Impact of Paranasal Sinus Surgery in Granulomatosis With Polyangiitis: A Longitudinal Computed Tomography Study

Sigrun S. Holme, MD; Jon M. Moen, MD; Karin Kilian, MD; Heidi B. Eggesbø, PhD; Øyvind Molberg, PhD

Objectives/Hypothesis: Severe chronic rhinosinusitis (CRS) in patients with granulomatosis with polyangiitis (GPA) failing medical therapies can be treated with paranasal sinus surgery. Whether this surgery protects from progressive sinonasal damage remains unknown. Here, we aimed to analyze time-dependent relations between sinus surgeries and computed tomography (CT) imaging features in the CRS of GPA.

Study Design: Longitudinal observational study.

Methods: We assessed CRS features including bone thickening by global osteitis scoring scale, bone erosions, and mucosal thickening by Lund-Mackay scores in serial paranasal sinus CT scans (742 CT scans in total) from a cohort of 127 well-characterized GPA patients. Data on sinonasal surgical procedures were from a mandatory national registry and from chart review. We defined the time from baseline CT to last CT as the study observation period in each patient. Datasets were analyzed by linear mixed models.

Results: We found that 23/127 cohort patients had one or more paranasal sinus surgical procedures, and 96% of these (22/23) had osteitis by CT after surgery. In patients with nasal surgery alone or no surgery, we identified osteitis in 7/11 (64%) and 45/93 (48%), respectively. During the observation period of a median of 5 years, 38 patients had progression of their sinus osteitis, with the highest annual osteitis progression rates observed around the time of surgery.

Conclusions: In this cohort, paranasal sinus surgery was associated with prevalence, severity, and progression rate of sinus osteitis, indicating that sinus surgery does not reduce the bone damage development in the CRS of GPA.

Key Words: Granulomatosis with polyangiitis, longitudinal study, computed tomography, paranasal sinuses, osteogenesis.

Level of Evidence: 4

Laryngoscope, 130:E460–E468, 2020

INTRODUCTION
Granulomatosis with polyangiitis (GPA), previously known as Wegener’s granulomatosis, is one of the three small vessel vasculitides syndromes associated with antineutrophil cytoplasmic antibodies (ANCAs). The hallmark feature of GPA is progressive and destructive end organ inflammation that primarily targets the upper and lower airways and the kidneys. Reported prevalence of GPA ranges from 140 to 250 per million adults in Northern Europe, with the mean age at disease onset at around 50 years and male: female ratio of 1.3:1.1–3 Diagnostic criteria for GPA does not exist, but classification for clinical trial purposes is usually by an algorithm developed for the European Medicines Agency.4,5 This algorithm combines serology (ANCAs), histopathology, and major clinical features, including upper airway disease, which is highly prevalent in GPA.4 In a study reporting on 138 GPA patients from European Vasculitis Study Groups trials, nearly 90% had involvement of the upper airways, with more than one-third having chronic rhinosinusitis (CRS).6

Recently, D’Anza and coworkers systematically reviewed the work published on paranasal sinus computed tomography (CT) in GPA.7 They identified seven cross-sectional studies that described sinonasal CT findings in GPA similar to those identified in CRS of other etiologies, including mucosal thickening, bone erosions, and bone thickening, referred to as osteitis. One of the studies reviewed reported obliterating osteitis in 18% of GPA patients.8 As there is no CT scoring system specific for GPA-related CRS, previous GPA studies8,9 assessed CT findings by generic CRS scores. The scores applied were the Lund-Mackay (LM) score for mucosal thickening,10 thought to reflect sinus inflammation, and the Global

DOI: 10.1002/lary.28639

Laryngoscope 130: August 2020

E460

Holme et al.: Sinus Surgery in a GPA Longitudinal CT Study
Osteitis Scoring Scale (GOSS) for osteitis, reflecting inflammation-related damage. Recently, we reported the first longitudinal CT study on CRS development in GPA. We found that extent and progression tendency of CRS features differed between patients, and we identified patient subsets with distinct sinus osteitis trajectories. One subset had stable osteitis over time, whereas the other displayed progressive osteitis.9

CRS in GPA is primarily treated with immunosuppressive drugs, and the goal of the treatment is symptom control and prevention of damage to sinonasal structures.12 Paranasal sinus surgery is approved as a second-line treatment if medical therapies fail, and this surgery appears to reduce CRS symptoms.13 However, little is known about the potential effects of surgery on sinonasal damage development.

Sinus osteitis is a radiological marker of CRS, but whether the presence or severity of osteitis is associated with clinical CRS symptoms is unclear.11,14–16 Cross-sectional work on CRS outside GPA showed correlations between sinonasal surgery and osteitis,17 and others found that the number of surgical procedures performed, correlated with osteitis severity.11,16 Knowledge on sinus surgery in GPA is limited, but a Cleveland study reported high prevalence of persistent or recurrent CRS symptoms after surgery.13 A cross-sectional study from the same center found higher frequency of sinus osteitis in GPA patients having undergone sinus surgery, and asked for longitudinal studies to clarify the effects of surgery on osteitis.8

Herein, the study hypothesis was that paranasal sinus surgery would aggravate sinus osteitis. To approach this hypothesis, we analyzed associations between sinus osteitis and surgery in a longitudinal CT study including patients from a well-characterized and largely unselected GPA cohort.

MATERIALS AND METHODS

Study Cohort and Surgery Groups

The Regional Committee for Medical and Health Research Ethics in South East Norway approved this study.

Patients included in the study cohort were from the Norwegian Systemic Connective Tissue Disease and Vasculitis Registry, a consent-based rheumatology research registry at Oslo University Hospital that includes >200 adult ANCA vasculitis patients classified as GPA by the updated European Medicines Agency algorithm.4,5 We recently published data on 121 GPA patients from this registry in a study on methods for longitudinal sinus osteitis assessment.9 Herein, we included the 127 GPA patients in the registry with two or more paranasal sinus CT scans performed ≥12 months apart during the period 2002 to 2016. As the majority of the patients had performed three or more CT scans, there were 742 paranasal CT scans available for analyses. We defined the time period from the baseline CT to the last CT as the observation period for each patient.

We retrieved individual-level data on sinonasal surgical procedures from electronic chart review and from the Norwegian Patient Registry, a mandatory national registry that since 2008 contains patients identifiable data expressed as International Classification of Diseases, Tenth Revision and procedure codes.

We defined two types of surgical procedures: 1) sinus surgery and 2) nasal surgery, including nose reconstructions, septoplasties, and surgery involving the nasal conchae. We grouped the patients according to type of surgery, and defined patients who had performed both sinus surgery and nasal surgeries as patients belonging to the sinus surgery group.

![Fig. 1. The granulomatosis with polyangiitis cohort. The patients were divided depending on history of sinonasal surgery. Thirty-three of the patients from the group without any surgery and the group with sinus surgery had osteitis that progressed during observation. The 16 sinus surgery patients were further subdivided into two groups according to when the sinus surgery was performed in relation to the baseline computed tomography.](image-url)
TABLE I.
Demographics, Clinical Data, and CT Findings of the Granulomatosis With Polyangiitis Cohort.

| Demographics and clinical data | Total, n = 127 | No Surgery, n = 93 | Sinus Surgery, n = 23 | Nasal Surgery, n = 11 |
|-------------------------------|---------------|------------------|---------------------|---------------------|
| Females, n (%)                | 60 (47)       | 47 (51)          | 8 (35)              | 5 (45)              |
| Mean age at diagnosis, yr (SD)| 45 (19)       | 48 (18)          | 37 (19)             | 40 (24)             |
| ANCA directed against proteinase 3, n (%) | 108 (85) | 80 (86) | 19 (83) | 9 (82) |
| ANCA directed against myeloperoxidase, n (%) | 12 (9) | 11 (12) | 1 (4) | 0 (0) |
| ANCA negative, n (%)          | 2 (2)         | 0 (0)            | 2 (9)               | 0 (0)               |
| Saddle nose by CT scout view, n (%) | 19 (15) | 8 (9) | 7 (30) | 4 (36) |
| Median time from diagnosis to baseline CT, yr (range) | 0 (−4.0 to 25.0) | 0 (−4.0 to 25.0) | 1.0 (−1.0 to 21.0) | 0 (−1.0 to 11.0) |
| Median observation period, yr (range) | 5.1 (1.0 to 14.7) | 4.7 (1.0 to 13.7) | 7.3 (1.9 to 14.7) | 7.6 (1.7 to 13.7) |
| Median time from diagnosis to first surgery, yr (range) | 2.0 (−6.0 to 26.0) | NA | 2.0 (−6.0 to 26.0) | 2.0 (−2.0 to 11.0) |
| Number of patients with surgery before the baseline CT, n (%) | 17 (13) | NA | 12 (52) | 5 (45) |
| Median number of surgical procedures per patient (range) | 0 (0 to 5) | NA | 2 (1 to 5) | 1 (1 to 3) |
| Median time between last surgery and last CT, yr (range) | 5.4 (0.4 to 11.9) | NA | 6.7 (0.4 to 11.9) | 4.5 (0.7 to 9.3) |

Baseline CT
- Patients with osteitis (GOSS > 0), n (%) | 55 (43) | 35 (38) | 17 (74) | 3 (27) |
- Median number of sinuses with osteitis (range) | 0 (0 to 10) | 0 (0–9) | 2 (0 to 10) | 0 (0 to 10) |
- Patients with bone destruction, n (%) | 32 (25) | 13 (14) | 14 (61) | 5 (45) |
- Patients with sinon opacifications (LM score > 0), n (%) | 106 (83) | 73 (78) | 23 (100) | 10 (91) |

Last CT
- Patients with osteitis (GOSS > 0), n (%) | 74 (58) | 45 (48) | 22 (96) | 7 (64) |
- Median number of sinuses with osteitis (range) | 1 (0 to 10) | 0 (0 to 9) | 6 (0 to 10) | 1 (0 to 10) |
- Patients with bone destruction, n (%) | 54 (43) | 26 (28) | 21 (91) | 7 (64) |
- Patients with sinon opacifications (LM score > 0), n (%) | 103 (81) | 70 (75) | 23 (100) | 10 (91) |

ANCA = antineutrophil cytoplasmic antibodies; CT = computed tomography; GOSS = Global Osteitis Scoring Scale; LM = Lund-Mackay; NA = not applicable; SD = standard deviation.

Fig. 2. (A) The level of osteitis of the baseline and last computed tomography (CT) measured by the Global Osteitis Scoring Scale (GOSS) in the three surgery groups of the granulomatosis with polyangiitis cohort. (B) The frequency of each subscore of GOSS (no osteitis = 0 and scores 1–5) for each sinus in the baseline and the last CT.
By electronic chart review, we collected the number of patients having sinonasal symptoms such as pain, congestion, crusts, and epistaxis at the time of the baseline CT and the last CT. Additionally, we recorded symptoms before and after the surgery in patients who had undergone sinus surgery during the observation period, and we registered information about indications for surgery.

Assessment of Paranasal CT Scans and Stratification by Surgery

We reviewed the CT scans for presence and extent of osteitis by two independent methods: 1) the GOSS, where osteitis is graded 0 to 5 in 10 sinuses (range = 0–50),11 and a sinus gets a GOSS subscore of 5 when the wall thickness is $\geq 5$ mm and $\geq 50\%$ of the sinus walls is involved and 2) diameter ratio measure, a recently described diameter-based surrogate measure that estimates volume of the maxillary and sphenoid sinuses. Sinus opacifications were assessed by LM score (range = 0–24).10 Bone destruction was identified as absent or present in 18 defined sinonasal structures (range = 0–18).9 We compared CRS scores across the surgery groups.

Grouping of Patients With Progressive Osteitis by Sinus Surgery Status

For the analyses of association between sinus osteitis and sinus surgery, we focused on the GPA patients with progressive osteitis. Progressive osteitis was defined as decreasing diameter ratio measure, a surrogate for decreasing sinus volume, and an increase of GOSS $>1$ from baseline CT to last CT. The GPA patients with progressive osteitis were divided into three subsets defined by sinus surgery history. The three subsets were: 1) patients with no sinus surgery, 2) patients with sinus surgery performed before the start of the study observation period, and 3) patients with sinus surgery performed during the study observation period. The flowchart in Figure 1 shows the patient groups of the study.

Statistical Analysis

We have used the open source software R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria) and the commercially available software Stata (version 15.1; StataCorp, College Station, TX). Variables were given as median (range = minimum–maximum), mean (standard deviation), or proportions. Average group differences were given with 95% confidence interval (CI) calculated by $t$ distributions.

We modeled development of osteitis over time by linear mixed models with patients as random intercept, time as random slope, and GOSS as outcome variable in the group of patients with progressive osteitis. The linear mixed models included fixed effects for age at diagnosis, sex, surgery groups, and time, which was modeled by piecewise linear spline with a knot at a time point zero ($T_0$). $T_0$ was defined as the date of the first postoperative CT for the group of patients with surgery during the observation period, and as the date of the baseline CT for the group with surgery performed before the observation period and the group without surgery. Variables with $P$ values $<.05$ were included in the final model, and estimates were given with 95% CI. For independent testing of break point in osteitis development, we used results from linear mixed models with diameter ratio measurements as outcome variable.

We performed an inter- and intraobserver study where two independent readers with >10 years experience scored osteitis by GOSS on 112 CT scans from 20 randomly selected GPA cohort patients. We estimated intraclass correlation coefficient by a three-level linear mixed model with readers and patients as random effects. The reader who did the intraobserver study performed the rest of the CT scoring.

RESULTS

Demographics, Presence of CRS Features, and Surgical Procedures

We assessed a median of five (range = 2–17) serial paranasal sinus CT scans per patient in the GPA study cohort, and the average time gap between each CT in a patient was 1 year. The patients were mean 45 (standard deviation = 19) years old at time of GPA diagnosis, 53%...
were men, and 85% had ANCACs directed against proteinase 3 (Table I).

The CT analyses showed that CRS features were highly prevalent in the GPA cohort. At the baseline CT, we identified sinus opacifications (LM score > 0) in 83% of the patients, sinus osteitis (GOSS > 0) in 43%, and bone destructions in 25%. At last CT, frequencies of patients with osteitis and bone destructions had increased to 58% and 43%, respectively, indicating progression of CRS-related damage during the observation period (Table I). For the rest of this study, we used osteitis as surrogate marker for progressive CRS-related damage, because we regarded it as a more robust marker than bone destructions, which may be directly caused by surgery and opacifications, which appear to fluctuate over time.

The 34/127 GPA patients who had ≥1 sinonasal surgical procedures performed, had been through 58 procedures from 1998 to 2016, with two-thirds performed at Oslo University Hospital. Twenty-three of the 34 patients had sinonasal surgery performed (with combined antrostomies and ethmoidectomies in 19/23), whereas 11 had surgery confined to the nose (Table I). In 29% of the patients (10/34), the first surgery was performed within the first year after GPA diagnosis, and in 50% the first surgery antedated the baseline CT.

We were able to retrieve data on indications for surgery from the original surgery report or associated medical records for 60% of the sinus surgery patients (14/23). The indications for the sinus surgeries were pain or congestion in three-fourths of these patients.

Information derived from chart review indicated that sinus surgery reduced local pain by near 90%, whereas congestion symptoms were less reduced (Supporting Information, Supporting Table I, in the online version of this article).

**Presence, Extent, and Progression of Sinus Osteitis in the Different Surgery Groups**

By the end of the study observation period, we found that 96% of the patients with a history of sinus surgeries had developed sinus osteitis (defined by GOSS > 0) compared to 64% of patients with surgeries confined to the nose, and 48% of patients with no history of sinonasal surgery (Fig. 2 and Table I). Detailed analyses of individual sinuses showed that 96% of the patients in the sinus surgery group had osteitis in the maxillary sinuses, whereas osteitis in the sphenoid, ethmoidal, and frontal sinuses were identified in 70% (16/23), 65% (15/23), and 41% (9/23), respectively (Fig. 2).

We observed an increase in osteitis (by GOSS) from baseline CT to end of observation in the entire GPA cohort, but group comparisons showed that GOSS increased most in the sinus surgery group, with an increase of a median of 9 points. The increasing GOSS in the sinus surgery group had two causes: 1) progression of osteitis in sinuses already afflicted at baseline, and 2) de novo development

### TABLE II.

**Demographics, Model Estimates, and CT Findings in the Granulomatosis With Polyangiitis Cohort Patients With Progressive Osteitis.**

| Demographics and clinical data | No Surgery, n = 17 | Sinus Surgery Before Observation Period, n = 8 | Sinus Surgery During Observation Period, n = 8 |
|--------------------------------|--------------------|-----------------------------------------------|-----------------------------------------------|
| Females, n (%)                 | 7 (41)             | 2 (25)                                        | 4 (50)                                        |
| Mean age at diagnosis, yr (SD) | 53.6 (16.5)        | 34.4 (15.3)                                   | 33.2 (17.6)                                   |
| Median time from diagnosis to baseline CT, yr (range) | 0 (−2.0 to 7.0) | 10.5 (0 to 20.0)                              | 0 (−1.0 to 3.0)                               |
| Median observation period, yr (range) | 4.7 (1.2 to 8.1) | 8.1 (3.6 to 14.7)                            | 6.8 (4.7 to 11.2)                             |
| Median time from diagnosis to first surgery, yr (range) | NA | 9.5 (−6.0 to 16.0)                           | 2.5 (0 to 6.0)                                |
| CT data compared to model estimates |                    |                                              |                                               |
| Mean GOSS at baseline (range) | 3 (0 to 14)        | 17 (4 to 38)                                  | 6 (0 to 33)                                   |
| Mean GOSS preoperatively (range) | NA                | NA                                            | 11 (0 to 47)                                  |
| Mean GOSS at T₀ (range)        | 3 (0 to 14)        | 17 (4 to 38)                                  | 19 (4 to 49)                                  |
| Model estimate: mean GOSS at T₀ (95% CI) | 4.2 (−0.4 to 8.8) | 18.1 (11.5 to 24.7)                           | 20.7 (14.1 to 27.3)                           |
| Mean time from baseline to T₀ (range) | 0                | 0                                             | 3.1 (0.8 to 7.3)                               |
| Change in GOSS divided by the interval between baseline and T₀, mean (range) | NA         | NA                                            | 6.4 (0.1 to 18.4)                              |
| Model estimate for change in GOSS in the interval between baseline and T₀, estimate (95% CI) | NA | NA                                            | 7.2 (5.8 to 8.5)                               |
| Mean time from T₀ to last CT (range) | 4.8 (1.2 to 8.1) | 9.6 (3.8 to 14.7)                            | 4.4 (1.7 to 9.0)                               |
| Change in GOSS divided by the interval between T₀ and last CT, mean (range) | 2.3 (0.3 to 10.1) | 1.7 (0.4 to 4.4)                             | 1.3 (0.0 to 3.9)                               |
| Model estimates for change in GOSS in the interval between T₀ and the last CT, estimate (95% CI) | 1.5 (0.7 to 2.2) | 1.5 (0.7 to 2.2)                             | 1.5 (0.7 to 2.2)                               |
| Mean GOSS at last CT (range)   | 12 (3 to 27)       | 29 (17 to 44)                                 | 24 (5 to 49)                                  |

The model is a linear mixed model with random intercept (patients) and slope (time), osteitis scored by the GOSS as outcome variable, and surgery groups and time with a breakpoint at T₀ as explanatory variables.

CI = confidence interval; CT = computed tomography; GOSS = Global Osteitis Scoring Scale; NA = not applicable; SD = standard deviation; T₀ = time point of first postoperative CT for the group with sinus surgery during observation, and the baseline CT for the other two groups.
of osteitis in sinuses not afflicted at baseline (Fig. 2 and Table I).

**Stratification of Patients With Progressive Osteitis by Sinus Surgery Status**

The subset with progressive sinus osteitis included 38 patients, five of whom had surgery confined to the nose, 16 had undergone sinus surgery, and 17 had no history of sinonasal surgeries (Fig. 1). We found that the osteitis progression differed between the surgery groups. The mean difference in GOSS increase between the 17 patients with no surgical history and the 16 patients with sinus surgeries was 7 (95% CI = 1–13).

In Figure 3, we show two examples of GPA patients with progressive osteitis. The upper panel depicts three serial CT scans with accompanying GOSS and diameter ratio measures from a patient with sinus surgery performed during the observation period, whereas the lower panel shows corresponding data from a patient with no history of sinus surgery.

**Associations Between Progressive Osteitis and Sinus Surgery**

Further analyses of the patient subset with progressive osteitis showed that the 16 patients having undergone sinus surgeries were on average 20 years younger (95% CI = 8–31) than the 17 patients with no history of sinus surgery and had a longer observation period, with a mean difference 3.8 years (95% CI = 1.6–6.0) (Table II). As detailed in the Materials and Methods, we subdivided the 16 sinus surgery patients with progressive osteitis in two groups, one in which surgery was performed before the start of the study observation period (n = 8) and one in which surgery was done during the observation period (n = 8, Fig. 1).

Interestingly, we found that the patient subsets with sinus surgery during observation and no surgery had equal median GOSS values of 1 point at the baseline CT (Fig. 4). At the preoperative CT, the mean GOSS in the subset with sinus surgery during observation had increased to 11 points (Table II, Fig. 4), and at the time of the first postoperative CT, the mean GOSS had increased further to 19 points. By the end of the observation period,
Fig. 5. The development of osteitis measured by the Global Osteitis Scoring Scale (GOSS) in three subgroups of patients with progressive osteitis. The black line is the mean predicted GOSS of patients having no history of surgery. The blue line is the mean predicted GOSS of patients who had sinus surgery before the study observation period. The red line is the mean predicted GOSS of patients who had sinus surgery during the observation period (i.e., between the baseline and last computed tomography [CT]). The individual data points, which are the actual data (not predicted values), are colored similarly to the lines. $T_0$ is the timepoint of the baseline CT for the no surgery and sinus surgery before observation period groups, and the time point of the first postoperative CT for the sinus surgery during observation group. The predicted GOSS values are calculated by a linear mixed model with patients as random intercept, time as random slope, and the surgery groups and time with a break point at $T_0$ as fixed effects.

The mean GOSS in this patient subset had increased to 24 points, and was now at the same level as in the subset with sinus surgery performed before the start of the observation period (Table II, Fig. 4).

We applied a linear mixed model to estimate differences in GOSS development between the three patient subsets with progressive osteitis. The final model included surgery groups and time as explanatory variables (Table III). As explained in the Materials and Methods, the time $T_0$ in the model denoted time of the first postoperative CT for the patient subset with surgery during observation, and time of baseline CT for the two other subsets. In the time interval leading up to the postoperative CT (i.e., $T_0$), the subset with surgery during observation had a very high GOSS annual progression rate (estimated at 7.2 with 95% CI [5.8–8.5] points by the model). This decreased to a rate of 1.5 (95% CI = 0.7–2.2) points per year in the time interval from the first postoperative CT to the last CT (Table II and Fig. 5). This progression rate was in the same range as the rates estimated in the two other patient subsets.

The models with diameter ratio measurement as outcome variable confirmed the high rate of osteitis progression before $T_0$ in patients with sinus surgery during observation (Table III).

**Intra- and Interobserver Variability**

The intraclass correlation coefficient for the inter- and intraobserver variability for the GOSS was 0.72 (95% CI = 0.56–0.83).

Laryngoscope 130: August 2020

Holme et al.: Sinus Surgery in a GPA Longitudinal CT Study
DISCUSSION

Main Findings

Cross-sectional studies in GPA and CRS have indicated associations between paraanasal sinus surgery and sinus osteitis, and surgery has been suspected to aggravate osteitis instead of preventing progression of CRS. In the current study, we observed the highest osteitis scores in patients with a history of sinus surgeries, supporting that surgery is associated with osteitis. We further corroborated this by longitudinal data showing the highest osteitis progression rates around the time of sinus surgery.

Chart review on the patients who had sinus surgery during study observation, indicated pain as the dominant preoperative symptom. After surgery, the patients reported pain relief, whereas the effects on congestion were more modest. One could speculate that the modest effects on congestion were due to poor sinus drainage, because the postoperative CT scans in these patients showed extensive sinus opacifications and increased osteitis.

Hence, it does not appear from this study that surgery inhibits progression of GPA-related CRS, even though it partly relieves symptoms. This finding has potential implications for indications of sinus surgery in patients with GPA, but the results need to be confirmed in larger prospective studies.

Results Compared to Literature

The proportion of sinus surgery patients with osteitis in our cohort (22/23, 96%), was in the same range as the 91% (40/44) reported by Grindler et al. However, their GPA cohort had more surgery patients (44/74, 59%) than ours (23/127, 18%), probably reflecting differences in cohort origin. Grindler’s cohort was from a head and neck clinic, whereas our cohort was from a rheumatology referral hospital where CT scanning of the paraanasal sinuses is part of routine follow-up.

Grindler’s study and the studies in CRS showing an association between sinus surgery and osteitis, are all cross-sectional studies. A time-dependent association of sinus surgery and osteitis has not been shown in earlier studies in GPA.

Limitations

Our study inclusion criterion of at least two paraanasal CT scans may have introduced a selection bias for patients with paraanasal sinus disease. The high frequency in the cohort of patients with no osteitis at the last CT (42%, 53/127) argues against this possibility. The inclusion into the research and quality patient registry was consent based and could introduce bias. However, the inclusion is set up as a simple one-time process, and more than 95% of the patients consent.

The current study was not designed to explain why the accelerated osteitis progression occurred around the time of surgery, but we speculate that it may be due to the surgical intervention per se, or to GPA-related active, aggressive sinonasal inflammation prompting referral to surgery. We believe that the high degree of preoperative pain reported by the patients in this study who had surgery during observation, supports the notion that GPA patients referred to surgery have more aggressive disease. To properly address this question, a large prospective study with serial CT scans before and after sinus surgeries would be required.

We have earlier shown that the utility of GOSS is limited by a ceiling effect, meaning that it will not capture the most extensive osteitis. To account for this problem, we proposed another method for osteitis assessment, the diameter ratio measurement based on diameter measurements of the two maxillary and sphenoid sinuses. In our material, the maximum subcore of GOSS was most commonly found in these four sinuses (Fig. 2). The break point and the high osteitis progression around the time of surgery were therefore tested and confirmed in linear mixed models with diameter ratio measurement as outcome variable.

Due to a limited number of patients with progressive osteitis, we restricted the explanatory variables in the model of the osteitis development to the surgery variables. The model and our results are proposed as proof-of-principle work in an area where the knowledge is limited, and we hope that other groups will be able to test the reproducibility of the suggested break point in osteitis development in relation to surgery.

CONCLUSION

This longitudinal observational study suggests that there is no inhibitory effect of sinus surgery on progression of GPA-related CRS. Rather, the datasets indicate a time-dependent association between a high rate of osteitis progression and sinus surgery, questioning the role of surgery to stop CRS progression in this population of GPA patients.

ACKNOWLEDGMENTS

Data from the Norwegian Patient Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

The authors thank Cathrine Brunborg at the Oslo Centre for Biostatistics and Epidemiology for valuable help with the linear mixed models.

BIBLIOGRAPHY

1. Koldingsnes W, Nosent H. Epidemiology of Wegener’s granulomatosis in northern Norway. Arthritis Rheum 2000;43:2481–2487.
2. Mohammad A, Jacobsson L, Mahr A, Sturfelt G, Segelmark M. Prevalence of Wegener’s granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg–Strauss syndrome within a defined population in southern Sweden. Rheumatology 2007;46:1329–1337.
3. Watts RA, Al-Taiar A, Scott DG, Macgregor AJ. Prevalence and incidence of Wegener’s granulomatosis in the UK general practice research database. Arthritis Rheum 2009;61:1412–1416.
4. Watts R, Lane S, Hanslik T, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 2007;66:222–227.
5. Abdulkader R, Lane SE, Scott DG, Watts RA. Classification of vasculitis: EMCLASS classification using CHCC 2012 definitions. Ann Rheum Dis 2013;72:1888.
6. Del Pero MM, Walsh M, Luqmani R, et al. Long-term damage to the ENT system in Wegener’s granulomatosis. Eur Arch Otorhinolaryngol 2011;268:735–739.
7. D’Anza B, Langford CA, Sindwani R. Sinonasal imaging findings in granulomatosis with polyangiitis (Wegener granulomatosis): a systematic review. *Am J Rhinol Allergy* 2017;31:16–21.

8. Grindler D, Cannady S, Batra PS. Computed tomography findings in sinonasal Wegener’s granulomatosis. *Am J Rhinol Allergy* 2009;23:497–501.

9. Holme SS, Moen JM, Kiliam K, Haukeland H, Molberg O, Eggesbo HB. Development of CT-based methods for longitudinal analyses of paranasal sinus osteitis in granulomatosis with polyangiitis. *BMC Med Imaging* 2019;19:13.

10. Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology* 1993;31:183–184.

11. Georgalas C, Videler W, Freling N, Fokkens W. Global Osteitis Scoring Scale and chronic rhinosinusitis: a marker of revision surgery. *Clin Otolaryngol* 2010;35:455–461.

12. Hernández-Rodríguez J, Hoffman GS, Koening CL. Surgical interventions and local therapy for Wegener’s granulomatosis. *Curr Opin Rheumatol* 2010;22:29–36.

13. Cannady SB, Batra PS, Koening C, et al. Sinonasal Wegener granulomatosis: a single-institution experience with 120 cases. *Laryngoscope* 2009;119:757–761.

14. Bhandarkar ND, Mace JC, Smith TL. The impact of osteitis on disease severity measures and quality of life outcomes in chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2011;1:372–379.

15. Sacks P-L, Snidvongs K, Rom D, Earls P, Sacks R, Harvey RJ. The impact of neo-ostegogenesis on disease control in chronic rhinosinusitis after primary surgery. *Int Forum Allergy Rhinol* 2013;3:823–827.

16. Huang Z, Hajij A, Li G, Naylor JV, Zhou B, Hwang PH. Clinical predictors of neo-osteogenesis in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2015;5:305–309.

17. Lee JT, Kennedy DW, Palmer JN, Feldman M, Chiu AG. The incidence of concurrent osteitis in patients with chronic rhinosinusitis: a clinicopathological study. *Am J Rhinol* 2006;20:278–282.