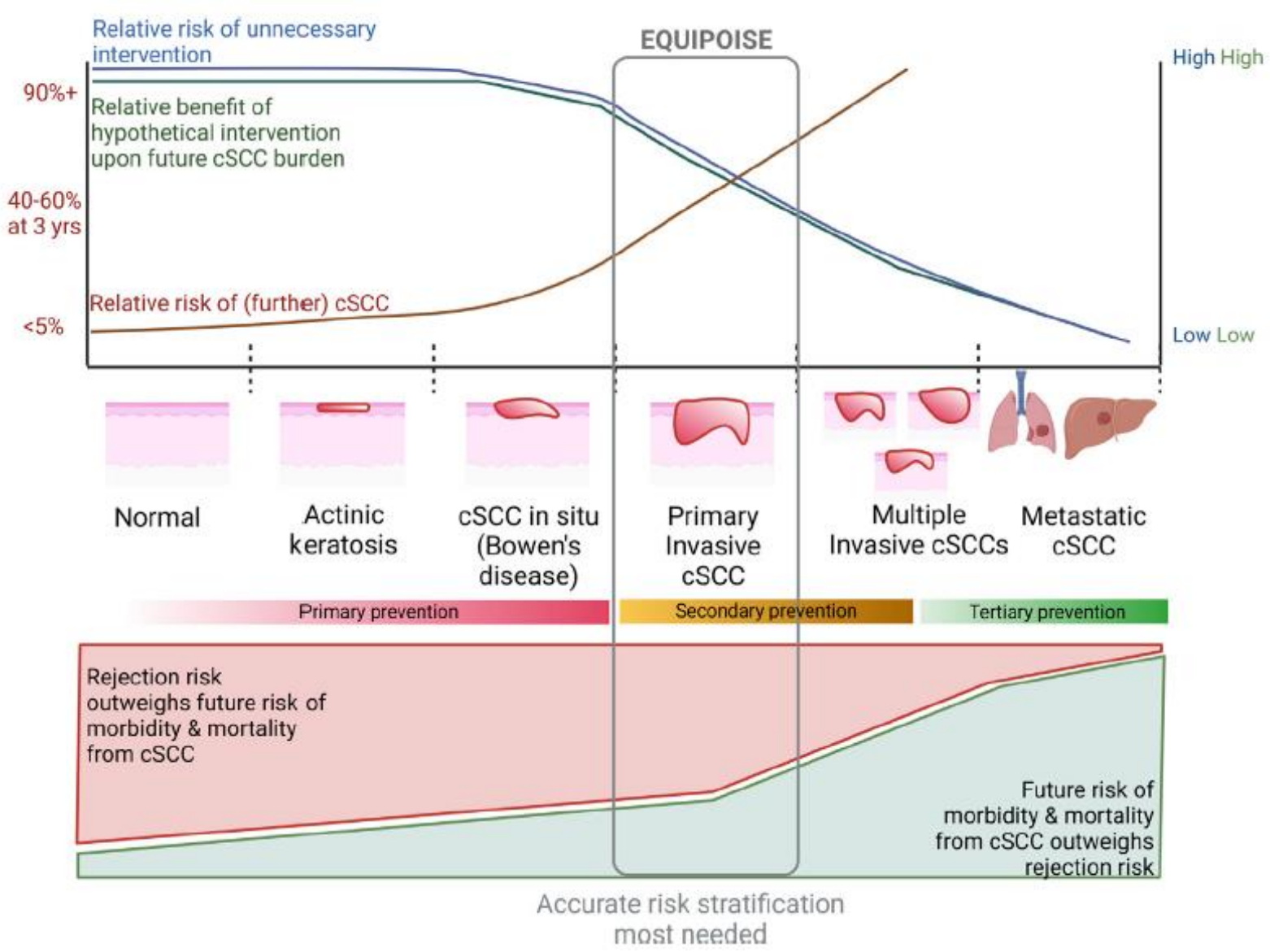
events in the first year after conversion. The absence of a high loading dose, unlike in previous investigations[1–3] and in agreement with most recent reports[14–16], and the maintenance of blood sirolimus concentrations close to 10 ng/mL were critical to achieving this outcome. Renal function was maintained, no episodes of acute allograft rejection occurred, and there was no de novo DSA within the 3-years follow-up, suggesting the effectiveness of sirolimus monotherapy in selected non-sensitized patients.

Reduction in Immunosuppression Intensity

- Graft function
- Pre-existing sensitization
- History of rejection
- Perceived balance between rejection and future malignancy risk
- ‘optimal’ immunosuppression intensity
  - circulating/urinary transcriptomics, HLA eplet mismatch profiling and donor derived cell-free DNA

Immunosuppression reduction or cessation (following graft failure) is associated with reduced risk and improved outcomes for virus-associated post-transplant malignancy such as lymphoma and Kaposi sarcoma (58), presumably by allowing greater immune control of cancer-associated viruses (59). However, data to support this approach for secondary prevention of CSCC is limited to retrospective cohort analyses, usually for advanced disease (3, 56).

Timing


Relative risk of unnecessary intervention
EQUIPOISE
High High
90%+
Relative benefit of hypothetical intervention upon future cSCC burden
40-60% at 3 yrs
Relative risk of (further) cSCC
<5%
Low Low
Normal
Actinic keratosis
cSCC in situ (Bowen's disease)
Primary Invasive cSCC
Multiple Invasive cSCCs
Metastatic cSCC
Primary prevention
Secondary prevention
Tertiary prevention
Rejection risk outweighs future risk of morbidity & mortality from cSCC
Future risk of morbidity & mortality from cSCC outweighs rejection risk
Accurate risk stratification most needed

Timing

- After first SCC
  - transition off older agents, particularly azathioprine.
  - Reduction of CNI target levels may also be appropriate.
- high risk of multiple subsequent CSCC
  - Sirolimus may be an option

re-transplantation

- CNI to mTOR inhibitor (Sirolimus or Everolimus) switch should be considered for recipients with a history of skin cancers, particularly squamous cell skin cancer
- No waiting period before re-transplantation is required for basal or low-risk squamous cell carcinoma of the skin (surgical excision with clear margins)
- Following surgical excision with clear margins, high-risk squamous cell carcinoma of the skin without perineural invasion requires a two-year waiting period before re-transplantation
- If the perineural invasion is found or adjuvant radiation therapy is required, a two to three-year waiting period is required

Drug side effects

Table 2: Cutaneous side-effects of immunosuppressive drugs used post renal transplant

Immunosuppresive drug	Cutaneous side-effects
Cyclosporine	Hypertrichosis, gingival and sebaceous hyperplasia, trichodysplasia spinulosa, non-melanoma skin cancer
Mycophenolate mofetil	Increased risk of herpes simplex, herpes zoster and and CMV infections; cutaneous side-effects are extremely rare
Tacrolimus	Non-melanoma skin cancer, virus-associated trichodysplasia
Sirolimus	Acneiform eruption, scalp folliculitis, inflammatory facial papules and nodules, aphthous ulceration, impaired wound healing, onychopathy, periungual infections, chronic gingivitis

Goel V, Sil A, Das A. Cutaneous manifestations of chronic kidney disease, dialysis and post-renal transplant: a review. Indian Journal of Dermatology. 2021 Jan 1;66(1):3-11.

Skin infection

- Acneiform folliculitis and pustules
  - early phase after transplantation, steroid dose
- Group A streptococci and *Staphylococcus aureus*
- Fungal infections of nails and soles
- Mucocutaneous candidiasis
  - arises in the first year after transplantation or after treatment for tissue rejection
- Systemic mycoses
  - Pulmonary *Aspergillus spp*. or *Candida albicans*
    - maculopapular exanthems, single ulcerated plaques, disseminated painful erythematous nodules
  - *Mucor spp.*, *Alternaria spp.*, pheohyphomycetes, disseminated cryptococcosis

Viral infection

- Reactivation of HSV and VZV: 0–30% within 6 months
  - high-dose immunosuppression— larger, sometimes necrotizing lesions
  - multi-dermatomal and generalised
- Primary infection
  - may spread systemically :pneumonia, vasculitis, hepatitis, or encephalitis
- HPV
  - prevalence of 50% at one year and over 90% at five years
  - predilection of viral warts for sun-exposed sites
  - multiple and tend to resist treatment and to recur
  - multiple types of treatment in combination
  - Multiple verrucous skin changes are a clinical warning sign of a markedly increased risk for SCC
- HHV-8
  - may cause Kaposi's sarcoma
- Trichodysplasia spinulosa polyoma virus

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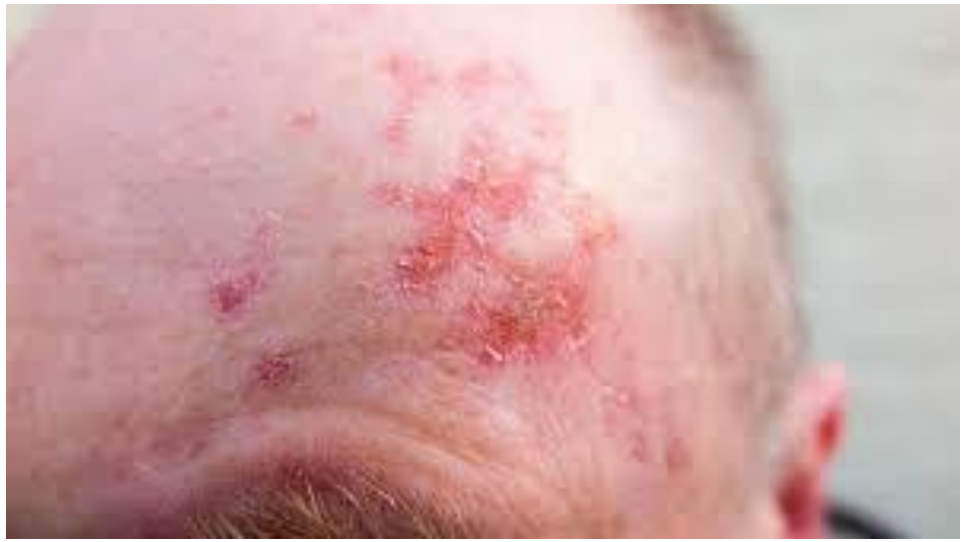
Table 2. Epidemiology of Skin Conditions

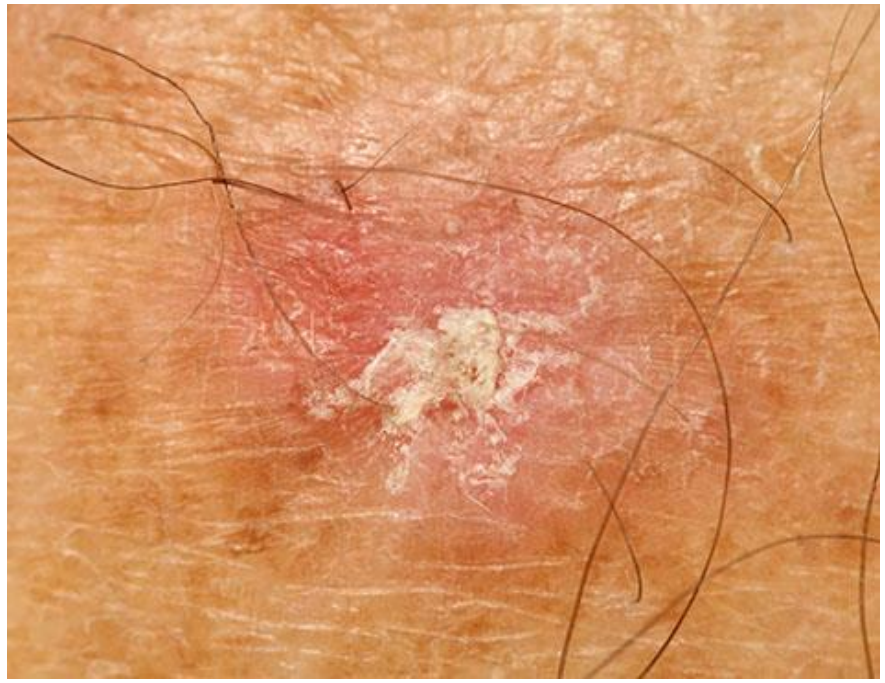
Skin Lesion	Number of Patients (%) (N = 97)
Viral infections	31 (32.0%)
Viral warts	13
Herpes	7
Varicella	6
Zoster	5
Bacterial infections	7 (7.2%)
Fungal lesions	29 (30.0%)
Pityriasis versicolor	17
Dermatophytosis	6
Onychomycosis	3
Candidiasis	3
Druginduced condition	58 (59.8%)
Acne	35
Seborrheic dermatitis	17
Hyperkeratosis	6
Kaposi sarcoma	3 (3 %)

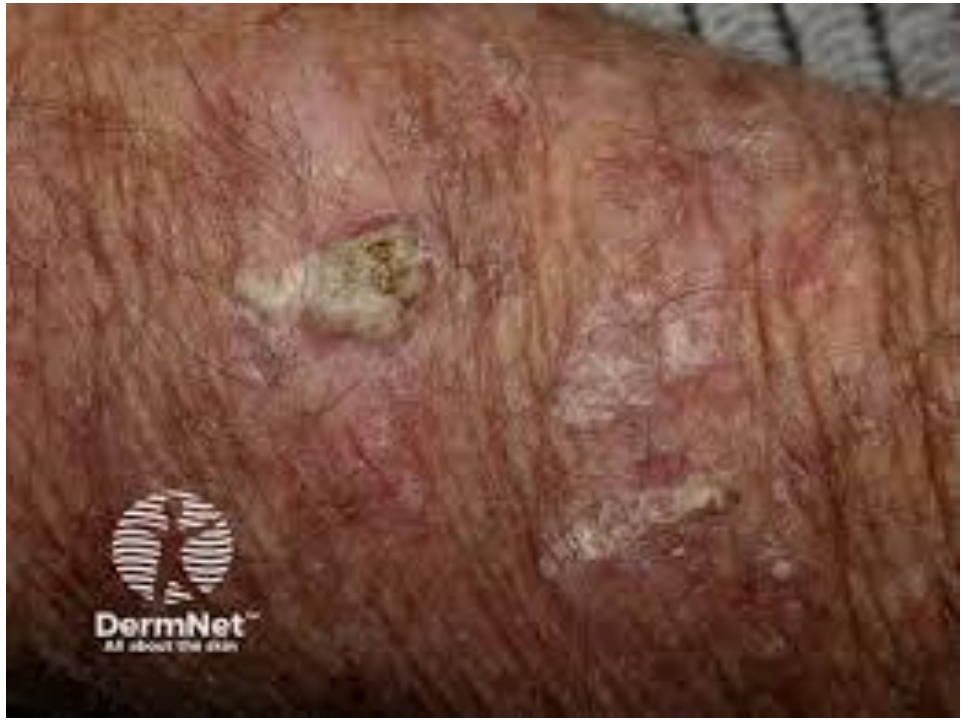
Table 3. Correlation Between Demographic and Clinical Data with Skin Lesions After Kidney Transplant

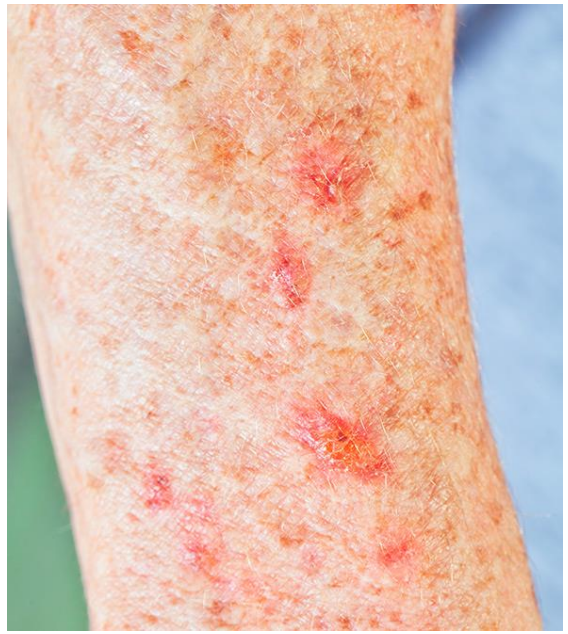
Variable	With Skin Lesion, No. (%)	Without Skin Lesion, No. (%)	*P* Value
Sex			.046
Male	77 (79.3)	54 (52.4)	
Female	20 (20.7)	49 (47.6)	
Type of donor			.9
Living	94 (96.9)	93 (96)	
Deceased	3 (3.1)	4 (4)	
ERE duration			.13
ERE <12 months	50 (51.5)	46 (44.6)	
ERE ≥12 months	47 (48.5)	57 (55.4)	
ERE method			.12
Hemodialysis	80 (81.6)	76 (74.5)	
Peritoneal dialysis	18 (18.3)	26 (25.5)	
Immunosuppressive medication			
Mycophenolate mofetil	15 (60)	10 (40)	.2
Cyclosporine	44 (66.6)	22 (33.3)	.03
Tacrolimus	56 (51.3)	53 (48.6)	.36

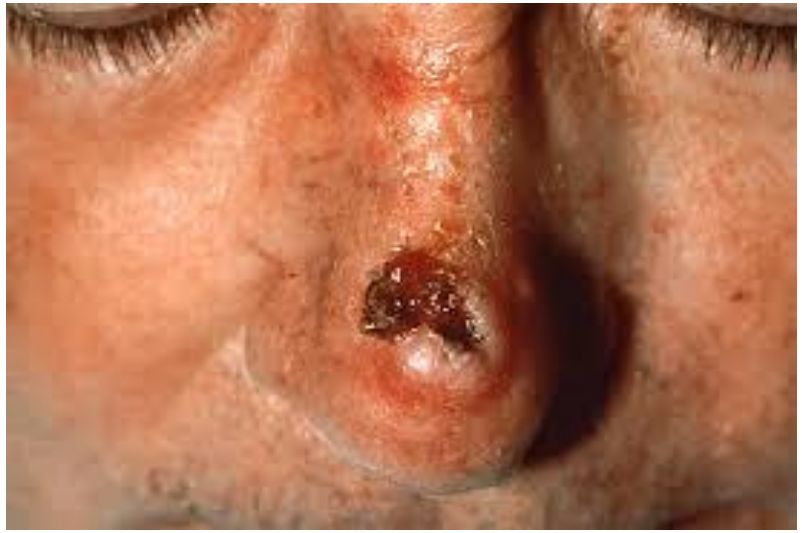
Dziri S, Azzabi A, Tilli G, Sahtout W, Azouz M, Aicha NB, Fradi A, Boukadida R, Mrabet S, Guedri Y, Zellama D. Dermatological conditions seen in kidney transplant recipients: prevalence and risk factors. Exp Clin Transplant. 2024 Jan 1;22(Suppl 1):310-4.

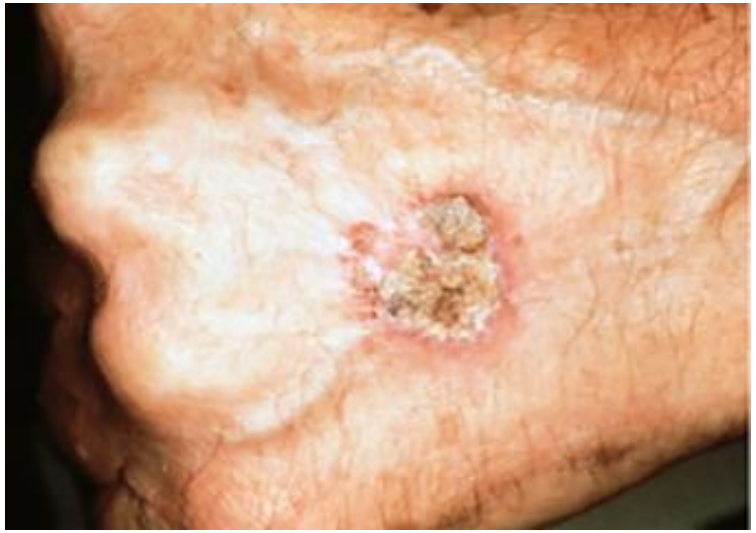


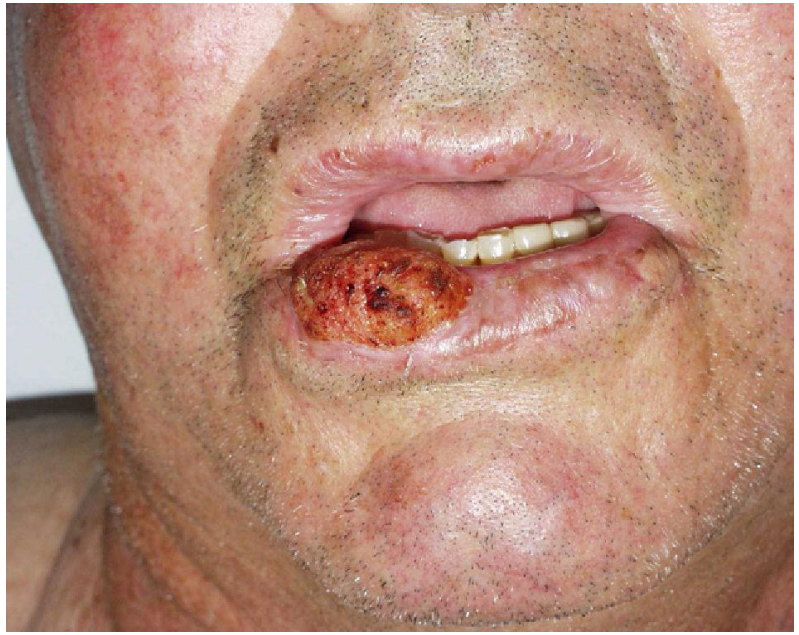


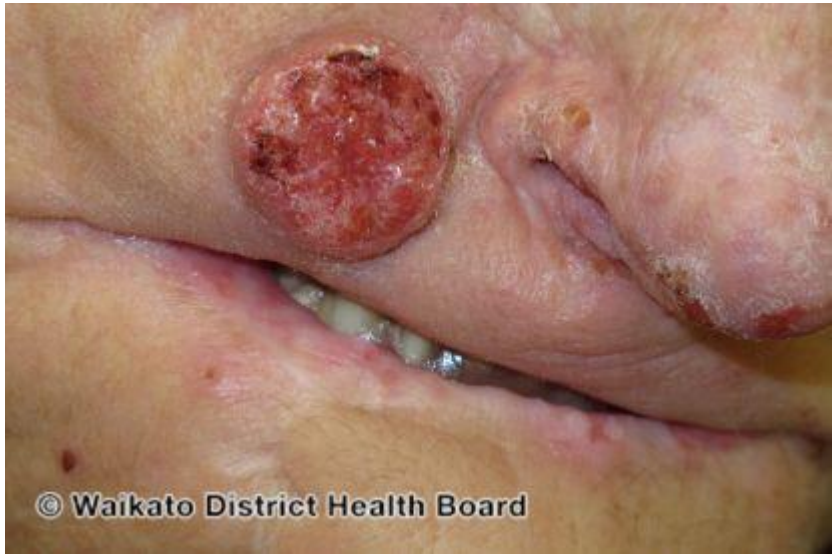

DermNet







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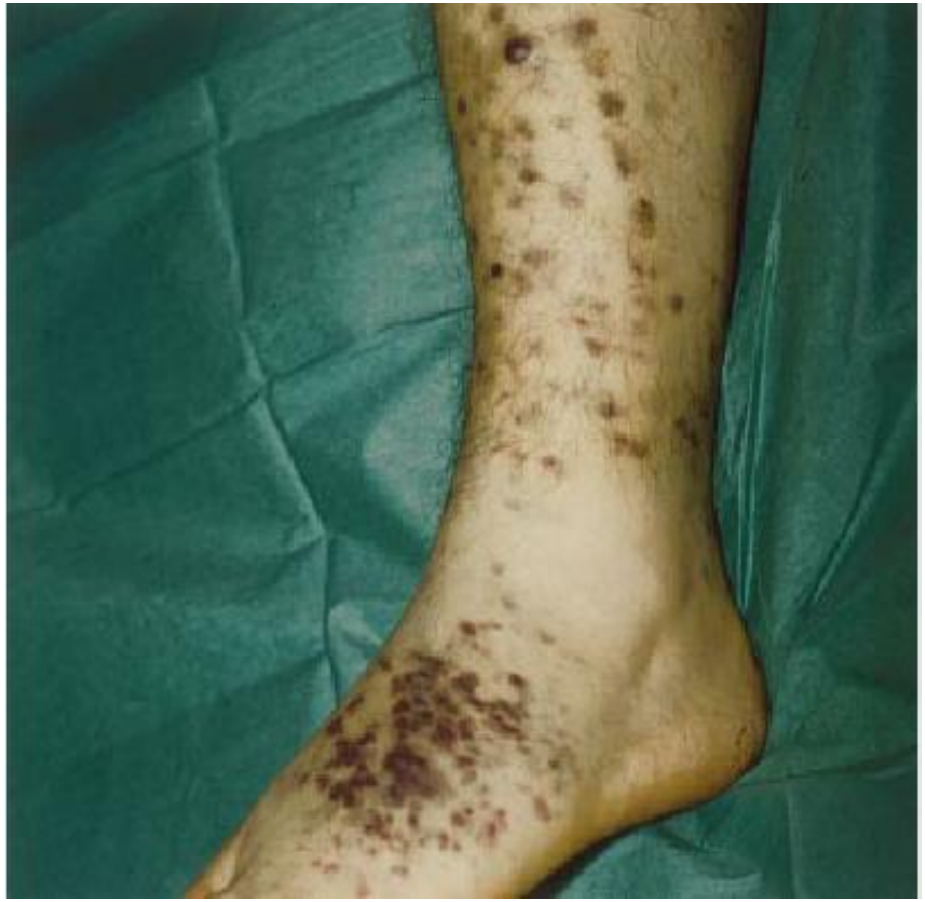

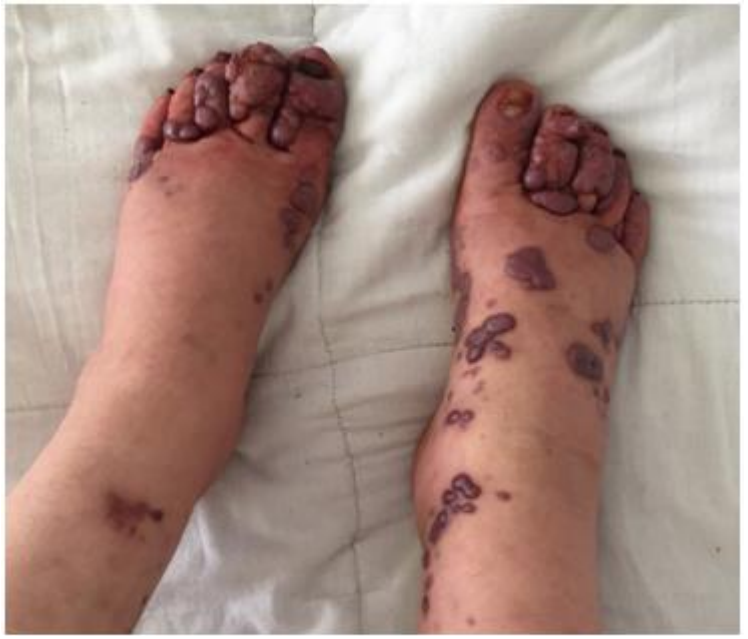

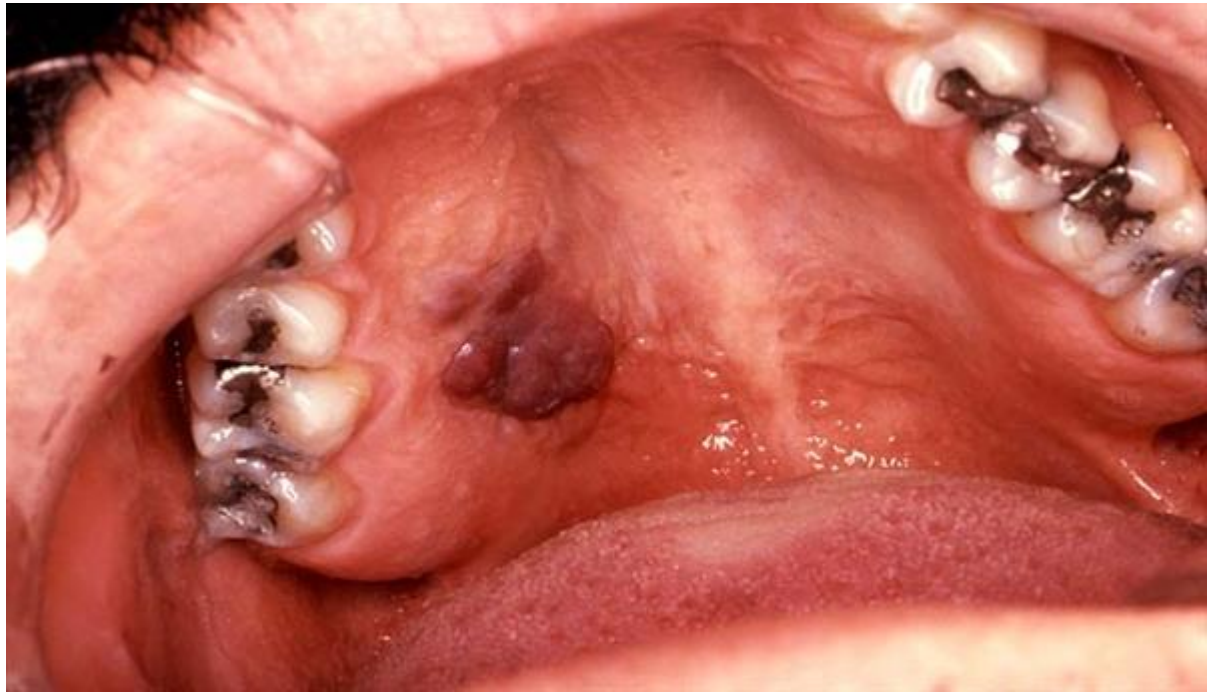

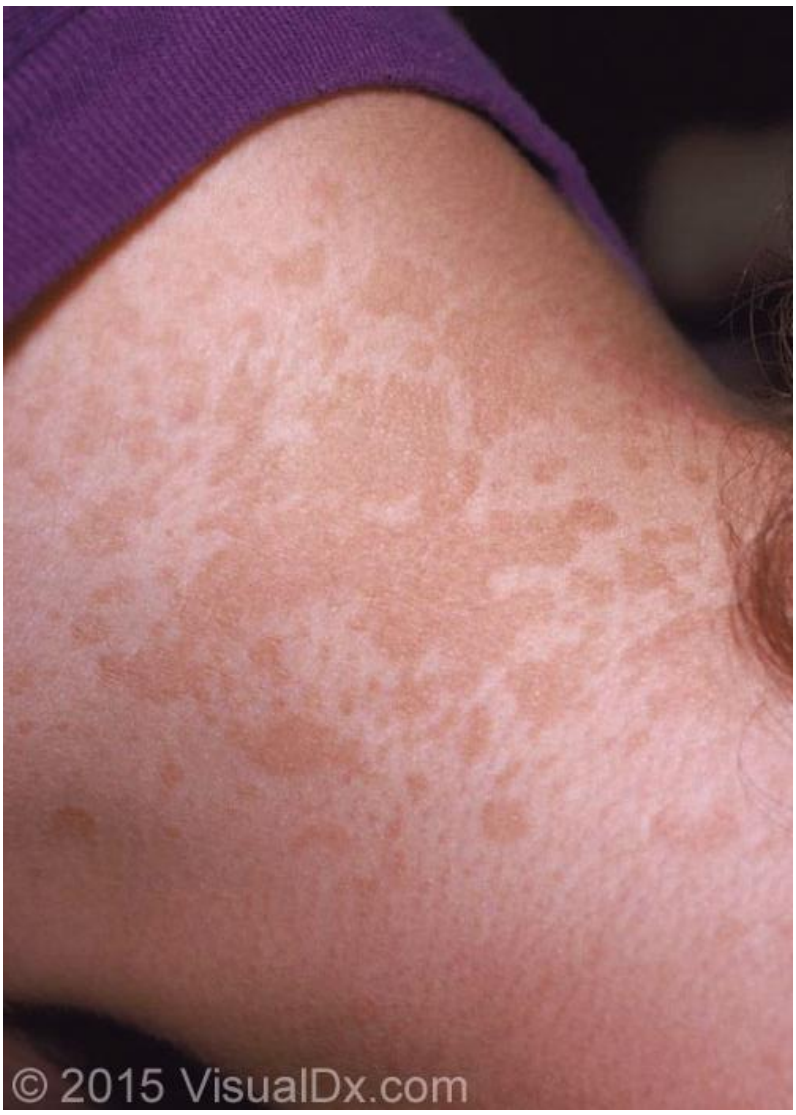
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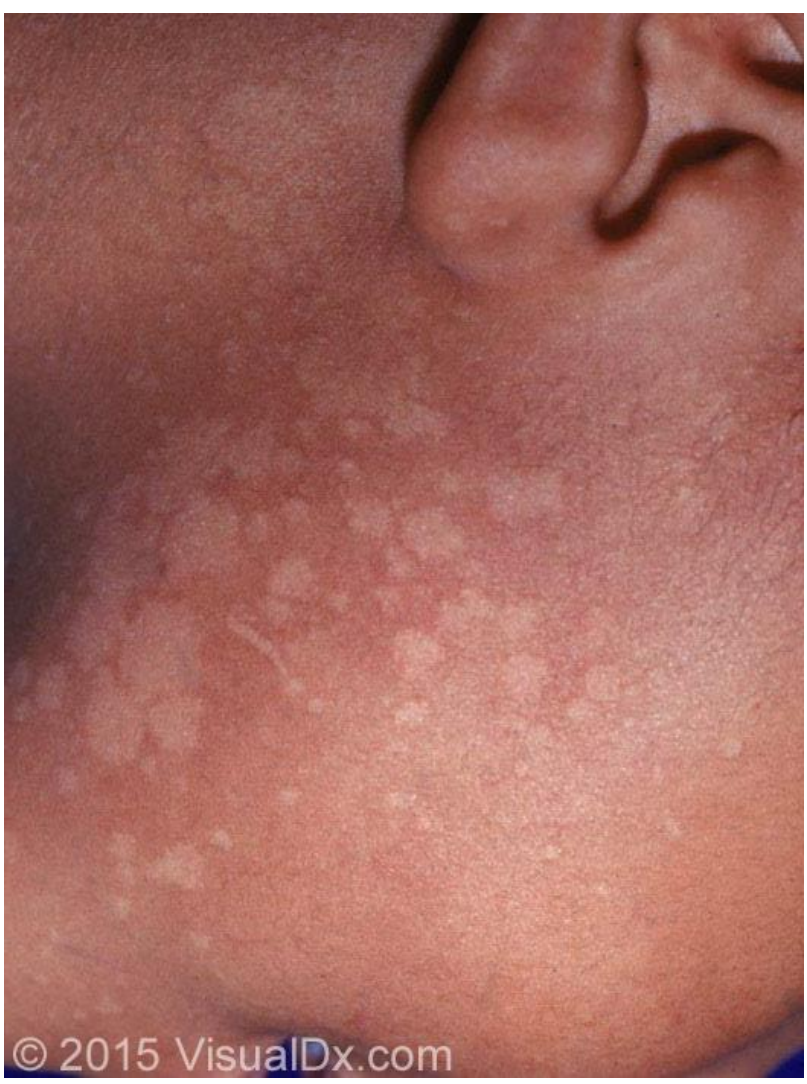
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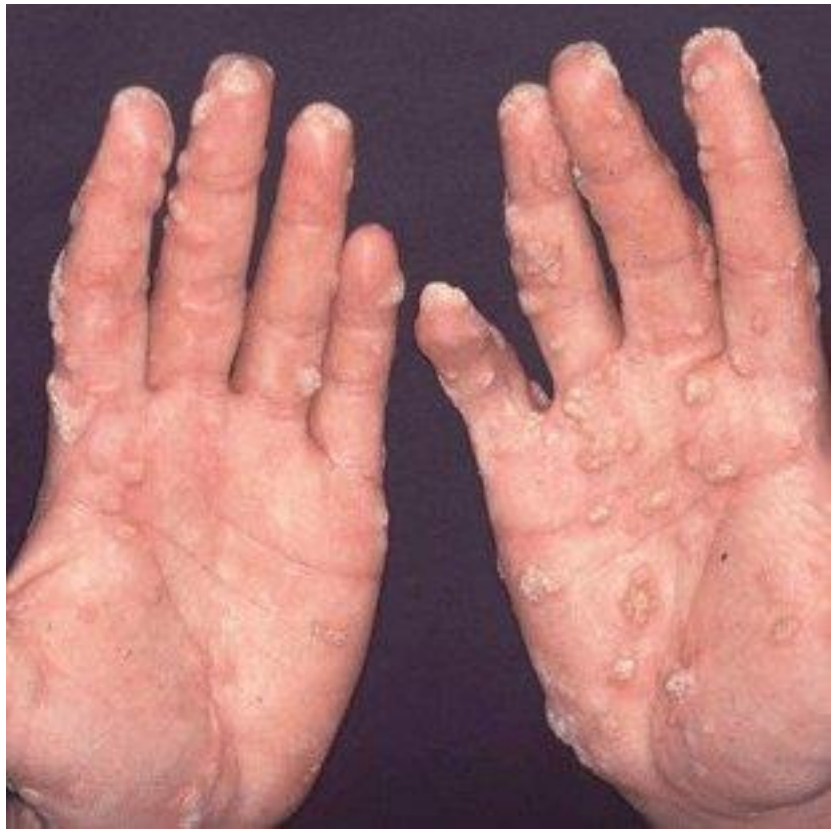

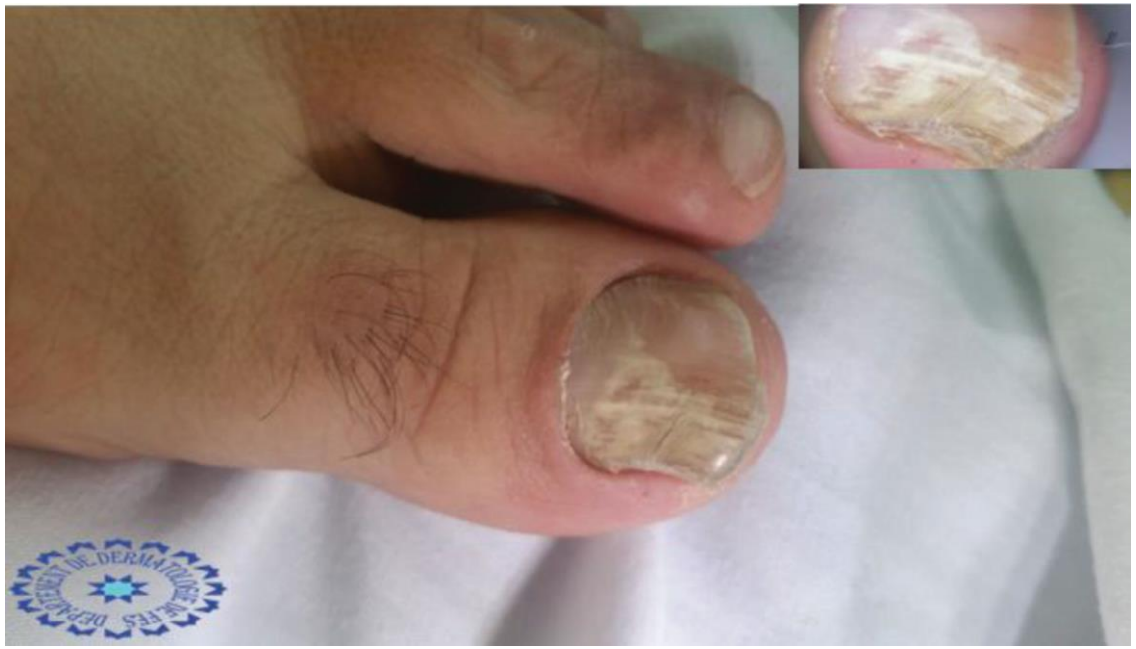

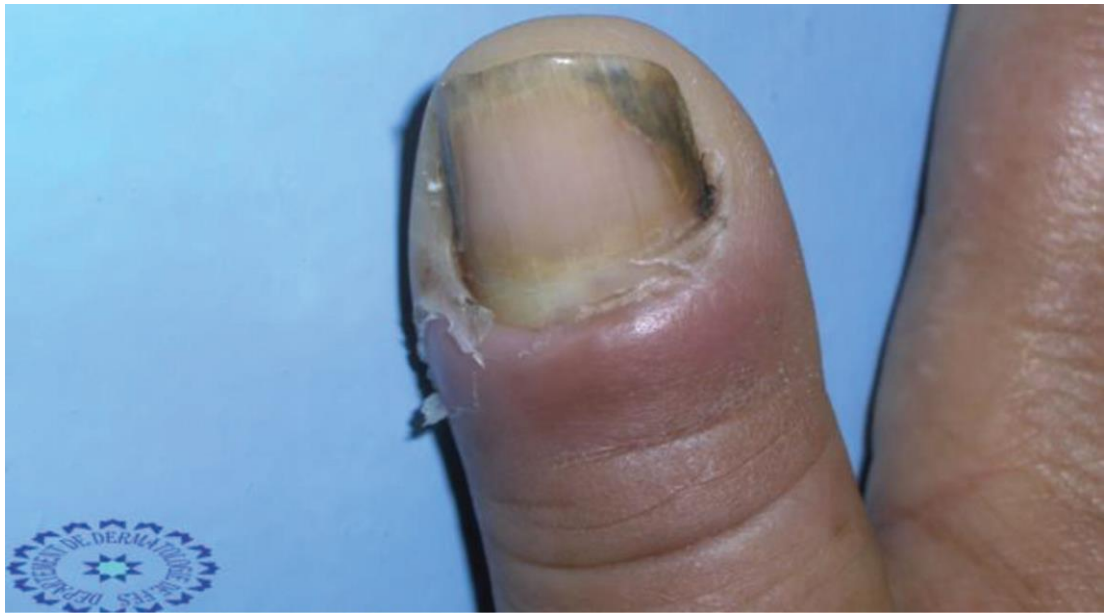

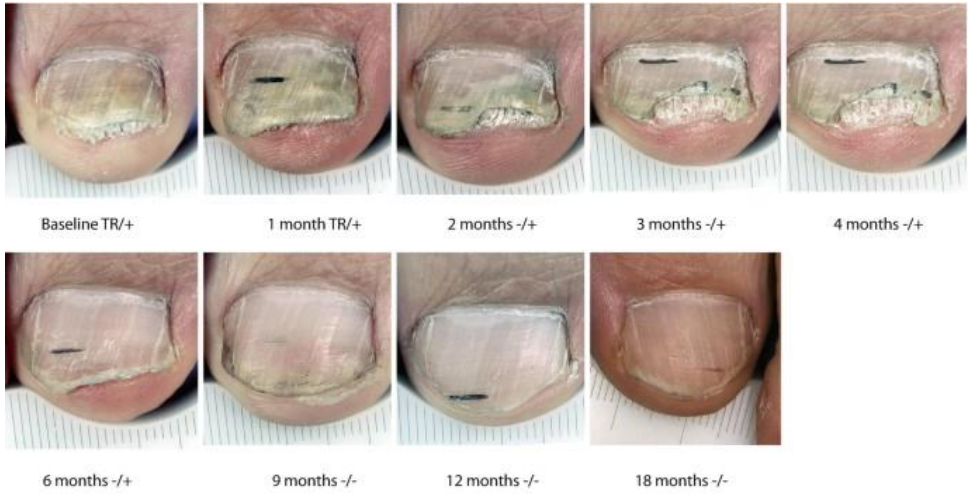
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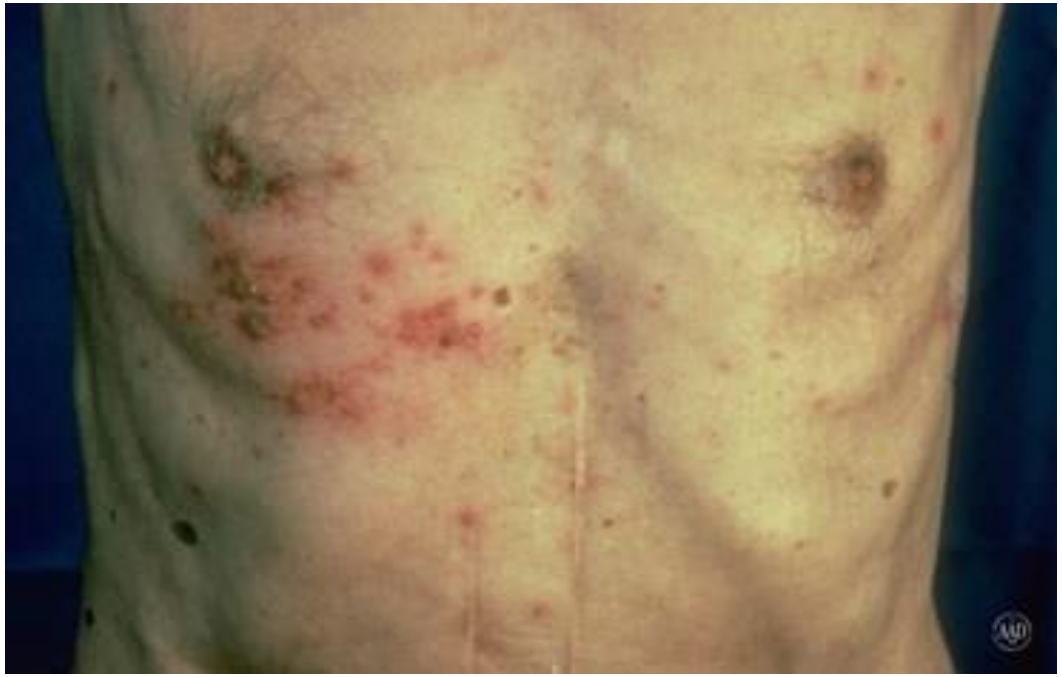
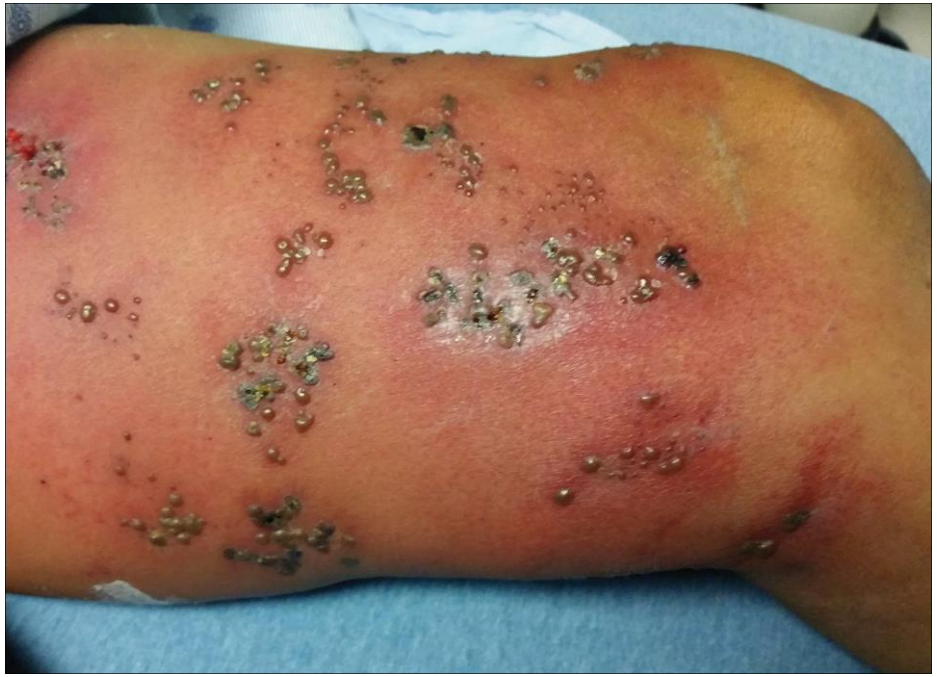
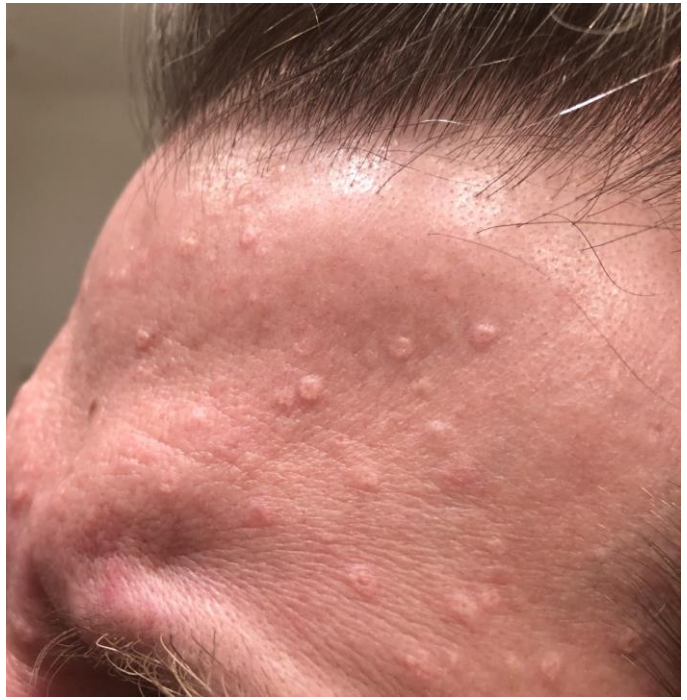
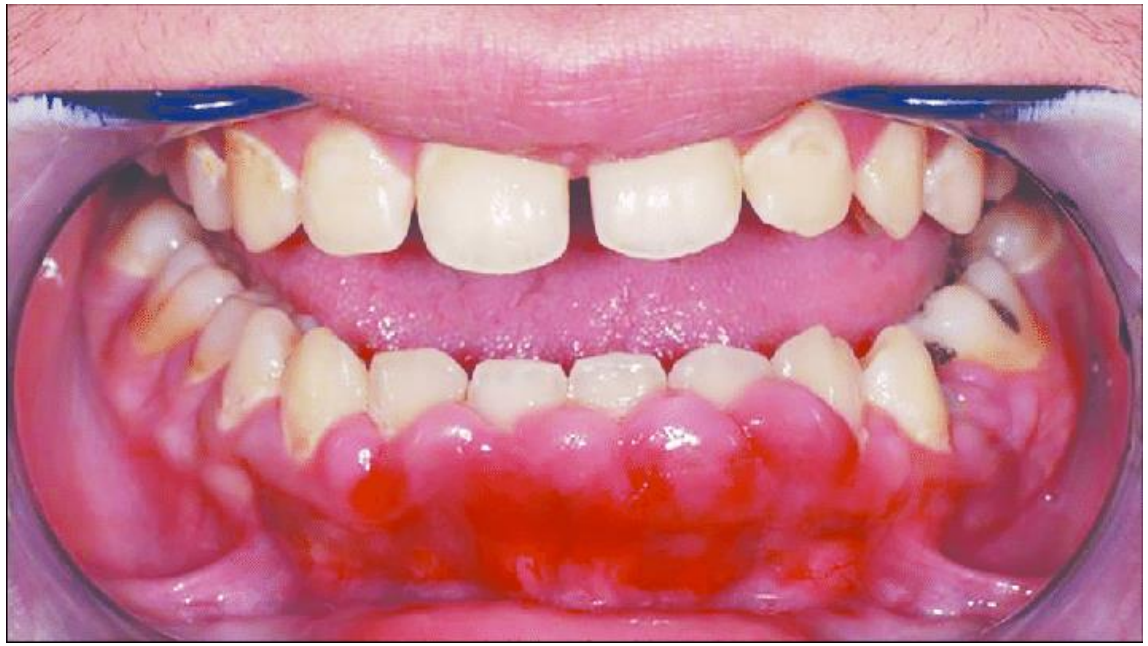
1 month TR/+
2 months -/+
3 months -/+
4 months -/+
6 months -/+
9 months -/-
12 months -/-
18 months -/-





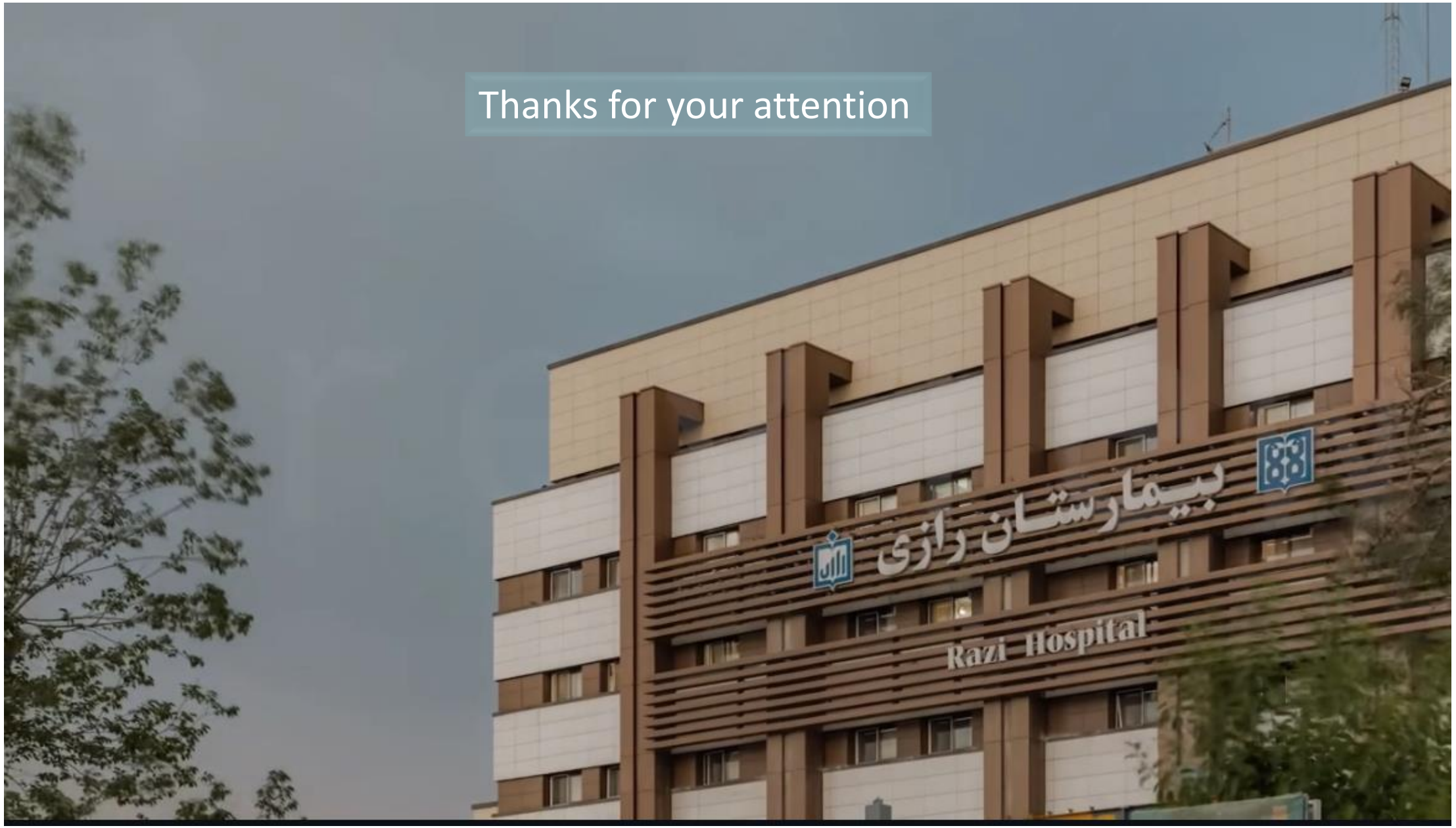




Take home message

- Patient Education
  - Adverse effects of sun exposure
  - Use total sunblock. SPF>50
  - Self-examination

- Reduced immunosuppression at appropriate dosage and time


Thanks for your attention
بیمارستان رازی
Razi Hospital