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Research Paper

Presentation and outcomes of chronic rhinosinusitis following liver and kidney transplant

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KEYWORDS
Rhinosinusitis;
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Kidney transplant;
Liver transplant;
Immunocompromised;
Immunosuppressed

Abstract *Objective:* This study aims to describe presenting characteristics of patients diagnosed with non-invasive chronic rhinosinusitis (CRS) following liver or kidney transplant and determine factors associated with disease-related complications, selection of endoscopic sinus surgery (ESS), and disease resolution in this population.
Study design: Retrospective chart review.
Setting: An academic tertiary care center (Mayo Clinic, Rochester, Minnesota).
Subjects and methods: Liver and kidney transplant recipients evaluated by Mayo Clinic otolaryngologists for CRS between 1998 and 2018 were identified. Univariate and multivariate logistic regression analyses were used to determine patient factors and treatment modalities associated with developing complications, selection of ESS, and disease resolution.
Results: Fifty-seven patients met inclusion criteria. No patients developed intraorbital or intracranial complications of their CRS. Multivariate modeling demonstrated that the presence of polyps ($P = 0.036$) was associated with undergoing ESS within one year of presentation. A higher Lund–Mackay (LM) computed tomography score ($P = 0.023$) and older age ($P = 0.018$) were significantly associated with decreased disease resolution. No other factors were significantly associated with the use of endoscopic sinus surgery within one year of otolaryngology presentation or resolution of CRS in this cohort.
Conclusion: The risk of developing CRS-related intraorbital or intracranial complications in this immunecompromised patient cohort may be lower than originally thought. For liver- and

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kidney-recipients stable on immunosuppressive medication for many years, prognostic factors for CRS may mirror those for immunocompetent patients.

Introduction

Otolaryngologists are increasingly managing diseases of the head and neck in populations of immunocompromised patients. One of the major contributors to this phenomenon is the rapid increase in liver and kidney transplantation in recent years. These two organs account for approximately 80% of organs transplanted in the United States each year. In the most recent Annual Data Report from the Organ Procurement and Transplantation Network (OPTN), there were 8082 liver transplants and more than 20 000 kidney transplants performed in 2017 alone.[1,2] This brings the total number of liver and kidney recipients living with functioning grafts in the United States to 83 925 patients and more than 220 000 patients respectively.[1,2] These post-transplant patients require life-long medication to suppress the immune system and minimize the chance for organ rejection. With long-term outcomes continuing to improve for both liver and kidney transplant recipients, the population of immunosuppressed transplant patients will only continue to increase.

This post-transplant population is of particular interest to the otolaryngologist because of the impaired ability to mount an immune response to sinonasal pathogens, especially in the setting of acute rhinosinusitis (ARS) or chronic rhinosinusitis (CRS).[3] The potential development of invasive fungal sinusitis is a well-recognized and feared complication in this patient cohort.[4—6] However, not all rhinosinusitis in transplant patients is invasive or fulminant, and the otolaryngologist must be prepared to counsel a patient and manage the nuances of non-invasive rhinosinusitis in the transplant recipient. In addition, the risk of intraorbital and intracranial spread of disease is often cited as a concern in this population, potentially leading to consideration of more aggressive disease treatment than in immunocompetent patients.[5,7] Robust evidence based recommendations for the treatment of CRS in the transplant patient is lacking.[8] Previous studies have examined the utility of baseline sinonasal evaluation and treatment of rhinosinusitis prior to liver or kidney transplant, but offer limited explanation regarding the patient and treatment factors that influence the clinical course and outcomes of patients who develop rhinosinusitis following transplantation.[7,9,10] One recent study suggests that the incidence of rhinosinusitis-related complications in solid organ transplant recipients may be significantly lower than in bone marrow transplant patients.[11]

Currently, treatment recommendations for transplant patients are extrapolated from studies looking at a broad population of immunosuppressed patients including patients with diabetes, HIV, cancer, and those in critical care settings.[12] Dao et al[12] found surgical management to be one important factor that may improve outcomes of broadly immunocompromised patients presenting with CRS and ARS. A recent retrospective review of a nationwide hospital database showed that in patients undergoing hematologic transplant, the presence of sinusitis is associated with higher total hospital charges and increased length of stay.[13]

Given the lack of specific data for the management of CRS in liver and kidney transplant recipients, the aim of this study is to describe the presentation of CRS in this patient population, characterize its clinical course, and to determine patient and treatment factors that impact CRS outcomes in this population.

Material and methods

Protocol and eligibility criteria

After gaining approval from the Mayo Clinic Institutional Review Board (IRB: 18—000486), International Classification of Diseases (ICD-9) codes were used to query a retrospective institutional database for patients diagnosed with CRS following a kidney and/or liver transplant. Inclusion criteria comprised a diagnosis of CRS following transplant confirmed by an otolaryngologist at our institution; and an accompanying maxillofacial computed tomography (CT) scan within 12 months of CRS diagnosis. Patients lacking a CT scan within 12 months of diagnosis and whose CRS was not confirmed by an otolaryngologist were excluded. Patients with a documented pre-existing CRS diagnosis prior to transplant were included in the study so long as ongoing disease was confirmed by an otolaryngologist following transplant and so long as they had a recent (within 12 months of post-transplant otolaryngology evaluation) maxillofacial CT scan. Diagnosis of CRS was determined using current criteria outlined in the Adult Sinusitis Guidelines provided by the American Academy of Otolaryngology.[14] Initial institutional database screening revealed 153 potential subjects.After careful chart review, a total of 57 patients diagnosed with CRS following kidney and/or liver transplantation met the aforementioned eligibility criteria and were included in this study.

Patient characteristics

Pertinent patient characteristics and findings recorded include demographics, smoking history, comorbidities, transplant type and indication, symptomology, laboratory studies, physical exam findings, and LM CT scores. A smoking history of at least 5 pack-years was considered positive. Treatments recorded included medical and

surgical management, with only medical treatments prescribed following transplant and before endoscopic sinus surgery (ESS) being recorded. Outcomes measured include disease resolution confirmed either by CT or nasal endoscopy, continued disease with improved symptoms, continued symptomatic disease, and disease complications.CRS disease resolution was defined as a normalized CT scan or endoscopic exam following treatment.

Statistical analysis

Patient factors, treatment modalities, disease outcomes, and complications were calculated using descriptive statistics. Univariate logistic regression was used to determine patient and treatment factors associated with disease resolution, complications, and undergoing ESS within one year of otolaryngology evaluation. Using a backwards stepwise variable selection model, factors with a $P < 0.2$ on the univariate analysis were carried forward to be used in a multivariable logistic regression model. For multivariate analysis, the significance level was set at $P < 0.05$.

Results and analysis

Baseline and presenting characteristics

Of the 57 patients in the study, 36 (63.2%) were kidney transplant recipients, 20 (35.1%) were liver recipients, and 1 (1.8%) patient received both a kidney and a liver. The median follow-up time with otolaryngology after the initial evaluation was 16.1 months (interquartile range: 3.9–56.7 months). The most common medication regimen used for maintenance immunosuppression was triple therapy consisting of prednisone, tacrolimus, and mycophenolate. Fourteen (24.6%) patients had a pre-existing diagnosis of CRS prior to transplant, while 43 (75.4%) had no previous history of CRS prior to transplant (Table 1).The median time interval between the date of transplant and date of the initial otolaryngology evaluation at our institution was 6.5 years (interquartile range: 3.0–12.8 years).

Upon presentation to an otolaryngologist, the most common symptom was nasal discharge (82.5%) followed by nasal congestion (71.9%). Thirty-two (56.1%) patients in this study had evidence of mucopurulent drainage on endoscopic examination. Over half (54.5%) of intranasal microbiology cultures, obtained within 6 months of presentation, were positive, with *Staphylococcusaureus* being present in 50% of positive cultures. The mean absolute neutrophil count (ANC), obtained within 6 months of the otolaryngology evaluation, was 4.3, or within normal limits (Table 2). All patients had a CT scan within 12 months of initial otolaryngology evaluation, with an average LM CT score of 9.9. For patients treated with ESS, the mean presenting LM CT score was 11.0. For those who were managed solely with medical treatment, the mean presenting LM score was 8.5.

Treatment patterns and outcomes

Medical management of CRS included systemic corticosteroids (33.3%), systemic antibiotics (91.2%), intranasal corticosteroids (78.9%), and topical antimicrobials (43.9%). The most commonly prescribed oral antibiotics were amoxicillin and amoxicillin clavulanate (47.4%), and fluoroquinolones (38.6%). The most commonly prescribed topical antibiotics were and Gentamicin (31.6%) and Mupirocin (14.0%). Surgical intervention was offered for patients for whom a trial of medical management failed to achieve clinically confirmed CRS resolution — determined either by endoscopy or a follow-up sinus CT scan — and for those who experienced persistent symptoms. A total of 33 (57.9%) patients underwent surgical intervention for their CRS after organ transplant, with 25 (43.9%) patients having surgery within one year of presenting to an otolaryngologist at our institution (Table 3).

Thirty patients (52.6%) experienced disease resolution with CT or endoscopic confirmation after treatment, nineteen (33.3%) of whom underwent ESS at any point following transplant, and eleven (19.3%) of whom were managed with medical treatment alone. Nine patients (15.8%) experienced continued disease with improved symptoms and 9 patients (15.8%) experienced continued symptomatic disease. The remaining 9 patients (15.8%) were lost to follow-up. No patients in this study developed intraorbital or intracranial complications (Table 4).

Table 1 Baseline characteristics of 57 patients diagnosed with chronic rhinosinusitis following transplant.

Demographics	Frequency: *n* (%)
Sex	
Male	29 (50.9)
Female	28 (49.1)
Asthma	11 (19.3)
Diabetes	18 (31.6)
Smoking history	16 (28.1)
Transplant Type	
Kidney	36 (63.2)
Liver	20 (35.1)
Kidney and liver	1 (1.8)
Immunosuppressive Medications	
Azathioprine	6 (10.5)
Cyclosporine	8 (14.0)
Mycophenolate	30 (52.6)
Prednisone	39 (68.4)
Sirolimus	7 (12.3)
Tacrolimus	35 (61.4)
Other	1 (1.8)
None	1 (1.8)
Otolaryngologist evaluation setting	
Inpatient	3 (5.3)
Outpatient	54 (94.7)
Pre-transplant CRS diagnosis	
No history of CRS	43 (75.4)
CRS without nasal polyps	8 (14.0)
CRS with nasal polyps	6 (10.5)
Surgical treatment prior to transplant	9 (15.8)

CRS = chronic rhinosinusitis; the mean age is 49.9 years old and the SD is 16.1.

Table 2 Presenting symptoms and findings of chronic rhinosinusitis in post-transplant patients.

Symptoms	Frequency: *n* (%)
Nasal discharge	47 (82.5)
Congestion	41 (71.9)
Cough	22 (38.6)
Face pain/pressure	28 (49.1)
Aural fullness	13 (22.8)
Hyposmia	13 (22.8)
Incidental imaging without significant symptoms	6 (10.5)
Endoscopic Findings	
Mucopurulence	32 (56.1)
Polyps	10 (17.5)
Laboratory Results	**Mean [SD]**
WBC[a]	6.4 (2.8)
ANC[a]	4.3 (2.4)
Cultures	**Frequency: *n* (%)**
Positive	12 (21.1)
S. *aureus*	6 (10.5)
Coagulase-negative staphylococci	4 (7.0)
Fungus	4 (7.0)
S. *pneumoniae*	2 (3.5)
H. *flu*	2 (3.5)
P. *aeruginosa*	1 (1.8)
Serratia	1 (1.8)
Enterobacter	1 (1.8)
Burkholderia	1 (1.8)
Escherichia coli	1 (1.8)
Mycobacterium	1 (1.8)
M. *catarrhalis*	0 (0.0)
Negative	10 (17.5)
Not preformed	35 (61.4)

ANC = absolute neutrophil count; WBC = white blood count.
[a] Drawn from peripheral blood.

Table 3 Post-transplant treatment patterns of chronic rhinosinusitis.

Medical Management	Frequency: *n* (%[b])
Steroids (oral or intramuscular)	19 (33.3)
Steroids (intranasal)	45 (78.9)
Antibiotics	
None	5 (8.8)
Oral antibiotics	51 (89.5)
Type of oral antibiotics	
Augmentin/amoxicillin	27 (47.4)
Fluoroquinolone	22 (38.6)
Macrolide	11 (19.3)
Bactrim	11 (19.3)
Cephalosporin	9 (15.8)
Doxycycline	5 (8.8)
Clindamycin	4 (7.0)
Other	2 (3.5)
Length oral of antibiotics use	
0–6 days	0 (0.0)
7–13 days	3 (5.3)
14–20 days	1 (1.8)
21–30 days	9 (15.8)
31+ days	26 (45.6)
Unknown[a]	12 (21.1)
Intravenous antibiotics	5 (8.8)
Topical antimicrobials	25 (43.9)
Type of topical antimicrobial	
Gentamicin	18 (31.6)
Mupirocin	8 (14.0)
Other	4 (7.0)
Antifungal	3 (5.3)
Unknown[a]	1 (1.8)
Surgical Management	**Frequency: *n* (%)**
ESS at any point following transplant	33 (57.9)
ESS within one year of otolaryngology evaluation	25 (43.9)
Multiple ESS following transplant	8 (14.0)

ESS = endoscopic sinus surgery.
[a] Antibiotics prescribed, but exact type or duration not recorded.
[b] % of total study subjects.

Predictors of undergoing ESS within one year of presentation in CRS patients

On univariate analysis, a co-diagnosis of asthma, LM CT score, mucopurulence on presenting endoscopy, polyps on presenting endoscopy, and positive bacterial or fungal cultures (for all, $P < 0.20$) were identified as potential predictors of undergoing ESS within one year of otolaryngology evaluation. These factors were carried forth on a multivariate analysis; only polyps on endoscopy (odds ratio [OR] = 6.18; confidence interval [CI] = 1.30, 45.53; $P = 0.036$) was identified as a statistically significant predictor of undergoing ESS within one year of presentation (Table 5).

Predictors of disease resolution in CRS patients

Regarding CRS resolution, univariate analysis demonstrated patient age at the time of otolaryngology evaluation ($OR = 0.95$; CI 0.90, 0.99; $P = 0.129$), length of oral antibiotics ($OR = 0.59$; CI 0.27, 1.01; $P = 0.079$) and LM CT score ($OR = 0.86$; CI 0.74, 0.99; $P = 0.029$) as potential predictors of clinically confirmed disease resolution. Subsequent multivariate analysis followed by stepwise variable selection identified decreased CRS resolution in patients with a higher presenting LM CT score ($OR = 0.79$; CI 0.62, 0.95; $P = 0.023$) and those of older age ($OR = 0.93$; CI 0.87, 0.98; $P = 0.018$) (Table 6). Positive smoking history, co-diagnosis of diabetes or asthma, whether CRS was first diagnosed prior to or post-transplant, mucopurulent drainage on presenting endoscopy, presence of polyps, neutrophil and leukocyte counts (both drawn from peripheral blood), type of maintenance immunosuppressive medication, daily dosage of prednisone, medical management with either systemic steroids or antibiotics, duration ofmedical management, and ESS at any point following transplant had no significant influence on disease resolution in CRS patients.

Table 4 Outcomes after treatment of CRS in post-transplant patients.

Outcome	Total (57 patients) Frequency: *n* (%)	Treated with surgery (33 patients) Frequency: *n* (%)	Medical treatment only (24 patients) Frequency: *n* (%)
Disease resolution with CT or endoscopic confirmation	30 (52.6)	19 (57.6)	11 (45.8)
Continued disease with improved symptoms	9 (15.8)	5 (15.2)	4 (16.7)
Continued symptomatic disease	9 (15.8)	6 (18.2)	3 (12.5)
Lost to follow up	9 (15.8)	3 (9.1)	6 (25.0)
Disease complication	0 (0.0)	0 (0.0)	0 (0.0)

CT = computed tomography.

Table 5 Multivariate analysis of predictors of useof ESS within one year of otolaryngology evaluation in patients with CRS.

Item	Odds-Ratio (95% CI)	*P* value
Higher Lund—Mackay CT score	1.12 (0.99, 1.29)	0.071
Polyps on endoscopy	6.18 (1.30, 45.53)	0.036

CT = computed tomography.

Table 6 Multivariate analysis of predictors of disease resolution in patients with CRS.

Item	Odds-Ratio (95% CI)	*P* value
Higher Lund—Mackay CT score	0.79 (0.62, 0.95)	0.023
Age at ENT evaluation	0.93 (0.87, 0.98)	0.018
Length of pre-transplant oral antibiotics	0.58 (0.25, 1.05)	0.108

CT = computed tomography; ENT = ear, nose, and throat.

Discussion

Management of non-invasive rhinosinusitis in liver and kidney transplant recipients poses a unique challenge given the immunocompromised state of these patients. Given the lack of robust data in this patient population, otolaryngologists have held widely varying practices for the management of this entity.[8] With an ever-expanding liver and kidney transplant recipient population, it is likely that the number of post-transplant patients with rhinosinusitis will continue to grow.

Lack of complications

In this study, none of the 57 post-transplant patients developed intraorbital or intracranial complications of CRS. It is well-recognized that immunosuppression following organ transplant provides an opportunity for pathogens to cause infectious spread of disease in both ARS and acute exacerbations of CRS.[14–16] It is notable that we did not find any instances of intraorbital or intracranial complications in our cohort given the widely held concern for this in patients who have previously undergone solid organ transplant and remain on long-term immunosuppression.[6,7,9,10,16,17] A recent retrospective study similarly found no instances of rhinosinusitis-related complication in 30 solid organ transplant recipients diagnosed with post-transplant CRS.[11] The authors also noted no signs of complications in 25 patients diagnosed with post-transplant ARS; although two ARS patients developed invasive fungal infection (mucormycosis) with no evidence of disease complications or recurrences following surgical intervention.[11]

Some patient factors that could potentially account for the lack of complications seen in the current study are that the majority of patients were initially evaluated in the outpatient setting with a mean ANC of 4.3 and there was a median time interval of 6.5 years between the date of transplant and that of otolaryngology evaluation. Given that our patients represent a more 'mature' cohort of transplant patients, our results may potentially underrepresent the frequency of CRS complications compared to if the cohort had a larger proportion of representation from immediate post-transplant patients. In the immediate post-transplant period, when the patient is under maximal immunosuppression, the index of suspicion for invasive fungal disease or secondary complications would be much higher. The lack of extra-sinus involvement in this patient cohort provides some degree of reassurance regarding disease progression in the 'mature' post-transplant patient population.

Microbiology

It is interesting to note that roughly half of the tested patients in this study had positive culture results and the most frequent culture results were fairly common pathogens such as S. *aureus*, S. *pneumoniae*, and H. *flu*. This is in contrast to other studies which identify the majority of culture swabs in transplant patients being positive and the culture results frequently including more unusual organisms such as P. *aeruginosa*.[11,18] It is possible that more routine pathogens were identified in this cohort of liver and kidney transplant patients because they are less commonly placed on daily prophylactic antibiotics as opposed to other transplanted organs, such as lungs or bone marrow. The presence of more routine pathogens may also be attributed to the fact thatmost patients were initially evaluated in the outpatient setting and not in the immediate post-transplant period under maximal immunosuppression. This finding highlights the importance of culture-directed antibiotics which allows for improved direction of systemic

antimicrobial therapy. Such culture-directed antibiotic treatment may help to avoid unnecessary exposure of immunocompromised patients to undirected broad spectrum antibiotics, which may increase the risk of microbial resistance in this vulnerable population.

Factors for resolution

Both older age and higher presenting LM scores were significantly associated with decreased CRS resolution in this study. These factors have also been associated with poor CRS outcomes in immunocompetent patients.[19–22] Furthermore, peripheral blood neutrophil and leukocyte counts, and the types of maintenance immunosuppressive medication had no significant impact on disease resolution or the development of complications in this study. This data suggests that liver and kidney transplant recipients who have been stable on immunosuppressive medication for several years may be similar to immunocompetent patients regarding their propensity for CRS resolution and the development of intracranial and intraorbital complications. The mundane pathogens identified on nasal swabs in this patient cohort further demonstrate the similarity between these two populations regarding their susceptibility to virulent sinonasal pathogens.

Although not captured in our data, one striking difference previously reported in solid organ recipients is a low incidence of CRS compared to the general population.[10,11] In 1503 adult kidney transplant recipients, Ryu et al[10] found a mere 0.6% incidence of post-transplant CRS. Tzelnick et al[11] similarly reported a post-transplant CRS incidence of $<$1% in 4562 solid organ patients, including heart, lung, kidney, and liver recipients. The latter study attributed the low incidence to the effects of anti-rejection medication on suppressing the inflammatory response to sinonasal pathogens.[11] Certainly, the notion that patients on immunosuppressive medication have an altered immune response to sinonasal pathogens has been demonstrated in a recent study that found histopathological variances in sinus tissue removed from patients on immunosuppressive therapy patients compared to tissue removed from immunocompetent CRS patients: sinus tissue from patients on immunosuppressive medication trended towards increased neutrophils and reduced fibrosis compared to immunocompetent patients diagnosed with CRS without nasal polyps, and significantly reduced fibrosis and eosinophil aggregates compared to immunocompetent patients diagnosed with CRS with nasal polyps.[23] Future study into the interaction between immunomodulatory medications and the inflammatory response to sinonasal pathogens may elucidate novel opportunities for medical management of CRS in transplant patients.

Surgical decision making

Notably, this study did not identify a statistically significant association between surgery and CRS resolution in post-transplant patients. This conclusion is in contrast to prior studies, which have shown that ESS may be associated with increased CRS resolution in both immunocompetent and immunocompromised populations.[12,24] It is also important to note that disease resolution was defined objectively as a lack of persistent inflammation on endoscopy or sinus CT following treatment, which does not take into account the potential for symptomatic improvement following ESS with some degree of ongoing disease. Given that the study timeframe occurred over a 20-year period when most patients were not routinely recording validated patient reported subjective outcome measures, this factor was not incorporated into our analysis models. Regardless, the otolaryngologist should have a comprehensive patient-centered discussion that considers all available evidence in tailoring an individualized treatment plan.

Generalizability to other transplant patients

The focus of this paper was limited to liver and kidney recipients because these patients account for the majority of organs transplanted in the United States each year. Given the shared immunosuppressive agents used among solid organ recipients, it is possible that the findings of this study may be translatable to recipients of other solid organs, such as heart.[25] However, this study may be less applicable to lung transplant recipients, such cystic fibrosis patients, who have a fundamental physiologic association with CRS beyond post-transplant immunosuppressive medication.[26,27] Bone marrow transplant patients are reported to experience increased rates of invasive fungal complications; it is therefore unlikely that the findings of this study apply to these populations.[11,18,28]

Limitations

Despite our efforts to adjust for confounding effects by using multivariate regression analysis, the retrospective nature of this study limits the recommendations we can make regarding definitive medical or surgical interventions as standard practice for liver and kidney recipients with non-invasive CRS. Given the 20-year timeframe of this study, there was also a lack of widely available validated patient-reported symptom scores, such as Sinonasal Outcome Test-22 (SNOT-22), which did not allow for a detailed analysis in this regard. When possible, subjective symptoms were recorded and reported (i.e. presenting symptoms), but these were not recorded in a validated fashion. Additionally, the extent of sinus surgery, which may influence patient outcomes, was not recorded in this study. Further study in well-designed prospective trials that utilize standard patient-reported outcome measures is required to investigate impact of surgical intervention on disease course and outcomes in this population.

Conclusions

Robust, evidence-based recommendations for the management of CRS in immunosuppressed patients following organ transplantation is lacking.[8] To the best of our knowledge, this study is the first to use regression analysis

in an attempt to determine factors associated with complications, selection of ESS, and disease resolution specifically in kidney and liver recipients with documented post-transplant CRS. Our findings indicate that prognostic factors for CRS in liver and kidney recipients who have been stable on anti-rejection medication for several years are similar to those for immunocompetent patients. Additionally, the risk for intracranial and intraorbital complications of CRS in solid organ transplant patients may be lower than once thought. An improved understanding of the distinct pathogenesis of CRS in transplant patients may provide opportunities to better tailor management options.

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Declaration of Competing Interest

None.

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