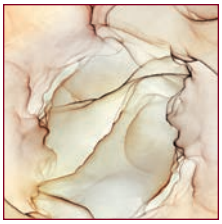

A Review of Cutaneous Diseases Observed in Solid Organ Transplant Recipients

by LISA FRONEK, DO; DERREK GIANSIRACUSA, BS, MS; NIKI NOURMOHAMMADI, BS, MPH; CASSANDRA JOHNSON, DO; ALLYSON YELICH, DO; and DANIEL HOGAN, MD

Dr. Fronek is with Bighorn Mohs Surgery and Dermatology Center, Scripps Clinic, La Jolla, California. Mr. Giansiracusa and Ms. Nourmohammadi are with Lake Erie College of Osteopathic Medicine in Bradenton, Florida. Drs. Johnson, Yelich, and Hogan are with HCA Healthcare and USF Morsani College of Medicine at Largo Medical Center in Largo, Florida. Dr. Hogan is additionally with the Department of Dermatology at Bay Pines Veterans Affairs Healthcare System in Bay Pines, Florida.

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Solid organ transplant recipients are at increased risk for numerous cutaneous conditions that fall within four categories: pre-neoplastic, neoplastic, infectious, or idiopathic. Many of these diseases can be attributed to immunosuppressive medications, including mycophenolate mofetil, cyclosporine, azathioprine, tacrolimus, or glucocorticoids. Iatrogenic lessening of the immune system places the patient at risk of malignancies, opportunistic infections, immune-mediated dermatoses, and adverse effects of medications. As the life expectancy of patients with solid organ transplants continues to increase, dermatologists and transplant physicians must stay abreast of this spectrum of dermatologic conditions, their respective prognoses, prevention, mitigation, and treatment.

KEYWORDS: Solid organ transplant recipient, immunosuppressants, cutaneous neoplasms, infectious disease, inflammatory dermatoses

Organ transplantation has become a frequent and efficacious treatment for end organ failure. In the year 2019, there were approximately 153,863 organ transplants performed worldwide according to the Global Observatory on Donation and Transplantation.[1] Success of a transplant requires an immunosuppressive and antiproliferative pharmacologic regimen; unfortunately, these medications create long-term complications for solid organ transplant recipients (SOTRs), including carcinogenesis and increased risk of infections.[2,3] The report below details the most common cutaneous conditions encountered among SOTRs, followed by clinicopathologic correlation and treatment options. Thorough skin examinations pre- and post-transplant are of significant benefit for transplant recipients.

Pre-neoplastic. Due to the increased risk of actinic keratoses (AK) and keratinocyte carcinomas (KC) in SOTRs, namely cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC), sufficient protection from ultraviolet radiation (UVR) is imperative.[4,5] Transplant recipients should be advised on the importance of sunscreen application and protective clothing to reduce UV exposure.[5,6,7] Regular use of sunscreen leads to significantly fewer precancerous lesions in addition to cSCC in SOTRs.[8] Organ transplant recipients should be screened routinely for AKs, as these lesions more rapidly transform into cSCC compared to the general population.[9] Topical therapies to eradicate field cancerization are recommended, with 5-fluorouracil (5-FU) 5% cream being the most common.[6,9] Imiquimod cream 2.5% and 3.75% are indicated in immunocompetent adults for the topical treatment of AKs.[10] There was initial concern with using this immunostimulatory topical medication in the SOTR population given a theoretical risk for organ rejection; while studies show it is safe and effective, it remains prudent to practice caution and limit application to a small surface area, which is facilitated by prescribing imiquimod in small packets.[7,9,11] It is important for the clinician to know that immunosuppressive medications may reduce the effectiveness of imiquimod overall. Diclofenac 3% gel is another option for the treatment of AKs.[12] This is disfavored by some renal transplant physicians, as it is a nonsteroidal anti-inflammatory drug, but it can be safe and effective when used in limited areas.[12] Weinstock et al[13] determined that the use of tretinoin cream is not effective at inhibiting the development of KC; however, 0.1% adapalene gel has shown modest improvement of AKs.[14] Tirbanibulin ointment, a novel microtubule inhibitor, was recently approved for field treatment of AKs, but its safety and efficacy in SOTRs has yet to be studied.[15]

Photodynamic therapy (PDT) demonstrates greater efficacy than topical therapy at clearing field disease in SOTRs.[6] The systemic retinoid acitretin is successful in preventing AKs and cSCC in SOTRs.[6,9,16] Capecitabine is a prodrug of 5-FU and has shown promising results in chemoprevention in SOTRs with one study showing that the incidence rate declined by 0.33 for cSCC, 0.04 for BCC and 2.45 for AK ($p<0.05$).[17] The role of capecitabine in chemoprevention needs to be further elucidated in larger randomized control trials, and caution must be exercised in patients with renal

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CORRESPONDENCE: Lisa Fronek, DO; Email: drlisafronek@gmail.com

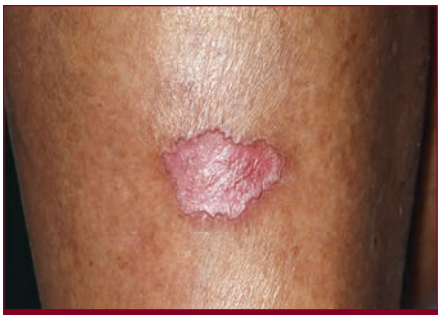

FIGURE 1. Porokeratosis is a disorder of atypical keratinization that presents as a skin colored circular plaque with a distinctive hyperkeratotic border.

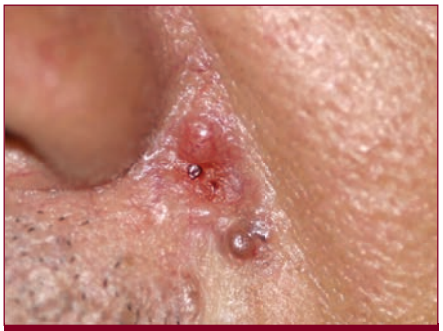

FIGURE 2. Nodular basal cell carcinoma presenting as a pink pearly papule with rolled borders, overlying telangiectasias and central ulceration. Pigmentation may or may not be a present feature.

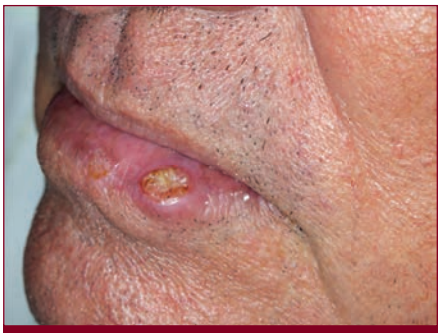

FIGURE 3. Cutaneous squamous cell carcinoma demonstrating a crusted, hyperkeratotic papule on the lower lip.

impairment.[9] Nicotinamide has emerged as a safe prophylactic agent for AK and KC development.[18-20] A Phase 2 trial in kidney transplant recipients showed a statistically nonsignificant 35 percent and 16 percent relative difference in rate of KCs and AKs, respectively, when treated with nicotinamide 500mg twice a day compared to placebo; additional studies are necessary for further guidance of nicotinamide's role in cutaneous chemoprevention.[6,9,18-20]

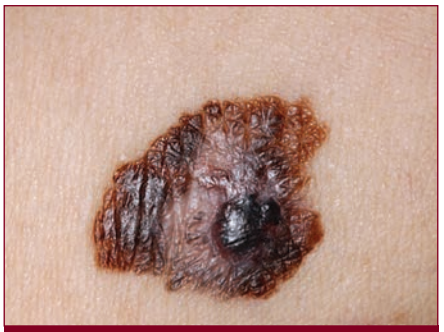

FIGURE 4. Malignant melanoma presenting as an asymmetric dark brown macule with loss of pigment centrally and a black nodular component.

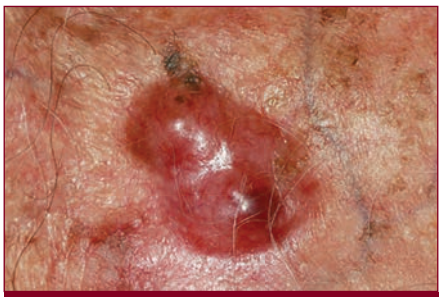

FIGURE 5. Merkel cell carcinoma presenting as a pink, rapidly growing nodule. The head and neck is the most common location.

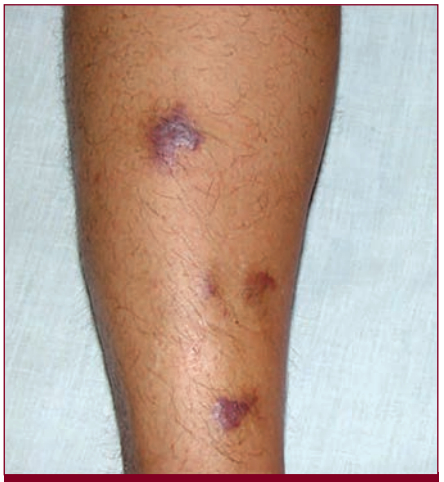

FIGURE 6. Kaposi sarcoma presenting as multiple violaceous plaques on the lower extremity.

Porokeratosis (PK) comprises a group of acquired skin disorders of aberrant keratinization that presents with sharply demarcated papules or red-brown annular plaques with central atrophy.[21,22] Risk factors for PK include UVR, immunosuppression, and germline mutations in genes encoding components in the mevalonate pathway.[21,23] The most frequent variants of PK in the immunosuppressed population include disseminated superficial actinic porokeratosis and porokeratosis of Mibelli.[21,22] The incidence of PK after renal transplantation varies from 0.38 percent to 10.86 percent with an average onset of four to five years. Due to the 7.5–11% risk of evolving into cSCC, PK in SOTRs should be treated to prevent malignant transformation.[21] Cryotherapy, electrosurgery, and PDT are potential treatment options for smaller lesions. Larger or multiple lesions can be treated with topical retinoids, 5-FU, diclofenac 3%, imiquimod 5% or vitamin D analogs.[21] A recent study showed that application of 2% cholesterol/2% lovastatin ointment results in significant clinical improvement after four weeks with no adverse effects.[24]

Neoplastic. Post-transplant malignancy presents a significant risk for morbidity and mortality to all SOTRs.[24,25] Both duration and intensity of the immunosuppressive regimen are positively correlated with diagnosis of cutaneous malignancies.[26,27] Immunosuppressive medications impair cell-mediated cancer surveillance mechanisms, allowing uncontrolled cell proliferation. Downregulation of B and T lymphocytes allow oncogenic viruses to replicate with consequent adverse effects on the genome.[27] Importantly, a prior history of skin cancer is one of the strongest risk factors for developing a subsequent skin cancer.[28] Wehner et al[3] reported that two years following the initial posttransplant skin cancer diagnosis, SOTRs had up to 57 percent risk of a successive skin cancer.

Cutaneous squamous cell carcinoma is the most common skin cancer in SOTRs.[29-31] Not only is there a 65–250 times increased incidence in SOTRs, cSCC is more likely behave aggressively, with higher rates of recurrence, metastasis, and mortality.[6,29] Risk factors for cSCC in SOTRs include cumulative UVR, history of KC prior to transplant, fair skin, male gender, and age greater than 50 years at time of transplantation.[28–30] Immunosuppressants contribute to the development of cSCC via enhancement of UV-induced carcinogenic effects or by adversely modulating cellular compounds.[27,29] Calcineurin inhibitors, such as cyclosporine and tacrolimus, induce activating transcription factor 3, leading to suppression of p53 and uncontrolled cellular proliferation.[6,9,27] Interestingly, 90 percent of cSCCs in SOTRs contain human papillomavirus (HPV) DNA,

demonstrating an important oncogenic role of high-risk strains of this virus.[6,9,32]

Higher levels of immunosuppression are independently correlated with an increased risk of cSCC, such as in lung and heart transplant recipients.[6,9] Immunosuppressive regimens generally include a calcineurin inhibitor (tacrolimus or cyclosporine), an antiproliferative agent (azathioprine or mycophenolate mofetil), and a corticosteroid.[30] Expert consensus guidelines suggest reducing or modifying the immunosuppressive regimen in SOTRs who develop multiple skin cancers (10 cSCCs per year) and those with aggressive tumors.[6,9,27,30] Research shows that switching from tacrolimus to sirolimus (a mammalian target of rapamycin (mTOR) inhibitor with antiproliferative properties), particularly in renal transplant patients, might prevent cSCC development.[6,29] Mycophenolate mofetil may reduce cSCC development compared with azathioprine, yet may increase the risk of BCC.[9] Therefore, a switch from tacrolimus to sirolimus and azathioprine to mycophenolate mofetil should be considered in SOTRs who develop cSCC. Additional studies are necessary to determine the optimal conversion regimens and dosing in these transplant patients.[30] A recent Delphi Consensus Statement listed acitretin as the sole chemoprevention therapy to be utilized in SOTR's developing cSCC at a high rate (at least 10 dermally invasive cSCC per year) or high risk cSCC (American Joint Committee on Cancer T3 or Brigham and Women's Hospital T2b tumor).[16,29]

While surgical excision remains the first line treatment for KC, we may also consider topical chemotherapeutics in the appropriate patient.[27] The surgical management of cSCC in SOTRs depends on tumor staging and the patient's surgical candidacy.[33] Patients with SCC in situ can be managed with surgical excision or electrodesiccation and curettage (EDC). Mohs micrographic surgery (MMS) has the highest cure rates of all treatment modalities for invasive cSCC. When MMS is not available, traditional excision with complete circumferential peripheral and deep margin assessment (CCPDMA) by frozen sections in place of the bread loaf technique is an adequate alternative.[6,9] In the case of locally advanced cSCC, radiation therapy (RT) can be incorporated as an adjuvant to surgical resection. The rates of locoregional metastasis in immunocompromised patients are significantly higher than in the general population.[9] Systemic therapy is the primary treatment option for those with metastatic cSCC. Checkpoint inhibitor (CPI) therapy has been successfully employed for unresectable and metastatic cSCCs in immunocompetent patients, but fear of its immunomodulatory effects has limited its use in SOTRs. Case reports demonstrate that program death receptor-1 (PD-1) inhibitor therapy can lead to acute transplant rejection in renal transplant patients.[34,35] There have been a few cases suggesting that cytotoxic T lymphocyte-associated protein-4 (CTLA-4) inhibitors may be more tolerable in SOTRs; however, a recent study with the largest series of SOTRs treated with CPIs to date determined that rejection rates were similar with inhibitors of both CTLA-4 and PD-1.[36-38] It is crucial that more research is conducted to help elucidate the role the immune system plays in the tumor and graft environment and to establish the feasibility of incorporating these agents in SOTRs.[6]

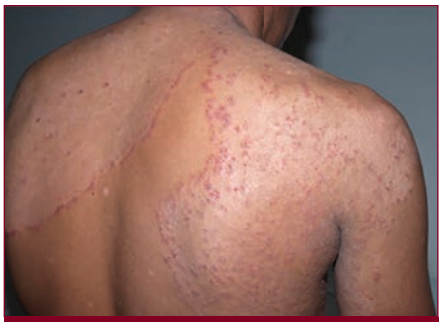

FIGURE 7. Tinea corporis is a superficial fungal infection that can be widely disseminated in immunocompromised patients. Here this patient has widespread erythematous pink plaques with scaling and central clearing.

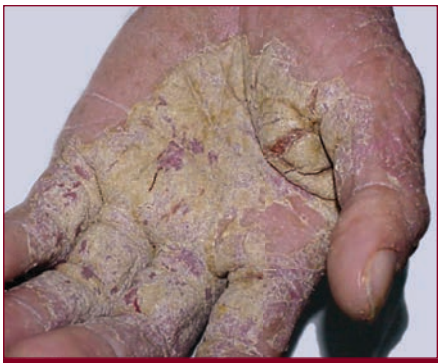

FIGURE 8. Crusted (Norwegian) scabies is a severe presentation of Sarcoptes scabiei infection that presents with extremely thick, crusted plaques with underlying red patches. Common locations include acral surfaces such as the hands and feet.

Basal cell carcinoma is the second most common skin cancer in SOTRs with 10-16 times increased incidence compared to the general population.[9,30] Risk factors for BCC include Fitzpatrick phototypes I to III and UVR. Despite an increased risk of BCC in SOTRs, these lesions do not have a greater propensity to become aggressive or metastasize compared to the general population. The clinical appearance and management of BCC in SOTRs follows National Comprehensive Cancer Network (NCCN) guidelines where surgical excision is standard of care.[39] In rare cases of locally advanced or metastatic BCC, newer targeted therapies inhibiting the hedgehog (Hh) pathway may be considered. The Hh inhibitors vismodegib and sonidegib are approved for locally advanced BCC not amenable to RT or surgery.[9,39] Vismodegib has additional approval for metastatic BCC.[9] Despite its approval for use in the immunocompetent population, there is limited research on efficacy of Hh inhibitors in SOTRs. Case reports of vismodegib use in SOTRs have demonstrated effective tumor regression without adverse effects or graft rejection.[40,41] Further research is essential in determining efficacy and safety of vismodegib with immunosuppressants.[9,40]

The incidence of malignant melanoma (MM) in SOTRs is 2–8 times higher compared to the general population and represents the most common non-KC skin cancer in SOTRs.[9,38,42] Among African American SOTRs, the incidence of MM is 17.2 times greater than their immunocompetent peers.[25,43] There is a specific increased risk of amelanotic and nodular subtypes of MM in this population, both of which portend poor prognosis.[42] The risk of MM in SOTRs peaks in the second year following transplant, and then decreases linearly.[38,44] Risk factors for MM include a personal history, family history, UVR exposure, white race, male sex, and age greater than 50 years and less than 18 years at the time of transplant.[6,30,38]

Primary treatment of MM in SOTRs is surgical excision with wide margins based on Breslow depth, per NCCN guidelines.[9,38,44] Per American Joint Committee on Cancer (AJCC) guidelines, sentinel lymph node biopsy (SLNB) should be discussed and considered for stage T1b melanomas, and discussed and offered for stage T2a and above.[44,45] Alterations of the immunosuppressive regimen are individualized based on the stage of the tumor and chance

of graft survival. The CONVERT trial showed a lower incidence of MM in kidney transplant recipients who received sirolimus.[38] Importantly, mTOR inhibitors is associated with a 25 percent decrease in MM risk, highlighting the possible role of these agents in preventing MM.[42] Targeted therapies and immunotherapies have been successful, resulting in longer survival times in certain patients with metastatic disease. However, evidence is lacking on the safety and efficacy of these agents in SOTRs, as these patients have been excluded from clinical trials.[38] Several studies demonstrate adequate responses to treatment with a combination of BRAF and MEK inhibition in SOTRs.[9, 38] Checkpoint inhibitors or talimogene laherparepvec (T-VEC) injections can be considered in SOTRs with advanced non-BRAF-mutant melanoma.[37,46,47] The decision to incorporate these agents should be made by a multidisciplinary team, as the increased risk of organ rejection must be carefully weighed with the potential benefits of treatment.[37–39]

Merkel cell carcinoma (MCC) is a rare and aggressive primary neuroendocrine cutaneous malignancy. This neoplasm classically presents as an erythematous, rapidly growing nodule on the head or neck.[47-49] Risk factors include increased age, UVR, white race, male sex, and immunosuppression.[9,48,51] The risk of MCC has been reported to increase 24-fold in SOTRs.[9,50] The average age of onset in SOTRs is approximately 53 years old compared with an average of 75 years old in the general population.[30,48,50] The prognosis of MCC in SOTRs is worse than in the general population, with a one year survival rate of 46.8 percent versus 88.6 percent, respectively.[9,30,48]

Merkel cell polyomavirus (MCPyV) has been implicated in the pathogenesis of MCC in most cases. The prevalence of this virus is up to 80 percent in adults, although most individuals exposed to MCPyV do not develop MCC. Therefore, other factors, such as immunosuppression, likely contribute to viral integration and carcinogenesis.[48,49] The development of MCC is accomplished through two separate etiologic pathways: MCPyV mediated and non-MCPyV mediated. The large T-antigen, which inhibits retinoblastoma tumor suppressor gene, is frequently mutated in MCPyV-positive MCC tumor cells, whereas the tumor suppressor gene TP53 is exclusively mutated in MCPyV-negative tumors.[48] It is thought that immunocompromised individuals have higher viral loads and antibody titers, which could be explained if humoral immunity plays a role in generating antitumor activity.[48,49] Additionally, cellular immunity hinders MCPyV replication via virus-reactive CD8+ and CD4+ T cells.[48,49]

Recommendations for management of MCC are based on studies of immunocompetent individuals, and specific data for SOTRs is limited.[9] The combination regimen of cyclosporine and azathioprine is associated with the highest incidence of MCC in SOTRs.[9] There is minimal evidence regarding altering or reducing the immunosuppressive regimens to improve survival following diagnosis of MCC.[48] Management of MCC includes wide local excision with 1–2cm margins often followed by adjuvant RT.[9,48,49,51] Positron emission tomography-computed tomography scans are crucial in adequate staging and locating distant metastasis.[51] Sentinel lymph node biopsy can be implemented in patients with localized lesions and clinically negative lymph nodes. Evaluating nodal status may guide treatment and have positive effects on the clinical course.[9,51] Radiation is considered if a tumor is inoperable or has significant local invasion.[51] Systemic chemotherapy and targeted immunotherapy can be considered for advanced or metastatic MCC.[9,51] Recent studies demonstrate that MCC is susceptible to PD-1 and PD-L1 inhibition.[51] The PD-L1 inhibitor avelumab was approved by the Federal Drug Administration in 2017 to treat metastatic MCC. In a recent study, avelumab achieved an objective response rate (ORR) of 37.5 percent and a complete response of 18.8 percent in immunocompromised patients.[52,53] Pembrolizumab was approved in 2018 for locally recurrent or metastatic MCC. A recent study reported the overall response rate to pembrolizumab was 58 percent (complete response 30% + partial response 28%) as a first-line therapeutic.[54] Similar to the use of CPI's in cSCC and MM, there is limited data available on their use in SOTRs and their implementation should be coordinated by a multidisciplinary team.

Kaposi sarcoma (KS) is a cutaneous malignancy of blood or lymphatic endothelial cell origin, caused by the human herpesvirus 8 (HHV-8).[55] In patients with iatrogenic immunosuppression, HHV-8 infection is reactivated in lymphatic endothelial cells which are then converted to spindle cells.[9,56] Kaposi sarcoma is seen in patients with acquired immunodeficiency syndrome (AIDS), older men of Mediterranean and Central/Eastern European descent (classic KS), in sub-Saharan Africa (endemic KS) and in SOTRs (iatrogenic KS).[56] The incidence of KS in SOTRs is between 60 and 500 times that of the general population.[9,55,57] The mean time of onset of KS in SOTRs is approximately 13 months post-transplant.[9,30] Clinically, KS presents as a violaceous patch, plaque, or nodule, commonly on the lower extremities. Visceral involvement has been reported to be as high as 25 to 30 percent for kidney transplant recipients and 50 percent for heart and liver transplant recipients who develop KS after transplantation; therefore, patients may benefit from consultation with gastroenterology for esophagogastroduodenoscopy or colonoscopy.[9] HHV-8 seropositivity in SOTRs prior to kidney transplantation carries an increased risk of developing KS, with 23–28 percent of seropositive and only 0.7 percent seronegative patients developing KS.[9,31,56] Screening patients for HHV-8 antibody levels prior to transplant may reduce the occurrence of this malignancy.[58] Calcineurin inhibitors, particularly cyclosporine, are associated with a high risk of KS; thus, reducing the levels of immunosuppression or switching to mTOR inhibitors forms the basis of treatment of KS in SOTRs.[9,59] In SOTRs who do not respond to alteration of the immunosuppressive regimen, localized disease can be treated with surgical excision, RT, or laser ablation. Topical alitretinoin has orphan drug designation for the treatment of AIDS-related KS with 33–50% of patients responding to treatment.[9] Patients with visceral disease or widespread mucocutaneous disease may require systemic chemotherapy.[9]

Post-transplantation lymphoproliferative disorders (PTLDs) account for 21 percent of all neoplasms after transplantation and are the second most common cancer in SOTRs.[60–62] Fifty percent of PTLDs in SOTRs are attributed to Epstein Barr Virus (EBV). Additional risk factors include EBV mismatch at time of transplantation (EBV negative transplant recipient with EBV positive donor), and the organ transplanted. Highest risk of PTLD is associated with a multiorgan transplant, followed by small intestine.[60] The World Health Organization reclassified PTLD in 2017 into

six categories: three nondestructive PTLD subtypes (plasmacytic hyperplasia, infectious mononucleosis-like PTLD, and florid follicular hyperplasia), polymorphic PTLD, monomorphic PTLD (B cell, T cell, natural killer cell), and classic Hodgkin's lymphoma-like PTLD.[60,62] A recent cohort study identifying non-KC skin cancers in SOTRs found elevated risk specifically for anaplastic large cell lymphoma, diffuse large B cell lymphoma, and extranodal NK/T-cell lymphoma in SOTR.[42]

Early-onset PTLD occurs in the first year after transplantation and is more likely to be EBV-positive. Late onset PTLDs are typically EBV negative but are more likely to be the monomorphic subtype and have extranodal disease.[60] Cutaneous involvement occurs in about 5 percent of PTLD cases, usually presenting as erythematous to violaceous nodules or plaques with or without ulceration; rarely, PTLD can present as a maculopapular eruption.[61] Treatment strategies include reduction of immunosuppression, surgical excision of local disease, radiation, rituximab, and chemotherapy.[60] Primary cutaneous PTLDs respond well to reduction in immunosuppression and exhibit a good prognosis. Systemic PTLDs with secondary cutaneous involvement and monomorphic PTLDs generally portend a worse prognosis.[61]

Infectious. Dermatophytoses represent a range of infections of the hair, skin or nails caused by Trichophyton, Epidermophyton, and Microsporum spp. Dermatophytoses have a prevalence of 5.6 percent in SOTRs and are named according to the body area affected: tinea corporis, tinea manuum, tinea pedis, tinea capitis, onychomycosis, etc.[64] *Trichophyton rubrum* is the most common cause of dermatophyte infection in SOTRs. While dermatophytes are confined to the superficial keratinized structures, such as the stratum corneum, nails, and hair in immunocompetent patients, in SOTRs the dermatophytes may invade deeper structures due to an impaired ability to eliminate infection.[64] Dermatophyte infections in SOTRs tend to be diffuse and recurrent compared to immunocompetent patients.[64] In Majocchi's granuloma (MG), fungal elements are found in the hair follicle and perifollicular infiltrate of the dermis, which is due to the rupture of the hair follicle wall. Majocchi's granuloma presents as erythematous red-brown papules coalescing into a plaque, studded with pustules and peripheral scaling.[64,65] Atypical presentations of *Trichophyton rubrum*, such as widespread molluscum contagiosum-like lesions on the face and back, have also been reported in SOTRs.[65,66] Onychomycosis, caused by dermatophyte infection of the nails, typically results in nail thickening, yellowing, and accumulation of subungual debris. Proximal subungual onychomycosis involves the proximal nail fold and extends to the ventral nail plate, which is pathognomonic of immunosuppression.[64]

Diagnosis of dermatophyte infection in SOTRs is supported with potassium hydroxide (KOH) skin scrapings demonstrating segmented hyphae. Culture of the skin lesion is warranted for definitive diagnosis as the KOH preparation is nonspecific.[64] Topical azole antifungals are the preferred therapy for superficial dermatophytosis, although infections in SOTRs may require alternative treatments with topical allylamines, ciclopirox or oral antifungals. Oral terbinafine 100mg daily for 2 to 4 weeks is the first line agent for treating MG and for dermatophyte infections refractory to topical treatments.[64]

Candida spp. are another common cause of fungal infections in SOTRs with oral candidiasis affecting up to 64 percent of transplant recipients within a year of transplantation.[64] Cutaneous disease is noted in up to 13 percent of SOTRs and *C. albicans* is the most frequently identified species. *C. glabrata* is the second most common species implicated in SOTRs and one out of every three *Candida* infections in liver transplant recipients are caused by non-albicans species.[67,68] Risk factors for cutaneous candidiasis include diabetes, corticosteroid therapy, and antibiotic therapy.[64,68] Nail infections with *Candida* spp. typically present with edema, discoloration at the lateral proximal nail fold, and occasional pus formation.[64] Superficial *Candida* infections are treated with topical antifungals, including imidazoles, allylamines, and nystatin. *Candida* infections with nail involvement are treated with oral antifungals, such as fluconazole, itraconazole, or terbinafine.[68]

Cutaneous manifestations of systemic candidiasis in SOTRs include small, disseminated macules and papules, frequently involving the trunk and extremities. These patients are often febrile and present with other constitutional symptoms, such as myalgias.[64] Ulcers mimicking ecthyma gangrenosum and intradermal bullae have been reported in multiple cases.[69,70] The gold standard for diagnosing disseminated candidiasis is blood culture; however, this may require up to five days to complete and up to 50 percent of cases are negative. *Candida* infection can be identified within five hours using T2 magnetic resonance, which has a high sensitivity and specificity.[64,71] Prophylaxis for *Candida* infections are not routinely used, except in pancreatic transplant recipients who receive fluconazole therapy following transplant.[64,72] Intravenous echinocandins are recommended as first line treatment for invasive candidiasis, as these agents have higher survival rates in comparison to triazoles and amphotericin B.[64,73]

Malassezia spp. colonize human skin and constitute part of the natural skin flora. Immunosuppression in SOTRs enables *Malassezia* overgrowth which leads to an increased risk of infection. Common infections caused by *Malassezia* include pityriasis versicolor (PV) and *Malassezia* folliculitis (MF). Pityriasis versicolor appears as hypo- or hyperpigmented oval macules, patches, or plaques with or without a scale, commonly on the chest, back, and upper arms.[64] *Malassezia* folliculitis appears as erythematous follicular papules and pustules; in severe cases, molluscoid comedonal papules are common. This infection has a predilection for sebum-rich areas, such as the face, upper back, scalp, neck, and arms.[64,74] The presence of *Malassezia* spp. has shown to play an important role in the development of seborrheic dermatitis (SD).[64] Seborrheic dermatitis presents as well-demarcated pink plaques with a yellow greasy scale classically in sebum rich and intertriginous areas.[75] In addition to *Malassezia* overgrowth, proposed mechanisms include the degradation of sebum and consumption of fatty acids by *Malassezia* species and an altered immune reaction.[75]

Diagnosis of *Malassezia* infections is accomplished via KOH preparation, although punch biopsy may be necessary to diagnose MF. *Malessezia* folliculitis and PV are treated with topical antifungals, such as imidazoles, ciclopirox, and ketoconazole shampoo. Refractory cases may require oral fluconazole or itraconazole.[64] Treatment for SD frequently includes topical 1-2% ketoconazole cream or shampoo, 1% ciclopirox, 1% zinc pyrithione, and low potency topical corticosteroids. Topical calcineurin inhibitors, such as 1% pimecrolimus,

may be used in areas that may be adversely affected by topical corticosteroid therapy, such as the face, eyelids and skin folds.[75]

Molluscum contagiosum (MC) is a member of the poxviridae family that presents in immunocompetent individuals as small, dome-shaped, flesh-colored papules with a central umbilication.[76,77] Molluscum occurs in up to 7 percent of SOTRs and frequently presents with widespread disease due to the underlying immunosuppression.[76,78] Atypical presentations of MC occur in SOTRs, with cases mimicking tinea barbae and condyloma acuminata.[78] Giant molluscum with lesions greater than 1cm has been reported in multiple cases of SOTRs.[79–81] Additionally, MC infection in these patients may lead to progressive, recurrent, or treatment refractory cases.[76,78] Diagnosis of MC is clinical; however, atypical lesions may require histologic confirmation of molluscum bodies, also termed Henderson Patterson bodies.[76] Treatment options include cryotherapy, cantharidin, podophyllin, trichloroacetic acid, and topical retinoids.[77] Particularly recalcitrant lesions in SOTRs may require intralesional interferon alpha, topical cidofovir, imiquimod, or pulsed dye laser.[76,77]

Human papillomavirus (HPV) is one of the most frequently identified infections in SOTRs, as immunosuppressive therapy reduces the ability to eliminate HPV infection and permits enhanced HPV replication in latently infected cells.[32,77,82] The increased burden of HPV infection in SOTRs results in widespread or treatment resistant disease and elevated risk of HPV-associated malignancies, most notably cSCC.[32,77,82,83] Cutaneous verrucae are the most common manifestation of HPV in SOTRs with a 50–92% prevalence within five years post-transplantation.[32,82] Verrucae manifest as hyperkeratotic, flesh-colored papules. Periungual and subungual verrucae can alter nail structure, resulting in nail dystrophy and onycholysis.[76,77] Common warts are caused by HPV Types 1, 2, 3, and 10.[32] Anogenital warts (condyloma acuminata), a common sexually transmitted disease, are most frequently due to infection by low-risk HPV Types 6 and 11.[32,82] Perianal giant condyloma acuminata is of high concern due to its potential to develop into verrucous carcinoma.[76] Immunosuppressed patients with anogenital warts are frequently coinfected with high-risk HPV types, such as HPV 16, 18, 31 and 33.[32] The prevalence of anogenital SCC caused by HPV is 10 times greater in the immunosuppressed population.[76] Therefore, SOTRs with anogenital warts should be thoroughly monitored and screened for malignancy.[32]

Professional societies recommend the inactivated nonavalent HPV vaccine for SOTRs that meet age and sex restrictions, although the safety and efficacy in SOTRs is not well established.[83,84] There are multiple treatment options for verrucae in SOTRs, including cryotherapy, electrodessication, laser, podophyllotoxin, salicylic acid, trichloroacetic acid, topical retinoids, 5-FU, bleomycin, cidofovir, imiquimod, and modulation of the immunosuppressive regimen.[83] Use of surgery, chemotherapy, and immunotherapy are generally reserved for recalcitrant lesions, as these methods are associated with more severe side effects.[76,77] Biopsy is recommended for lesions that do not respond to typical treatments, as there is a concern for malignancy.[76]

Infections caused by the eight human herpesviruses are of important clinical relevance to SOTRs.[85] Herpesviruses may be dormant but are later reactivated in the host, leading to recurrent infections. Herpes simplex virus (HSV-1; human herpesvirus 1) and sexually transmitted human herpesvirus 2 (HSV-2) are alpha herpesviruses that infect individuals in childhood or adolescence. After the primary episode, the virus remains latent in the dorsal root ganglion (DRG) of the affected dermatome. HSV-1 has a predilection for the trigeminal ganglion, while HSV-2 has a predilection for the sacral DRG. The virus may be reactivated with emotional stressors, physical stressors, immunosuppressive medications, or UVR.[85] Diagnosis of HSV is assisted by viral culture from lesional skin or mucosa, followed by direct staining of cells with fluorescent-dye-conjugated monoclonal antibodies specific for HSV-1 and HSV-2 antigens.[86] Oral acyclovir or valacyclovir are used to treat an active episode, as prophylaxis or as suppressive therapy. Due to the high usage of acyclovir, many patients may become infected with acyclovir-resistant strains and should be treated with cidofovir or foscarnet.[87]

Varicella-zoster virus (VZV; human herpesvirus 3) is an alpha herpesvirus where primary infection presents as varicella, commonly termed chicken pox. After initial infection, VZV remains dormant in the DRG of the initially infected dermatome. Upon reactivation, the virus disseminates along the associated peripheral nerve leading to the presentation of herpes zoster (HZ) as a dermatomal distribution of vesicles on an erythematous base.[85] Solid organ transplant recipients are a high-risk population for VZV, with African Americans and heart transplant recipients having the highest incidence of HZ.[88] Solid organ transplant recipients are also at a higher risk for disseminated VZV, which requires aggressive therapy to prevent complications of viremia, such as encephalitis or pneumonia. Complications of HZ depend on the dermatome involved, and include post-herpetic neuralgia, uveitis, hearing impairment, meningoencephalitis, etc.[89,90] Herpes zoster-attributable resource utilization has led to a significantly increased cost burden in SOTRs.[91] To evaluate immunity against VZV infection amongst SOTRs, IgG antibody avidity and VZV-specific cellular responses may serve as antibody markers, in addition to IgG-anti VZV antibodies. Available vaccines should be highly recommended to SOTRs as they are safe and effective in this population.[92,93] Standard treatment of VZV infections in transplant patients is high-dose intravenous acyclovir.[94] Alternative treatments include high-dose oral acyclovir, valacyclovir, and famciclovir.[94]

Epstein-Barr virus (EBV; human herpesvirus 4) is a gamma herpesvirus implicated in infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, and PTLD.[95] The virus is excreted in saliva and spread by direct contact. Primary infection is often asymptomatic and can present as mononucleosis in young adults. Amongst SOTRs, development of EBV is accompanied by the risk of developing PTLD and organ rejection. Treatment for EBV-driven PTLD includes acyclovir or ganciclovir.[95] Intravenous immunoglobulin (IVIG) has also been used in combination with other treatment regimens; however, its use in PTLD prophylaxis has not been reported.[96,97]

Human cytomegalovirus (CMV; human herpesvirus 5) is a member of the beta herpesvirus subgroup. Transmission requires direct contact through tears, urine, saliva, semen, breast milk, or cervical secretions of infected patients.[98] It may also be transmitted through blood and blood products, transplantation of infected organs, or passed

vertically via maternal-fetal transmission.[98] Cytomegalovirus infection in SOTRs may be the result of the reactivation of an existing latent infection, infection with a donor strain of CMV, or a primary infection in a previously CMV-naive individual.[99] Chronic CMV infections in SOTRs can lead to acute or chronic graft failure, including secondary immune deficiency and an increased risk of subsequent bacterial or fungal infections.[100] Ganciclovir is the treatment of choice for CMV infections; foscarnet or cidofovir are used in ganciclovir-resistant cases. Valganciclovir and valacyclovir are under investigation for CMV treatment in transplant recipients.[101,102]

Trichodysplasia spinulosa (TS) is a rare cutaneous infection associated with immunosuppression and caused by the trichodysplasia spinulosa- associated polyomavirus (TSPyV).[103] This condition presents as skin-colored follicular spiculated papules on the face, ears, eyebrows, and neck.[103] Most cases present when immunosuppression is the highest within a year of transplant.[104] Delay in diagnosis may occur as TS mimics numerous disorders, such as keratosis pilaris atrophicans and hyperkeratotic spicules of multiple myeloma.[103,105] Treatment is considered to prevent disfigurement. Reduction in immunosuppressive regimen is the first line option, followed by topical cidofovir, oral valganciclovir, topical retinoids, and keratolytics.[104]

Human Polyomavirus 9 (HPyV9) was first detected in 2011 in kidney transplant patients.[106] Further studies identified HPyV9 viremia in over 20 percent of SOTR patients, most often within the first three months of transplantation, which was thought to correlate with the higher doses of immunosuppression during this period.[106] About 30 percent of healthy controls are positive for HPyV9 antibodies; however, HPyV9 DNA has never been detected in healthy individuals.[106] Historically, HPyV9 was not associated with any significant clinical findings. Mishra et al[107] recently described three cases of HPyV9 associated cutaneous and pulmonary disease. Cutaneous findings included acrally distributed pink plaques which progressed to hyperkeratotic lesions. HPyV9 DNA levels were found to be significantly elevated in cutaneous and pulmonary pathologic specimens.[107] All three patients later experienced nonspecific symptoms dyspnea, weakness, and ultimately passed away. Interestingly, all three patients began to experience symptoms at least seven years after transplantation while immunosuppression was presumably stable. At this time, there are no commercially available HPyV9 diagnostic tests. Acitretin and cidofovir improved skin lesions in one patient, there is currently no definitive treatment regimen.

Crusted (Norwegian) scabies is a severe presentation of scabies occurring in immunocompromised patients and can present in SOTRs with an onset between 2–20 years post-transplant.[108–111] Cases are predominantly male (74%) with median age of 35 years.[107] Misdiagnosis of crusted scabies at initial presentation is common (84%), as it can mimic psoriasis, drug exanthems, and allergic contact dermatitis.[110] Diagnosis is supplemented with skin scraping utilizing a mineral oil preparation. Treatment includes topical agents, such as permethrin or lindane, oral ivermectin, or a combination.[108–111] Crusted scabies often requires systemic antiparasitic agents, such as oral ivermectin. Topical agents, such as ammonium lactate or salicylic acid, may also be employed to reduce the overlying hyperkeratotic plaques and optimize anti-parasitic penetration. Affected individuals have a high burden of Sarcoptes scabiei, and secondary infections in close contacts and healthcare workers are frequent.

Malakoplakia is a chronic granulomatous inflammatory condition due to recurrent infection, typically *E. coli* urinary tract infections (UTIs), and the macrophages inability to kill phagocytized bacteria.[111] Malakoplakia can manifest as inflammatory plaques, nodules or ulcers with predilection for cutaneous, gastrointestinal, and genitourinary systems.[113] Malakoplakia results in significant comorbidity owing to misdiagnoses as malignancy or other granulomatous processes.[113–115] Visualization of distinct pathological findings, including Michaelis-Gutmann bodies, basophilic intracytoplasmic inclusions that undergo calcification, and von Hansemann cells, foamy macrophages containing basophilic granules on histopathological analysis aids in diagnosis. Von Kossa or Periodic acid- Schiff may assist in histologic diagnosis.[112] First line treatment is surgical excision; however, for many patients who are poor surgical candidates, fluoroquinolone antibiotics may be employed.[113,114]

Inflammatory dermatoses. Eosinophilic folliculitis (EF) is an idiopathic inflammatory follicular disease divided into three categories: eosinophilic pustular folliculitis (Ofuji's disease), neonatal eosinophilic pustular folliculitis, and immunosuppression-associated EF, which will be discussed herein.[116] Immunosuppression-associated EF is most commonly appreciated in HIV positive individuals but may be seen in SOTRs on immunosuppressive therapy as well. This disorder is characterized by pruritic follicular papules and pustules on the face, scalp, trunk or upper extremities.[117] Diagnosis is made by clinicopathologic correlation with biopsy demonstrating an eosinophilic inflammatory infiltrate surrounding adnexae and negative skin cultures. Treatment options include topical corticosteroids and antihistamines. If these are unsuccessful, clinicians may also utilize TCIs, tetracyclines, indomethacin, or isotretinoin.[116,117]

Nephrogenic systemic fibrosis (NSF) is a systemic fibrosing disorder seen in the setting of renal insufficiency. It is classically thought that NSF is caused by exposure to gadolinium, predominantly via contrast media.[118] While NSF commonly occurs in the setting of acute kidney injury of chronic kidney disease, cases of NSF after liver and kidney transplantations have also been reported.[119,120] Nephrogenic systemic fibrosis presents clinically with symmetric hyperpigmented plaques on the extremities, which become indurated over time resulting in a "pseudocellulite" appearance.[119] Diagnosis requires a deep punch or incisional biopsy to fascia, which demonstrates a dermal proliferation of CD34+ spindled fibrocytes, occasionally infiltrating into the deep fat and fascia.[118] Treatment is limited as NSF is typically refractory to systemic steroids and the focus falls to controlling the underlying renal disease.[120] Physical therapy is an important part of the management because these patients are at risk of developing joint/limb contractures.

Graft-versus-host-disease (GVHD) is a multisystem condition that primarily occurs after hematopoietic stem cell transplantation (HSCT) and, in rare cases, SOT (<1%).[121] The largest contributing risk factor for developing GVHD is human leukocyte antigen (HLA) mismatch, followed by African American race, CMV infection, and neoadjuvant chemotherapy.[121,122] Acute GVHD (aGVHD) presents with a morbilliform rash, diarrhea,

transaminitis and hyperbilirubinemia that occurs within the first 100 days after transplantation.[122] Additional cutaneous features of aGVHD include acral erythema, perifollicular erythema and, in severe cases, confluent blistering and desquamation that can mimic Steven Johnson Syndrome and Toxic Epidermal Necrosis.[123–128] Chronic GVHD (cGVHD) presents over 100 days after transplantation, occurs in about 50 percent of those with aGVDH, and manifests with either a lichenoid or sclerodermoid appearance.[129] Treatments for GVHD depend on organ involvement and severity. For mild disease, topical corticosteroids and optimization of immunosuppressive regimen can be employed.[130,131] In severe disease, oral glucocorticoids, mTOR inhibitors, TNF-alpha inhibitors, imatinib, or rituximab can be utilized.[132–134]

CONCLUSION

There is a plethora of dermatologic conditions that SOTRs are more prone to. Solid organ transplant recipients have a heightened risk for malignancies, such as cSCC, BCC, KS, and MCC, due to a combination of weakened cancer surveillance and oncogenic viruses taking advantage of lymphocyte inhibition.[3,63] Because of this predisposition to neoplastic conditions, SOTR's should maintain consistent visits with the dermatology department. Most SOTRs will see their dermatologist once a year; however, the frequency may be increased to once every three months with the presence of multiple KCs or particularly aggressive or metastatic tumors.[24] Other consequences of anti-rejection immunosuppressive medication are severe cases of indolent infections ranging from fungal, viral, bacterial, and parasitic agents. Finally, there are a few inflammatory dermatoses that SOTRs may be susceptible to. Ultimately, it is important for SOTRs to be treated with a multidisciplinary team consisting of dermatology and transplant teams for most effective care.

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All figures presented in this article were sourced from Dermatology Atlas (Available at: https://www.atlasdermatologico.com.br/). All images on the Dermatology Atlas are free to use for non-commercial purposes.

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