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Different patterns and specific outcomes of large-vessel involvements in giant cell arteritis

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ABSTRACT

Large-vessel involvement (LVI) in giant cell arteritis (GCA) includes different clinical and imaging patterns that are rarely described separately at diagnosis and whose specific cardiovascular outcomes are unknown.

We conducted a nationwide retrospective study and included GCA patients with LVI demonstrated on imaging at diagnosis between 2007 and 2017. We analyzed the prognosis of three different imaging patterns of LVI present at diagnosis, with some of them overlapping but with the first one present in all patients: 1) inflammation of the aorta and/or its branches; 2) dilation of the aorta; and 3) stenosis of the aortic branches. A control group of GCA patients without LVI was constituted.

We included 183 patients with LVI and 105 controls without LVI. Altogether, among the 183 patients who all showed inflammation of the aorta and/or its main branches, concomitant aortic dilation and large-vessel stenosis were observed in 27 (15%) and 55 (30%) patients, respectively. During the follow-up period, new cardiovascular events occurred in 49% and 11% of LVI patients and controls, respectively ($p < 0.0001$). Inflammation of the aorta and/or its branches (HR: 3.42 [2.09–5.83], $p < 0.0001$) and large-artery stenosis (HR: 2.75 [1.80–4.15], $p < 0.0001$) were independent predictive factors of new cardiovascular events. Conversely, the use of an immunosuppressant besides corticosteroids was a protective factor against new cardiovascular events (HR: 0.44 [0.29–0.66], $p < 0.0001$) and the development of aortic dilation (HR: 0.43 [0.23–0.77], $p = 0.005$).

This study suggests different forms of cardiovascular events according to the initial imaging pattern of LVI.

1. Introduction

Giant cell arteritis (GCA) is a systemic vasculitis that typically affects cranial vessels in patients over 50. However, in addition to the cranial presentation, proximal large vessels, i.e., the aorta and its main branches, can be affected in 30%–80% of GCA patients [1–9], whereas the involvement of peripheral limb arteries is more rarely reported [10–13]. Radiological assessment of large vessels is currently widely performed in GCA to demonstrate vasculitis, even replacing the histological criterion in some large-scale studies [14]. Imaging patterns of vascular changes on imaging described in GCA include inflammation of the aorta and/or of its main branches, solely or in association with

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aortic dilation or large-vessel stenosis [4,8,12,15–19]. Subsequent clinical consequences of these large-vessel involvements (LVI) range from acute symptomatic vascular events (e.g., aortic dissection or vascular occlusions) to non-symptomatic presentations (inflammation of the aorta and/or of its main branches or aortic dilation detected on systematic radiologic assessment) [5,20,21]. Therefore, LVI in GCA covers a large spectrum of different clinical and radiological patterns that are often pooled together in the published cohorts (often under the generic term “large-vessel vasculitis").

Previous studies reported a worse vascular outcome in patients with LVI, especially more cardiovascular events and lower survival, due to early or late aortic dissections [5,19,22,23]. It has been suggested that late aortic dilation – increasing the risk of aortic dissection – occurs more readily in patients with demonstration of aortic inflammation [3,15,24,25]. However, the analysis of the different imaging patterns in GCA patients with LVI and their relationships with patients’ prognosis have been poorly investigated.

In this retrospective multicenter study, we analyzed the patients’ characteristics and subsequent prognosis according to the imaging patterns of LVI at GCA diagnosis.

2. Patients and methods

2.1. Patients and subgrouping

We conducted a nationwide retrospective study in six referral centers for GCA (Caen, Limoges, Nantes, Marseille, Lille, and Paris - La Pitié Salpêtrière) and included patients if they satisfied the three following criteria: 1) a diagnosis of GCA with LVI demonstrated on imaging made between 2007 and 2017; 2) at least one large-vessel imaging was repeated during the follow-up period; and 3) patients had to be followed-up at least 6 months, unless they died earlier.

LVI was demonstrated in all patients on a CT angiography (CTA) or a magnetic resonance angiography (MRA) to have a morphological assessment of the large vessels’ lumen and these procedures were performed at diagnosis, i.e., no later than 10 days after the start of treatment. Some patients also underwent, besides CTA or MRA, a positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG) coupled with computed tomography (PET/CT) but this imaging was not sufficient for patient inclusion in this study as it is not suitable for assessing the morphology of the arterial walls.

A standardized electronic form was used to collect data in each center, and the main investigator of the study gathered the forms from the 6 centers to constitute a common database.

Based on previous publications [6–8,12,13], we distinguished three different imaging patterns of LVI present at diagnosis, some of them overlapping but the first one being present in all patients: 1) inflammation of the aorta and/or of its branches; 2) dilation of the aorta; and 3) stenosis of the aortic branches. We decided to include only patients with demonstration of inflammation on the aorta and/or its branches on imaging to reduce the risk of considering other causes of vascular abnormalities, especially atherosclerosis, in those with aortic dilation or large-vessel stenosis. We considered that aortic dilation or vascular stenosis were related to GCA only if there existed a concomitant parietal inflammation on the same considered or the adjacent arterial segments. We therefore noted in each patient which pattern(s) of LVI was observed on imaging. We did not include in this study patients with initial aortic dissection as they represent a small subset of patients with a poor vascular prognosis at diagnosis. Moreover, in most cases, GCA is fortuitously diagnosed after the aortic dissection.

Finally, a control group was constituted with patients from Caen and Limoges. We included in this control group all patients diagnosed with GCA between 2007 and 2017 with a positive temporal artery biopsy (TAB) and negative large-vessel imaging performed at diagnosis. All of them also performed at least one other imaging of the aorta during the follow-up period that did not show occurrence of large-vessel inflammation. However, we noted in these patients if an aortic dilation or dissection appeared on imaging as well as large-vessel stenosis.

In the six centers, since many studies have shown LVI in 30–80% of GCA patients, large-vessel imaging is performed in a high proportion of patients at diagnosis, even in the absence of LVI-related symptoms. Each imaging was specifically asked to search for LVI.

This study was conducted in compliance with good clinical practices and the Declaration of Helsinki principles. In accordance with French public health law (Art. L 1121-1-1, Art. L 1121-1-2), written consent from the patient is not required for this type of retrospective study. Our local ethics committee confirmed the observational non-interventional retrospective nature of our cohort.

2.2. Studied parameters and definitions

In each patient, we analyzed demographics, cardiovascular risk factors, past history of cardiovascular ischemic disease (myocardial infarction and stroke), clinical manifestations including cranial symptoms (headaches, scalp tenderness, jaw claudication, abnormalities on the temporal artery, and visual ischemic signs), extracranial signs (limb claudication or distal limb ischemic signs, pulseless limb and vascular murmurs) and polymyalgia rheumatica (PMR). The delay between the first symptoms/signs and the diagnosis of GCA was also recorded in each group. We also recorded whether or not patients satisfied the criteria from the American College of Rheumatology (ACR) [26].

Laboratory tests and histology findings (on TAB or on extratemporal vascular sample), when available, were also recorded.

Imaging results were recorded from the initial radiological reports. Adapted from previous reports, large-vessel inflammation (i.e., aortitis and/or inflammation of aortic branches) corresponded on CTA and MRA to a circular vascular thickening ≥ 2.2 mm [1,8,27,28] +/− with contrast enhancements, and on PET/CT to a vascular uptake superior to the physiologic uptake of the liver (grade 3 according to the classification from Meller et al.) [29]. Stenotic lesions were analyzed on morphologic procedures, such as CTA or MRA, and corresponded to a reduced vascular lumen > 50%. We differentiated on imaging vascular inflammation from atherosclerosis on the following points: no atheromatous plaque was observed within vascular thickening or vascular uptakes on the considered arterial segment and vascular thickening or uptakes had to be circumferential and homogeneous on imaging. Adapted from previous reports, the aortic root, aortic arch, and descending aorta were considered to be dilated when the aortic diameter was ≥ 4.5 cm, $\geq$ 4 cm and ≥ 3.5 cm, respectively [15]. Repetitive imaging during the follow-up period were CTA, MRA or PET/CT, and were performed in patients with initial LVI and in controls.

Treatments were analyzed, especially glucocorticoid (GC) management (starting dose, GC tapering schedule, and duration) and the use of a GC-sparing agent. The GC tapering schedule in France is not strictly standardized. However, in the absence of ischemic complications, a starting dose of 0.7 mg/kg/day is consensual and a progressive tapering is planned within the following months with the aim to discontinue GC at 12 months. However, many patients continue a maintenance prednisone dose < 5 mg/day thereafter [30]. Outcomes included the GC discontinuation rate, the occurrence of a relapse (defined as a re-occurrence of clinical signs attributable to GCA along with increased acute phase reactants that required an increase in treatment and with a subsequent clinical and biological improvement) or a GC-dependence (defined when GC dose could not be tapered below 0.30 mg/kg after 6 months or 0.20 mg/kg after 12 months and was maintained without a decrement over 2 years to assure a permanent disease control and avoid a relapsing course).

All patients included in this study were longitudinally followed-up at each hospital in a department of internal medicine and were regularly seen for medical controls by their treating physician at a frequency left to their own choice (from two to six visits per year).

Repeated imaging were performed during follow-up at time intervals left to the choice of the treating physician. No patient was lost during follow-up. In each patient (including patients with initial LVI and controls), we analyzed the occurrence of new cardiovascular complications during the follow-up period, namely, stroke, myocardial infarctions, limb or any other organ ischemia (e.g., mesenteric infarction), aortic dilation (not observed on the first imaging), aortic dissection and any vascular surgery. We differentiated vascular surgeries performed for an aortic complication (aortic root surgery or valvular surgery) from those performed for a revascularization (arterial bypass, stenting or vascular surgery for an ischemic complication). We did not analyze the progression of aortic dilations present at diagnosis but we recorded whether an aortic dissection occurred or whether a vascular surgery was required.

2.3. Statistical analyses

Categorical variables are expressed as numbers (%), and quantitative variables are expressed as medians [range]. To compare two groups, categorical variables were analyzed using the Pearson or Fisher Chi-square test, as appropriate, and quantitative variables were analyzed using Wilcoxon's rank-sum test. To compare the three subgroups of imaging patterns, we used the Chi-square for homogeneity for the categorical analyses and the Kruskal-Wallis test for quantitative variables.

A Cox proportional hazards model was used to assess predictive factors associated with new cardiovascular complications, ischemic events and aortic dilation. Hazard ratios (HRs) and 95% confidence intervals (CI) were computed for each predictor in the univariate analysis and in the multivariate model using the backward stepwise approach using variables that reached $p < 0.1$ in univariate analyses. We analyzed the cardiovascular event-free survival in patients with LVI and in controls, as well as in each different pattern of LVI using life tables and the Kaplan-Meier method, and these were compared using the log-rank test. To account for death as a possible competing event, we also compared the cumulative incidence function of cardiovascular events between LVI (and different LVI subgroups) and controls using Gray's test in a sensitivity analysis.

The statistical analyses were computed using JMP 9.0.1 (SAS Institute Inc., Cary, NC, USA). A $p \leq 0.05$ defined statistical significance, except for the survival curves pairwise comparisons between each LVI pattern and controls, in which we applied a Bonferroni correction ($p < 0.016$).

3. Results

3.1. Characteristics and imaging patterns of patients with large-vessel involvement at diagnosis

One hundred and eighty-three patients with LVI were included in this study and were compared to 105 control patients without LVI on imaging at diagnosis. Their characteristics are described and compared in Table 1. An arterial biopsy was performed in 169 patients with LVI that showed giant cell vasculitis in 110 (65%) of them, including 103/165 (62%) on TAB and 7 on large-vessel samples obtained during a vascular surgery. Among the last 7 patients, three also underwent a TAB that was negative. Twenty-nine (16%) patients with LVI on imaging had 2 ACR criteria.

At GCA diagnosis, when compared to controls, patients with LVI were younger ($p < 0.0001$) and showed less frequent cranial signs ($p < 0.0001$) but more frequent disease–related limb claudication ($p < 0.0001$). The LVI was evidenced on CTA in 101, on CTA and PET/CT in 81 and on MRA in one of them. In the control group, no LVI was evidenced on PET/CT performed in 68 patients and on CTA performed in the 37 others. Control patients underwent at least one other aorta imaging procedure at a median delay of 11 [6–134] months after GCA diagnosis that did not show inflammation of the aorta and/or its branches.

Table 1
Characteristics of patients with giant cell arteritis-related large-vessel involvement compared to GCA controls without large-vessel involvement.

	GCA patients with large-vessel involvement at diagnosis (n = 183)	GCA control patients (n = 105)	P
Demographics			
Female	128 (70)	69 (66)	0.46
Age	69 [50–92]	76 [49–90][a]	< **0.0001**
Cardiovascular risk factors			
Hypertension	89 (49)	52 (50)	0.88
Diabetes mellitus	19 (10)	13 (12)	0.60
Dyslipidemia	46 (25)	37 (35)	0.07
Tobacco use	52 (28)	17 (16)	**0.02**
Previous stroke	5 (3)	5 (5)	0.37
Previous coronary disease	10 (5)	6 (6)	0.93
Aspirin use	144 (80)	79 (75)	0.50
Delay of diagnosis, days	82 [5–410]	33 [13–180]	**0.02**
Clinical manifestations			
Fever	60 (33)	31 (30)	0.57
Any cranial sign	121 (66)	97 (92)	< **0.0001**
Headaches	101 (55)	79 (75)	**0.0007**
Jaw claudication	38 (21)	46 (44)	< **0.0001**
Scalp tenderness	36 (20)	52 (50)	< **0.0001**
Abnormalities on TA	35 (19)	39 (37)	**0.0008**
Ophthalmological signs	28 (15)	23 (22)	0.16
Polymyalgia rheumatica	57 (31)	41 (39)	0.17
Limb claudication	48 (26)	0	< **0.0001**
ESR, mm	80 [18–140]	91 [11–138]	0.53
CRP, mg/l	73 [3–312]	89 [3–421]	**0.043**
Hemoglobin, g/dl	11.1 [7.5–15.1]	11.5 [7.4–14.7]	0.18
Positive histology	110/169 (65)	105 (100)	< **0.0001**
On TAB	103/165 (62)	105 (100)	< **0.0001**

Values are number (%) or medians [range]. GCA: giant cell arteritis; TA: temporal artery; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TAB: temporal artery biopsy.
[a] The 49-year-old patient showed typical features of GCA and a positive TAB.

Supplementary Fig. 1 depicts the different imaging patterns observed in the 183 patients with LVI at diagnosis. All of them showed inflammation of the aorta and/or its main branches. The aorta and its main branches were affected in 117 (64%) patients, while only the aorta and only the main aortic branches were involved in 49 (27%) and 17 (9%), respectively. Isolated inflammation of the aorta and/or of its branches was the only pattern observed in 104 (57%) patients, whereas the 79 (43%) other patients also exhibited another imaging pattern (76 and 3 patients presented two and three concomitant imaging patterns, respectively). Altogether, among these 183 patients, a concomitant aortic dilation was observed in 27 (24 on the thoracic aorta and 3 on the suprarenal abdominal aorta) patients (15%), and large-vessel stenosis in 55 (30%). Locations of large-vessel stenosis are indicated in (Supplemental Table 1). Subclavian and axillary arteries were more frequently involved, both in 54% of patients. Among the 55 patients with vascular stenosis, 27 (49%) showed multiple stenoses affecting different non-adjacent arteries.

Only 3 (1.6%) of the 183 patients with LVI showed concomitant aortic dilatation and large-vessel stenosis.

When comparing the characteristics at diagnosis of the 104 patients with the pattern of isolated inflammation of the aorta and/or its branches to each other pattern (aortic dilation and large-vessel stenosis, Supplementary Fig. 1), patients with isolated inflammation of the aorta and/or of its branches presented more frequently with fever than the other patterns ($p = 0.0008$). Moreover, patients with large-vessel stenosis showed more frequent limb claudication ($p < 0.0001$) and lower

Table 2
Outcomes of patients with giant cell arteritis according to the presence of a large-vessel involvement at diagnosis.

	Patients with large-vessel involvement at diagnosis (n = 183)	GCA control patients (n = 105)	P
GC doses, mg/kg			
At onset	0.82 [0.50–1]	0.73 [0.60–1.2]	0.63
At month 6	0.2 [0.08–0.45]	0.18 [0.07–0.70]	0.20
At month 12	0.135 [0.05–0.21]	0.115 [0.01–0.59]	0.59
Relapse	125 (68)	52 (50)	**0.002**
GC-dependence	89 (49)	38 (36)	**0.04**
GC duration, months	28 [0–212][a]	23 [8–84]	0.15
Use of immunosuppressant	54 (30)	19 (18)	0.03
Follow-up, months	49 [0–243][a]	43 [1–158]	0.56
New cardiovascular events	89 (49)	12 (11)	**< 0.0001**
Delay after diagnosis, months	30 [1–134]	46 [1–64]	0.68
New events in the first-year post-diagnosis	21/89 (24)	2/12 (17)	0.59
Events occurring after 12 months	68/89 (76)	10/12 (83)	0.59
Any ischemic event	39 (21)	7 (7)	**0.001**
Stroke	19 (10)	3 (3)	**0.02**
Myocardial infarction	12 (7)	2 (2)	0.08
New aortic dilation during follow-up	42 (23)	4 (4)	**< 0.0001**
New aortic dissection	8 (4)	0	**0.03**
Vascular surgery	34 (19)	0	**< 0.0001**
Aortic surgery	14/34	–	–
Revascularization	22/34	–	–
Death	26 (14)	17 (16)	0.65

Values are number (%) or medians [range]; GC: glucocorticoids.
[a] Two patients died during the first month.

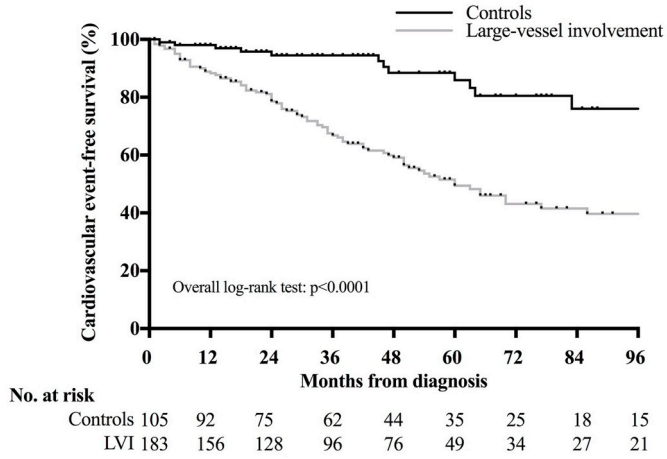

Fig. 1. Kaplan-Meier curves of cardiovascular event-free survival in patients with giant cell arteritis-related large-vessel involvement on imaging at diagnosis (gray line) and in control patients without large-vessel involvement on imaging at diagnosis (black line).

inflammatory parameters (lower CRP levels and higher hemoglobin levels, p = 0.0002 and p = 0.003, respectively). Their demographics, especially their age at GCA diagnosis, and previous cardiovascular risk factors were not different. The delay of diagnosis was not different in the three groups (data not shown).

3.2. Outcomes of patients with large-vessel involvement at diagnosis compared to control patients and according to the different imaging patterns

In Table 2, we compared the treatment regimen and the outcomes of patients with LVI to those of controls. GC doses at initiation and at months 6 and 12 were not different in both groups, nor were the GC durations. However, patients with LVI showed more frequent relapses (p = 0.002) and more GC-dependent disease (p = 0.04) than control patients, although their follow-up durations were not different (49 [0–243] months versus 43 [1–158] months, p = 0.56). In our study, 73 patients (54 with LVI and 19 without) were prescribed an immunosuppressant during follow-up, as a GC-sparing agent in 70 of them (median delay of introduction: 8 [5–122] months after diagnosis). The three other patients received an immunosuppressant at GCA diagnosis following severe stenosis of the limbs. Methotrexate was the most commonly used agent, prescribed to 58 patients (79%). Tocilizumab was used in 8 patients, dapsone in 4, a TNF-alpha blocker in 2 and anakinra in 1.

New cardiovascular events occurred during the follow-up period in 89 (49%) and 12 (11%) of patients with initial LVI and controls, respectively (p < 0.0001), at a median delay of 30 [1–134] months after diagnosis in the former group and 46 [1–64] months in the latter (p = 0.68). Among all patients who experienced a new cardiovascular event, GCA was relapsing at that time in 31 (35%) out of the 89 patients with initial LVI and in one (8%) of the 12 control patients (p = 0.06). In patients with LVI, 13 (15%) out of the 89 patients who experienced a new cardiovascular event and 36 (38%) out of the 94 remaining patients without a cardiovascular event were receiving an immunosuppressant at the time of the event (p = 0.0003). The comparison of patients with LVI according to whether or not they experienced a new cardiovascular event is shown in Supplemental Table 2. Patients with new cardiovascular events were older (p = 0.001), showed more hypertension (p = 0.0005), more limb claudication (p = 0.01) and died more frequently (25% versus 4% in patients without cardiovascular events, p < 0.0001).

Fig. 1 shows poorer cardiovascular event-free survival in patients with LVI than in controls (log-rank test: p < 0.0001). The results of the sensitivity analyses considering death as a competing rather than censored event were consistent (p < 0.0001, by Gray's test) for the comparison between LVI and controls (Supplemental Fig. 2).

Ischemic events (21% in patients with LVI versus 7% in controls, p = 0.001), especially stroke (10% in patients with LVI versus 3% in controls, p = 0.02), were more frequent in patients with initial LVI. Among the 19 patients with initial LVI who experienced a stroke, the vertebrobasilar territory was affected in 14 (74%) of them. Patients with initial LVI also showed more frequently a new aortic dilation (23% in patients with LVI versus 4% in controls, p < 0.0001) and more frequently a new aortic dissection during follow-up (4% in patients with LVI versus none in controls, p = 0.03) than controls. A vascular surgery was required in 19% of the patients with initial LVI versus none in the control group (p < 0.0001). Histological evidence of active vasculitis was obtained in 8 of the 15 available surgical vascular samples.

Table 3
Outcomes of patients with GCA-related large-vessel involvement according to their imaging pattern.

	Isolated inflammation of the aorta and/or its branches (=104)	Aortic dilation (n = 24)	Large-vessel stenoses (n = 55)	p
GC doses, mg/kg				
At onset	0.80 [0.50–1]	0.82 [0.52–1]	0.82 [0.7–1]	0.6
At month 6	0.25 [0.09–0.44]	0.2 [0.08–0.44]	0.28 [0.08–0.45]	0.35
At month 12	0.12 [0.05–0.45]	0.14 [0.06–0.21]	0.15 [0.08–0.20]	0.36
Relapse	71 (68)	17 (71)	37 (67)	0.95
GC-dependence	45 (43)	15 (63)	29 (53)	0.18
GC duration, months	27 [7–82]	25 [0–118][a]	30 [10–212]	0.82
Immunosuppressant use	30 (29)	11 (46)	13 (24)	0.13
Aspirin use	77 (74)	18 (75)	49 (89)	0.08
Follow-up, months	49 [2–190]	48 [0–172][a]	50 [1–243]	0.77
New cardiovascular events	46 (44)	6 (25)	37 (67)	**0.001**
Delay after diagnosis, months	35 [3–134]	117 [1–131]	21 [1–132]	0.07
New events in the first-year post-diagnosis	8/46 (17)	2/6 (33)	11/37 (30)	0.36
Events occurring after 12 months	38/46 (83)	4/6 (67)	26/37 (70)	0.36
Stroke	8 (8)	1 (4)	10 (18)	0.07
Myocardial infarction	4 (4)	0	8 (15)	**0.01**
Limb ischemia	0	0	14 (25)	**< 0.0001**
New aortic dilation during follow-up	35 (34)	0	7 (13)	**0.0002**
New aortic dissection	2 (2)	4 (17)	2 (4)	**0.006**
Vascular surgery	10 (10)	3 (13)	21 (38)	**< 0.0001**
Aortic surgery	8/10 (80)	3/3 (100)	3/21 (14)	**0.0002**
Revascularization	3/10 (30)	0	19/21 (90)	**0.0002**
Death	10 (10)	4 (17)	12 (22)	0.10

Values are number (%) or medians [range]; GC: glucocorticoids.
[a] Two patients died during the first month.

Aspirin use at the time of the cardiovascular event did not differ between the groups.

Finally, the death rate did not differ between the groups (p = 0.65). Three patients with LVI died during the first month.

3.3. Clinical and radiologic outcomes of the different LVI patterns

Outcomes of patients according to the initial imaging pattern are detailed in Table 3. We included the 3 patients with concomitant aortic dilation and vascular stenosis in the group of patients with vascular stenosis (Supplementary Fig. 1). GC management did not differ between the three groups.

Regarding the occurrence of new cardiovascular events during follow-up, patients with initial large-vessel stenosis experienced a higher rate of vascular complications (in 67% of them versus ≤44% in all other groups, p = 0.001), especially limb ischemia in the territory of the stenosis (25% versus none in all other groups, p < 0.0001) and the need for vascular surgery (38% in patients with vascular stenosis versus ≤13% in other patients, p < 0.0001). Revascularization was the most frequent vascular surgery in patients with vascular stenosis (in 19 out of the 21 patients who underwent surgery). The cardiovascular event-free survival in the three patterns and in controls is shown in Fig. 2. Patients with large-vessel stenosis showed the worst outcomes (log-rank test: p < 0.0001). The results of the sensitivity analyses considering death as a competing rather than censored event were consistent (p < 0.0001, by Gray's test) for the comparison between different LVI subgroups and controls (Supplemental Fig. 3).

Patients with isolated inflammation of the aorta and/or of its branches developed more frequently new aortic dilations during the follow-up period (in 34% of them versus ≤13% in other groups, p = 0.0002) on a previous inflammatory segment in 33 out of the 35 involved patients at a median delay of 33 [3–120] months after GCA diagnosis. Patients with aortic dilations at diagnosis developed more aortic dissections during the follow-up period (17% versus ≤4% in the other groups, p = 0.006), at a median delay of 116 [8–131] months after GCA diagnosis and always on the previously dilated segment. At the last follow-up, the death rate was not different in the different subgroups.

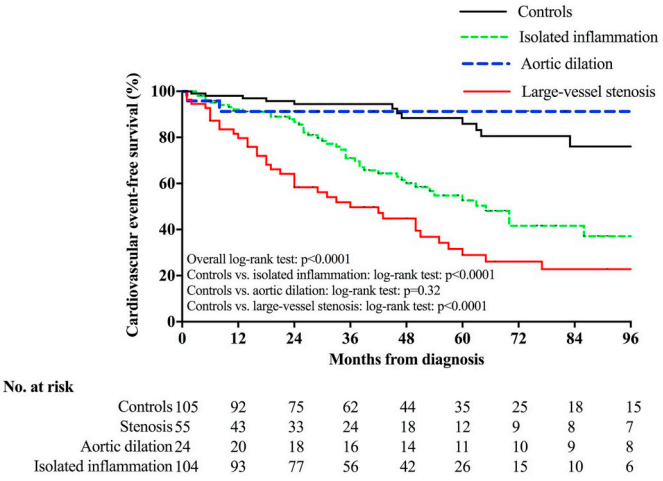

Fig. 2. Kaplan-Meier curves of cardiovascular event-free survival in patients with three patterns of giant cell arteritis-related large-vessel involvement on imaging at diagnosis and in control patients without large-vessel involvement on imaging at diagnosis.

3.4. Predictive factors associated with new cardiovascular events

Table 4 shows the uni- and multivariate analyses conducted to identify predictive factors associated with the occurrence of new cardiovascular events during the follow-up period. Diabetes (hazard ratio (HR): 2.03 [1.14–3.41], p = 0.02), inflammation of the aorta and/or its branches (HR: 3.42 [2.09–5.83], p < 0.0001) and large-artery stenosis (HR: 2.75 [1.80–4.15], p < 0.0001) were independent predictors. Conversely, the use of an immunosuppressant (HR: 0.44 [0.29–0.66], p < 0.0001) and the presence of cranial signs at diagnosis (HR: 0.64 [0.42–0.98], p = 0.04) were protective factors against new cardiovascular events.

Supplemental Table 3 shows the uni- and multivariate analyses conducted to identify predictive factors associated with the occurrence of new ischemic events during the follow-up. GCA-related large-artery stenosis at diagnosis (HR: 6.08 [3.44–10.87], p < 0.0001), previous

Table 4
Factors associated with the occurrence of new cardiovascular events in patients with GCA.

	Univariate analysis		Multivariate analysis	
	HR [95% CI]	P	HR [95% CI]	P
Female	0.90 [0.60–1.38]	0.63		
Age	2.25 [0.84–6.23]	0.11		
Hypertension	1.70 [1.14–2.55]	0.009		
Diabetes mellitus	1.64 [0.93–2.73]	0.08	2.03 [1.14–3.41]	0.02
Dyslipidemia	1.40 [0.92–2.11]	0.12		
Tobacco use	1.03 [0.64–1.59]	0.90		
Previous stroke	1.97 [0.60–4.75]	0.23		
Previous coronary disease	2.44 [1.08–4.74]	0.03		
Aspirin use	0.85 [0.57–1.27]	0.14		
Delay of diagnosis	0.54 [0.03–2.80]	0.54		
Any cranial signs	0.49 [0.32–0.74]	0.001	0.64 [0.42–0.98]	0.04
Limb claudication	2.03 [1.30–3.10]	0.002		
Polymyalgia rheumatica	0.70 [0.45–1.06]	0.097		
C-reactive protein level	0.71 [0.22–2.16]	0.56		
Inflammation of aorta and/or its branches	3.44 [2.15–5.77]	< 0.0001	3.42 [2.09–5.83]	< 0.0001
Large-artery stenosis at diagnosis	2.74 [1.80–4.11]	< 0.0001	2.75 [1.80–4.15]	< 0.0001
Initial aortic dilation	0.75 [0.35–1.42]	0.40		
Glucocorticoid dose at diagnosis	1.02 [0.56–1.87]	0.76		
Glucocorticoid duration[a]	1.57 [0.03–12.95]	0.77		
Glucocorticoid dependency	0.69 [0.41–1.07]	0.13		
Immunosuppressant use	0.61 [0.40–0.91]	0.08	0.44 [0.29–0.66]	< 0.0001
Total patient's follow-up duration	0.998 [0.993–1.001]	0.34		

HR: Hazard ratio; CI: confidence interval.
[a] At glucocorticoid discontinuation or at last follow-up if treatment is ongoing.

coronary disease (HR: 5.10 [2.02–11.21], p = 0.001), diabetes mellitus (HR: 3.61 [1.70–7.17], p = 0.001) and inflammation of the aorta and/or its branches at diagnosis (HR: 1.86 [1.01–3.59), p = 0.045) were independent predictors.

Inflammation of the aorta and/or its branches was the unique independent predictive factor associated with the occurrence of an aortic dilation during the follow-up period (HR: 9.30 [3.74–31.05, p < 0.0001), whereas the use of an immunosuppressant was protective (HR: 0.43 [0.23–0.77], p = 0.005) (Supplemental Table 4).

The small number of aortic dissections that occurred during the follow-up period did not allow a multivariate analysis to be run. However, among the eight patients with LVI who developed an aortic dissection, all of them had a previous aortitis, and 4 had an aortic dilation at onset.

Finally, multivariate analyses failed to identify predictive factors associated with complications occurring before 12 months after diagnosis (data not shown).

4. Discussion

Large-vessel involvement in GCA is proteiform and includes different clinical and imaging patterns. This distinction between the different patterns of LVI has been poorly studied, and we found some relevant findings suggesting different cardiovascular outcomes in patients with LVI. New cardiovascular events were significantly more frequently observed in patients with initial LVI when compared to control patients without LVI at diagnosis. Interestingly, GCA was relapsing, i.e., vasculitis was active, in 35% of patients with initial LVI who experienced new cardiovascular events, suggesting a possible role of GCA in the vascular event. Our study suggests a protective role of immunosuppressants in the occurrence of cardiovascular events. In patients with LVI, those who were taking an immunosuppressant showed less new cardiovascular events.

This study exhibited different subsets of new cardiovascular events according to the pattern of the initial LVI. Indeed, in accordance with previous works, we showed that aortic complications, especially aortic dilation, mainly occurred in patients with isolated inflammation of the aorta and/or its branches [15,24,25]. In addition, aortic dissection during the follow-up period always occurred in this study in patients with previous aortic inflammation and mainly in patients with previous aortic dilation. On the other hand, ischemic events affecting visceral or limb arteries occurred mainly in patients with large-vessel stenosis and required more frequent revascularization surgeries in addition to the medical treatment. Except in patients with a vascular sample showing active vasculitis on the site of the cardiovascular event, the differential diagnosis between GCA and atherosclerosis remains difficult in front of an ischemic event in a GCA patient. However, all limb ischemia during follow-up occurred on the side where vascular stenosis was observed, and imaging showed inflammatory vascular findings rather than atherosclerosis signs. Moreover, most strokes occurring during the follow-up period in these patients affected the posterior territory, which is most often affected in GCA [31]. Interestingly, we found in multivariate analysis that the use of an immunosuppressant was a protective factor against new cardiovascular events, suggesting an effect against vascular inflammation that may favor these new vascular events in GCA. Little is known about the link and interaction between inflammation, atherosclerosis and cardiovascular complications. Although we did not observe more cardiovascular risk factors in patients with initial LVI in comparison with controls at diagnosis, diabetes mellitus and previous coronary disease were both independent predictive factors of new ischemic events, suggesting a possible pathogenic role of atherosclerosis in the occurrence of such complications. Some studies have indicated a higher risk of vascular calcifications in large-vessel vasculitis, especially in Takayasu arteritis (TAK), in areas of vascular inflammation [32–34]. Altogether, these studies support the existence of a probable link between vascular inflammation and the development of vascular calcifications. Patients with vasculitis-related large-vessel stenosis might thus have developed accelerated fibrosing atherosclerosis that leads to ischemic events. However, we did not analyze the link between microcalcifications within vessels and inflammation in this study. Our study did not analyze the impact of aspirin or statin use on the occurrence of cardiovascular events, and most of our patients already received aspirin at the time of the complication. Altogether, this observational study showed an increased risk of cardiovascular events in patients with LVI, but no conclusion can be made on the individual impact of GCA, treatments (including GCs,

immunosuppressants and cardiovascular protective drugs) and atherosclerosis in the occurrence of such events. To date, immunosuppressants are mainly used in GCA as GC-sparing agents or in the setting of a GC-dependency.

Further studies are required to determine whether treatments can be adapted according to these patterns, especially the use of immunosuppressants in the setting of LVI. Recent prospective studies dealing with anti-interleukin-6 receptors [14,35,36] or CTLA-4Ig [37] showed different outcomes, with some patients being unresponsive to these drugs. This suggests, as shown in some biological studies [12] that different cytokine networks are involved in GCA patients with LVI. Thus, a more personalized therapeutic strategy is probably required in patients with GCA, especially in those with LVI. Our finding regarding the protective impact of immunosuppressants on the occurrence of cardiovascular events in patients with LVI should be replicated in other studies.

We did not observe an increased mortality in patients with LVI when compared to controls, as already suggested in other studies [5,23,38]. The younger age of patients with LVI and the relatively short follow-up duration might explain this absence of differences.

Some limitations should be discussed. The retrospective design and the selection of patients do not allow any determination of the prevalence of the different patterns. The retrospective retrieval of data on imaging reports did not include the presence of vessels' dilation on sites other than aorta, although some studies indicated different outcomes in patients with subclavian arteries' dilations [25]. Moreover, our study did not analyze the beneficial value of Doppler ultrasonography at diagnosis and during follow-up. There probably still remains some slight differences among the different centers regarding the interpretation of imaging, especially the positivity criteria for large-vessel vasculitis. However, we used positivity criteria already used and validated in other studies [1,8,9,27,28]. Although the results from imaging were retrospectively retrieved on imaging reports and no central reviewing of imaging was performed, radiologists who performed the procedures were specifically asked to search for a GCA-related LVI. They were thus aware of the need to assess the large vessels. The absence of consensual guidelines regarding the frequency and the means of large-vessel screenings have led to heterogeneity regarding the control of aorta morphology during the follow-up period. Some cardiovascular complications were probably not captured given the relatively short follow-up period or because the repetitive imaging was performed too early to detect a complication. Some complications are described as occurring nearly 10 years after GCA diagnosis. Except in patients with vasculitis demonstration on the vascular area responsible for cardiovascular complications, the link between new cardiovascular events and GCA is uncertain. However, the different frequency of complications in different groups remains of clinical significance and is probably relevant. The mandatory criteria of inflammation of the aorta and/or its branches in the LVI group did not allow us to analyze GCA patients with isolated initial aortic dilation and those with isolated vascular stenosis. However, in the absence of any evidence of vascular inflammation, the link between GCA and aortic dilation or vascular stenosis is difficult to prove.

In the absence of recommendations regarding steroids' tapering schedule, some slight differences might exist in our patients, with a possible subsequent influence on outcomes. However, at onset, and at month 6 and 12, no significant differences of steroid doses were observed in the different groups. Given the retrospective retrieval of data, we did not record the cumulative dose of GC at the time of cardiovascular complications and one can hypothesize that patients with such complications might have higher cumulative doses.

Defining relapses by both clinical reoccurrence and increase of acute phase reactants could lead to an underestimation as some flares can occur without clinical symptoms or without increase of acute phase reactants [39].

Finally, further studies are needed to analyze patients who develop LVI during the follow-up period, as our study only focused on patients with LVI at diagnosis. Moreover, other imaging studies dedicated to vascular outcomes under treatment are needed to assess the evolution of LVI.

In conclusion, this study highlights that large-vessel involvement in GCA includes different clinical and imaging patterns that might influence cardiovascular outcomes. In this study, the use of immunosuppressants in patients with LVI showed a protective impact on the occurrence of new cardiovascular events. A validation of this finding in other studies is required.

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Disclosures

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jaut.2019.05.011.

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