

Rhinosinusitis in Solid Organ Transplant Recipients: Analysis of 4562 Transplanted Patients

American Journal of Rhinology & Allergy

2019, Vol. 33(1) 56–61

© The Author(s) 2018

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/1945892418808717

journals.sagepub.com/home/ajr



Sharon Tzelnick, MD, MPH¹  and Ethan Soudry, MD^{1,2}

Abstract

Introduction: Survival rates of solid organ transplant recipients are steadily increasing. Chronic immunosuppression is a key to sustain the transplanted organ. Thus, these patients are at a higher risk for fulminant disease and severe complications of rhinosinusitis (RS). Surprisingly, this has been scarcely discussed in the literature.

Objective: To analyze the characteristics and disease course of RS in solid organ transplant recipients.

Materials and Methods: Retrospective study. Medical records of all solid organ transplant recipients with a diagnosis RS treated at a national transplant center between the years 2001 and 2016 were reviewed.

Results: Of 4562 solid organ transplant recipients, a documented diagnosis of RS was identified only in 61 (1.3%) patients. Sixty-four patients presented with posttransplantation RS; of them, 54.5% had chronic RS (CRS) and the remaining 45.5% patients were diagnosed with acute RS. Microbial cultures grew almost exclusively bacterial pathogens. A documented invasive fungal infection was noted in only 2 patients. A total of 24 (40%) patients underwent endoscopic sinus surgery, the majority (22) for CRS. On subgroup analysis, surgical intervention was more frequent in lung transplant recipients ($P = .005$). Neither specific disease nor surgical complications were found.

Conclusions: Interestingly, acute fulminant infection or sinusitis complications in solid organ transplant patients were much lower than expected. CRS in this patient group was less frequent than expected as well. Whether chronic immunosuppression minimizes the likelihood for CRS deserves further investigation. A more surgically oriented approach in CRS patients may be favored early in the management course of medically refractory patients in light of patients excellent outcomes.

Keywords

rhinosinusitis, solid organ transplantation, immunosuppression

Introduction

In the last 2 decades, solid organ transplantation of lung, kidney, heart, and liver has become increasingly common. Transplant recipients are regularly maintained on chronic immunosuppression to avoid rejection of the transplanted organ. Posttransplantation infection is a major complication associated with high morbidity and mortality rates.^{1,2}

Rhinosinusitis (RS), whether acute (ARS) or chronic (CRS), is a frequent infection.³ Immunocompromised patients may be at increased risk for sinusitis complications and invasive fungal infections. Of note, an occult course of RS is not uncommon in immunosuppressed patients, and RS should be sought in any such patient with fever.⁴

Surprisingly, there is limited data in the literature regarding RS in solid organ transplant recipients. There are no clear guidelines for the management of RS in immunosuppressed patients and specifically in the solid organ transplant recipient patient group. Furthermore, data regarding the characteristics, disease

¹Department of Otolaryngology, Head and Neck Surgery, Rabin Medical Center, Petah Tikva, Israel

²Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Corresponding Author:

Ethan Soudry, Department of Otolaryngology, Head and Neck Surgery, Rabin Medical Center, 39 Jabotinsky Street, Petah Tikva, Israel.

Email: ethanso@clalit.org.il

course, and outcomes of RS in this patient group are scarce. In this study, we therefore aimed to analyze the characteristics, disease course, and outcomes of RS in solid organ transplant recipients.

Materials and Methods

The medical records of all adult patients (age > 18 years) who underwent solid organ transplantation and were treated in our hospital (as inpatients or outpatients) during the years 2001 to 2016 were identified. Of note, patients who underwent transplantation prior to the study period but were treated in our hospital during the study period were included as well. All such patients with a diagnosis of RS were retrieved. Noteworthy, the majority of organ transplants in our country are performed in our hospital, and the vast majority of patients are regularly being followed up in our institution as well. Excluded from our analysis were patients who underwent bone-marrow transplantation, cornea transplant, or heart valve transplantation; patients with cystic fibrosis; patients not receiving immunosuppressive therapy; and patients with incomplete medical record data.

For each patient included in our study, data were collected retrospectively from the first follow-up or surgery date. Data included patient demographics, comorbidities, type of transplant, immunosuppressive treatment, preoperative Lund–Mackay CT score (LMS), clinical presentation, disease complications, microbial cultures, surgical procedures, and operative and postoperative complications.

ARS was defined when symptoms of nasal congestion, facial pain/pressure, anterior or posterior nasal drainage, and reduced or absent sense of smell lasted up to 4 weeks or when there was evidence on imaging for sinus disease associated with acute onset symptoms of fever.

CRS was diagnosed when symptoms lasted longer than 12 weeks and were associated with objective findings on nasal endoscopy or imaging.^{5,6}

Disease severity was determined by one of the following: Lund–Mackay score (LMS) above 16, need for surgical (endoscopic sinus surgery [ESS]) intervention, or evidence for multiple surgical interventions.

Statistical analysis was performed with SPSS software, version 21.0 (IBM Corp., Armonk, NY). Categorical variables were described using frequency and percentage. Normally distributed variables were described using mean and standard deviation (SD), whereas abnormally distributed variables were described using median and range. Association between categorical variables was calculated using χ^2 test. Association between normally distributed variables was compared with the *t* test, and association between nonparametric variables was performed using Mann–Whitney test,

as appropriate. A value of $P < .05$ was considered significant.

Ethical Considerations

This study has been approved by the institutional review board (protocol number 0413-17-RMC).

Results

A total of 4602 solid organ recipients (heart, lungs, kidney, or liver) were identified. Of them, 40 patients were excluded from our study: 31 patients with missing data and 9 patients with a diagnosis of cystic fibrosis. Thus, a total of 4562 solid organ recipients were included in our study. The majority (71%) were kidney transplant recipients. Table 1 depicts patients' distribution according to the solid organ transplanted.

Sixty-one solid organ recipients (1.3%) were diagnosed with RS in our institution during the years 2001 to 2016: 27 (44.3%) with ARS and 34 (55.7%) with CRS. Thirty-five patients (57.3%) were male and 26 (42.7%) were female. Mean age at transplantation was 41.9 years ($SD \pm 16.2$). Mean age of diagnosis of sinusitis was 46.7 ($SD \pm 15.2$) years. Median follow-up was 10 years (range 1–36 years).

Thirty-three patients had at least 1 additional comorbidity such as hypertension, diabetes, dyslipidemia, ischemic heart disease, chronic renal failure, or chronic obstructive pulmonary disease. Twelve patients (19.6%) had more than 2 comorbidities. Twenty-eight patients (45.9%) were without additional comorbidities.

Sixty patients (98.3%) received 2 or more immunosuppressive agents. Fifty-eight (95%) patients received chronic low-dose prednisone treatment, 44 (72.8%) received tacrolimus, and 33 patients received mycophenolic acid. Other immunosuppressive agents recorded less frequently were azathioprine, cyclosporine, and everolimus.

Pretransplant RS

Six patients were diagnosed with RS prior to organ transplantation: 2 with ARS and 4 with CRS. Three of the CRS patients underwent ESS prior to

Table 1. Distribution of Solid Organ Recipients by Transplanted Organ and Rhinosinusitis Presentation.

Organ	Number	ARS	CRS
Kidney	3262 (71%)	16	18
Liver	574 (12.5%)	5	2
Lung	468 (10.5%)	5	12
Heart	258 (6%)	1	2
Total	4562	27	34

Abbreviations: ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis.

transplantation. None had disease recurrence documented in the posttransplantation period.

Posttransplant ARS

Of the 55 patients who were diagnosed in the posttransplantation period, 25 (45.4%) were patients hospitalized for inpatient treatment of an ARS infection. Twenty (80%) presented with the typical symptoms of ARS and were hospitalized. The other patients presented with nonspecific complaints of fever (3 patients) or gastrointestinal manifestations such as vomiting and diarrhea (2 patients). In the latter patients, diagnosis of RS was confirmed by computed tomography (CT) scan performed as a part of the diagnostic work-up. In total, 11 patients with ARS (40%) underwent CT with a median LMS of 12 (range 2–20). Microbial cultures were taken in 7 patients. In 4 patients, cultures grew *Haemophilus influenza*, and in 1 patient, *Staphylococcus aureus*. In 2 patients, *Mucor* species was isolated.

The majority of ARS patients (92%) were managed conservatively with intravenous antibiotics. Surgery was indicated in only 3 patients: 2 patients with invasive fungal infection (mucormycosis) and 1 patient who failed conservative treatment. In none of these patients, disease or surgical complications were noted. Moreover, both patients who were diagnosed with mucormycosis were alive at the time of the current study. Disease recurrence was not observed in any of these patients.

Posttransplant CRS

Thirty patients (54.5%) were referred to our Otolaryngology department and clinics for the management of CRS. CRS was relatively more common in lung transplant patients. None of the patients had a documented history of symptomatic RS prior to transplantation. All patients presented with the typical symptoms of CRS lasting longer than 12 weeks. Nasal endoscopy confirmed the diagnosis in all patients. Twelve patients (45.9%) had polyposis. Twenty-seven patients (90%) underwent a CT scan with a median LMS of 12 (range 2–24). In 20 (66.6%) patients, microbial cultures were taken. Table 2 depicts culture results. *Pseudomonas* was the most common pathogen isolated and was documented in 8 patients (40%). In 1 patient, a fungal ball was isolated (*Aspergillus*).

Sinusitis complications were observed in none of these patients. Twenty-two patients (73.3%) underwent ESS for medically refractory disease: 18 patients underwent a single procedure and 4 patients underwent multiple procedures (median 2, range 2–3) for disease recurrence. No surgical complications were noted in this patient group.

Table 2. Cultured Isolates in Chronic Rhinosinusitis Patients.

Pathogen	Culture Distribution
<i>Pseudomonas aeruginosa</i>	8 (46%)
<i>Streptococcus pneumonia</i>	4 (15%)
<i>Staphylococcus aureus</i>	1 (4%)
<i>Proteus mirabilis</i>	1 (4%)
Coagulase-negative staphylococci	1 (4%)
<i>Escherichia coli</i>	1 (4%)
<i>Enterobacter</i>	1 (4%)
<i>Branhamella catarrhalis</i>	1 (4%)
<i>Citrobacter</i>	1 (4%)
<i>Aspergillus</i>	1 (4%)

Table 3. Surgical Interventions (Endoscopic Sinus Surgery) According to Transplanted Organ.

Organ	Operated Patients	Multiple Operations
Lung	12/16	3/16
Heart	2/3	0/3
Liver	10/31	1/31
Kidney	2/8	0/8
P	.005	.021

Statistical analysis was performed to reveal whether age, gender, type of immunosuppressive medication, number of immunosuppressive medications, type of transplanted organ, or comorbidities were risk factors for disease severity or invasive fungal infection. No significant correlation was identified.

Overall, surgical (ESS) interventions were more commonly performed in lung transplant recipients, and a higher number of ESS interventions (more than 2) were noted in this group as well (12/16 vs 14/44, $P = .019$ and 3/16 vs 1/44, $P = .021$, respectively). Table 3 depicts the incidence of surgical interventions according to the type of organ transplanted. Overall, surgical interventions were more frequent in CRS patients compared to ARS patients (22/30 vs 3/25, $P < .001$). Invasive fungal infections were noted only in ARS patients.

Discussion

In this present study, we found a low incidence (1.3%) of RS in a cohort of 4562 solid organ transplant recipients cared at a tertiary referral center during a 15-year period.

According to a recent analysis of U.S. National Health Interview Survey data,⁷ the prevalence of RS was 12% among adults. Berlinger⁸ evaluated

27 immunodeficient and immunosuppressed patients with RS; among them, only 2 patients were solid organ (kidney) transplant recipients. The authors of that study suggested that RS is less common in the organ transplant recipients as less severe immunosuppression is caused when compared to patients with primary immunodeficiency or hematologic diseases. In contrast, the incidence of RS in bone marrow transplant patients has been reported to be up to 44%.^{5,6,9,10}

Dhong et al.¹¹ analyzed 278 transplant recipient patients; 12% (n = 34) were bone marrow transplant recipients and the remainder were liver, kidney, and heart transplant recipients. No lung transplant recipients were included. In that study, an RS incidence of 11.5% was found, similar to the general population, with a slightly higher incidence of RS (14.7%) in the bone marrow transplant recipients; 6.8% had RS in the pretransplantation period and 4.7% had RS in the posttransplantation period. Whether patients were diagnosed with ARS or CRS is not clear. A high surgical intervention (ESS) rate was noted in that study—47.3% in the pretransplantation patients and 76.9% in the posttransplantation patients.

In a recently published, large cohort study on RS in kidney transplant recipients, Ryu et al.¹² analyzed 1589 kidney transplant adult patients. A low RS incidence was also noted in the pretransplantation and posttransplantation period (4.2% and 0.9%, respectively). In their study, the majority of patients underwent functional ESS, both in the pretransplantation period and in the posttransplantation period (61.5% and 74%, respectively), the majority of whom had CRS.

Acute RS

Interestingly, in this study, only a minority (less than 1%) of solid organ transplant recipients presented with an ARS infection that required hospitalization and inpatient treatment. None had evidence of disease complications, and in the vast majority of patients conservative treatment alone was successful. When surgery was indicated, no surgical complications were noted and patients recovered uneventfully.

Analysis of the microbial culture results in patients diagnosed with ARS revealed predominantly bacterial isolates. Most common being *H. influenza*.

Interestingly, invasive fungi were isolated in only 2 patients (2%) with an acute infection. This rate is lower than the 10% incidence reported by Dhong et al. who included bone marrow transplant recipients in their analysis.¹¹ In contrast to solid organ transplant recipients, bone marrow transplant recipients have a considerably higher rate of invasive fungal infections (up to 68%).^{13,14} These patients are much more susceptible to fungal infections, as they are commonly severely

neutropenic for prolonged periods of time.^{15,16} In neutropenic patients, defects in phagocytic cell activity enable invasive fungal infection.¹⁷ In a study by Stuehler et al.¹⁸ that examined the association between invasive aspergillosis and hematopoietic stem cell transplantation, defects in polymorphonuclear cells (PMN) function and reduced restoration of natural killer (NK)-cell counts were suggested to account for increased susceptibility to these invasive infections.

In contrast to hematologic patients, the mechanism of immune suppression in solid organ recipients is dependent on the immunosuppressive therapy that these patients are receiving. Most patients are maintained on prednisone, tacrolimus, and mycophenolic acid with a high percentage (94%) of combined therapy. Glucocorticoids have a dose-dependent effect on all immune cells by blocking promotor sites of pro-inflammatory genes, stimulating production of anti-inflammatory genes and inhibition of the synthesis of inflammatory cytokines. Glucocorticoids specifically affect T-cells and myeloid cell function^{19–21} and are associated with an increased risk of bacterial, viral, and fungal infection in a dose-dependent fashion. Tacrolimus is a macrolide antibiotic with potent immunosuppressive activity that inhibits the T-cell receptor-mediated signal transduction required for transcription of interleukin 2 and other lymphokines²² and mycophenolate mofetil has an effect on both B and T lymphocytes.²³ In a recent meta-analysis by Singh et al.²⁴ that examined the risk of serious infections with immunosuppressive drugs and glucocorticoids, a low risk for infection in patients receiving tacrolimus and mycophenolate mofetil was observed, compared to patients receiving glucocorticoids, demonstrating the highest risk for infection.

In our study cohort, patients exhibited a low infection rate, likely as the majority of patients received only low-dose prednisone treatment with combination of tacrolimus and mycophenolate mofetil.

Chronic RS

The incidence of CRS observed in this patient group was also very low (<1%). We speculate that this low incidence may be associated with the chronic immunosuppressive treatment, particularly low-dose prednisone, these patients are maintained on, suppressing the inflammatory responses commonly leading to CRS. On their study on kidney transplant adult patients, Ryu et al.¹² presented a low incidence (0.6%) of CRS in this patient group as well. Nonetheless, this remains to be studied more thoroughly.

Interestingly, none of these patients suffered from sinusitis complications. The majority (73.3%) of the CRS patients in our cohort underwent ESS without

surgical complications, which is line with data from previous studies.^{11,12,25} In light of the excellent outcomes observed in these patients, a surgically oriented approach may be advocated earlier in the management course of these patients. This is further supported by a recent study²⁶ that compared survival rates among lung transplant recipient patients with CRS who underwent ESS with those who were managed conservatively. In that study, ESS correlated with increased survival rates.

Study Limitations

Several limitations to our study should be mentioned. Primarily, this is a retrospective study with the inherited limitations. Second, although all patients with heart, lung, and liver transplantation, and the vast majority patients with kidney transplant are being regularly followed up and treated in our institution either as inpatients or outpatients and are instructed to report immediately to our hospital in any event of infection or change in their health status or as soon as possible, there may have been a minority patients who might had been treated in the community or other institutions and may have been excluded from the analysis. Nonetheless, any patient in need of hospital admission or surgery would most likely be captured in this analysis.

Conclusions

In conclusion, chronic immunosuppression did not put these patients at a high risk for sinusitis complications or invasive fungal infection as opposed to data on bone marrow transplant recipients. No complications were associated with surgical interventions (ESS) in these patients. Moreover, a low incidence of CRS in solid organ transplant recipients was noted which may be associated with the combination of immunosuppressive drugs, mostly low-dose prednisone. A more surgically oriented approach in CRS patients may be favored early in the management course of medically refractory patients in light of patients excellent outcomes. Further studies are warranted in this unique patient group.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Sharon Tzelnick  <http://orcid.org/0000-0001-7973-3212>

References

- Gupta RK. Opportunistic infections in renal allograft recipients. *Transplant Proc.* 2007;39(3):731–733.
- Chiu LM, Domagala BM, Park JM. Management of opportunistic infections in solid-organ transplantation. *Prog Transplant.* 2004;14(2):114–129.
- Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl.* 2012;3:1–298.
- Drozd-Sokolowska JE, Sokolowski J, Wiktor-Jedrzejczak W, Niemczyk K. Sinusitis in patients undergoing allogeneic bone marrow transplantation—a review. *Braz J Otorhinolaryngol.* 2017;83(1):105–111.
- Shibuya TY, Momin F, Abella E, et al. Sinus disease in the bone marrow transplant population: incidence, risk factors, and complications. *Otolaryngol Head Neck Surg.* 1995;113(6):705–711.
- Won YW, Yi SY, Jang JH, et al. Retrospective analysis of paranasal sinusitis in patients receiving hematopoietic stem cell transplantation. *Int J Hematol.* 2011;93(3):383–388.
- Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: National Health Interview Survey, 2012. *Vital Health Stat 10.* 2014;260:1–161.
- Berlinger NT. Sinusitis in immunodeficient and immunosuppressed patients. *Laryngoscope.* 1985;95(1):29–33.
- Bento LR, Ortiz E, Nicola EM, Vigorito AC, Sakano E. Sinonasal disorders in hematopoietic stem cell transplantation. *Braz J Otorhinolaryngol.* 2014;80(4):285–289.
- Sekine L, Manica D, Piltcher OB, Lopes CJ, Segatto MM, Paz AA. Rhinosinusitis in autologous and allogeneic bone marrow transplantation: a retrospective study on the performance of imaging studies on severity and prognostic evaluation. *Rev Bras Hematol Hemoter.* 2010;32:29–33.
- Dhong HJ, Lee JC, Ryu JS, Cho DY. Rhinosinusitis in transplant patients. *Clin Otolaryngol Allied Sci.* 2001;26(4):329–333.
- Ryu G, Seo MY, Lee KE, et al. Clinical course of rhinosinusitis and efficacy of sinonasal evaluation in kidney transplant recipients: review of 1589 patients. *Eur Arch Otorhinolaryngol.* 2018;275(5):1183–1188.
- Ortiz E, Ng RT, Alliegro FC, Teixeira C, Muranaka EB, Sakano E. Microbiology of rhinosinusitis in immunosuppressed patients from the University Hospital. *Braz J Otorhinolaryngol.* 2011;77(4):522–525.
- Imamura R, Voegels R, Sperandio F, et al. Microbiology of sinusitis in patients undergoing bone marrow transplantation. *Otolaryngol Head Neck Surg.* 1999;120(2):279–282.
- Morrison VA, McGlave PB. Mucormycosis in the BMT population. *Bone Marrow Transplant.* 1993;11(5):383–388.
- Marr KA. Fungal infections in hematopoietic stem cell transplant recipients. *Med Mycol.* 2008;46(4):293–302.
- Chinn RY, Diamond RD. Generation of chemotactic factors by *Rhizopus oryzae* in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis. *Infect Immun.* 1982;38:1123–1129.
- Stuehler C, Kuenzli E, Jaeger VK, et al. Immune reconstitution after allogeneic hematopoietic stem cell

- transplantation and association with occurrence and outcome of invasive aspergillosis. *J Infect Dis.* 2015;212(6):959–967.
19. McEwen BS, Biron CA, Brunson KW, et al. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. *Brain Res Brain Res Rev.* 1997;23(1–2):79–133.
 20. Herold MJ, McPherson KG, Reichardt HM. Glucocorticoids in T cell apoptosis and function. *Cell Mol Life Sci.* 2006;63:60–72.
 21. Kleiman A, Tuckermann JP. Glucocorticoid receptor action in beneficial and side effects of steroid therapy: lessons from conditional knockout mice. *Mol Cell Endocrinol.* 2007;275:98–108.
 22. Joseph A, Raj D, Shanmuganathan V, Powell RJ, Dua HS. Tacrolimus immunosuppression in high-risk corneal grafts. *Br J Ophthalmol.* 2007;91(1):51–55.
 23. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology.* 2000;47(2–3):85–118.
 24. Singh JA, Hossain A, Kotb A, Wells G. Risk of serious infections with immunosuppressive drugs and glucocorticoids for lupus nephritis: a systematic review and network meta-analysis. *BMC Med.* 2016;14(1):137.
 25. Dao AM, Rerreddy SK, Wise SK, DelGaudio JM, Patel ZM. Management of non-invasive rhinosinusitis in the immunosuppressed patient population. *Laryngoscope.* 2015;125(8):1767–1771.
 26. Kariya S, Okano M, Oto T, Higaki T, Haruna T, Noda Y, Nishizaki K. The impact of chronic rhinosinusitis on long-term survival in lung transplantation recipients. *Acta Otolaryngol.* 2017;137(5):529–533.