Non-infectious aortitis: a report of 32 cases from a single tertiary centre in a 4-year period and literature review

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ABSTRACT

Objective. *Non-infectious aortitis often presents with non-specific symptoms leading to inappropriate diagnostic delay. We intend to describe the clinical spectrum and outcome of patients with aortitis diagnosed at a single centre.*

Methods. *We reviewed the clinical charts of patients diagnosed with non-infectious aortitis between January 2010 and December 2013 at the Rheumatology Division from a 1.000-bed tertiary teaching hospital from Northern Spain. The diagnosis of aortitis was usually based on FDG-PET-CT scan, and also occasionally on CT or MRI angiography or helical CT-scan.*

Results. *During the period of assessment 32 patients (22 women and 10 men; mean age 68 years [range, 45–87]) were diagnosed with aortitis. The median interval from the onset of symptoms to the diagnosis was 21 months. FDG-PET CT scan was the most common tool used for the diagnosis of aortitis. The underlying conditions were the following: giant cell arteritis (n=13 cases); isolated polymyalgia rheumatica (PMR) (n=11); Sjögren's syndrome (n=2), Takayasu arteritis (n= 1); sarcoidosis (n=1), ulcerative colitis (n=1), psoriatic arthritis (n=1), and large-vessel vasculitis that also involved the aorta (n=2). The most common clinical manifestations at diagnosis were: PMR features, often with atypical clinical presentation (n=23 patients, 72%); diffuse lower limb pain (n=16 patients, 50%); constitutional symptoms (n=12 patients, 37%), inflammatory low back pain (n=9 patients, 28%) and fever (n=7 patients, 22%). Acute phase reactants were increased in most cases (median erythrocyte sedimentation rate 46 mm/1st hour, and a median serum C-reactive protein 1.5 mg/dL).*

Conclusion. *Aortitis is not an uncommon condition. The diagnosis is often delayed. Atypical PMR features, unexplained low back or limb pain, constitutional symptoms along with increased acute phase reactants should be considered "red flags" to suspect the presence of aortitis.*

Introduction

Aortitis is the inflammation of the aortic wall (1, 2), and can be idiopathic or associated with a cluster of infectious or non-infectious diseases (1-11). Giant cell arteritis (GCA) (12, 13) and Takayasu arteritis (TA) are the most common underlying conditions associated with aortitis (14, 15), although it can be a manifestation of other systemic diseases (16-23).

Non-infectious aortitis is often an underrecognised condition usually presenting with non-specific symptoms. Thus, high index of clinical suspicion is required (1, 2). Early diagnosis is of main importance to prevent serious complications, such as an aneurysmal rupture or an aortic dissection (24).

Aortitis is a hystopathological term (Fig. 1). However, in the clinical practice, the diagnosis is based on imaging techniques (25, 26). Thus, the introduction in the last decade of ^{18}F(fluoro)-D-glucose (FDG) positron emission tomography (PET) computed tomography scan (FDG-PET/CT scan) and contrast-enhanced magnetic resonance imaging (MRI) (Fig. 2) has improved the diagnosis of large-vessel vascultides (23, 26-30).

In the present study we aimed to: a) analyse the presenting features and clinical spectrum of patients with aortitis diagnosed at a single centre, and b) establish the clinical and laboratory data that may be considered as "red flags", which may help to establish an early diagnosis of aortitis.

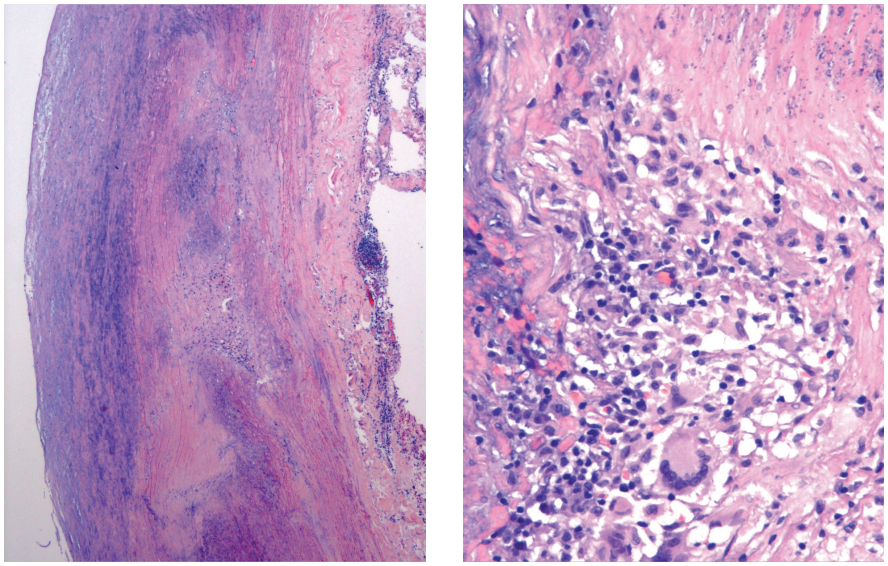

Fig. 1. A. Microscopic panoramic view of the aortic wall showing medial necrosis with inflammatory response (H&E, original magnification x25).
B. Microscopic higher power view showing inflammatory infiltrate with lymphocytes and a Langhans type giant cell (H&E, original magnification x200).

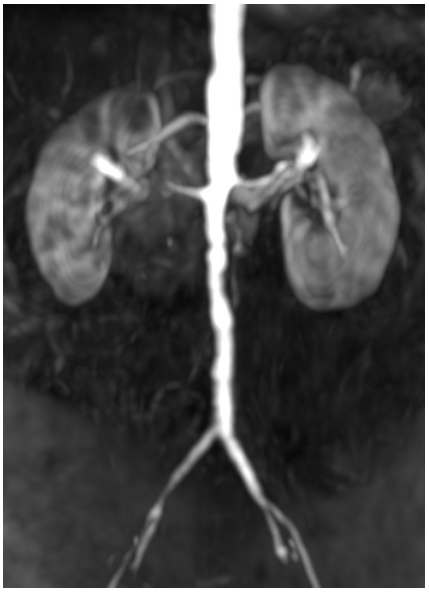

Fig. 2. Coronal MRA of the abdominal aorta. Irregular lumen stenosis of the infrarenal abdominal aorta.

Patients and methods

Patient population

We reviewed the clinical charts of patients diagnosed with non-infectious aortitis between January 2010 and December 2013 at the Rheumatology Division from a 1.000-bed tertiary teaching hospital from Northern Spain. The diagnosis of aortitis was usually based on FDG-PET-CT scan, and also occasionally on CT or MRI angiography or helical CT-scan. In all the cases clinical features and/or laboratory abnormalities were also present.

GCA (31) and TA (32) were diagnosed according to the American College of Rheumatology classification criteria.

Under the term "polymyalgia rheumatica" (PMR) we included patients with typical and atypical polymyalgia features. Typical PMR was defined when the patient fulfilled the PMR criteria proposed by Chuang *et al*. (33). On the other hand, we defined atypical PMR when patients did not fulfill the criteria for PMR shown above (33). These patients had aches and pain resembling PMR and at least one of the following features: a) inflammatory low back pain, b) diffuse pain in the lower limbs, c) persistent fever, d) constitutional symptoms and/or e) lack of improvement of PMR with low-medium dose oral corticosteroids (in all cases prednisone range: 10–15 mg/day). We also assessed whether patients with PMR features fulfilled the classification criteria proposed by EULAR/ACR 2012 (34).

Sjögren's syndrome was diagnosed according to the European-American classification criteria (35), and psoriatic arthritis was diagnosed on the basis of CASPAR criteria (36).

Data collection and clinical definitions

Clinical and laboratory data were retrieved according to a pre-established research protocol. To minimise entry error, all the data were double-checked. Fever was defined as a temperature >38ºC. Constitutional symptoms were asthenia, anorexia or weight loss greater than 5% of the normal body weight. Lower limb pain was defined as a diffuse pain involving the thighs. Inflammatory low back pain was diagnosed according to the Assessment of Spondyloarthritis International Society (ASAS) (37). ESR was considered increased when it was higher than 20 or 25 mm/1st hour for men or women, respectively. Serum CRP levels above 0.5 mg/dL were considered as high values.

FDG-PET CT scan acquisition and image analysis

Patients had to be in fasting state for at least 6 hours before the examination. Serum glucose level was lower than 160 mg/dL in all the patients. Whole-body FDG-PET uptake was assessed 180 minutes after injection of 7 MBq/kg of ^{18}F-FDG, using a Biograph LSO Pico 3D from Siemens Healthcare Molecular Imaging (Hoffman Estates, IL, USA). A low dose CT scan for attenuation correction and anatomic localisation was first obtained, followed by a FDG-PET scan (acquiring 250 s/bed position). Images were reconstructed using the ordered subsets-expectation maximisation (OSEM) algorithm (2 iterations, 8 subsets). Images were visually evaluated by two experienced nuclear medicine specialists according to the intensity of the ^{18}F-FDG uptake by the vessel wall at the supraaortic trunks, thoracic aorta, abdominal aorta, iliac arteries and femoral/tibioperoneal arteries.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) or as median, range and/or interquartile range (IQR) as appropriate. Analysis was performed with the STATISTICA software package (Statsoft Inc. Tulsa, OK, USA).

Results

Overall results

We studied 32 patients (22 women/10 men) with non-infectious aortitis. The mean age±SD at the time of diagnosis was 68±11 years (range 45–87 years).

Table I. Main features of 32 patients finally diagnosed as having aortitis.

Case	Age/ sex	Associated disease	Delay to the diagnosis of aortitis (months)		Fever	Constitutional symptoms	Inflammatory low back	Lower limb pain pain	PMR	ESR/CRP at the time of aortitis diagnosis	Temporal artery biopsy	Imaging technique and result
			From the initial symptom	From first physician consultation								
1	56/F	GCA, PMR	6	5	Yes	Yes	No	Yes	Typical	75/NP	NP	PET-CT: supraaortic vessels, left common iliac artery, femoral and tibial arteries
2	59/M	GCA, PMR	2	0	Yes	Yes	Yes	No	Typical	67/13.4	Negative	PET-CT: aorta, supraaortic vessels and both common iliac arteries
3	68/M	GCA	4	0	Yes	Yes	No	No	No	101/11.75	Positive	PET-CT: supraaortic vessels and subclavian arteries
4	69/F	GCA, PMR	0.3	0	Yes	No	No	Yes	Atypical	126/28.2	Positive	PET-CT: large arteries of lower limbs Scintigraphy: uptake along the venous-arterial route of both popliteal fossas
5	70/F	GCA, PMR	36	0	No	Yes	No	No	Typical	78/3.3	Negative	PET-CT: thoracic aorta, supraaortic vessels, medium and large vessels of lower limbs
6	63/F	GCA, PMR	77	72	No	No	No	No	Typical	4/0.16	Positive	PET-CT: descending thoracic aorta and abdominal aorta
7	65/F	GCA, PMR	18	15	Yes	Yes	Yes	Yes	Typical	12/0.9	Positive	PET-CT: aorta, supraaortical vessels, subclavian arteries and both common carotid arteries
8	72/F	GCA, PMR	31	30	No	No	No	No	Typical	10/0.15	Positive	PET-CT: ascending and descending aorta, aortic arch, supraaortic vessels, iliac and femoral arteries
9	73/F	GCA	100	99	No	No	No	No	No	46/NP	Positive	PET-CT: supraaortic vessels, thoracic and abdominal aorta and iliac arteries
10	79/F	GCA, PMR	47	23	No	Yes	No	No	Typical	32/1.2	Positive	PET-CT: aortic arch, thoracic and abdominal aorta
11	81/F	GCA, PMR	27	17	No	No	No	No	Atypical	43/0.2	Positive	PET-CT: ascending aorta, aortic arch, thoraco-abdominal aorta, supraaortic vessels, femoral, popliteal and tibial arteries
12	82/M	GCA, PMR	10	8	No	No	No	No	Typical	119/1.6	Negative	PET-CT: large vessels, including supraaortic, thoracic and abdominal aorta and bifurcation of iliac and femoral arteries
13	85/F	GCA	21	19	No	No	Yes	Yes	No	27/1.2	Positive	PET-CT: ascending and descending aorta and aortic arch
14	52/F	Isolated atypical PMR	8	2	No	No	No	Yes	Atypical	53/0.9	NP	PET-CT: thoracic aorta and supraaortic vessels
15	56/F	Isolated atypical PMR	14	2	No	No	Yes	Yes	Atypical	43/NP	Negative	PET-CT: thoracic aorta and supraaortic vessels
16	63/F	Isolated atypical PMR	9	6	No	No	Yes	Yes	Atypical	25/0.1	NP	PET-CT: thoracic aorta and supraaortic vessels
17	68/M	Isolated atypical PMR	120	119	No	No	No	Yes	Atypical	2/0.1	NP	PET-CT: ascending aorta, aortic arch, femoral and popliteal arteries
18	76/M	Isolated atypical PMR	3	0	No	Yes	No	No	Atypical	62/2.1	Negative	PET-CT: thoracic aorta, supraaortic vessels and pulmonary artery trunk
19	53/F	Isolated typical PMR	27	26	No	No	No	Yes	Typical	46/0.4	NP	PET-CT: aortic arch
20	62/M	Isolated PMR	2	0	No	No	No	No	Typical	70/7.7	NP	PET-CT: thoracic aorta
21	65/F	Isolated PMR	ND	ND	No	No	Yes	No	Typical	65/5.5	NP	PET-CT: thoracic aorta
22	79/F	Isolated PMR	11	8	No	No	No	Yes	Typical	25/1.5	NP	PET-CT: supraaortic vessels and thoracic aorta
23	79/F	Isolated typical PMR	13	1	No	Yes	No	Yes	Typical	33/0.6	NP	PET-CT: thoracic aorta
24	81/F	Isolated PMR	142	136	No	Yes	Yes	Yes	Typical	78/2.1	Negative	PET-CT: descending aorta and aortic arch. MRA: aortic elongation and thickening of descending aorta.
25	71/F	Sjögren's syndrome	180	170	No	Yes	No	No	No	111/0.99	NP	PET-CT: thoracic aorta and supraaortic vessels
26	79/F	Sjögren's syndrome	69	9	No	No	No	No	No	92/4	Negative	PET-CT: thoracic aorta
27	48/F	TA	156	0	No	No	No	Yes	No	28/2.6	NP	PET-CT: without inflammatory activity Carotid Doppler-ultrasound: wall thickening of both common and external carotid. MRA: decreased caliber of the infrarenal abdominal aorta. Lower limb arteriography: decreased caliber of the infrarenal abdominal aorta and stenosis. Stenosis of left subclavian artery
28	56/M	Sarcoidosis, PMR	44	39	Yes	Yes	Yes	Yes	Typical	33/2.1	Negative	PET-CT: ascending and descending aorta, aortic arch, femoral and tibial arteries
29	69/F	Ulcerative colitis, PMR	26	24	No	No	No	Yes	Atypical	12/<0.1	NP	PET-CT: thoracic aorta and femoral and tibial arteries
30	45/M	Psoriatic arthritis	156	71	No	No	No	Yes	No	4/0.1	NP	PET-CT: ascending and descending thoracic aorta, aortic arch, supraaortic vessels
31	64/M	Idiopathic	2	0	Yes	No	No	No	No	104/12.6	Negative	PET-CT: thoracic and abdominal aorta, supraaortic vessels and iliac arteries
32	87/M	Idiopathic	4	0	No	Yes	Yes	No	No	110/12.4	NP	PET-CT: thoracic aorta, supraaortic vessels and large vessels of lower limbs CT: atherosclerosis with aortocoronary calcification and elongated aorta

M: male; F: female; GCA: giant cell arteritis; PMR: polymyalgia rheumatica; TA: Takayasu arteritis; CT: computed tomography; MRA: magnetic resonance angiography; PET: 18FDG positron emission tomography. NP: Not performed; ESR: Erythrocyte sedimentation rate (mm/1st hour); CRP: C-reactive protein (mg/dL).

Table II. Main features of 13 patients with giant cell arteritis (GCA) and aortitis.

		Features at GCA diagnosis								Features at aortitis diagnosis			Aortitis: therapy and outcome			
Case	Age (yrs) /sex (at aortitis diagnosis)	Headache*	Jaw claudi-cation	Visual symptoms	PMR	Abnormal temporal artery exploration	ESR / CRP	Temporal artery biopsy	Initial prednisone dose / response at first month	Clinical features	ESR / CRP	Time from GCA to aortitis diagnosis (months)	Initial prednisone dose) and other therapy / response at 1 month	Other therapy in follow-up	Follow-up (months)	Outcome
1	56/F	No	No	No	Yes	No	75/ND	NP	40/ PclinR, ClabR	Fever, ILBP, ConsS	-	Synchronous	-	MTX 10 mg/w	36	CclinR, ClabR
2	59/M	Yes	Yes	Yes	Yes	Yes	67/13.4	Negative	40/ CclinR, ClabR	Fever, sweating, ConsS	-	Synchronous	-	-	36	CclinR, ClabR
3	68/M	Yes	Yes	No	No	Yes	101/11.75	Positive	50/ PclinR, PlabR	Malaise, fever, sweating, ConsS	-	Synchronous	-	MTX 15 mg/w	66	CclinR, PlabR
4	69/F	No	No	No	Yes	No	126/28.2	Positive	45/ PclinR, PlabR	Fever, pain in thighs, diffuse pain in lower limbs	-	Synchronous	-	MTX 15 mg/w	24	CclinR, ClabR
5	70/F	No	No	No	Yes	No	78/3.3	Negative	30/ CclinR, ClabR	ConsS	-	Synchronous	-	-	3	CclinR, ClabR
6	63/F	No	No	No	Yes	Yes	131/24	Positive	50/CclinR, PlabR	Chest pain	4/0.16	72	45/CclinR, ClabR	MTX 15 mg/w	6	CclinR, ClabR
7	65/F	Yes	Yes	Yes	Yes	Yes	108/13.2	Positive	40/ PclinR, ClabR	Headache and loss of weight when prednisone is tapered below of 25 mg/d	12/0.9	6	25+TCZ (8 mg/kg/m)/ PclinR, ClabR	-	36	CclinR, ClabR.
8	72/F	Yes	No	No	Yes	Yes	46/1.9	Positive	40/ CclinR, ClabR	Headache, pain in scapular guirdle when prednisone is tapered below 10 mg/d	10/0.15	30	10+ MTX 7.5// PclinR, ClabR	-	7	CclinR, ClabR
9	73/F	Yes	No	No	No	Yes	85/4.6	Positive	30/ CclinR, ClabR	Asthenia	46/ND	99	TCZ (8mg/k/m)// CclinR, ClabR	-	20	CclinR, ClabR
10	79/F	Yes	No	No	Yes	Yes	84/ND	Positive	20 /PclinR, PlabR	ConsS, PMR, headache, asthenia	32/1.2	35	7.5+MTX (12.5mg/w) // CclinR, ClabR	-	5	CclinR, ClabR
11	81/F	Yes	Yes	Yes	Yes	Yes	76/2.92	Positive	45/ CclinR, ClabR	Asymptomatic	43/0.2	17	20+ MTX10// CclinR, PlabR	-	7	CclinR, PlabR
12	82/M	No	No	No	Yes	Yes	49/5.5	Negative	10/ CclinR, ClabR	Asymptomatic but ↑of acute phase reactants	119/1.6	8	40//CclinR, ClabR	-	15	CclinR, ClabR
13	85/F	Yes	No	No	No	Yes	113/1.4	Positive	45/ CclinR, ClabR	ILBP and lower limbs pain	27/1.2	19	7.5+MTX (25 mg/w)// PclinR, PlabR	-	34	CclinR, PlabR

*Headache: recent onset or different from usual.
F: female; M: male; CclinR; complete clinical response; PclinR: partial clinical response; ClabR: complete laboratory response; PlabR: partial laboratory response; MTX: metothrexate; ILBP: inflammatory low back pain; ConsS: constitutional symptoms; ESR: Erythrocyte sedimentation rate (mm/1st hour); CRP: C-reactive protein (mg/dL); NP: Not performed.

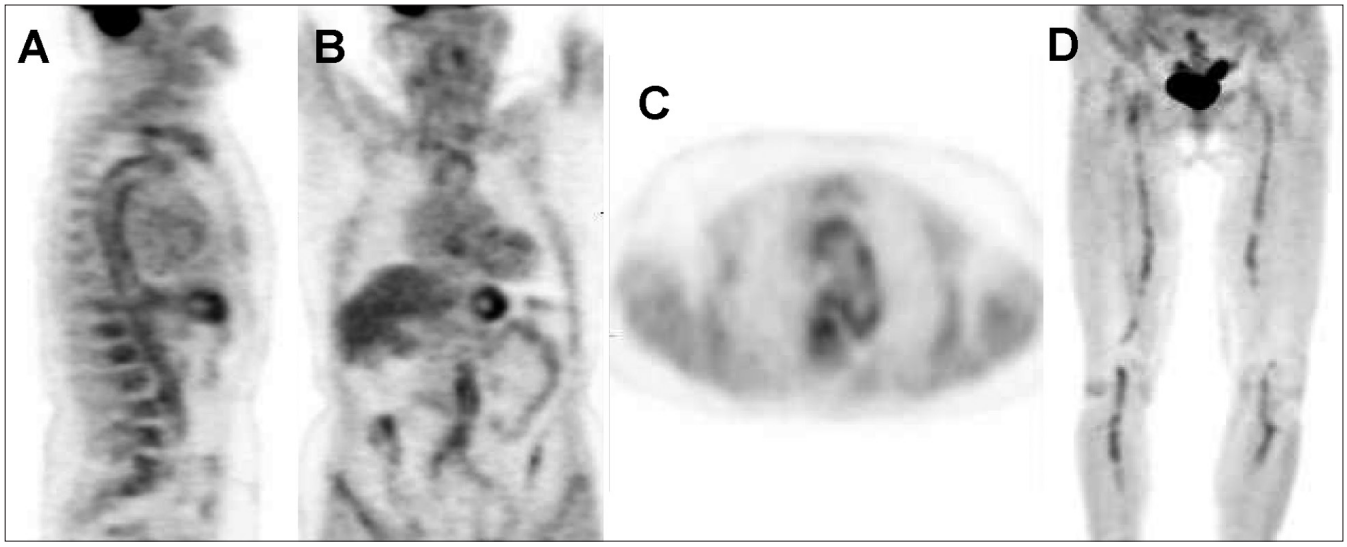

Fig. 3. An 81-year-old woman (case **11** in **Tables I** and **II**) with GCA confirmed by temporal artery biopsy. FDG-PET CT scan was perfomed. Sagittal **(A)** and coronal **(B)** PET images showed an intense and well defined FDG lineal uptake along the thoracic and abdominal aortic wall. Axial view through the aortic arch **(C)** revealed intense FDG uptake by the arterial wall. Maximum intensity projection image of the lower extremities **(D)** also showed an intense lineal FDG uptake along the femoral and tibioperoneal arteries.

The median interval from the onset of the symptoms to the diagnosis of aortitis was 21 (IQR: 6–69) (range 0.3–180) months. Table I summarises the main features of the patients included in our series.

Clinical subtypes of aortitis

– Giant cell arteritis and aortitis

We diagnosed 13 patients (10 women/3 men) with aortitis associated with GCA. The mean age±SD was 71±9 years (range 56–85 years). GCA was histologically confirmed in 9 of 13 cases. The main clinical and laboratory characteristics of these patients are summarised in Table II. Of note, in 8 cases initially diagnosed of GCA, the diagnosis of aortitis was made later (median [IQR]: 24.5 (8–72) months; range 6–99 months).

– Typical and atypical polymyalgia rheumatica associated with aortitis

Twenty-three patients had PMR (typical in 15 cases). It was isolated in 11 (typical in 6 cases and atypical in 5), and associated with other conditions in the remaining (10 cases with GCA, 1 with sarcoidosis and 1 with ulcerative colitis).

Patients (8 women and 3 men) with isolated PMR had a mean age of 67±10 years (range 52–81 years). Table III shows the main clinical features and laboratory parameters of patients with isolated PMR. Noteworthy, patients with atypical PMR experienced, more commonly, symptoms such as thigh pain, low back pain or lower limb pain, and they had a poor response to low-medium doses of prednisone (10–15 mg/day). Besides, none of the 5 patients with isolated atypical PMR fulfilled the ACR/EULAR criteria (34).

– Sjögren's syndrome and aortitis

Two patients were diagnosed with Sjögren's syndrome and aortitis. The first one was a 71-year-old woman diagnosed with Sjögren's syndrome in 1997. Aortitis was suspected because persistently high ESR levels despite treatment with low-dose corticosteroids. A FDG-PET CT scan showed increased vascular uptake with a typical pattern suggestive of aortitis. Rituximab (375 mg/m^2 weekly for 4 weeks) was added with an excellent clinical response at 3 months.

The second patient was a 79-year-old woman diagnosed with Sjögren's syndrome with persistently elevated ESR and anaemia. The patient underwent a FDG-PET CT scan that disclosed an increased FDG uptake in the thoracic aortic wall consistent with aortitis.

– Aortitis related to other diseases

We found a patient with Leriche syndrome and exertional angina pectoris in which TA was diagnosed on the basis of raised acute phase reactants and an arteriography with high-grade stenosis in the infrarenal aorta, dilation of the arc of Riolan and 50% left subclavian artery stenosis. She was started on prednisone (30 mg/day) and MTX (15 mg/week). Normalisation of acute phase reactants and resolution of asthenia was achieved 2 months later. Then, prednisone was tapered until complete discontinuation one year later.

Sarcoidosis and ulcerative colitis associated with aortitis was diagnosed in two patients previously reported (16, 17).

Finally, a 45-year-old man with psoriatic arthritis and aortitis was diagnosed in our centre. He suffered a stroke and then began with diffuse pain in lower limbs. Because of the lower limb pain and the previous history of stroke, a large-vessel vasculitis was suspected and confirmed by increased FDG uptake in the ascending and descending thoracic aorta, aortic arch and supraaortic vessels. Successful response to adalimumab (40 mg every other week subcutaneously) in combination with MTX (15 mg/week) was achieved.

– Large-vessel vasculitis that also involved the aorta

Two cases of large-vessel vasculitis that also involved the aorta were included in this series. The first one was

Table III. Main features of 11 patients with isolated typical and atypical polymyalgia rheumatica (PMR) and aortitis.

		Features at PMR diagnosis							Features at the time of aortitis diagnosis			Aortitis: therapy and outcome			
Case*	Age (yrs)/ sex	Cervical pain	Scapular pain	Pelvic pain	Other features	ESR / CRP	Typical or atypical PMR	Initial prednisone dose / response at 1 month	Clinical features	ESR/ CRP	Time from PMR diagnosis to aortitis diagnosis (months)	Predisone dose and other therapy / Response at 1 month	Other therapy in the follow-up	Follow-up (months)	Outcome
14	52/F	No	No	Yes	Pain in thighs and lower limbs pain	87/1.1	Atypical	10/ No clinical improvement and PlabR	Pain in thighs and shoulder girdle	53/0.9	2	10/CclinR, PlabR	-	3	CClinR, PlabR
15	56/F	No	No	Yes	Lower limbs pain	33/ND	Atypical	No corticosteroids// No improvement	Pain in thighs, lower limbs and arms	43/NP	2	20/PclinR, PlabR because the patient discontinued the treatment for fear of side effects	-	15	PclinR, PlabR
16	63/F	No	No	Yes	Pain in thighs, ILBP	98/0.1	Atypical	10/C clinR, ClabR	Pain in thighs, ILBP and abdominal pain	25/0.1	6	5/PCclinR, PlabR	MTX 20 mg/w	8	CclinR and PlabR
17	68/M	No	No	Yes	-	10/0.1	Atypical	10/ CclinR, ClabR	Pain in thighs	2/0.1	119	40//CclinR, ClabR	MTX 10 mg/w, HQ 300 mg/d	16	CclinR, ClabR
18	76/M	No	No	Yes	ConsS	62/2.1	Atypical	30/ CclinR, ClabR	ConsS	62/2.1	Synchronous	30/CclinR, PlabR	-	8	CclinR, PclinR
19	53/F	No	Yes	Yes	-	59/2.9	Typical	10/PclinR, PlabR	Pain in thighs	46/0.4	26	40/CclinR, ClabR	-	6	CclinR, ClabR
20	62/M	Yes	Yes	No	Shivering, shore throat	70/7.7	Typical	20/ PclinR, PlabR	Shivering, shore throat	70/7.7	Synchronous	20/PclinR, PlabR	-	3	PclinR, PlabR
21	65/F	Yes	Yes	No	ILBP	65/5.5	Typical	5/PclinR, PlabR	ILBP	65/5.5	Synchronous	5/PclinR, PlabR	-	1	PclinR, PlabR
22	79/F	No	Yes	Yes	Headache	30/1.0	Typical	10/CclinR, ClabR	Reactivation of the symptoms when prednisone is tapered	25/1.5	8	6.25/PclinR, PlabR.	-	0	Exitus
23	79/F	No	Yes	Yes	Asthenia, pain in thighs, headache	33/0.6	Typical	20/ PclinR, ClabR	Asthenia, pain in thighs	33/0.6	Synchronous	20/PclinR, ClabR	-	2	PclinR, ClabR
24	81/F	Yes	Yes	Yes	ConsS	28/2.2	Typical	10/CclinR, ClabR	Pain in cervical, shoulder and pelvic girdles	78/2.1	136	30/PclinR, ClabR	MTX 10 mg/w	16	CclinR, PlabR

* Related to case number from Table I.

F: female; M: male; CclinR: complete clinical response; PclinR: partial clinical response; ClabR: complete laboratory response; PlabR: partial laboratory response; MTX: metothrexate; ILBP: inflammatory low back pain; ConsS: constitutional symptoms. HQ: hidroxichloroquine; ESR: Erythrocyte sedimentation rate (mm/1st hour); CRP: C-reactive protein (mg/dL); Prednisone dose: mg/day; NP: Not performed.

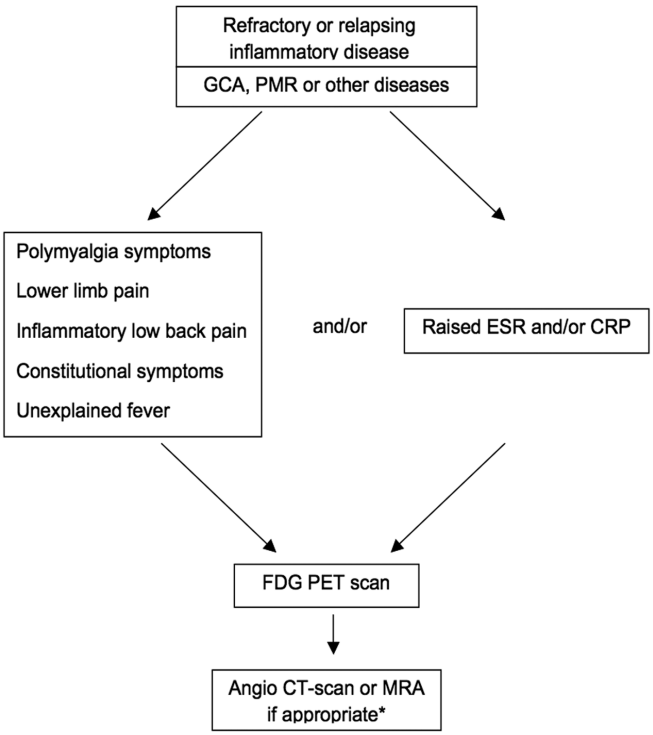

Fig. 4. Suggested work-up in patients presenting with an autoimmune or inflammatory condition to determine the presence of aortitis.

a 64-year-old man presented with high-grade fever and dyspnea. He had mild leucocytosis, ESR 104 mm/1st hour and serum CRP 12.6 mg/dL. Complete microbiological studies were all negative. Temporal artery biopsy was normal. A body CT-scan disclosed sligthy enlarged left paratracheal lymph nodes, and a biopsy showed reactive lymphadenitis. A ^{18}F-FDG PET/CT scan revealed an increased uptake in the thoracic and abdominal aorta, supraaortic vessels and iliac arteries. The patient started on prednisone (40 mg/day) and MTX (10 mg/week) reaching complete clinical remission.

The second patient was an 87-year-old man who was sent to the hospital because of chest wall pain and inflammatory low back pain as well as asthenia, anorexia and weight loss of 3 months´ duration. The ESR was 110 mm/1st hour and serum CRP 12.4 mg/dL. A body-CT scan showed diffuse atherosclerosis with aortocoronary calcification and an elongated aorta. A ^{18}F-FDG PET/CT scan revealed homogeneous and diffuse increased FDG uptake in the thoracic aorta, supraaortic vessels and large vessels of lower extremities. Prednisone (30 mg/day) was initiated with complete resolution of the symptoms and normalisation of the acute phase reactants.

Discussion

We describe a series of 32 patients diagnosed with aortitis at a single tertiary hospital from Northern Spain over a 4-year period. As expected, aortitis was mainly observed in the setting of GCA and PMR.

Non-infectious aortic disease presents with a wide range of symptoms. Apart from fever, headache, back pain, and PMR manifestations (38), severe aortic insufficiency, aortic aneurysms and rarely, aortic disection and rupture have been described at the time of disease diagnosis (1, 13, 39, 40). In our series, the most common clinical manifestations of aortitis were PMR, diffuse lower limb pain, constitutional symptoms, inflammatory low back pain, and fever. Most of these manifestations are non-specific. Therefore, a high index of suspicion for aortitis is needed. Thus, in patients with chronic or relapsing inflammatory diseases, these clinical features along with elevated acute phase reactants should be considered as "red flags" to suspect the presence of aortitis (Fig. 4).

Regarding imaging techniques, angiography has been replaced by angioCT-scan and MRI in the diagnosis and assessment of distribution and activity of aortitis (23, 41-43). MRI is recommended in patients in whom close follow-up is needed as this technique is very useful to assess wall thickening and wall oedema, and to determine the presence of specific lesions such as the presence of aneurysms or thrombus, (1, 41, 42, 46). In recent years, however, FDG-PET CT scan has gained considerable acceptability as a non-invasive tool potentially useful for the diagnosis and management of patients with large-vessel vasculitis by providing a metabolic functional image of the vessel wall inflammation before structural changes are seen (47-52). This technique is especially helpful in atypical presentations of vasculitis (17, 53). Previous studies have shown good results evaluating the aortic involvement in patients with large-vessel vasculitis (28).

GCA is more common in Caucasian individuals older than 50 years (54-57), and may affect the aorta and its major branches (12, 13, 29, 58-63). Table IV summarises the main series on patients with GCA and aortic involvement. The use of new imaging techniques has disclosed that extracranial large-vessel involvement in GCA is more common than initially thought (26). Aortitis in the setting of GCA is a potentially serious and usually underdiagnosed complication (64). A prospective study using CT-scan within the month after GCA diagnosis showed that aortic thickening occurs frequently at the time of diagnosis of GCA, and that this condition predominantly affects the ascending aorta (65). In keeping with these observations, using CT angiography Prieto-González *et al*. found aortitis in 67% of 40 newly diagnosed GCA patients (66). Histopathology studies disclosed ascending aorta involvement in 8–13% of GCA patients (13, 61, 62). Aortitis in patients with GCA may lead to aortic aneurysms. The risk of aneurysmal rupture and aortic dissection is increased in patients with GCA. They occur mostly in the ascending thoracic aorta. Comparing with people of the same age and sex, Evans *et al*. reported that patients with GCA had a 17-fold increased risk of thoracic aortic aneurysm and a 2.4-fold increased risk of abdominal aortic aneurysm (39). Simi-

Table IV. Former series describing the main features of GCA patients with aortic and/or its major branches involvement.

Reference	n/sex	Age (years)	Fever (n)	Constitutional symptoms (n)	PMR (n)	Headache (n)	Abnormal temporal artery on physical exam (n)	Jaw claudication (n)	Visual manifestations (n)	ESR	Positive temporal artery biopsy (n)	Imaging techniques
Ghinoi *et al*. (60)	15 (15 F)	Mean: 71±11	NA	NA	8	9	NA	2	2	Mean: 90±20	9	CDS, PET
González-Gay *et al*. (52)	20 (12F/8M); all with aortic aneurysm	Mean: 71.1±6.4	1	16	13	18	14	12	3	Mean: 101±21	20	Angiography, CT, MRI, US
Nuenninghoff *et al*. (13)	30 (24F/6M); all with aortic aneurysm and/ or dissection	Median: 74.7 [70.7–83.1]	6	NA	10	24	NA	15	4	Median: 81.5 [IQR 64–116]	27	Angiography, CT, MRI, US
Nuenninghoff *et al*. (13)	21 (17F/4M); all with large artery stenosis	Median: 75.2 [68.8–80.9]	5	NA	4	15	NA	6	6	Median: 79 [IQR 58–97]	17	Angiography, CT, MRI, US
Brack *et al*. (58)	74 (65F/9M)	Mean: 66	NA	17	21	7	NA	NA	NA	Mean: 61	33	Angiography
Narváez *et al*. (29)	4(3F/1M)	Mean 77±7	NA	NA	1	NA	NA	NA	NA	Mean: 56±25	4	MRI
Lie (63)	72 (51F/21M)	Median: 69 (range 54–92)	NA	NA	ND	NA	NA	NA	NA	Mean: 96	67	Angiography
Evans *et al*. (59)	41(31F/10M)	Median:67 (range 52–88)	14	NA	22	25	25	14	9	Median: 104 (range 40–139)	36	CT, angiography, echocardiogram

M: male; F: female; CDS: colour Doppler sonography; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; US: ultrasonography; NA: not available. ESR: erythrocyte sedimentation rate (mm/1st hour).

Table V. Review of published cases of polymyalgia rheumatica and involvement of the aorta and/or its major branches.

Reference	n/sex	Age (years)	Fever	Stiffness	Cervical pain	Shoulder pain	Pelvic pain	Thighs pain	ESR	CRP	Imaging technique	Response to corticosteroids (initial dose)	Outcome
Kataoka *et al*. (74)	1/M	61	Yes	Yes	Yes	Yes	No	Yes	120	11.57	CT and MRA: thickening of aortic arch and its branches, descending and abdominal aorta PET: FDG uptake in aortic arch branches, thoracic and abdominal aorta.	Yes (prednisolone, 30 mg/day).	Rapid resolution
Kataoka *et al*. (74)	1/F	63	No	Yes	Yes	Yes	No	No	90	6.01	CT and MRA: thickening of thoracic and abdominal aorta and mild stenosis of the right internal carotid artery.	Yes (prednisolone, 15 mg/day)	Relapse
Koga *et al*. (75)	1/F	64	Yes	Yes	No	Yes	No	No	105	12.6	CT: soft tissue thickening of the descending thoracic aorta.	Yes (prednisolone, 40 mg/day)	6 months later the patient required surgery for a dissecting aortic aneu rysm, recovering without complications
Narváez *et al*. (29)	1/F	73	NA	NA	NA	NA	NA	NA	82	40	MRI: vessel wall thickening, wall edema, increased mural contrast enhancement, stenosis of left subclavian artery.	Yes(prednisone, 20 mg/day)	Treatment failure
Narváez *et al*. (29)	1/F	67	NA	NA	NA	NA	NA	NA	42	19	MRI: vessel wall thickening, wall edema, increased mural contrast enhancement.	Yes (prednisone, 20 mg/day)	Treatment failure
Milchert *et al*. (76)	1/F	66	NA	NA	NA	NA	NA	NA	NA	NA	CT: aortic wall thickening	Yes (methyl-prednisolone, 500 mg/day/3 days)	Rapid resolution

M: male; F: female; CT: computed tomography; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; PET: positron emission tomography; NA: not available. ESR: erythrocyte sedimentation rate (mm/1st hour); CRP: C-reactive protein (mg/dL)

Table VI. Reported series on main features of patients with Takayasu arteritis.

Reference	n (Sex)	Age (years)	Fever n (%)	Fatigue/ malaise n (%)	Joint manifestations n (%)	Weight loss n (%)	Hypertension n (%)	Upper limb claudication n (%)	Bruits (n)	ESR (Median)	CRP (Median)	Imaging technique
Noosin *et al.* (85)	15 (11F/4M)	Median: 36 (range 19–51)	10 (67%)	7 (47%)	4 (27%)	3 (20%)	8 (53%)	13 (87%)	Subclavian: 13 Carotid: 7 Abdominal: 6 Femoral: 3	88 (range 30–125)	NA	Angiography
Schmidt *et al.* (86)	126 (115F/11 M)	Median: 31.5 [IQR: 22.9–39.8]	30/103 (29%)	58/107 (54%)	36/103 (35%)	37/104, (36%)	41/109 (new-onset), (38%)	50/125 (40%)	Subclavian: 60/121 Carotid: 60/121 Abdominal: 44/122 Femoral: 17/120	45 [IQR: 17.5–96.5]	3.75 [IQR: 0.7–9.5]	CTA, PET, US, angiography
Bicakcigil *et al.* (82)	248 (221F/27M)	Mean: 33.1±12	68 (27%)	139 (56%)	116 (47%)	62 (25%)	106 (43%)	ND	Subclavian: 121 Carotid: 146 Abdominal: 55 Femoral: 24	NA	NA	Aortography, DSA, Doppler-US
Kerr *et al.* (83)	60 (58F/2/M)	Median: 25 (range 7–64)	16 (27%)	20 (33%)	18 (30%)	9 (15%)	20 (33%)	37 (62%)	Subclavian: 13 Carotid: 42 Abdominal: 17 Femoral: 2	NA	NA	Angiography

M: male; F: female; CTA: computed tomography angiography; DSA: digital subtraction angiography; PET: positron emission tomography; US: ultrasonography; NA: not available. ESR: erythrocyte sedimentation rate (mm/1st hour); CRP: C-reactive protein (mg/dL)

lar data have been reported in biopsy-proven GCA patients from Northwest Spain (61). Of note, Liozon *et al*. indicated that the presence of classic cranial features of GCA at the time of disease diagnosis may be a negative predictor of an aortic complication (67).

Overall, patients with large-vessel involvement in the setting of GCA are younger than patients with classic cranial temporal arteritis (66 *vs*. 72 years) and most of them are women (83% *vs*. 66%). Moreover, the time between the onset of symptoms and the diagnosis of the disease is usually longer in patients with aortitis (7 months *vs*. 2 months) (26).

Patients with large-vessel GCA may present with typical cranial temporal arteritis or PMR, but they may also present with non-specific symptoms such as fever, sweating, malaise, anorexia, weight loss, fatigue, lower extremity claudication or arthralgias (26, 42, 68). Therefore, in many GCA patients the diagnosis of aortitis may be extremely difficult, leading to a long diagnostic delay. Thus, in a series of biopsy-proven GCA patients from Northwest Spain, the mean time between the diagnosis of GCA and the diagnosis of aortic involvement was 57 months (61). Similar results have been reported in other studies (29, 58).

Aortic complications may be the cause of death in 3–12% of patients with large-vessel GCA (13). A recent epidemiologic study on large-vessel involvement in GCA patients from Olmsted County (MN) has shown that incidence of any large-vessel event is high within the first year of GCA diagnosis. The incidence of aortic aneurysm/dissection is also increased 5 years after GCA diagnosis (69). Survival of GCA patients with aortic aneurysm or dissection was found decreased (standardised mortality ratio, 2.63; 95%CI 1.78–3.73) (69).

PMR is also a common disorder in individuals older than 50 years from Western countries (55, 56). This may appear as an isolated disease or associated with ischemic features of GCA (70, 71). In the literature a handful of case reports emphasise the presence of aortitis in patients with PMR (29, 57, 70, 72-76). Table V summarises the lit-

erature cases of PMR with involvement of aorta and/or its major branches.

The diagnosis of PMR is very straightforward when typical features, such as pain in the neck, and shoulder and pelvic girdles are present (77, 78).

However, the presence of atypical symptoms or a poor response to corticosteroids should be considered warning signs for the presence of a condition mimicking this disease but different from isolated and typical PMR (79). It was also the case for some of our patients diagnosed with aortitis. Compared to the vast majority of patients with PMR reported in clinical studies, complications of large-vessel vasculitis in PMR patients are extremely rare. A search for aortitis should only be undertaken in PMR under special circumstances. This may be the case if atypical findings such as low back pain or pain involving mainly the legs associated to elevation of acute phase reactants are present.

TA is a large-vessel vasculitis uncommon in Western countries (54). However, it has been widely described in people from Asia, Africa and Latin America (80). TA affects commonly young people (81). The aorta, carotid and subclavian are the arteries most frequently involved (82, 83). The development of arterial stenosis and aneurysms leads to claudication, bruits, limb pain, and diminished or even absent pulses (84). Sometimes patients may also complain of visual loss or stroke, constitutional symptoms, fever, malaise, weight loss or anorexia (84). Table VI shows a set of series of patients with TA in which information on major branch involvement is described (82, 83, 85, 86).

In our study, we only disclosed one patient with multiple arterial stenosis features and complications related to severe vascular involvement in the setting of a delayed diagnosis of TA.

Aortitis may be associated with other diseases. It may occur in the setting of sarcoidosis, a multisystemic disease that involves the lungs, eyes and skin (87). Sarocidosis may coexist with rheumatic diseases including PMR (16, 88). Although uncommonly reported (89), sarcoidosis may be associated with vascular involvement (90-96), mostly with small-vessel vasculitis (90). Sarcoidosis has also been associated with Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and TA (19, 90, 96). Association of sarcoidosis with aortitis and Crohn's disease has also been described (97).

Inflammatory bowel disease is characterised by diarrhoea with blood and mucus, and may be accompanied by extraintestinal symptoms. Although aortitis has been reported in patients with Crohn's disease (98-100), large-vessel involvement in ulcerative colitis is very uncommon (83, 101, 102).

Sjögren's syndrome is a heterogeneous systemic autoimmune disease characterised by keratoconjuctivitis sicca, xerostomy and a wide spectrum of systemic symptoms and signs. Although vascular involvement is very uncommon, in the present study we described two cases associated with aortitis. We also reported a patient with aortitis and psoriatic arthritis. This association has previously been reported as single case reports (103-106).

In our series, we described two patients with large-vessel vasculitis that also involved the aorta. The main features were unexplained fever along with high ESR in one patient and low back pain in the other.

Idiopathic aortitis is an uncommon disorder characterised by giant cells or lymphoplasmacytic inflammation of the aorta (107). Female gender, smoking, and older age are risk factors for the disease (108-111). Two related entities have been proposed: isolated idiopathic thoracic aortitis, and chronic periaortitis, that encompass idiopathic retroperitoneal fibrosis, inflammatory abdominal aortic aneurysm, perianeurysmal aortitis and idiopathic isolated abdominal periaortitis (1). Isolated aortitis usually manifests as an aneurysm of the ascending aorta, and is often an incidental finding during the histopathological study of the aortic wall after thoracic surgery (107). Nevertheless, sometimes it may present with symptoms related to aortic inflammation. Liang *et al*. published 64 patients who underwent an aortic aneurysm dissection at Mayo Clinic. Most of them (81%) were classified as isolated aortitis. Forty-five percent of the patients had aneurysm-related symptoms, 33% were asymptomatic, 12.5% had constitutional symptoms, 9.4% polymyalgia and 4.7% suffered symptoms related to the involvement of cranial arteries. Seventy-two per cent of patients had additional vascular imaging abnormalities (109). Miller *et al*. found isolated aortitis in 47% of patients from a series of 45 patients who underwent an ascending aortic resection (112).

Patients with retroperitoneal fibrosis, inflammatory abdominal aortic aneurysms or perianeurysmal aortitis may develop constitutional symptoms, abdominal or back pain, fever, fatigue, night sweats and elevated inflammatory markers (1, 4, 5, 9, 113-117). In patients with retroperitoneal fibrosis, ureteral obstruction and renal failure have been reported (1, 5); and sometimes blood and lymphatic vessels may be also involved (116, 118).

There are other diseases that may be also included under the term "idiopathic aortitis". This is the case of Erdheim-Chester disease and immunoglobulin G4-related disease. Erdheim-Chester disease is a rare systemic disease characterised hystopathologically by histiocytosis of no-Langerhans cells. It may present with retroperitoneal infiltration and cardiovascular involvement. When the aorta is affected, the periaortic tissue is infiltrated circumferentially from ascending aorta to the iliac bifurcation (7, 42, 119, 120). Immunoglobulin G4-related disease encompasses a broad spectrum of disorders presenting with fibrosis of several organs, increase of serum IgG and IgG4 and autoantibodies. The aorta and its major branches show a lymphoplasmacytic infiltration and irregular fibrosis in the adventitial layer (42, 121). In this entity, chronic periaortitis is more frequent than aortitis. Differences between isolated aortitis and GCA have recently been described by Talarico *et al*. (122).

In conclusion, aortitis is not an uncommon entity. However, the search for aortitis should only be undertaken in patients presenting with typical PMR under special circumstances. It may be the case in the evaluation of corticosteroid-resistant PMR patients (123).

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