A 4-year retrospective assessment of postoperative complications in immunosuppressed patients following Mohs micrographic surgery

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Background: Many patients undergoing Mohs micrographic surgery for basal and squamous cell carcinomas are immunocompromised, yet postoperative complications associated with different types of immunosuppression are largely unstudied.

Objective: To determine the incidence and nature of postoperative complications in immunosuppressed patients undergoing Mohs micrographic surgery.

Methods: A retrospective cross-sectional chart review of patient characteristics, clinical characteristics, and complications.

Results: Univariable analysis showed that compared with immunocompetence, immunosuppression was associated with 9.6 times the odds of postoperative complication (P = .003), with solid organ transplant recipients having 8.824 times higher odds (P = .006) and immunosuppressive therapy use displaying 5.775 times higher odds (P = .021). Surgical site infection (2.5%) and dehiscence (0.51%) were more prevalent among immunosuppressed patients, with an overall complication rate of 5.4% in the immunosuppressed population. Multivariable analysis of the association between immunosuppression and postoperative complication closely trended toward, but did not meet, significance (P = .056).

Limitations: This was a single-center, retrospective study. Other limitations include lack of non–solid organ transplants, limited medication-related data on nontransplant patients, and exclusion of cases involving patients with double transplants or multiple sources of immunosuppression.

Conclusions: Immunosuppression overall, particularly owing to solid organ transplant and immunosuppressive therapy use, places patients at higher risk for postoperative complications, including surgical site infection and wound dehiscence following MMS. (J Am Acad Dermatol 2019;80:1594-601.)

Key words: dermatologic surgery; immunosuppression; Mohs micrographic surgery.

Nonmelanoma skin cancer (NMSC) is the most prevalent form of skin cancer, with an estimated incidence of more than 5 million new cases per year in the United States.[1] Previous studies have demonstrated a clear relationship between immunosuppressed status and NMSC incidence, with a predominance of squamous cell carcinoma (SCC) over basal cell carcinoma (BCC) in the immunosuppressed population (reported incidence ratio, 4:1).[2] Immunosuppressed status has been shown to increase the probability of development of SCCs and cancers with high

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recurrence and metastasis risk, as determined by size, thickness, histology, location, and invasiveness.[3,4]

Mohs micrographic surgery (MMS) is the criterion standard treatment for NMSC and is reported to be very safe with a low incidence of intraoperative and postoperative complications.[5] In 1 large prospective cross-sectional study, the most common adverse events reported were infections, dehiscence, partial or full necrosis, and bleeding, as well as hematoma formation.[6] Another prospective study reports that most perioperative surgical complications involve difficulties with hemostasis.[7]

Immunosuppression has been associated with increased complication rates following cutaneous surgery.[6] These patients also tend to have aggressive subclinical extension, multiple lesions, and longer procedure durations, all of which may increase the risk of complication.[8] Previous studies have shown that a significant proportion of surgical site infections after MMS occurred in immunosuppressed patients. Specifically, Alam et al reviewed more than 20,000 cases in which MMS was performed, showing an overall adverse event rate of 0.72%, of which 61.1% were infectious in nature.[6] Although more than 95% of these were associated with the use of nonsterile gloves during surgery, this study was not powered to detect a difference, and more recent studies have shown no increased infection rate in resection or reconstruction with sterile versus nonsterile gloves.[9] Among the remaining cases of infectious complication that Alam et al analyzed, 2.4% had immunosuppression resulting from causes other than transplantation and 1.2% had immunosuppression secondary to organ transplantation.[6] However, the authors did not elaborate further on the effects of immunosuppression on surgical outcomes; specific postoperative complication rates for patients with various types of immunosuppression who are undergoing MMS are less well studied.[10,11]

Consequently, the limitations of prior studies include the lack of data on other complications such as dehiscence, necrosis, or bleeding, as well as absence of risk stratification based on the type of immunosuppression. The challenges in assessing these outcomes include the relatively low incidence of complications with MMS and the overall complexity in managing high-risk patients with multiple comorbidities requiring comprehensive medical treatment.[12] From a patient perspective, prior studies may have been limited in discussing patient-centered outcomes; in a recent survey, patients identified 2 additional complication outcomes to be considered for inclusion within the American College of Mohs Surgery registry: wound dehiscence and scarring.[13]

Our retrospective study aimed to analyze the incidence and nature of postoperative complications in patients who are immunosuppressed following MMS compared with in those who are immunocompetent. The findings will allow dermatologic surgeons to provide appropriate counseling to immunosuppressed patients and more accurately guide management of these patients preoperatively and postoperatively.

CAPSULE SUMMARY

- Solid organ transplant and immunosuppressive medications confer a higher risk of complications such as infection and dehiscence because of larger defect size, complex repair, and impaired healing.
- Dermatologists should take the higher risk of complications into account when counseling and managing immunosuppressed recipients of solid organ transplants who are undergoing Mohs micrographic surgery.

METHODS

Our retrospective review was performed at the Dermatologic and Mohs Surgery Center of University of California San Diego and granted exemption status from the University of California San Diego Institutional Review Board. All MMS cases presenting between July 2011 and June 2015 were assessed by using data gathered via electronic medical record review.

Patient characteristics such as age at surgery, sex, immunosuppression status, history of tobacco and alcohol use, and medication history were collected. Clinical characteristics included tumor location and histologic diagnosis.

Complications were defined as any adverse event within 2 weeks of MMS that was directly related to the procedure and assessed by the medical staff at the follow-up visit. Any adverse event was further defined as a clinical diagnosis of wound bleeding, dehiscence, tissue necrosis, or surgical site infection (as assessed by a clinical provider to include a combination of purulence, tenderness, erythema, and/or warmth at the site of the lesion with or without patient fever). The 2-week duration was

Abbreviations used:

BCC: basal cell carcinoma
MMS: Mohs micrographic surgery
NMSC: nonmelanoma skin cancer
SCC: squamous cell carcinoma
SOTR: solid organ transplant recipient

chosen in accordance with the standard follow-up period after a surgical procedure within our practice. Cases were arranged into 2 statistically independent groups (complication and no complication). To avoid double inclusion of participants who had multiple surgical procedures within both the complication and no-complication groups, 603 cases (involving a total of 107 patients) were removed from both groups. This permitted the creation of 2 independent comparison groups and diminished selection bias stemming from an unequal removal of cases from either group. The total number of patients included in the initial database search was 2576; our final analysis included 2468 unique patients and 4151 total cases. Current cigarette use or alcohol use were defined as activity within 6 months of MMS. Immunocompromised status was defined as history of a solid organ transplant (kidney, liver, heart, or lung), concurrent immunosuppressive therapy use, concurrent diagnosis of hematologic cancer (leukemia or lymphoma), or HIV-positive status. Cases of double transplantation or multiple causes of immunosuppression (eg, solid organ transplant and hematologic malignancy) were excluded from our analysis. The immunosuppressive medications assessed included oral cyclosporine, prednisone, sirolimus, tacrolimus, and mycophenolate mofetil.

Lesion location was separated into zones consistent with the 2013 National Comprehensive Cancer Network Guidelines to strengthen the power of each area: zone 1 included the "mask areas" of the face (central part of the face, eyelids, eyebrows, periorbital area, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, and ear), genitalia, hands, and feet; zone 2 included the cheeks, forehead, scalp, neck, and pretibial area; and zone 3 included the trunk and extremities, excluding the pretibial area, hands, feet, nail units, and ankles.[14] These anatomic areas respectively correspond to the areas H, M, and L, as delineated in the American Academy of Dermatology's appropriate use criteria or MMS.[15] Preoperative and postoperative dimensions, final surgical margins, number of stages required to achieve histologically clear margins, histologic diagnosis, level of training of the surgeon, and closure type were included in the analysis. The tumor sizes were recorded as 2 orthogonal dimensions (x axis and y axis) by the surgeon as preoperative size I and II and postoperative size I and II. Smaller orthogonal length of the tumor was recorded as size I, whereas longer length was recorded as size II. Consequently, differences between preoperative and postoperative size I and II, respectively, yielded 2 final surgical margin values for each tumor. The closure types included linear closure, granulation tissue (healing by secondary intention), a flap, or a graft. The linear closure was used as a reference group in the comparison, as this is the standard closure technique in dermatologic surgical procedures.

Data were analyzed via independent t test for continuous variables, Fisher's exact test for binary variables, and a logistic regression model with backward likelihood ratio technique with removal set at a P value of .1 by using SPSS software (version 21, IBM Inc, Armonk, NY). Our primary outcome measure was incidence of complications, and our primary analysis focused on the associations between independent variables of immunosuppression and the dependent variable of a complication.

RESULTS

The overall rate of complications among all cases in our analysis was 5.0%. Complications were statistically significantly more likely to occur in older patients than in younger patients (70.7 years vs 67.8 years, $P = .005$), and no significant differences by sex were observed ($P = .093$). Cases involving MMS within zone 1 were 5.1 times less likely to have a complication ($P = .028$), whereas cases involving MMS in zone 3 had 4.79 higher odds of complication ($P = .040$). Overall, patients with SCC, as compared with patients with BCC, had 12.7 times the odds of having a complication ($P < .001$). Among cases involving an immunosuppressed patient, the incidences of SCC and BCC were 62% and 38%, respectively. The average postoperative size for all SCC cases was 20 by 22 millimeters compared to 17 by 19 mm for all BCC cases.

As illustrated in Table I, immune compromise of any type was associated with 9.6 times the odds of having a postoperative complication ($P = .003$). Among immune compromise subtypes, cases involving patients with hematologic malignancy or HIV-positive status did not show significantly higher odds of complication compared with all other cases involving an immunocompetent patient. Solid organ transplant recipients (SOTRs) had 8.824 times the

Table I. Demographics of patients undergoing Mohs micrographic surgery

Characteristic	Any complication, n (%) (n = 198)*	No complication, n (%) (n = 3953)	OR (95% CI)	*P* value
Age, y				
Mean (SD)	70.7 (13.3)	67.8 (13.87)	—	**.005**
Sex			3	.093
F	58 (29.3)	1396 (35.3)		
M	140 (70.7)	2557 (64.7)		
Location[15,†]				
Zone 1	74 (37.4)	1800 (45.5)	5.1	**.028**
Zone 2	84 (42.4)	1579 (39.9)	0.483	.504
Zone 3	40 (20.2)	575 (14.5)	4.79	**.040**
NMSC type			12.7	**<.001**
BCC	103 (52)	2535 (64.1)		
SCC	94 (47.5)	1385 (35)		
Immunosuppressed				
All	49 (24.7)	644 (16.3)	9.694	**.003**
SOTR	22 (11.1)	245 (6.9)	8.824	**.006**
Hematologic malignancy[‡]	15 (7.6)	211 (6)	2.704	.131
HIV	12 (6.1)	195 (5.6)	1.030	.294
Organ received by SOTR[§]				
Kidney	7 (3.8)	94 (2.5)	1.281	.230
Heart	5 (2.7)	29 (0.8)	7.891	**.019**
Liver	2 (1.1)	29 (0.8)	0.258	.651
Lung	6 (3.3)	59 (1.6)	3.193	.123
Immunosuppressive medication				
Any	22 (11.1)	264 (6.7)	5.775	**.021**
Cyclosporine	1 (0.5)	81 (2)	2.32	.185
Prednisone	17 (8.6)	204 (5.2)	4.389	.049
Sirolimus	13 (6.6)	79 (2)	18.148	**<.001**
Tacrolimus	14 (7.1)	124 (3.1)	9.079	**.007**
Mycophenolate mofetil	3 (1.5)	22 (0.6)	2.894	.114
Total number of immunosuppressive meds mean (SD)	0.25 (0.750)	0.14 (0.541)	—	**.039**
Tobacco use	9 (4.5)	244 (6.2)	0.872	.446
Alcohol use	126 (63.6)	2140 (54.1)	6.865	**.010**
Preoperative size *x*				
Mean (SD)	13.86 (9.28)	9.45 (6.853)	—	**<.001**
Preoperative size *y*				
Mean (SD)	14.91 (9.7)	10.48 (7.29)	—	**<.001**
Postoperatove size *x*				
Mean (SD)	25.31 (15.79)	17.46 (10.41)	—	**<.001**
Postoperative size *y*				
Mean (SD)	27.14 (15.98)	19.47 (10.95)	—	**<.001**
Margin 1[‖]				
Mean (SD)	11.2 (9.05)	8.10 (7.27)	—	**<.001**
Margin 2[¶]				
Mean (SD)	12.05 (9.66)	9 (7.06)	—	**<.001**
Mohs stage, mean (SD)	2.43 (1.183)	2.18 (1.016)	—	**.005**
Closure type				
Granulation	13 (6.6)	48 (1.2)	6.67	**<.001**

Continued

Table I. Cont'd

Characteristic	Any complication, n (%) (n = 198)*	No complication, n (%) (n = 3953)	OR (95% CI)	*P* value
Linear (ref)	86 (44.3)	2120 (53.6)	—	—
Flap	48 (24.2)	947 (24)	1.248	.229
Graft	47 (23.7)	615 (15.6)	1.884	**.001**

Boldface indicates statistical significance.
BCC, Basal cell carcinoma; *CI*, confidence interval; *OR*, odds ratio; *ref*, reference; *SCC*, squamous cell carcinoma; *SD*, standard deviation; *SOTR*, solid organ transplant recipient.
*Data on tumor type are missing for 1 case.
†National Comprehensive Cancer Network Guidelines version 2.2013 for BCC and SCC: zone 1 includes the "mask areas" of the face (central part of the face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermillion], chin, mandible, preauricular and postauricular skin/sulci, temple, and ear), genitalia, hands, and feet; zone 2 includes the cheeks, forehead, scalp, neck, and pretibial area; and zone 3 includes the trunk and extremities, excluding the pretibial area, hands, feet, nail units, and ankles.
‡Hematologic malignancy includes acute myeloid leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia.
§Data on transplant type are missing for 2 cases.
‖Margin 1 is the difference between postoperative size *x* and preoperative size *x*.
¶Margin 2 is the difference between postoperative size *y* and preoperative size *y*.

odds of having a postoperative complication ($P = .006$); specifically, patients who had received a heart transplant had 7.89 times higher odds of complication as compared with all immunocompetent patients. Noncardiac solid organ transplantation, in contrast, did not demonstrate significantly higher odds of complication. Taking any immunosuppressive medication was associated with 5.775 times the odds of having a postoperative complication ($P = .021$), with patients taking sirolimus and tacrolimus showing 18 and 9 times the odds of having a postoperative complication, respectively ($P < .001$ and $P < .007$). Prednisone use showed 4.4 times higher odds of development of a complication ($P = .049$), but no statistically significant association was observed with cyclosporine and mycophenolate mofetil use. Alcohol use was associated with 6.8 times the odds of having a postoperative complication as compared with no alcohol use ($P = .010$).

The results were further adjusted by using a logistic regression model (Table II). Histologic subtype of SCC, clinical location of zone 3, history of alcohol use, tumor margin size, and repair type of granulation and graft remained significant predictors for postoperative complications, which is consistent with the univariate findings in Table I. In this model immunosuppression was closely approaching significance as a predictor of postoperative complication ($P = .056$).

The prevalence of specific complications in both immunosuppressed and immunocompetent patients is shown in Table III. Surgical site infection (2.5%), bleeding (0.61%), and dehiscence (0.51%) were the highest subtypes of complications among immunosuppressed patients who developed a complication (5.4%). Immunocompetent patients who developed a complication (4.0%) showed the greatest prevalence of surgical site infection (1.6%) and bleeding (0.95%).

DISCUSSION

Our data suggest that immunosuppression overall closely approaches significance in its association with complication development when controlled for repair type, tumor margin size, anatomic location, alcohol use, and tumor subtype. Specifically, heart transplant recipients and those receiving immunosuppressive therapy are the subgroups accounting for the significantly increased complication risk among immunosuppressed patients. The increased odds of complication among patients with SCC compared with among patients with BCC are likely due to a higher incidence of SCC in immunosuppressed patients in addition to increased average postoperative size.[16]

The types of complications more likely to occur in the immunocompromised group included surgical site infection and wound dehiscence. This is consistent with the results of prior studies showing higher rates of infectious complication following dermatologic surgery among immunocompromised patients, as well as with the well-established literature indicating that subacute infection and impaired wound healing are significant risk factors for wound dehiscence.[5-7,17,18] Interestingly, there was only 1 case involving an immunocompetent patient who developed both infection and dehiscence simultaneously; all other reported infections or instances of dehiscence occurred in isolation. Our findings reiterate the importance, as identified in patient survey–based studies, of including dehiscence as a complication in the American College of Mohs Surgery registry.[13]

Table II. Adjusted results

Characteristic	*B*	*P* value	OR	95% CI
Age	0.011	.060	1.011	1-1.024
Sex	0.019	.913	1.019	0.729-1.423
SCC	0.322	**.042**	1.379	1.012-1.881
Zone 3	0.523	**.010**	1.687	1.134-2.510
Alcohol use	0.415	**.008**	1.514	1.116-2.055
Immunosuppression	0.365	**.056**	1.441	0.991-2.094
Margin 1*	0.017	**.034**	1.018	1.001-1.034
Margin 2†	0.023	**.012**	1.023	1.005-1.042
Granulation	1.329	**<.001**	3.779	1.819-7.850
Flap	0.230	.247	1.258	0.853-1.857
Graft	0.593	**.003**	1.810	1.218-2.691

Variables included in the logistic regression model with backward likelihood ratio technique were sex (fixed), age, zone 3, basal cell carcinoma, SCC, any immunosuppressed status, size margins, Mohs stages, closure type (linear closure as reference), alcohol use. Only variables included in the final model step are displayed. One binary outcome of complication (yes/no). Boldface indicates statistical significance.

CI, Confidence interval; *OR*, odds ratio; *SCC*, squamous cell carcinoma.

*Margin 1 is the difference between postoperative size *x* and preoperative size *x*.

†Margin 2 is the difference between postoperative size *y* and preoperative size *y*.

Table III. Prevalence of complications by subtype

Complication	Immunosuppressed, n (%) (n = 973)	Immunocompetent, n (%) (n = 3772)
Any complication	49 (5.4)	149* (4.0)
Stroke	0	1
Bleeding	6 (0.61)	36 (0.95)
Surgical site infection	24 (2.5)	62 (1.6)
Swelling	0	7
Necrosis	4	11
Hypertrophic scar	4	7
Bruising	1	1
Spitting sutures	0	7
Dehiscence	5 (0.51)	3
Ulceration	2	5
Granuloma	1	5
Pruritus	0	1
Nonhealing wound	2	0

*Data on complication type are missing for 3 cases.

SOTRs were 8.8 times more likely to have a postoperative complication as compared with all other immunocompetent patients. In particular, heart transplant recipients alone had 7.89 times higher odds of complication ($P < .019$), whereas other solid organs did not approach statistical significance in their associations, suggesting that heart transplants primarily account for the higher odds of complications among transplant recipients.

Prior studies have noted that heart transplant recipients are especially prone to skin cancer because of the intensive immunosuppression needed to prevent transplant rejection, as well as because they are, on average, older at time of transplant.[19] The present study highlights the fact that heart transplant—associated skin cancer risk applies not only to incidence and tumor burden but also to treatment complication. The increased complication risk may also be related to patient age, white race, and male sex, which have been associated with both development of skin cancer and need for a cardiac transplant.[20] Ischemic cardiomyopathy is also associated with a high-fat diet, which is thought to be an independent risk factor for incidence of actinic keratosis and promotion of ultraviolet carcinogenesis.[19]

In addition, patients taking immunosuppressive medications were found to have 5.78 times higher odds of complication. Those patients who were taking multiple immunosuppressive medications at the time of surgery also carried higher risk of postoperative complications ($P = .039$) that were likely secondary to the medications' combined effects. Although both prednisone and tacrolimus demonstrated a greater complication risk (at 4.39 and 9.08 times higher odds, respectively [$P = .049$ and $P = .007$]), the complication risk was most salient for sirolimus (at 18.1 times higher odds of complication [$P < .001$]).

Interestingly, prior studies have linked sirolimus and other mechanistic target of rapamycin inhibitors with a reduced risk of skin cancer incidence in kidney transplant patients,[21-23] and more recently, in a cohort of patients with various organ transplants and a history of post-transplant cancer, rendering this drug a favorable option for patients at risk of post-transplant cancer.[24] A recent meta-analysis has illustrated an increase in overall mortality with sirolimus use but no elevation of mortality in studies of low-dose sirolimus.[25] Our findings thus underscore the potential disadvantages associated with sirolimus therapy in post-transplant immunosuppression and possible dose-dependent risk of complication in patients who do develop a cutaneous malignancy.

The mechanisms whereby corticosteroids such as prednisone impair wound healing and increase infection risk are not completely understood. It is thought that the treatment doses for anti-inflammatory conditions are generally below the level required for dramatic inhibition of wound healing; higher doses such as those indicated in

maintenance regimens for post-transplant patients may increase this complication risk.[26] Tacrolimus, a drug routinely used in post-transplant regimens, has been shown to produce reduced infectious complications in kidney transplant recipients at lower doses while maintaining transplant tolerance.[27] Although our study did not distinguish between higher and lower doses of immunosuppressive therapy, whether dose-dependent relationships with complication risk exist would be worthwhile to explore in a future study.

There are several limitations of this study, including its retrospective nature and restriction to a single institution. Non–solid organ transplants, such as bone marrow transplants or stem cell transplants, were also not included in our analysis. One important limitation is that medication data were available only for SOTRs rather than for all immunosuppressed patients and consequently were not included in the multivariate analysis. This may introduce confounding as to the effect of the immunosuppressive medication itself versus that of its underlying indication (ie, transplant) on complication rates. For example, 9 of the 34 heart transplant patients were taking sirolimus and 15 reported alcohol use. Moreover, the complications documented were made by the diagnosing providers at the time of clinical visit, and as our study is a retrospective chart review, fully standardizing complication definitions and ensuring thorough recording of complications is challenging. Additionally, cases with double transplantation and multiple causes of immunosuppression were excluded from our analysis not only because of very small sample size but also to avoid confounding the association of a particular immunosuppressive diagnosis with complication risk. However, future study is warranted to explore how extent of immunosuppression affects the likelihood of complication. Prospective studies are also needed to validate the findings presented in this article and to explore additional factors that may affect postoperative complication rates.

On the basis of our data, we conclude that the high odds of postoperative complication observed for cases involving patients with a heart transplant and sirolimus use suggest that these subgroups of patients may benefit from close monitoring in the postoperative period and vigilant counseling about wound care and follow-up. Administering the lowest dose of immunosuppressive drugs to facilitate transplant tolerance while preventing cutaneous surgical complications remains an important clinical consideration warranting further study. Nonetheless, complication rates are very low overall, even when the immunosuppressed population is included, thus reinforcing the idea that MMS is a safe and effective treatment for NMSCs.

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