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Granulomatosis with Polyangiitis and Nasal Involvement - What Radiological Markers

Point the Disease

Short title: Granulomatosis with Polyangiitis - sino-nasal involvement

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WHAT'S NEW?

This paper describes a new, previously not described, radiologic marker observed in patients with granulomatosis with polyangiitis (GPA). Otorhinolaryngologists with nasal endoscopy are able to observe the changes involving nasal mucosa, most commonly in GPA - crusting. For those who do not perform nasal endoscopy it is more difficult to observe this nasal symptom attributed to necrotizing changes of the nasal mucosa. When analyzing computed tomographies of patients with GPA we have come across the strands occurring in the nasal cavities. We also found them in chronic rhinosinusitis but significantly less and they were thinner. Moreover we found that when the number of nasal strands was 5 or more, a statistically significant positive correlation with proteinase 3 antineutrophil cytoplasmic antibodies (PR3-ANCA) was found.
ABSTRACT

Introduction: Granulomatosis with polyangiitis (GPA) as an autoimmune disease leads to necrotizing changes in the affected tissues. Computed tomography (CT) of paranasal sinuses reveals multiple changes in GPA: sinus opacification, bone/cartilaginous destruction and neoosteogenesis.

Objectives: To describe and compare CT changes in GPA with chronic rhinosinusitis (CRS) patients. To propose a new radiological marker of GPA - nasal strands.

Patients and methods: A retrospective study (2014–2019) enrolled 53 patients with GPA (22M, 31F), mean age 47.3 (17.1). Mucosal changes in paranasal sinuses, neoosteogenesis, bony and cartilaginous changes were noted. The nasal strands were described as inter-mucosal adhesion resembling bands. Patients with CRS (n=71) were assessed for the presence of nasal strands and CT changes as in GPA. The differences were statistically significant for p <0.05.

Results: CT scans showed mucosal changes in the sinuses of 35 patients (66%) with GPA. Nasal septum perforation was observed in 19 patients (35.8%), neoosteogenesis in 17 (32.1%), bone damage in 14 (26.4%). External nose deformity was present in 16 patients (30.2%). The nasal strands in CTs were present in 36 patients (68%) with GPA and in 32 patients with CRS (45%). Strands ≥5 were more characteristic of GPA than CRS (<0.001). A positive correlation was found between strands ≥5 and PR3-ANCA (p=0.046).

Conclusions: Nasal strands, a parameter showing pathologic mucus and atrophic changes (tissue loss), should have a place in CT evaluation of the nasal cavities in patients either with suspicion of GPA or in the course of GPA.
Introduction

Autoimmune diseases develop in approximately 7–8% of the population. The number of autoimmune diseases exceeds 80, with some of the most common being celiac disease, Graves' disease, Hashimoto disease, diabetes type 1, rheumatoid arthritis, Sjögren's syndrome, and multiple sclerosis. Granulomatosis with polyangiitis (GPA) as an autoimmune disease belonging to ANCA-associated vasculitides (AAV) that leads to necrotizing changes in the affected tissues. Its etiology includes environmental factors as well as infectious and toxic agents, genetic background, and epigenetic regulation [1]. The disease involves small or small and medium-sized vessels. Its prevalence in Europe is 23 to 160 people per 1 million and affects primarily adult caucasians (rarely children), with no gender predilection [2,3]. Polish Vasculitis Registry encompassing 58.2% of Polish population showed that demographic characteristics and frequency of AAV in Poland is similar to other European countries [3].

The diagnosis of GPA according to the American College of Rheumatology (ACR) established in 1990 included hematuria, abnormal chest radiograph, ulcers in the oral and/or nasal cavity mucosa, and positive histopathological examination. The diagnosis of GPA requires two or more of the 4 above mentioned criteria [4].

Granulomatosis with polyangiitis is a type of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides [5], where C-ANCA/PR3-ANCA and P-ANCA/MPO-ANCA are involved in the damage to the vascular endothelium, leading to necrosis [6,7]. As in the early 1990s the ANCA tests were already known but not routinely performed, they reached their current status in the diagnosis of GPA in the late 1990s [8], in which their presence complements the ACR diagnostic criteria. In the localized form of the disease, ANCAs are present in 40–50% of patients, while in generalized form as many as 75–95% of the patients are C-ANCA positive. If uncertain, the diagnosis requires confirmation with a
biopsy of the affected area and histopathological examination [8,9].

The European Vasculitis Study (EUVAS) divided vascular diseases associated with ANCA (GPA) into 5 groups according to level of severity [10]: localized, early systemic, generalized, severe, and refractory. This division guides further treatment in patients with GPA. According to a retrospective analysis of POLVAS registry, in AAV patients, independent risk factors for death are permanent renal replacement therapy (PRRT), kidney involvement/respiratory involvement, age > 65 years, and the presence of c/PR3 ANCA. Ear, nose and throat (ENT) involvement was identified a factor negatively associated with PRRT [3].

Computed tomography (CT) reveals multiple changes in the head and neck region of patients with GPA, especially in the nose and paranasal sinuses. The most common changes involve sinus opacification, bone/cartilaginous destruction and neoosteogenesis. To date there is no description of CT changes in the nasal cavities of patients with GPA except for nasal septum perforation or lateral nasal wall destruction.

This study aims to provide a description of changes in sinonasal CT scans of patients with GPA and comparison with chronic rhinosinusitis patients (CRS) and to introduce a new radiological marker of the disease with its relation to PR3-ANCA. Since PR3-ANCA is considered a risk factor in AAV and given that there is a need to identify the subsets of patients at risk for relapses, or infectious complications [11] we decided to present an analysis of GPA patients with upper respiratory tract involvement.

**Patients and methods**

This retrospective study was performed between May 2014 and September 2019 in the academic referral center. Bioethical Committee approval was waived (AKBE/186/2018) due to the non-experimental character of the study. The inclusion criteria were: GPA
diagnosis based on ACR criteria and EULAR guidelines [12], computed tomography of the sinonasal region, and ORL examination with endoscopic assessment of nose, ear and larynx.

The patients enrolled into the study were either primarily diagnosed - in the first year of treatment due to GPA (12/53 patients) or were admitted to hospital in the course of the disease with a relapse (18/53 patients) or were in remission (23/53 patients). All of the patients in the study signed informed consent. Fifty-three patients (22M/31F) out of 68 with GPA (diagnosed according to ACR criteria and EULAR guidelines) met the inclusion criteria. The age of patients in the study group ranged between 14 and 86, with median 45 (IQR 34-60).

For the purpose of this study, all patients with GPA were divided into a group with rhinological manifestation of the disease R(+) or without it R(-). The division was based on ORL examination involving nasal endoscopy. Patients without rhinological manifestation presented either otological or orolaryngeal symptoms or none of them. The rhinological manifestation of the disease involved symptoms of rhinitis with nasal crusting, epistaxis, rhinosinusitis, septal perforation, and external nose deformity. Otological manifestation consisted of external, middle, and internal ear changes such as aural skin ulcers, acute/secretory otitis media, or sensorineural hearing loss and vertigo. Rarely, otitis media was complicated with facial nerve palsy. Orolaryngeal manifestation involved laryngeal stenosis with temporary tracheotomy, vocal cord paresis, and ulcerations in the oral cavity.

In the course of the disease, patients were treated with either glucocorticoids (GKS) with cyclophosphamide or GKS with azathioprine. Plasmapheresis was applied rarely in the course of treatment. None of the patients in the study group received biological treatment (rituximab). The disease duration in the study group was 0–24 years. Patients were examined at different time intervals of disease duration between 0 and 24 years.

In the study group, the PR3-ANCA results were collected and *Staphylococcus aureus*
nasal carriers were specified. The phase of disease was determined as either active or in remission.

To assess the sinus mucosal changes in the CT scans, a Lund-MacKay Score (LMS) was implemented, assigning each sinus a score [13]:

- 0 (no abnormality)
- 1 (partial opacification) or
- 2 (complete opacification).

The ostiomeatal complex was assigned a score of either 0 (not obstructed) or 2 (obstructed). The total score ranged between 0 and 24 and the evaluation included:

- frontal sinus
- anterior ethmoidal cells
- posterior ethmoidal cells
- maxillary sinus
- sphenoid sinus
- ostiomeatal complex.

To show the changes in the bones, a Kennedy Osteitis (neoosteogenesis) Score (KOS) and a Global Osteitis Score (GOS) [14] were applied. In KOS, the sinus wall of the sinuses mentioned above were scored 0 for a sinus wall thinner than 3 mm, 1 point for 3–5 mm sinus wall thickness, and 2 points for a sinus wall thicker than 5 mm (0–20). In GOS, the thickness of bones and obliteration of each sinus group as above were taken into consideration. The points were given as follows: 0: <3 mm, <50% of sinus; 1: 3–5 mm, <50% of sinus; 2: >5 mm, <50% of sinus OR <3 mm and >50% of sinus; 3: 3–5 mm, >50% of sinus; 4: >5 mm, >50% of sinus. The results may range from 0 and 40.

The CT scans were examined for the presence of intranasal soft-tissue changes called nasal strands (NS), which are dried mucus and atrophic tissue formations that form bridges...
between the walls of the nasal cavity. They are either straight or irregular in shape (Figure 1) and may represent tissue remnants or tissue loss in the nasal cavity of patients with GPA. Strands present in the nasal vestibule or nasal valve area were not taken into consideration. The number of nasal strands was counted in both nasal cavities and divided into three categories: 0-1; 2-4; 5 and more. 

As the reference group, patients with chronic rhinosinusitis were chosen. The diagnosis of CRS in this group was based on EPOS 2012 criteria [15]. LMS was assessed in 150 patients and KOS, GOS, and NS in 71 patients.

**Statistical analysis**

Statistical analysis was performed using the T-test and the Mann-Whitney U test. Correlations were analyzed using the Spearman correlation coefficient. Differences in dichotomous variables were tested using the chi-squared test and the Fischer test. For multiple comparisons Kruskal-Wallis test was applied. A receiver operating characteristic (ROC) curve was generated to show true positive rate (sensitivity) and false positive rate (1-specificity). ROC curve and odds ratio (95%CI) were estimated by means of logistic regression. The differences were statistically significant for p<0.05. Statistical analysis was performed with SAS software.

**Results**

Patients in the study group presented with involvement of the following sites: upper respiratory tract - 48 patients (90.5%), lower respiratory tract - 31 patients (58.5%), renal disease - 29 patients (54.7%), osteoarticular system - 19 patients (35.8%), peripheral nervous system - 13 patients (24.5%), orbital involvement - 10 patients (19.6%), skin involvement - 5 patients (9.4%), central nervous system - 3 patients (5.7%), heart - 2 patients (3.8%), muscles - 2 patients (3.8%), digestive tract - 1 patient (1.9%).
The results of the study comparing patients with GPA and CRS without any divisions into subgroups are presented in Table 1. The comparison between rhinological manifestation of GPA and CRSwP and CRSsP is presented in Table 2. In the GPA group, 36 patients presented with rhinological manifestation (68%) and 23 of those patients had a coexisting otological manifestation. Overall, 34 patients exhibited an otological manifestation (64%). Five patients were positive for orolaryngeal changes in the course of the disease (9%). One patient was diagnosed due to orbital pseudotumor. Four patients did not present head and neck symptoms.

In the study group (GPA), LMS ranged from 0 to 20, with a median of 3 (IQR 0-8) for the whole group (Table 1). Computed tomography scans showed mucosal changes in the sinuses of 35 patients (66%) with GPA. In patients with rhinological manifestation R(+) the median value of LMS was 6.50 (IQR 2.00-11.50) (Table 2). The sinus involvement was:

- maxillary sinus: 29 patients (80.6% in R(+) / 64.2% of all GPA patients),
- anterior ethmoidal cells: 22 (58.3%/41.5%),
- sphenoid sinus: 19 (52.8%/35.9%),
- frontal sinus: 19 (52.8%/35.9%),
- posterior ethmoidal cells: 15 (41.7%/28.3%).

Neoosteogenesis in GPA patients was evaluated with two scoring systems addressed to osteitis in paranasal sinuses [16]. It was observed in 17 cases (32.1% of total group) (Table 3) and the Kennedy Osteitis Score (0–20) was positive in 14 cases (26.4% of total group, 39% of the R(+) ). The results ranged from 1 to 14 and 0 results amounted to 73.6% of GPA group. The Global Osteitis Score was also positive in 14 patients and ranged from 1 to 22 (Tables 1–2). The sinus involvement was:

- maxillary sinus: 12 (33% R(+)/22,5% of total GPA),
- sphenoid sinus: 6 (17%/11%).
• posterior ethmoidal cells: 4 (11%/7.5%),
• anterior ethmoidal cells: 2 (5.5%/4%).

Neoosteogenesis was rarely observed in the early stages of the disease (2 out of 12 newly diagnosed patients), and the highest incidence was observed in the 3rd to 4th years of the disease.

Bone damage was noted in 14 patients (26.4% of the total group, 38.9% in R(+)) and affected nasal bones, nasal bony septum, nasal turbinates, or lateral nasal wall. Septal perforation (cartilaginous or mixed bony and cartilaginous) was present in 19 patients (35.8% of the total group; 52.8% in R(+)) and in 11 cases it coexisted with neoosteogenesis in the sinuses. External nose deformity was present in 16 patients (14F : 2M). Four of those patients had no septal perforation (cartilaginous nor bony) and 12 had developed septal perforation.

Patients with LMS higher than 10 (13 patients) presented with higher neoosteogenesis incidence (11 patients) and septal perforation incidence. Three of the previously operated-on patients (3/8 in R(+)) were either KOS or GOS positive. The difference in history of previous surgery in GPA and CRS patients was not significant (Tables 1–2).

*Staphylococcus aureus* was cultured in 29 nasal swabs of patients with GPA (65.9%) (Table 1) and in 24 patients R(+) (75%) (Table 2). GPA patients had a greater risk of *S. aureus* nasal carriage than patients with CRS (OR 11.07; 95% CI 4.53 to 27.06; p<0.001).

Most commonly, *S. aureus* was present in patients either with septal perforation (15 patients) or with neoosteogenesis (14 patients). Based on that, septal perforation together with *S. aureus* was established to be 6 times as high as without *S. aureus* (OR = 6.07; 95% CI: 1.16–31.82; p=0.045). Odds ratio for neoosteogenesis and *S. aureus* was insignificant.

Twenty-four patients were PR3-ANCA positive (46.2%) among all GPA patients (16 patients: 45.7% in R(+) subgroup). In one case data was unavailable. The disease was active in 28 patients (52.8%) and in remission in 25 patients (47.2%). In patients with rhinological
manifestation, an active phase was detected in 22 patients (61.1%). MPO-ANCA was positive in 4% of patients with GPA (3% R(+) group).

The analysis of CT scans showed one more feature—nasal strands between two sites in the nasal cavity—frequently on the opposite sides of the cavity either straight or irregular in shape (Figure 1). Those narrow strands in patients with GPA are dried mucus formations with atrophic tissues and may be attributed to tissue loss and crusting in endoscopic examination. In GPA patients, NS (>1) occurred in 36 patients (67.9% of total) and in rhinological manifestation of GPA, in 28 patients (77.8%). In the R(-) group they were observed in 8 patients (47%). Seventy-one CT scans of patients with CRS were assessed for the presence of NS. The results in GPA patients compared to CRS patients are presented in Table 4 and the multiple comparisons between GPA R(+), CRSsP and CRSwP are presented in Table 5.

The NS in GPA patients were correlated with LMS, KOS, GOS, and time of disease duration. A negative Spearman correlation coefficient (-0.26)(p=0.07) was established between the time of disease duration and NS. The associations between PR3-ANCA (n=52)/phase of disease (n=53) and NS were evaluated with a Fisher test. The results are presented in Table 6. NS ≥5 were significantly more common in PR3-ANCA(+) than in PR3-ANCA(-) patients (p=0.046). The associations between NS and phase of disease were not significant. Of 29 patients with S. aureus-positive cultures, 13 were found to have AS ≥5 (44.8%) (p=0.53)(Table 6). The sensitivity and specificity of NS ≥5 was respectively: 39.6% and 95.8%. In the presented group positive predictive value of this marker was 87.5% while negative predictive value was 68%. A receiver operating characteristic (ROC) curve was generated to show true positive rate (sensitivity) and false positive rate (1-specificity), i.e. to show how much the nasal strands are capable of distinguishing between GPA and CRS (Figure 2).
Discussion

Patients with GPA in study group showed higher prevalence of ENT involvement than described by POLVAS registry (90.5% vs 75.5%). The rest of organ involvement presented on a lower level according to the registry except for the neurological involvement (peripheral nervous system) - in our study group it was 24.5% compared to 18% in POLVAS registry [3].

Radiological features of granulomatosis with polyangiitis have already been outlined as mucosal thickening, bony destruction, septal erosion, neoosteogenesis, orbital involvement, and bony obliteration [17]. In this study, mucosal thickening was evaluated with a Lund-MacKay Score developed for patients with rhinosinusitis. Positive results were observed in 35 patients (66% of all patients). In their systematic review of the sinonasal changes in GPA, Danza et al. found mucosal thickening in sinuses in 87.7% patients [17]. For the present study only, if we take into consideration patients with rhinological manifestation of GPA, the prevalence of mucosal thickening in GPA amounts to 83.3%.

Thus, any discrepancies in results may be explained by patient selection bias, as the patients with GPA in studies usually present to the ENT specialist with a certain manifestation of the disease. Our study included all of the GPA patients diagnosed not only in ENT departments but also Family Medicine, Internal, and Metabolic Diseases Department. Table 3 presents a comparison of literature data on LMS and sinus opacification in studies exceeding 20 patients [18-21]. Benoudiba et al. described mucosal thickening together with nodular changes of the mucosa based on their observations in only 9 patients with GPA [22]. We observe that nodular changes are more typical for another autoimmune disease - sarcoidosis. Makary et al. described 53 patients with different autoimmune diseases and compared their sinus changes with chronic rhinusinusitis patients [23]. They found no significant difference in CT scores between the groups but they had only 8 patients with CT scans in autoimmune
study group. In the presented material comparison between GPA and CRS shows that LMS in GPA is significantly lower: 3(0-8) vs 11(8-16) (p<0.001) (Table 1). In multiple comparison of GPA R(+), CRSsP and CRSwP, the difference was also significant (<0.001), but when compared only GPA R(+) with CRSsP the difference came out insignificant (p=0.08)(Table 2).

Bony/cartilaginous damage in our study was observed in 20 patients, 19 of which had septal perforation: in 8 cases cartilaginous and in 11, bony/cartilaginous. D'Anza found bony destruction in 59.9% of GPA patients [17]. In our study, the result was similar: 55.5% in the R(+) group. However, the result was lower out of the total group of GPA patients due to the aforementioned patient selection issue.

Neoosteogenesis in our study affected 17 patients (47.2% R(+) patients) while D'Anza reported 56.1% [17]. We did not analyze obliteration of sinuses separately, as it was evaluated with GOS as a part of the neoosteogenesis process. Neoosteogenesis scales for KOS and GOS are significantly higher in patients with GPA than in CRS, whether with or without polyps (Tables 1–2). Holme et al. described the changes in CT scans with the duration of the disease - 23% of the GPA-patients had significant osteitis, defined as GOS ≥ 5 in the first year of the disease. This proportion had increased to 40% at the last CT, performed more than 12 months from the first one [24]. Similarly, in our material patients in the early stages of GPA had less changes than later, finally reaching 32.1% of the total group.

The analysis of external nose deformities revealed that 4 patients with a saddle nose deformity did not have septal perforation. The majority of patients with an external nose deformity were female (14F:2M), which allows us to conclude that GPA has a higher burden of nasal deformity in female patients, which is not always accompanied by septal perforation.

*S. aureus* carriage was found to be 11 times higher in GPA than in CRS (p<0.001). In GPA patients, *S. aureus* carriage was also connected with septal perforation.
Cannady et al. examined 120 patients with GPA and found that 89% of patients exhibited sinonasal changes, including nasal crusting (69%), chronic rhinosinusitis (61%), nasal obstruction (58%), bloody nasal discharge (52%), septal perforation (33%), saddle-nose deformity (23%), epiphora (13%), and mucocele formation (3.3%) [25]. Crusting in patients with GPA goes along with tissue loss following vasculitis and necrosis. Given that crusting is one of the most frequently described types of change in examination of nasal cavities in GPA patients and that crust removal usually requires aspiration with endoscopic procedures, this work also aimed at analysis of CT scans in the terms of crusting in nasal cavities. Measuring the crust in CT scans is difficult as it does not differ from mucosal tissues. Thus, we analyzed narrow strands between the opposite sites, frequently irregular in shape in the nasal cavity (Figure 1). Dryness and crusting may be present in the nasal vestibule up to the nasal valve in different conditions in patients without septal perforation and rarely occurs in the nasal cavity behind the nasal valve. Thus the nasal vestibule and nasal valve areas were excluded from the analysis. NS were found in 77.8% patients with rhinological manifestation of the disease (67.9% of total GPA). What is interesting is that those strands were also present in 35% patients without rhinological symptoms of vasculitis. The patients in the GPA R(-) group presenting with strands in CT scans did not complain of any rhinological issues. Comparison between GPA and CRS in terms of NS revealed that finding 5 or more strands was significantly more common in GPA than in CRS (p<0.001), while 2-4 strands occurred in both groups (more often in CRSwP than CRSsP). Having 0–1 strands was significantly more common in the CRS group (p<0.001). This analysis showed that when present at a level of 5 or more, NS can be a valuable predictive factor for GPA.

Interestingly, NS ≥5 was positively correlated with PR3-ANCA-positive results (p=0.046) but not within the active phase of the disease (p=0.34). Such divergence may be explained by the fact that patients with decreasing but still positive PR3-ANCA titers are
commonly identified as in remission. The analysis of nasal strands revealed that they are highly specific for GPA especially when ≥5, but it is possible to find them in other autoimmune diseases leading to tissue necrosis in nasal cavities (e.g., sarcoidosis). A negative Spearman correlation coefficient (-0.26) (p=0.07) between time of disease duration and NS could relate to the treatment efficacy and decrease in tissue loss in time, but the result did not meet the criteria of statistical significance. The sensitivity and specificity of NS ≥5 was respectively: 39.6% and 95.8%. The factor responsible for quite low sensitivity could probably be the characteristics of the study group including both rhinologic and non-rhinologic manifestation of the disease. If we analyzed only patients with rhinologic (n=36) manifestation of the disease, the sensitivity of the marker would amount 52.8%. Similarly the ROC curve would approach near to the 1 (better measure of separability) if we included only the rhinologic patients instead of the whole GPA group. The aim to compare rhinosinusitis with GPA refers to overlapping symptoms of the two entities and high prevalence of upper airway involvement in GPA. Analysis and group comparison in this paper refers to differentiation between rhinosinusitis and GPA patients, where the main difficulty for both ENT and internal medicine specialist is dealing with localized disease in upper respiratory tract and approximately 5 month delay in diagnosis. This difficulty is enhanced by the fact of intermittent steroid therapy in chronic rhinosinusitis patient (usually intranasal but sometimes systemic steroid therapy) is blurring the picture of the disease.

The limitation of this study was the diverse stage of disease at the time of CT examination (the duration of disease was from 0 to 24 years) and different treatment regimens. Some patients in the study group were examined due to inflammatory disease in the upper airways and were finally diagnosed as GPA, others were referred to ORL for routine examination to observe any signs of relapse in upper respiratory tract. This limitation applies to all the changes previously described in GPA such as sinus opacification,
neooosteogenesis, and perforation of the nasal septum. Nevertheless, by checking the level of PR3-ANCA we were able to address an important feature of the disease and correlate it with intranasal changes. And when mentioning PR3-ANCA it has to be annotated that PR3-ANCA were estimated in 52 patients with 24 positive results.

In summary, CT analysis in patients with GPA revealed the following abnormalities according to their occurrence:

- Nasal strands in the nasal cavities: 68% total GPA/78% GPA R(+)
- Mucosal thickening: 66% total GPA/83.3% GPA R(+)
- Cartilaginous or bony damage: 37.7% total GPA/55.5% R(+)
- Neoosteogenesis: 32.1% total GPA/47.2% R(+).

Comparison between GPA and CRS shows that LMS is significantly lower, while KOS and GOS are significantly higher, in patients with GPA than in CRS. *S. aureus* carriage is higher in GPA. *S. aureus* carriage was also more common in patients with GPA and septal perforation. Nasal strands can be a factor helping differentiate GPA from CRS patients.

Nasal strands, a parameter showing pathologic mucus and possible atrophic changes (tissue loss), should be recognized along with mucosal thickening, bone damage, and neoosteogenesis as part of CT evaluation of the nasal cavities in patients either with suspicion of GPA or in the course of GPA.

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References:

1. Csernok E, Gross WL. Current understanding of the pathogenesis of granulomatosis with polyangiitis (Wegener's). Expert Rev Clin Immunol. 2013; 9: 641-648.

2. Mohammad AJ, Jacobsson LT, Westman KW, et al. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology. 2009; 48: 1560-1565.

3. Wojcik K, Wawrzycka-Adamczyk K, Wludarczyk A, Sznajd J, Zdrojewski Z, Masiak A, et al. Clinical characteristics of Polish patients with ANCA-associated vasculitides- retrospective analysis of POLVAS registry. Clin Rheumatol. 2019; 38: 2553-2563.

4. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum. 1990; 33: 1101-1107.

5. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013; 65: 1-11.

6. Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. Nat Rev Rheumatol. 2014; 10: 463-473.

7. Xiao H, Hu P, Falk RJ, Jennette JC. Overview of the Pathogenesis of ANCA-Associated Vasculitis. Kidney Dis (Basel). 2016; 1: 205-215.

8. Savige J, Gillis D, Benson E, et al. International Consensus Statement on Testing and Reporting of Antineutrophil Cytoplasmic Antibodies (ANCA). Am J Clin Pathol. 1999; 111: 507-513.

9. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016; 75: 1583-1594.

10. Mukhtyar C, Guillemin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;
11. Padjas A, Sznajd J, Szczeklik W, Wojcik K, Wawrzycka K, Musial J. Rare disease registries: an initiative to establish vasculitis registry in Poland. Pol Arch Med Wewn. 2014; 124: 143-144.

12. Basu N, Watts R, Bajema I, et al. EULAR points to consider in the development of classification and diagnostic criteria in systemic vasculitis. Ann Rheum Dis. 2010; 69: 1744-1750.

13. Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology. 1993; 31: 183-184.

14. 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.

15. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012; 50: 1-12.

16. Snidvongs K, Earls P, Dalgorf D, et al. Osteitis is a misnomer: a histopathology study in primary chronic rhinosinusitis. Int Forum Allergy Rhinol. 2014; 4: 390-396.

17. 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.

18. Lloyd G, Lund VJ, Beale T, Howard D. Rhinologic changes in Wegener's granulomatosis. J Laryngol Otol. 2002; 116: 565-569.

19. Lohrmann C, Uhl M, Warnatz K, et al. Sinonasal computed tomography in patients with Wegener's granulomatosis. J Comput Assist Tomogr. 2006; 30: 122-125.

20. Grindler D, Cannady S, Batra PS. Computed tomography findings in sinonasal Wegener's granulomatosis. Am J Rhinol Allergy. 2009; 23: 497-501.
21. Zycinska K, Straburzynski M, Nitsch-Osuch A, et al. Lund-Mackay System for Computed Tomography Evaluation of Paranasal Sinuses in Patients with Granulomatosis and Polyangiitis. Adv Exp Med Biol. 2016; 884: 13-19.

22. Benoudiba F, Marsot-Dupuch K, Rabia MH, et al. Wegener's granulomatosis: CT characteristics. Neuroradiology. 2003; 45: 95-99.

23. Makary CA, Gill B, Parman B, Unsal AA, Holmes T, Reyes-Gelves C, et al. Subjective and Objective Measurements of Sinonasal Manifestations in Patients With Autoimmune Disorders. Laryngoscope. 2021; 131: 255-259.

24. Holme SS, Moen JM, Kilian 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: 1-11.

25. Cannady SB, Batra PS, Koenig C, et al. Sinonasal Wegener granulomatosis: a single-institution experience with 120 cases. Laryngoscope. 2009; 119: 757-761.
**Table 1.** Comparison of age, computed tomography parameters, *Staphylococcus aureus* presence, and previous surgery in patients with granulomatosis with polyangiitis and chronic rhinosinusitis.

|                | GPA                        | CRS                        | p 1 vs 2 |
|----------------|----------------------------|----------------------------|----------|
|                | n                          | Median 1 (IQR) or %        | n        | Median 2 (IQR) or % |        |
| Age            | 53                         | 45 (34-60)                 | 150      | 46 (35-61)         | 0.93    |
| LMS            | 53                         | 3 (0-8)                    | 150      | 11 (8-16)          | <0.001  |
| KOS ≥1         | 53                         | 0 (0-1) 73.6% 26.4%        | 71       | 0 (0-0) 91.6% 8.4% | 0.008   |
| GOS ≥1         | 53                         | 0 (0-1) 73.6% 26.4%        | 71       | 0 (0-0) 91.6% 8.4% | 0.006   |
| S.aureus (+)   | 44                         | 65.9%                      | 74       | 14.9%              | <0.001  |
| Prev.surg.     | 53                         | 15.1%                      | 71       | 29.6%              | 0.09    |

CRS - chronic rhinosinusitis; GOS - Global Osteitis Score; GPA - granulomatosis with polyangiitis; KOS - Kennedy Osteitis Score; LMS - Lund-Mackay Score; n - number; p - statistical significance; Prev.Surg. - previous surgery; S.aureus - *Staphylococcus aureus*; IQR - interquartile range;
Table 2. Comparison of age, computed tomography parameters, *Staphylococcus aureus* presence, and previous surgery in patients with granulomatosis with polyangiitis - rhinologic manifestation and chronic rhinosinusitis without polyps and chronic rhinosinusitis with polyps.

|          | GPA R(+) | CRSsP | CRSwP |
|----------|----------|-------|-------|
|          | n        | Median 1 (IQR or %) | Median 2 (IQR or %) | Median 3 (IQR or %) | p 1vs2 | p 1vs3 | p 2vs3 | P |
| **Age**  | 36       | 46 (31-63) | 74 | 42.5 (31-59) | 76 | 50 (39-64) | 0.36 | 0.38 | 0.009 | 0.04 |
| **LMS**  | 36       | 6.5 (2-11.5) | 74 | 8 (6-11) | 76 | 15 (11-18) | 0.08 | <0.001 | <0.001 | <0.001 |
| **KOS 0 ≥1** | 36     | 0 (0-3) | 24 | 0 (0-0) | 0 (0-0) | 0.003 | 0.004 | 0.34 | <0.001 |
| **GOS 0 ≥1** | 36     | 0 (0-5) | 24 | 0 (0-0) | 0 (0-0) | 0.003 | 0.002 | 0.34 | <0.001 |
| **S.aureus** | 32     | 75% | 47 | 6.4% | 27 | 29.6% | <0.001 | 0.001 | 0.01 | <0.001 |
| **Prev. Surg.** | 36     | 22% | 24 | 16.7% | 47 | 36.2% | 0.75 | 0.23 | 0.11 | 0.18 |

CRSsP - chronic rhinosinusitis without polyps; CRSwP - chronic rhinosinusitis with polyps; GOS - Global Osteitis Score; GPA R(+) - granulomatosis with polyangiitis, rhinologic manifestation; KOS - Kennedy Osteitis Score; LMS - Lund-Mackay Score; n - number; p - statistical significance; Prev.Surg. - previous surgery; *S.aureus* - *Staphylococcus aureus*; IQR - interquartile range;
Table 3. Comparison of literature data on sinus opacification/Lund-MacKay Score, neoosteogenesis, bony destruction, nasal septum perforation, and nasal strands.

|                          | sinus opacification | neoosteogenesis | bone destruction | septal perforation | nasal strands |
|--------------------------|---------------------|-----------------|------------------|--------------------|---------------|
| Lloyd et al. 2002 (n=28) | 85,7%               | 50%             | 75%              | -                  | -             |
| Lohrmann et al. 2006 (n=28) | 75%               | 21%             | 57%              | -                  | -             |
| Grindler et al. 2009 (n=74) | 90,5               | 78%             | 62%              | 35,1%              | -             |
| Życińska et al. 2015 (n=43) | 78%               | 9%              | 32%              | 21%                | -             |
| present study (total group) (n=53) | 66%               | 32,1%           | 26,4%            | 35,8%              | 68%           |
| present study (rhinological manifestation) (n=36) | 83,3%               | 47,2%           | 38,8%            | 52,8%              | 78%           |
Table 4. Nasal strands in patients with granulomatosis with polyangiitis and chronic rhinosinusitis.

| GPA      | CRS     | p     |
|----------|---------|-------|
|          | n      | %    | n    | %    |       |
| NS 0-1   | 53     | 32.08| 71   | 70.42| <0.001|
| NS 2-4   | 53     | 28.3 | 71   | 25.35| 0.84  |
| NS ≥ 5   | 53     | 39.62| 71   | 4.2  | <0.001|

CRS - chronic rhinosinusitis; GPA - granulomatosis with polyangiitis; NS - nasal strands; n - number; p - statistical significance

Table 5. Nasal strands in patients with granulomatosis with polyangiitis - rhinological manifestation and chronic rhinosinusitis without polyps and chronic rhinosinusitis with polyps.

| GPA R(+) | CRSSP  | CRSwP | p1vs2 | p1vs3 | p2vs3 | p     |
|----------|--------|--------|-------|-------|-------|-------|
|          | n      | %      | n     | %    |       |       |
| NS 0-1   | 36     | 22.2   | 24    | 79.2 | <0.001| <0.001| 0.29  | <0.001|
| NS 2-4   | 36     | 25     | 24    | 16.7 | 0.53  | 0.81  | 0.27  | 0.51  |
| NS ≥5    | 36     | 52.8   | 24    | 4.2  | <0.001| <0.001| 1.00  | <0.001|

CRSSP - chronic rhinosinusitis without polyps; CRSwP - chronic rhinosinusitis with polyps; GPA R(+) - granulomatosis with polyangiitis, rhinologic manifestation; NS - nasal strands; n - number; p - statistical significance
Table 6. Associations between nasal strands and proteinase 3 antineutrophil cytoplasmic antibodies, phase of disease and *Staphylococcus aureus* presence in patients with granulomatosis with polyangiitis.

|                     | NS<5 | NS ≥5 | TOTAL | p     |
|---------------------|------|-------|-------|-------|
| **PR3-ANCA**        |      |       |       |       |
| (-)                 | 21 (75%) | 7 (25%) | 28    |       |
| (+)                 | 11 (45,8%) | 13 (54,2%) | 24    |       |
| **Total**           | 32   | 20    | 52    | 0.046 |
| **Phase of disease**|      |       |       |       |
| Remission           | 17 (68%) | 8 (32%)  | 25    | 0.4   |
| Active              | 15 (53,6%) | 13 (46,4%) | 28    |       |
| **Total**           | 32   | 21    | 53    |       |
| **S.aureus**        |      |       |       |       |
| (-)                 | 10 (66,7%) | 5 (33,3%)  | 15    | 0.53  |
| (+)                 | 16 (55,2%) | 13 (44,8%) | 29    |       |
| **Total**           | 26   | 18    | 44    |       |

NS - nasala strands; p - statistical significance; PR3-ANCA - proteinase 3 antineutrophil antibodies; *S. aureus* - *Staphylococcus aureus*
Figure 1. Paranasal sinus computed tomography scans of patients with granulomatosis with polyangiitis (A,B,D - coronal section; C - horizontal section): white arrows show nasal strands - crusting and necrosis in the nasal cavities of four different patients with granulomatosis with polyangiitis, (*) shows nasal septum perforation, black arrows - neooosteogenesis of the maxilla with destruction of the lateral nasal wall.
Figure 2. Receiver operating characteristics (ROC) curve showing the capability of the nasal strands in distinguishing between granulomatosis with polyangiitis and chronic rhinosinusitis.