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Dermatologic Problems During COVID-19 Pandemics in Kidney Transplant Recipients

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Abstract

Introduction. Our stady aimed toinvestigate the rate of dermatologic disorders in kidney transplant recipients during the COVID-19 pandemic.
Methods. We performed a retrospective observational single-center cohort study including all adult renal transplant recipients with a functioning kidney allograft and who have recovered from the SARS CoV-2 infection. The study was conducted at a tertiary center in Croatia from March 2020 to August 2022. The study included 321 patients (57% were male). Data were obtained retrospectively from hospital charts and records, while self-reported cosmetic problems were reported prospectively.
Results. The study included 321 patients (57% were male). Overall, 59 patients (18%) reported or were diagnosed with dermatological conditions. Eleven patients presented with facial eruptions that were most pronounced in the area covered by the mask, one patient developed similar changes in the skin of her hands. Hair loss was reported by twenty female patients, with the hair loss persisting in three patients. Six patients were diagnosed with skin cancer in the areas covered by facial masks. Three had squamous cell skin cancer, two were diagnosed with basal cell skin cancer, and one had a neuroendocrine skin tumor on the chin.
Conclusion. Dermatologic problems are frequent in kidney transplant recipients recovered from acute COVID-19. Besides cosmetic problems, skin malignancies may be diagnosed with a delay. Kidney transplant recipients should be advised to regularly self-examine their skin for potential skin cancer with dermatologic evaluation when necessary.

Key words: dermatological disorders, skin cancer, facial mask, covid-19, kidney transplant recipients

Introduction

Many skin manifestations associated with SARS-CoV-2 infection have been reported, including chilblain-like lesions, maculopapular lesions, urticarial lesions, vesicular lesions, and livedoid lesions. Erythema multiforme-like lesions and multisystem inflammatory syndrome are rare but may occur in association with COVID-19 [1,2]. Besides the virus itself, COVID-19 vaccines can cause a variety of skin reactions. The most common are unspecific injection-site reactions, different hypersensitivity reactions, autoimmune-mediated skin findings, and less frequently, functional angiopathies [3]. Much less is known about dermatologic problems arising during the COVID-19 pandemic which are not a direct consequence of the virus.
Kidney transplant recipients (KTRs) are a specific group of patients with unique problems during the COVID-19 pandemics. They have an increased risk for the development of skin cancer and require regular dermatologic follow-up. Data on dermatologic problems in KTR during the COVID-19 pandemics are lacking. Therefore, we investigated the rate of dermatologic complications and their outcome in this group of patients.

Material and methods

The study was designed as a retrospective observational single-center cohort study, participants were recruited from tertiary center in Croatia to estimate dermatologic complications and their outcomes. Data were retrospectively obtained from hospital charts and records, while self-reported cosmetic problems were reported prospectively. The study included all adult renal transplant recipients with a functioning kidney allograft between March 2020 and August 2022, who have recovered from COVID-19. SARS-CoV-2 infection was proven by a positive SARS-CoV-2 real-time reverse transcripttase-polymerase chain reaction (RT-PCR) test. We have no data on the type of SARS-CoV-2 that caused the infection.
To assess clinical complications, patients were interviewed by a standardized survey by trained transplant nephrologists to recount their symptoms during acute

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Table 1. Patients' characteristics. ADPKD, autosomal dominant polycystic kidney disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus; BKV, BK virus; MMF, mycophenolate mofetil; Aza, azathioprine; CyA, cyclosporine; Tac, tacrolimus

Characteristics	Number (%) of patients	Range
Sex		
Male	183 (57)	
Age (years) [Median (IQR)]	55 (44 - 64)	22 - 81
Primary kidney disease		
Glomerulonephritis	98 (30,6)	
Diabetic nephropathy	12 (3,8)	
ADPKD	48 (15)	
Pyelonephritis	26 (8,1)	
Nephroangiosclerosis	26 (8,1)	
Other	110 (34,4)	
Time from transplantation (months) [Median (IQR)]	94,5 (52 - 135,8)	1 - 368
Height (cm) [Median (IQR)]	171 (163 - 180)	124 - 199
Body weight (kg) [Median (IQR)]	79 (67 - 92)	42 - 150
BMI [Median (IQR)]	26,5 (23,9 - 29,2)	17,36 - 45,79
Nutritional status		
Underweight (BMI< 18,5)	4 (1,3)	
Normal weight	105 (32,8)	
Pre-obesity (25 – 29,9)	144 (45)	
Obese (≥ 30)	67 (20,9)	
Previous thrombosis	30 (9,4)	
Previous myocardial infarction or stroke	32 (10)	
Previous CMV infection	36 (11,3)	
Previous BK infection	68 (21,3)	
Previous EBV infection	28 (8,8)	
Allograft rejection	46 (14,4)	
Creatinine value [Median (IQR)]	129 (98 - 165,8)	45 - 430
CKD EPI [Median (IQR)]	49 (35 - 64)	0,23 - 133
Biuret [Median (IQR)]	0,2 (0,1 - 0,5)	0 - 79
Vaccinated against COVID-19	246 (76,9)	
Before COVID-19 infection	149 (46,6)	
After COVID-19 infection	97 (30,3)	
Number of vaccine doses [Median (IQR)]	2 (2 – 3)	1 - 4
Number of vaccine doses (n = 246)		
One	21 (8,5)	
Two	138 (56,1)	
Three	83 (33,7)	
Four	4 (1,6)	
COVID-19 initial symptoms		
Febrility	245 (76,6)	
Diarrhea	39 (12,2)	
Respiratory	230 (71,9)	
Asymptomatic	21 (6,6)	
COVID-19 initial complications		
Hospitalisation	125 (39,1)	
Pneumonia	141 (44,1)	
Mechanical ventilation	4 (1,3)	
Other	66 (20,6)	
Initial immunosuppression		
Tacrolimus	222 (69,4)	
Cyclosporin A	70 (21,9)	
Mycophenolate	280 (87,5)	
Azathioprine	12 (3,8)	
Everolimus	48 (15)	
Prednisolone (dose) [Median (IQR)]	5 (5 - 5)	0 - 30
Acute COVID-19 treatment		
Cessation of MMF/Aza	133 (41,6)	
Decreasing MMF/Aza	102 (31,9)	
Cessation of Tac / CyA	1 (0,3)	
Decreasing Tac / CyA	29 (9,1)	
Hyperimmune anti-CMV globulin	30 (9,4)	
Intravenous immunoglobulin	13 (4,4)	

COVID-19, and additionally questioned on the persistence or new onset of any symptoms. After the interview, the patients underwent a detailed physical examination. Additional diagnostic methods were used per clinician judgment (laboratory, radiologic). Data on the immunosuppressive regimen and acute COVID-19 characteristics were recorded.
The study was approved by the University Hospital Center Zagreb Ethics committee.

Results

Study population

From March 2020 to August 2022, 408 out of the initial cohort of 1432 patients who received a renal allograft at our institution developed COVID-19 disease proven by a positive SARS-CoV-2 RT-PCR of a nasopharyngeal swab and were potentially eligible for study participation. Twenty-five patients died in the period during or after the infection and 62 patients have not been assessed in our clinic and were therefore excluded from the study population. Overall, 321 patients were included, 57% males with data presented in the table 1. One-hundred-and-fifty patients (46,7%) received at least one dose of the anti-SARS-CoV-2 vaccine before the infection. One hundred twenty-five (39,1%) patients required hospitalization, 141(44,1%) developed pneumonia and 4 patients (1,3%) required mechanical ventilation. Treatment included immunosuppression modification in 233 patients (77,1%) and remdesivir in 53 patients (16,6%), along with other supportive measures.

Self-reported cosmetic skin problems

Twenty-one patients (6.5%) reported severe acne, two of them on the chin, cheeks, and forehead, while four had acne on the back. They all received steroids for treatment of acute COVID-19.
Eleven patients presented with new onset facial eruptions that were most pronounced in the area covered by the mask. Six were diagnosed with contact dermatitis or "rosacea" and five as "seborrheic dermatitis" (Figures 1, 2, 3). Additionally, one patient developed similar changes in the skin of her hands due to excessive hygiene.

Fig. 1. Discoid rash of the area covered by the facial mask. The patient was diagnosed with contact dermatitis

Fig. 2. Local status 2 months later. The patient did not use her facial mask for two months

Fig. 3. Perioral seborrhoic dermatitis

Fig. 4. Telogen effluvium in a 46-year-old female

Hair loss was reported by twenty female patients. The problem was severe in 8 patients (Figure 4), while 12 reported moderate hair loss. The symptom of hair loss developed three to six weeks after the clinical manifestation of COVID-19. Increased shedding was most pronounced during the first three months, with gradual improvement over the next six months. Although most patients recover, three of them have persistent hair loss.
Twelve patients received topical treatment with minoxidil solution as per dermatologist recommendations.
Six patients were diagnosed with skin cancer in the areas covered by facial masks. They were all diagnosed when asked by the attending nephrologist to remove the mask and none of them reported the changes. Three had squamous cell skin carcinoma, two were diagnosed with basal cell skin cancer, and one had a neuroendocrine skin tumor on the chin (Figures 5 and 6).

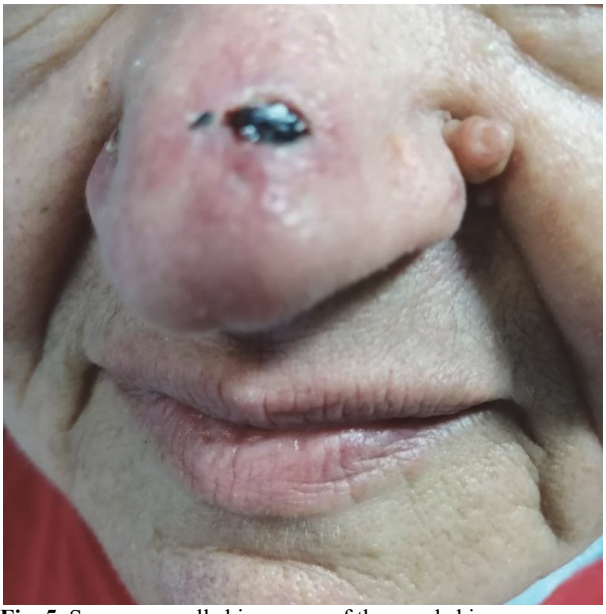

Fig. 5. Squamous cell skin cancer of the nasal skin

Fig. 6. Basocellular skin cancer of the cheek

Discussion

In our study, nearly every fifth patient (18%) was diagnosed with a dermatological condition following recovery from acute COVID-19, regardless of symptom severity. Most frequently diagnosed were acne, hair loss, seborrheic dermatitis, rosacea, and skin cancer. Most importantly, the discovered skin cancers were all in the areas covered by face masks, no patient self-reported the skin change, and the changes would not have been discovered had the clinician not asked specific questions and asked for the mask to be removed.
Since the outbreak of the COVID pandemic, outpatient visits are performed with strict epidemiological measures enforcing the use of facial masks. However, masks covering parts of the face during the examination and the lack of patients self-reporting skin changes may be associated with unrecognized problems beneath the mask [4]. Upon learning that patients don't report skin changes, our team introduced obligatory mask removal for a few seconds. This approach resulted in the discovery of different skin problems including malignancies. Several studies have recognized the problem of diagnostic delay of skin cancers during the COVID-19 pandemic [5-7], with postponed surgical excisions resulting in an increased incidence of advanced skin cancers [7)]. This problem might be additionally emphasized in kidney transplant recipients with skin cancers being more aggressive than in the general population due to the immunosuppressive drugs used for the prevention of rejections [8].
Our study's most common self-reported dermatologic problem was hair loss (telogen effluvium). Telogen effluvium is a well-known COVID-associated problem [9-11]. The most common triggers for telogen effluvium are severe infections and nutritional deficiencies, especially vitamin D, ferritin, and zinc deficiencies [12,13]. In COVID-19, both triggers are present, together with higher levels of inflammatory cytokines and microthrombi formation which may obstruct hair follicle blood supply [14].
The association between acne and prolonged use of protective face masks has been observed even before the onset of the COVID-19 pandemic [15]. Adverse skin reactions caused by prolonged wearing of masks include pressure injury, urticaria, contact dermatitis, skin dryness, and aggravation of preexisting skin diseases [16]. A greater number of individuals who suffered from acne associated with the prolonged wearing of protectt ive masks during COVID-19 pandemic have been referred to dermatologists, leading to the introduction of a new term for this variant of acne mechanica-"maskne" [17]. Possible mechanisms of acne pathogenesis include mechanical stress through pressure and friction caused by the mask [18], microbiome dysbiosis caused by heat, alteration of skin pH and humidity [19] which is stimulative for bacterial proliferation [20], but also increased

steroid dosages during acute COVID-19 [21]. Steroids may explain the occurrence of acne on the back and not only on the face of our patients. In the study by Ozkesici *et al* the course of acne during the COVID-19 pandemic in healthcare professionals was monitored. Almost half of the participants reported an increase in pre-existing acne, while more than one-third of the participants reported first occurrence or had a relapse. Among many factors, surgical masks have been found to be responsible for the development of acne [22].
KTRs are known to have a significantly increased risk of developing skin malignancy secondary to chronic immunosuppression [23]. In the study by Keeling *et al.* a slight increase in the number of diagnosed skin cancer during COVID-19 pandemic was observed in KTRs and finally, the importance of face-to-face outpatient examinations was emphasized [24].

Conclusion

In conclusion, dermatologic problems are frequent in kidney transplant recipients recovered from acute COVID-19. Besides cosmetic problems, skin malignancies may be diagnosed with a delay. Kidney transplant recipients should be advised to regularly self-examine their skin for potential skin cancer, report any changes to their physicians and to seek a dermatologic evaluation when necessary.

Conflict of interest statement. None declared.

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