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

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1 **Running title:** Endocarditic impairment of AAV.

2

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

5

6

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45 **Author declaration:**

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48

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53

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

56

57 **Key messages:**

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

63 **ABSTRACT:**

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

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

73 **RESULTS:** The retrospective cohort included ten patients (91%) with GPA and one (9%)
74 with MPA. Clinical presentation included acute valvular insufficiency (n=7, 64%), cardiac
75 failure (n=3, 27%), dyspnea (n=3, 27%), or no symptom (n=2, 18%). The aortic valve was
76 the most frequently affected (n=8/10, 80%), and vegetations were noted in 4/10 patients
77 (40%). Six patients (55%) underwent surgical valvular replacement. No death from
78 endocarditis was reported.

79 The systematic review retrieved 42 patients from 40 references: 30 (71%) had GPA, 21
80 (50%) presented with vegetations, the aortic valve (n = 26, 62%) was mostly involved.
81 Valvular replacement was required in 20 cases (48%) and 5 patients (13%) died from the
82 endocarditic impairment.

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

88 **INTRODUCTION:**

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

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

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

109

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

113 **Retrospective study**

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

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

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

135 **Systematic review**

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

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

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

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

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

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

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

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

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

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

176

177 **RESULTS:**

178 **Retrospective multicenter cohort:**

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

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

186 presentations included ENT impairment with rhinitis (n=7, 64%) and sinusitis (n=4, 36%),
187 followed by lung nodules (n=4, 36%), renal insufficiency (n=4, 36%), and neuropathy (n=4,
188 36%). The median BVAS at onset was 24 (IQR [21-25]).

189 Histological findings confirmed the diagnosis of AAV in 7 patients (87%, data missing for 3
190 patients), 2 patients (25%) had positive lung biopsies, 1 patient (12%) had ENT, 1 patient
191 (12%) had kidney and 1 (12%) had both kidney and ENT compatible histological data.
192 Valvular histology confirmed diagnosis of AAV in two patients (25%).

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

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

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

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

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

216 All patients had normalized echocardiography after treatment (data missing for 2 patients).

217 No death was linked to endocarditis after a median follow-up duration of 19 months (IQR
218 [10.5-28.5]).

219

220 **Systematic review results:**

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

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

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

236 (50%), p-ANCA in 6 (21%), unspecified in 1 (4%), while 7 patients were ANCA-negative
237 (25%). ANCA specificity was available in 17 cases: anti-PR3 in 76% and anti-MPO in 23%.
238 AAV most frequently presented with acute kidney insufficiency (n = 22, 55%), cutaneous
239 manifestations (n = 20, 50%), sinusitis (n = 15, 37%), intra-alveolar hemorrhage (n=15,
240 37%), and osteo-articular involvement (n=14, 35%). Non-valvular histological findings were
241 compatible with AAV in 23 patients, on skin (n=19, 45%), kidney (n=13, 31%), ENT (n=4,
242 9%) and/or lung (n=3, 7%) biopsies.

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

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

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

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

259

260 **DISCUSSION:**

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

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

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

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

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

291

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

303

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

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

313

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

319

320 **Author participation:**

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

324 AD conducted the literature search.

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

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

328 P. Charles designed and supervised the study.

329 All co-authors reviewed and approved the final manuscript.

1

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1 **FIGURE LEGENDS:**

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

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

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

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

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