Isolated aortitis *versus* giant cell arteritis: are they really two sides of the same coin?

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ABSTRACT

Objective. *The aim of the study was to compare epidemiological data, clinical findings and results of investigations in patients with isolated aortitis and those with giant cell arteritis (GCA) to establish whether patients with isolated aortitis differ from those with GCA.*

Patients and methods. *We reviewed the medical notes of all patients consecutively seen in two Rheumatology centres in the last two decades with a suspicion of GCA, searching for cases characterised by abnormal [^{18}F] fluorodeoxyglucose (FDG) PET uptake of the aorta. "Isolated aortitis" was defined as increased FDG uptake in the aorta not explained by atherosclerosis in the absence of FDG uptake in other large vessels.*

Results. *Comparing the epidemiological and clinical data of patients with isolated arteritis with those with GCA, we observed many statistical significant differences. First of all, the male/female ratio was reversed, with a predominant male involvement in isolated arteritis. Moreover, the mean age of patients with isolated arteritis was significantly lower than that of GCA patients (62 vs. 78.4 yrs; p<0.0001). None of the patients with isolated aortitis presented at any time of the disease course the typical symptoms of GCA, while in a low percentage of cases constitutional symptoms represented the only clinical features. Beside the aortic arch, the sites more frequent involved were the thoracic and abdominal tracts, in all cases without an uptake of the aortic branches.*

Conclusion. *It is not known whether our patients with isolated aortitis represent variants of GCA or TA, nor is it known how they will evolve, but we can certainly conclude that these patients have a different epidemiologic and clinical profile, and do not necessarily represent two sides of the same coin.*

Introduction

Giant cell arteritis (GCA) is the most common primary systemic vasculitis of the elderly, which usually involves the major branches of the aorta with predilection for the extra-cranial branches of the carotid artery, including the temporal arteries (1-3). The clinical profile of GCA can greatly vary, ranging from the typical cranial signs and symptoms, represented by prominent temporal arteries, headache, jaw claudication and visual impairment, to constitutional symptoms, such as fever, weight loss and fatigue. Imaging techniques indicate that aortic involvement is common even in the early stages of GCA or at the time of its diagnosis (4-6). Moreover, an inflammatory aortic involvement presenting at onset of GCA may predict a more chronic/relapsing course of disease, with more aggressive therapeutic requirements and an increased risk for vascular events in the long term (7). The prevalence of aortitis in GCA ranges from 33 to 65% (8-11), even though data from surgical case series and autopsy studies suggest a higher rate of it (12-14). Since aortitis can result in life-threatening complications (dissection and aneurysms) and is not as a rule clinically overt until complications appear, a careful screening for potential aortic involvement in GCA is mandatory.

Takayasu arteritis (TA) and GCA represent the most common rheumatologic causes of aortitis (11), but aortitis may also be idiopathic, part of the IgG4-related disease or caused by infectious diseases (15-16). Infectious aortitis may be secondary to syphilis, tuberculosis, or other bacterial or viral pathogens (17).

In addition to GCA patients with cranial manifestations, it is not so rare to observe patients with increased [^{18}F] fluorodeoxyglucose (FDG) PET up-

take of the aorta associated with constitutional symptoms or sometimes occurring even in the absence of specific clinical manifestation. In the routine clinical practice of these latter cases, we generally make a clinical diagnosis of GCA or TA (depending on the age of onset of the disease), but the main question remains: is aortitis invariably part of GCA or TA, or is isolated aortitis a nosologically different entity?

The aim of the study was to compare epidemiological data, clinical findings and results of investigation in patients with isolated aortitis and

Patients and methods

We reviewed the medical notes of all patients consecutively seen in two centers (Rheumatology Units of Pisa and Reggio Emilia) in the last two decades with a suspicion of GCA, searching for cases characterised by abnormal [^{18}F] fluorodeoxyglucose (FDG) PET uptake of the aorta. "Isolated aortitis" was defined as increased FDG uptake in the aorta not explained by atherosclerosis in the absence of FDG uptake in other large vessels.

The primary aim of the study was to evaluate the characteristics of patients with isolated [^{18}F] FDG PET uptake of the aorta. The secondary aim was to compare patients with isolated arteritis and patients diagnosed with GCA according to the American College of Rheumatology (ACR) criteria.

Data regarding gender, ages at onset, presenting signs and symptoms, laboratory results, temporal artery biopsy (TAB) findings, [^{18}F] FDG vascular uptake and its sites, and presence/recurrence of aneurysms were collected and stored in an electronic database. All the information regarding the cohort of GCA patients diagnosed according to the ACR criteria were retrieved from a dedicated database.

Statistical analysis

All results are expressed in means ± standard deviation (SD). Chi-square test, *t*-test and ANOVA were used to evaluate the differences among the subgroups. A *p*-value <0.05 was considered statistically significant. All calculations were done using StatView program ver. 5.0.

Results

Among the patients evaluated, we found 11 patients with isolated aortitis (M/F: 9/2; mean age at the diagnosis: 62 years). The main epidemiological, clinical and PET findings are summarised in Table I.

As control group a cohort of 199 (male/female: 32/167, mean age at the onset±SD: 78.4±4) GCA patients according to the ACR criteria was used. The clinical profile was mainly characterised by new onset of headache and/or scalp pain, reported by 88% of the subjects. Visual impairment was presented in 45% of the cases, followed by jaw claudication (37%), while constitutional symptoms were reported in a lower percentage of patients. TAB was performed in 161 patients and was positive in 61% of the cases. About one-fourth of the subjects underwent a [^{18}F] FDG PET, which was positive in 25% of the cases. The uptake of [^{18}F] FDG in GCA patients diagnosed according to the ACR criteria was mainly detected in the aortic arch (100%), and also in the aortic braches, thoracic aorta and abdominal aorta.

Comparing the epidemiological and clinical data of patients with isolated arteritis with those with GCA, we observed many statistical significant differences. First of all, the male/female ratio was reversed, with a predominant male involvement in isolated arteritis. Moreover, the mean age of patients with isolated arteritis was significantly lower than that of GCA patients (62 *vs*. 78.4 yrs; p<0.0001). None of the patients with isolated aortitis presented at any time of the disease course the typical symptoms of GCA, while in a low percentage of cases constitutional symptoms represented the only clinical features. Beside the aortic arch, the sites more frequent involved were the thoracic and abdominal tracts, in all cases without an uptake of the aortic branches.

A comparison of the epidemiological and clinical data between GCA and isolated arteritis patients is summarised in Table II.

Discussion

In the present paper we described eleven patients with isolated aortitis. The patients we have studied came to our attention referred by the surgeon after vascular surgery, or for the presence of constitutional symptoms and/or elevation of acute phase reactants that induced us to rule out a systemic autoimmune disease. All these patients underwent a careful work-up to investigate the presence of vasculitis, which allowed us to exclude TA and GCA according to the ACR criteria, as well as any kind of infections; TAB was not performed in all cases, but those who had undergone it resulted negative. In comparison with our cohort of patients with GCA, the group of patients with isolated aortitis are predominantly males and of younger age.

The term aortitis refers, strictly speaking, to the pathologic definition of inflammation of the aortic wall, although imaging signs of inflammation are used as a rule as surrogate markers (17-19). The causes of aortitis are usually divided into infectious and non-infectious. Among infectious agents, the most common pathogenic species involved are *Salmonella, Staphylococcus, Streptococcus pneumonia, Mycobacterium tuberculosis*, human immunodeficiency virus, and, even if now rare, *Treponema pallidum*. In most cases of infectious aortitis, the responsible microorganism is thought to colonize the aorta by entering via the vasa vasorum. Segment of the aortic wall with pre-existing injury, such as an atherosclerotic plaque or aneurysm sac may be particularly predisposed (19). The most common rheumatologic causes of aortitis are represented by GCA and TA; however, in a lower percentage of cases, aortitis may also be associated with other systemic autoimmune diseases, such as systemic lupus erythematosus, ANCA-associated vasculitides, rheumatoid arthritis, HLA-B27 associated spondyloarthropathies, sarcoidosis, Cogan's syndrome and Behçet's disease. Moreover, aortitis may also occur associated with the IgG4-related disease, or chronic periaortitis (12, 20). Beside these identifiable scenarios, there are growing data that aortitis may also occur in isolation, *i.e*. in the absence of other defined systemic diseases.

Literature data on the demographic pro-

Table I. Epidemiological and clinical data of patients with isolated aortitis.

Patients	Sex	Age	Main PET alterations	Presence/recurrence of aneurysms	Acute phase reactants	Clinical picture
1	male	60	aortic arch, thoracic aorta	_	raised	weight loss
2	male	68	aortic arch, thoracic and abdominal aorta	_	raised	fever
3	male	56	aortic arch, thoracic and abdominal aorta	aortic arch, thoracic and abdominal aorta	raised	_
4	male	55	aortic arch, thoracic and abdominal aorta	thoracic and abdominal aorta	raised	asthenia, weight loss
5	male	60	aortic arch, thoracic aorta	_	raised	_
6	male	57	aortic arch, thoracic and abdominal aorta	abdominal aorta	raised	_
7	male	63	aortic arch, thoracic and abdominal aorta	thoracic aorta	raised	fever, asthenia
8	male	68	aortic arch, thoracic and abdominal aorta	_	raised	_
9	female	61	aortic arch, thoracic and abdominal aorta	aortic arch, thoracic and abdominal aorta	raised	_
10	male	59	aortic arch, lower extremity	_	raised	fever
11	female	75	aortic arch, thoracic and abdominal aorta		raised	fever, weight loss

Table II. Comparison of epidemiological and clinical data between GCA and isolated arteritis patients.

	GCA according ACR criteria	Isolated aortitis
Number of patients	199	11
Male/Female	32/167	9/2
Mean age ± SD (min-max) (years)	78.4±4 (71-90)	62±6 (55-75)
Presenting sign and symptoms (%)		
New onset headache and/or scalp pain	88	0
Visual impairment	45	0
Jaw claudication	37	0
Temporal artery abnormality	36	0
Asthenia	15	2
Fever	6	4
Weight loss	5	3
Cough	0.5	0
Laboratory features *(n)* (%)		
Elevated ESR	*(197)* 99	*(11)* 100
Elevated CRP	*(197)* 99	*(11)* 100
Temporal artery biopsy (TAB) *(n)* (%)		
TAB performed	*(161)* 81	*(5)* 45
TAB positivity	*(121)* 61	*(0)* 0
18F-FDG PET (n) (%)		
18F-FDG PET performed	*(32)* 18	*(11)* 100
18F-FDG PET positivity	*(7)* 25	*(11)* 100
Site of 18F-FDG uptake *(n)* (%)		
Aortic arch	*(7)* 100	*(11)* 100
Aortic branches	*(2)* 29	*(0)*
Thoracic aorta	*(1)* 14	*(10)* 91
Abdominal aorta	*(1)* 14	*(9)* 82
Upper extremity artery	*(1)* 14	*(0)*
Lower extremity artery	*(1)* 14	*(1)* 9

file of isolated aortitis are contrasting. Since isolated aortitis may be asymptomatic, it is certainly possible that its frequency is underdiagnosed and only cases in which complications occur may come to our attention. Moreover, not all the surgical specimen undergo pathologic examination, making the real frequency of the disease difficult to assess. The selection criteria of the population studied may represent an important bias in the comparison of the demographic profile; in fact not all the studies so far published have homogeneous inclusion criteria. Finally, we do not know the effective frequency of an aortic PET uptake in those patients who underwent it for other reasons.

Bearing all these concepts in mind, a surgical pathology study of non-infectious ascending aortitis performed in Minnesota, USA (12), showed that the most frequent causes of aortitis were represented by isolated aortitis and GCA. The latter group was characterised by a high prevalence of women, with a mean age of 73 years. Similarly, in other reported series women were predominantly affected (13). On the other hand, a nation-wide Danish population-based study by Schmidt *et al*. (21) showed that the patients diagnosed with aortitis were predominantly men (62%), with a mean age of 65 years, which is more similar to our results. This study was aimed at assessing the prevalence of, and predictors for, pathologically-confirmed inflammation of the aorta. Notably, the prevalence of inflammation of the aortic wall was of 6.1%, with approximately three-fourths of the cases being idiopathic.

So far, the specific trigger for the inflammatory process underlying aortitis remains unknown, as it is for the majority of vasculitis, including GCA and TA. It would be also very interesting to further explore if the atherosclerotic plaque may have a role in the pathogenetic process of inflammatory aortic involvement.

The main clinical issue of isolated aortitis is related to its classification and prognosis, and we do not yet know if patients with isolated arteritis will develop a defined vasculitis in the future. If a patient presents with aortitis in the context of a systemic inflammatory disease, the choice of the therapy depends by the aortic involvement itself and by the underlying systemic disease; but which is the appropriate choice in a patient with isolated aortitis? As described by some authors, we partially know the risk factors for the development of aortitis (14, 22-23), but

little we know about predictive factors for poor outcome in isolated aortitis. In this regard, it is not clear which is the best approach in all patients with an incidental diagnosis of aortitis without complications such as aneurysms. There is certainly a point in performing a periodic follow-up to monitor for the development of new vascular lesions. Treatment is wholly empirical and consists essentially of glucocorticoids. It is desirable that further and larger studies be carried out to elucidate the clinical significance of isolated aortitis.

To sum up, it is not known whether our patients with isolated aortitis represent variants of GCA or TA, nor is it known how they will evolve, but we can certainly conclude that these patients have a different epidemiologic and clinical profile, and do not necessarily represent two sides of the same coin.

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