ANCA-Associated Vasculitides Valvular Impairment: Multicenter Retrospective Study and Systematic Review of the Literature

Lina Jeantin, Tiphaine Lenfant, Pierre Bataille, Hubert de Boysson, Pascal Cathébras, Christian Agard, Stanislas Faguer, Vincent Poindron, Marc Ruivard, Nicolas Martin Silva, et al.

Running title: Endocarditic impairment of AAV.

ANCA-Associated Vasculitides Valvular Impairment: Multicenter Retrospective Study and Systematic Review of the Literature.

Lina Jeantin MD[1*], Tiphaine Lenfant MD[1*], Pierre Bataille MD[2], Hubert de Boysson MD PhD[3], Pascal Cathébras MD [4], Christian Agard MD PhD [5], Stanislas Faguer MD PhD[6], Vincent Poindron MD[7], Marc Ruivard MD PhD [8], Nicolas Martin Silva MD[3], Matthieu Monge MD[9], Loic Guillevin MD PhD [10], Xavier Puéchal MD PhD [10], Benjamin Terrier MD PhD [10], Agnès Dechartres MD PhD[11], Pierre Charles MD[1] on behalf of the French Vasculitis Study Group.

* Both authors contributed equally to this work.

Funding source: this study received no funding.

[1] LJ MD https://orcid.org/0000-0001-6888-3311, TL MD https://orcid.org/0000-0001-8992-6675, PCh MD, Department of Internal medicine, Institut Mutualiste Montsouris, 42 Bd Jourdan, 75014 Paris, France

[2] PB MD, Department of Nephrology, CH Boulogne-sur-Mer, allée Jacques Monod, 62200 Boulogne-sur-Mer, France

[3] HB MD, PhD https://orcid.org/0000-0001-9083-8365, NMS MD https://orcid.org/0000-0002-1536-1373., Department of Internal medicine, CHU Caen, avenue de la côte de Nacre, 14000 Caen, France

[4] PCa MD, https://orcid.org/0000-0001-7570-3336 Department of Internal medicine, Hôpital Nord, CHU St Etienne, 42055 St Etienne Cedex 2, France

[5] CA MD, PhD, https://orcid.org/0000-0002-1156-0607, Nantes Université, CHU Nantes, Department of Internal medicine, 44000 Nantes, France

[6] SF MD PhD, Department of Nephrology and Organ ransplantation, Rangueuil Hospital, 1 avenue du Pr Jean Poulhès, 31400 Toulouse, France

[7] VP MD, Referral center for autoimmune and rare systemic diseases RESO, Strasbourg university hospital, 1 place de l'hôpital, 67000 Strasbourg, France

[8] MR MD, PhD, Department of Internal medicine, CHU Estaing, CHU Clermont-Ferrand,1 rue Lucie et Raymond Aubrac, 63100 Clermont-Ferrand, France

[9] MM MD, https://orcid.org/0000-0002-7355-9126, Hemodialysis department, Institut Mutualiste Montsouris, 42 Bd Jourdan, 75014 Paris, France

[10] LG MD, PhD, XP MD http://orcid.org/0000-0003-3573-9203, PhD, BT MD, PhD, National Referral Centre for Rare Systemic Autoimmune Diseases, department of Internal medicine, CHU Cochin, 27 rue du Faubourg St Jacques, 75014 Paris, France

[11] AD MD, PhD, http://orcid.org/0000-0003-0770-5567, Sorbonne Université, Institut National de la Santé et de la Recherche Médicale (INSERM), Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP. Hôpital Pitié Salpêtrière, Département de Santé Publique, Paris 75013

Author declaration:

S.F: received lecture fees from Vifor Pharma and Asahi Lt

All other authors have no conflicts of interest to declare.

Corresponding author: Dr Pierre Charles, Department of Internal Medicine, Institut Mutualiste Montsouris, 42 Bd Jourdan, Paris, France

pierre.charles@imm.fr

telephone: 33 1 56 61 67 70, fax: 33 1 56 61 67 29

Keywords: antineutrophil cytoplasmic antibodies, vasculitis, non-infective endocarditis, heart valve diseases

Key messages:

- The endocarditic presentation of AAV is a scarce form of valvular impairment that can be misleading.
- AAV-endocarditis might be under-diagnosed as some patients are asymptomatic.
- If diagnosed early, AAV-endocarditis might be accessible to immunosuppressive therapy before surgery is required.

ABSTRACT:

OBJECTIVE: While myocardial impairment is a predictor of poor prognosis in ANCA-associated vasculitides (AAV), little is known about valvular involvement. This study aims at describing the clinical presentation, management and outcome of endocarditis associated with AAV.

METHODS: We conducted a multicenter retrospective study in centers affiliated with the French Vasculitis Study Group. We included patients with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), or eosinophilic granulomatosis with polyangiitis (EGPA) with endocardial impairment. A systematic review was then performed through PubMed, Embase and Cochrane library up to September 2020.

RESULTS: The retrospective cohort included ten patients (91%) with GPA and one (9%) with MPA. Clinical presentation included acute valvular insufficiency (n=7, 64%), cardiac failure (n=3, 27%), dyspnea (n=3, 27%), or no symptom (n=2, 18%). The aortic valve was the most frequently affected (n=8/10, 80%), and vegetations were noted in 4/10 patients (40%). Six patients (55%) underwent surgical valvular replacement. No death from endocarditis was reported.

The systematic review retrieved 42 patients from 40 references: 30 (71%) had GPA, 21 (50%) presented with vegetations, the aortic valve (n = 26, 62%) was mostly involved. Valvular replacement was required in 20 cases (48%) and 5 patients (13%) died from the endocarditic impairment.

CONCLUSION: Endocarditis is a rare manifestation of AAV but might be underdiagnosed. Acute valvular insufficiency may lead to urgent surgery. Implementing transthoracic echocardiography in standard assessment at baseline and follow-up of AAV might reduce the delay to diagnosis and allow earlier specific immunosuppressive treatment before surgery is needed.

INTRODUCTION:

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are small-vessel vasculitides according to the Chapel Hill nomenclature (1) comprising microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). They affect respiratory tracts, renal glomeruli and less frequently other organs (e.g. peripheral nerve, gastrointestinal tract, heart) (1–5). This heterogeneity often leads to diagnosis delay which may cause organ damage and sequelae without an early treatment (3,6). Better knowledge of rare manifestations of AAV could allow prevention of their complications.

Myocardial injury is a severity factor of ANCA-associated vasculitides (4). Cardiac impairment was described for EGPA in up to two out of three patients (5). EGPA can be associated with pericarditis, rhythmic disorders, myocarditis, or coronary vasculitis (7). Pericardial effusion, wall motion defects, and altered systolic function are also frequent in GPA (8).

Libman-Sacks non-infectious endocarditis may be encountered in anti-phospholipid syndrome (9). However, data is scarce about the rare endocarditis-like presentations of AAV. Studies have found cardiac magnetic resonance imaging useful for detecting subclinical cardiac involvement in AAV. A prospective study found subclinical late gadolinium-enhancement in 8 out of 25 subjects (10), but the diagnostic significance of this abnormality remains uncertain, as it could remain or worsen in spite of appropriate treatment and not necessarily be associated with poor clinical outcome (11).

The objective of this study was to describe the endocarditic presentation of AAV, its therapeutic management and clinical outcomes, from both a retrospective cohort study and a systematic review of the literature.**MATERIALS AND METHODS:**

Retrospective study

Study design: This multicenter retrospective study was conducted in France under the auspices of the French Vasculitis Study Group (FVSG) and was following the good clinical practices protocol and the Declaration of Helsinki principles. The local ethics committee (CEPAR 2020-001) approved the study and waived the requirement for informed consent.

Selection of patients: To be included, patients had to have an AAV (GPA, EGPA, or MPA) fulfilling the ACR 1990 criteria (12) or the 2012 revised Chapel Hill consensus conference (1), together with a specific endocarditic disease (ultrasonographic images evoking endocarditis, *i.e.* vegetation, abscess, valvular insufficiency or perforation). Patients were excluded if they presented infectious endocarditis (positive bacterial or fungal blood cultures, positive serology for *Coxiella*), marantic endocarditis (active solid cancer), lupus or anti-phospholipid syndrome. Members of the FVSG were contacted by LJ and PC through the FVSG network for any suspected cases.

Data collection**:** The following information was recorded: general characteristics (age, gender, BMI), vasculitis subtype (GPA, EGPA, MPA), ANCA (pattern, titer, specificity), clinical presentation (cutaneous, ear/nose/throat (ENT), neurological, pulmonary, renal impairment…), cardiological symptoms, laboratory results at onset (estimated glomerular filtration rate (eGFR), C-reactive protein (CRP) and Birmingham Vasculitis Activity Score), blood cultures and serologic test for Coxiella, cardiological presentation, echocardiographic characteristics, electrocardiogram (EKG), histological data, treatment (valvular replacement, immunosuppressive drugs, antibiotic therapy), and outcome (echocardiography after treatment, mortality, follow-up duration).

Systematic review

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and was registered on PROSPERO (CRD42020213228).

Search strategy: A comprehensive search of the following electronic databases was conducted on September 2020 by the author AD: MEDLINE via PubMed, EMBASE, and Cochrane library. A dedicated search algorithm was developed for each database and included both MeSH or Emtree terms and free-text words related to AAV and valvular endocarditis. We also searched the reference lists of included studies. Since AAV valvular impairment is very rare, we chose not to limitate in time the literature search.

Eligibility criteria: All reports on patients with AAV with valvular involvement were eligible, without restriction on the publication date. We excluded articles describing the association between infectious endocarditis and ANCA positivity or systemic vasculitis, and articles unavailable in English or French.

Selection process: Eligible articles were independently selected by LJ and TL. All disagreements about inclusion were solved by a discussion with, if needed, the help of a third reviewer (PC) until consensus was reached. The review authors were not blinded to the names of the journals, authors, or institutions.

Data extraction: Two review authors (LJ and TL) independently extracted the following data from the included studies:

- General: authors, year, and journal, period of recruitment, country
- Study design: prospective or retrospective, single-center or multicenter study
- Population: age, gender, vasculitis type (GPA, MPA, EGPA), new diagnosis or relapse, organ involvement
- ANCA positivity and type, anti-myeloperoxidase (MPO), anti-proteinase 3 (PR3) antibodies

- AAV treatment (immunosuppressive therapy)
- Time between diagnosis of vasculitis and endocarditis
- Valvular involvement: location, valvular damage
- Pathological findings
- Endocarditis treatment (immunosuppressants, antibiotics, surgery)
- Evolution of valvular imaging
- Clinical outcome (mortality, follow-up duration)

Evaluation of the methodological quality: The methodological quality of the included studies was evaluated by the Critical Appraisal Skills Program checklist for cohort studies.

***Statistical analysis*:** Analyses were descriptive: we used frequencies and percentages for qualitative variables and median (interquartile range, IQR) for quantitative variables. Analyses were performed using R Studio (Version 1.4.1103).

Data availability: Dataset and R code are available upon reasonable request to the corresponding author.

RESULTS:

Retrospective multicenter cohort:

Twelve patients were identified in 9 French centers. One was excluded because of anticardiolipin positivity, eleven patients were assessed for final analysis. Results are shown in Tables 1-2 (see details per patient in Supp. Table 1).

Patients' characteristics: Of the 11 analyzed patients, 4 (36%) were male, the median age at diagnosis of the vasculitis was 58 (IQR 52.5-63) years. Nine patients (82%) had GPA, one had MPA (9%) and one unclassified anti-PR3 AAV. ANCA were positive in 90% of cases (n=10): 5 patients (45%) had anti-PR3 and 5 (45%) had anti-MPO antibodies. Initial clinical

presentations included ENT impairment with rhinitis (n=7, 64%) and sinusitis (n=4, 36%), followed by lung nodules (n=4, 36%), renal insufficiency (n=4, 36%), and neuropathy (n=4, 36%). The median BVAS at onset was 24 (IQR [21-25]).

Histological findings confirmed the diagnosis of AAV in 7 patients (87%, data missing for 3 patients), 2 patients (25%) had positive lung biopsies, 1 patient (12%) had ENT, 1 patient (12%) had kidney and 1 (12%) had both kidney and ENT compatible histological data. Valvular histology confirmed diagnosis of AAV in two patients (25%).

Endocarditic presentation: Non-microbial endocarditis was diagnosed simultaneously with the AAV in 5 patients (45%) and was a relapse of a previously diagnosed vasculitis in 6 patients (55%). The median time between vasculitis onset and relapse as endocarditis was 4.7 years (IQR [4.1-6.5]). Seven patients (64%) presented with acute valvular insufficiency, 3 patients (27%) had acute cardiac failure. Endocarditic impairment was diagnosed on routine echocardiography in 2 patients without cardiological symptoms (18%).

Endocarditis presentations included vegetation (n=4/10, 40%), followed by endocardium abscesses (n=3/10, 30%), isolated valvular insufficiency (n=2/10, 20%), and valvular thickening without vegetation (n=1/10, 10%). The most impaired valve was the aortic (n=8/10, 80%), followed by the mitral valve (n=2/10, 20%). One patient had two valves impaired (aortic and mitral, 10%). Left ventricular ejection fraction (LVEF) was globally preserved (median 58%, IQR [48-66]). Two patients had associated pericarditis (27%), one had myocarditis (9%) diagnosed by echocardiographical, EKG and biological data.

Treatments and outcomes: A total of 9 patients (82%) received immunosuppressive therapy: five patients (45%) had immunosuppressants alone and 4 patients (36%) underwent valvular replacement followed by immunosuppressants. Two patients (18%) had surgery alone. Indications for surgery were acute valvular insufficiency (4 patients, 36%) or acute cardiac and valvular insufficiency (2 patients, 18%). The most frequently prescribed

immunosuppressants were steroids pulses (n=6, 55%), cyclophosphamide (n=6, 55%), oral steroids (n=7, 64%), and rituximab (n=4, 36%).

Histology was available for 5 patients: 4 samples were compatible with AAV (3 granulomas, one inflammatory infiltrate) one was aspecific (sclerosis and calcifications). Macroscopic view and histology (compatible with GPA) for patient 1 are presented in Figure 1.

All patients had normalized echocardiography after treatment (data missing for 2 patients). No death was linked to endocarditis after a median follow-up duration of 19 months (IQR [10.5-28.5]).

Systematic review results:

Study selection: The screening retrieved 276 references, of which 34 duplicates were removed (Supp. Fig. 2). Of the remaining 242 records, 181 were excluded because not matching the selection criteria: 100 were AAV without valvular involvement, 60 were infective endocarditis, 14 did not involve AAV, 7 did not report patient cases. Sixty-one reports were sought for retrieval, 8 were not retrieved, without answer to author solicitation for missing papers. Fifty-three reports were assessed for eligibility, of which 11 were excluded because of unavailability in English or French, one did not present enough information to allow data extraction, one was already included in the retrospective cohort (13). Forty studies about 42 individuals were included in the systematic review (2 reports described 2 patients). (Supp. Table 2 and 3).

Study characteristics: All included studies were case reports (listed in Supp. Table 2, with individual data in Supp. Table 3).

Patient characteristics **(Table 1):** Twenty-eight patients (67%) were male with a median age of 45.5 (IQR 28-54) years. All patients had AAV: GPA (n=30, 71%), EGPA (n=5, 12%), or MPA (n=2, 5%), 5 patients (12%) had unspecified AAV. c-ANCA were found in 14 patients

(50%), p-ANCA in 6 (21%), unspecified in 1 (4%), while 7 patients were ANCA-negative (25%). ANCA specificity was available in 17 cases: anti-PR3 in 76% and anti-MPO in 23%. AAV most frequently presented with acute kidney insufficiency (n = 22, 55%), cutaneous manifestations (n = 20, 50%), sinusitis (n = 15, 37%), intra-alveolar hemorrhage (n=15, 37%), and osteo-articular involvement (n=14, 35%). Non-valvular histological findings were compatible with AAV in 23 patients, on skin (n=19, 45%), kidney (n=13, 31%), ENT (n=4, 9%) and/or lung (n=3, 7%) biopsies.

Endocarditic presentation (Table 2): Twenty-eight patients (67%) had a simultaneous diagnosis of AAV and endocarditic impairment, at a median age of 47 (IQR 31-56) years. Fourteen patients (33%) presented endocarditis as a relapse, in median 3 years after the AAV diagnosis (IQR [1-5]).

Twenty patients (49%) presented with acute heart failure, 32 (78%) had acute valvular insufficiency (data missing for 1 patient). The most frequent endocarditic presentation was vegetation (n = 21, 50%), followed by perforation (n = 5, 12%). Histology of the valves was available in 21 cases and consistent with AAV in 15 (n = 15/20, 75%).

Treatments and outcomes (Table 2): Immunosuppressors (IS) were prescribed to 39 of 42 patients (93%), alone (n = 20) or in addition to a valvular replacement (n = 19). One patient had surgery alone (without IS), two patients neither had surgery nor IS. The most frequently prescribed IS were oral steroids (n=33, 82%), followed by cyclophosphamide (n=21, 52%), steroid pulses (n = 13, 32%), and rituximab (n = 8, 20%). Among the 20 patients having received IS alone, 6 presented persisting valvular involvement at follow-up (30%).

After a median follow-up of 10 months (IQR [1.9-15.5]), five deaths linked to the valvular involvement were reported (13%).

DISCUSSION:

In this study, we report 11 cases of non-infective endocarditis in AAV, and 42 cases from a systematic review of the literature.

Similarly to the literature review, most patients from our cohort were diagnosed with GPA. However, the higher rate of patients with anti-MPO positivity than expected (45%) in our patients was not confirmed in the literature (28%) (14). Indeed, it has been suggested that ANCA specificity might not be sufficient to classify AAV (15). Studies focusing on anti-MPO-GPA (16–18) did not find an overrepresentation of cardiac involvement, but they were not powered to detect such a difference.

In AAV-endocarditis, the aortic valve was the most frequently impaired, followed by the mitral valve. Patients mostly had only one affected valve. Interestingly, the valvular damage was isolated from other cardiac impairments: very few patients had concomitant myocarditis or pericarditis. Vegetations or aseptic abscesses were the most common presentations but isolated regurgitation or valvular thickening were also observed: the echocardiographic features do not help to distinguish AAV endocarditis from infective (19) or Libman-Sacks endocarditis (20).

Most patients presented with good functional outcome after immunosuppressive therapy, with or without surgical valvular replacement. This might be explained by the rapid diagnosis and management of the valvular impairment in specialized centers, and the close follow-up of patients. We cannot draw definitive conclusions on the management of AAV endocarditis from our study: AAV management should be based on the current guidelines (21). We observed many patients with complete regression of the valvular damage with medical treatment alone. As in infective endocarditis (22), valvular surgery is mandatory in patients with heart failure. About half of the patients from our cohort underwent valvular replacement, which is similar to what we observed in the literature. Accordingly, steroids were the main immunosuppressive treatment used, followed by cyclophosphamide. However,

we observed no persisting valvular disease after immunosuppressive therapy alone in our cohort, while this was observed in 30% of the patients from the literature review. This might be an effect of our small cohort size, or on the contrary to an echocardiography controlled too early in the literature review, as the median follow-up duration was shorter in the literature than for our patients (19 months (IQR 11-29) vs 5.5 months (IQR 1.9-15.5)).

Overall, gathering data from our retrospective cohort and the literature review, 26 patients (49%) benefited from valvular surgery, mostly required because of acute cardiac or valvular insufficiency. We do not have sufficient data to draw conclusions about the vegetation size that would require surgery, thus cardiac and valvular dysfunction appear as logical requirements for valvular replacement. These results also suggest that half of the patients can have serious cardiac impairment, which could explain the overall 9% mortality rate. Immunosuppressants are required for AAV and showed effectiveness without surgery in some patients. Detecting endocarditic impairment before valvular or cardiac insufficiency and treating patients with immunosuppressants might be sufficient to avoid surgery in some cases, or guide the therapeutic decision towards stronger therapies (e.g. cyclophosphamide or corticoid pulses) if endocarditic impairment is associated to the AAV diagnosis or relapse.

Our study comports limitations: firstly, we had to face missing data given the retrospective design. However, AAV are a rare form of systemic diseases, and their low prevalence associated to the rarity of the endocarditic presentation would have made the creation of a prospective cohort difficult. Our study lacks functional evaluation of patients after treatment, with assessment of clinical scores such as NYHA (23) for dyspnea upon follow-up. Secondly, this study exposes to center bias as participating centers are familiar with such rare afflictions and have access to a large panel of complementary exams, while

this might be arduous in smaller centers. Thirdly, our cohort was small and did not allow us to study long-term outcome properly.

In conclusion, the endocarditic presentation of AAV is a scarce form of valvular impairment which might be under-diagnosed and require valvular surgery. Assessing valvular function in AAV patients with non-invasive techniques (*i.e.* transthoracic echography) might help to have an extensive assessment of newly diagnosed patients, and should be implemented during follow-up.

Author participation:

LJ reviewed the files, extracted and analyzed the data for the retrospective cohort, selected studies in the systematic review and extracted data, and wrote the first draft of the manuscript.

AD conducted the literature search.

TL selected the studies in the systematic review and extracted data.

PB, H de B, P Cathebras, CA, SF, VP, MR, N MS, MM, LG, XP, BT provided eligible files to the study.

P. Charles designed and supervised the study.

All co-authors reviewed and approved the final manuscript.

REFERENCES:

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

2. McGeoch L, Carette S, Cuthbertson D, et al. Cardiac Involvement in Granulomatosis with Polyangiitis. J Rheumatol 2015;42:1209-12.

3. Hunter RW, Welsh N, Farrah TE, Gallacher PJ, Dhaun N. ANCA associated vasculitis. BMJ 2020;m1070.

4. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Toumelin PL. The Five-Factor Score Revisited: Assessment of Prognoses of Systemic Necrotizing Vasculitides Based on the French Vasculitis Study Group (FVSG) Cohort. Medicine 2011;90:19-27.

5. Dennert RM, van Paassen P, Schalla S, et al. Cardiac involvement in churg-strauss syndrome. Arthritis Rheumatol 2010;62(2)627-34.

6. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. Arthritis Rheumatol 2021;73:1366-83.

7. Knockaert DC. Cardiac involvement in systemic inflammatory diseases. European Heart Journal 2007;28:1797-804.

8. Oliveira GH, Seward JB, Tsang TS, Specks U. Echocardiographic findings in patients with Wegener granulomatosis. Mayo Clinic proceedings 2005;80:1435-40.

9. Lee JL, Naguwa SM, Cheema GS, Gershwin ME. Revisiting Libman–Sacks Endocarditis: A Historical Review and Update. Clinic Rev Allerg Immunol 2009;36:126-30.

10. Giollo A, Dumitru RB, Swoboda PP, et al. Cardiac magnetic resonance imaging for the detection of myocardial involvement in granulomatosis with polyangiitis. Int J Cardiovasc Imaging 2021;37:1053-62.

11. Dunogué B, Terrier B, Cohen P, et al. Impact of cardiac magnetic resonance imaging on eosinophilic granulomatosis with polyangiitis outcomes: A long-term retrospective study on 42 patients. Autoimmunity Rev 2015;14:774-80.

12. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of churg-strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheumatol 2010;33:1094-100.

13. Lacoste C, Mansencal N, m'rad MB, et al. Valvular involvement in ANCA-associated systemic vasculitis: a case report and literature review. BMC Musculoskelet Disord 2011;12:50.

14. Cornec D, Gall EC-L, Fervenza FC, Specks U. ANCA-associated vasculitis — clinical utility of using ANCA specificity to classify patients. Nat Rev Rheumatol 2016;12:570-9.

15. Windpessl M, Bettac EL, Gauckler P, Shin JI, Geetha D, Kronbichler A. ANCA Status or Clinical Phenotype - What Counts More? Curr Rheumatol Rep 2021;23:37.

16. Schirmer JH, Wright MN, Herrmann K, et al. Myeloperoxidase-Antineutrophil Cytoplasmic Antibody (ANCA)-Positive Granulomatosis With Polyangiitis (Wegener's) Is a Clinically Distinct Subset of ANCA-Associated Vasculitis: A Retrospective Analysis of 315 Patients From a German Vasculitis Referral Center. Arthritis Rheumatol 2016;68:2953-63.

17. Monti S, Felicetti M, Delvino P, et al. Anti-neutrophil cytoplasmic antibody specificity determines a different clinical subset in granulomatosis with polyangiitis. Clin Exp Rheumatol 2021;39 Suppl 129:107-13.

18. Chang D-Y, Li Z-Y, Chen M, Zhao M-H. Myeloperoxidase-ANCA-positive granulomatosis with polyangiitis is a distinct subset of ANCA-associated vasculitis: A retrospective analysis of 455 patients from a single center in China. Semin Arthritis Rheum 2019;48:701-6.

19. Habib G, Badano L, Tribouilloy C, et al. Recommendations for the practice of echocardiography in infective endocarditis. Eur J Echocardiogr 2010;11:202-19.

20. Roldan CA, Tolstrup K, Macias L, et al. Libman-Sacks Endocarditis: Detection, Characterization, and Clinical Correlates by Three-Dimensional Transesophageal Echocardiography. J Am Soc Echocardiogr 2015;28:770-9.

21. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583-94.

22. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075-128.

23. Caraballo C, Desai NR, Mulder H, et al. Clinical Implications of the New York Heart Association Classification. JAHA 2019;8:e014240.

FIGURE LEGENDS:

Figure 1. Macroscopic and histological data from patient 1 (Granulomatosis with poly-angiitis, endocarditis with valvular replacement, aortic valvular abscess)

A, B: Macroscopic view of the aortic valve: thickened sigmoid leaflets

C: Histological findings of the aortic valve: granulomas with multinucleated giant cells, Hematoxylin and eosin (H&E) stain, x200

D: Fibrinoid necrosis of the aortic valve (H&E stain, x200)