Title: A Retrospective Cohort of Surgically Diagnosed Idiopathic Aortitis Cases in a Canadian Centre

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Abstract:

Objective: Idiopathic aortitis (IA) became recognized relatively recently; the body of knowledge related to this condition is scarce. This study aims to determine: the frequency of IA in aortic specimens; its clinical, laboratory, and radiological characteristics at diagnosis and during follow-up; and the approach to work-up, treatment and monitoring taken by the treating physicians.

Methods: Cases of aortitis diagnosed on pathologic specimens of aorta over a 10 year period at The Ottawa Hospital were identified. Charts were reviewed and data on patient demographics, clinical features, laboratory and imaging tests, treatment, and outcomes were analyzed.

Results: Six hundred and eighty four aortic specimens were analyzed during the study period; 47 cases of aortitis were identified, 32 of which were IA. Two thirds (21/32) of patients with IA had complete imaging of branch vessels and 16/21 (76%) had additional baseline aortic or branch vessel lesions. Corticosteroids were used in 12/32 (38%) of patients with IA; elevated perioperative inflammatory markers was the only significant predictor of corticosteroid use. Over mean follow-up of 47.5 months new aortic or branch lesions were diagnosed in 5 out of 12 (42%) imaged IA patients, three patients required additional vascular surgery and 2 were diagnosed with systemic conditions.

Conclusion: IA is commonly discovered incidentally on examination of pathologic specimen following ascending aortic aneurysm repair. No guidelines exist for the workup, treatment, and follow-up of IA resulting in great variability of practice. Good quality prospective studies are needed to address unanswered questions about IA.

Introduction:

Aortitis is a general term used to describe inflammation of the aorta (1). It is known to be associated with a variety of systemic vasculitides (most commonly giant cell arteritis (GCA)(2,3) and Takayasu's arteritis (Tak)(3,4)), connective tissue diseases such as rheumatoid arthritis (RA) (5), systemic lupus erythematosus (SLE) (6), ankylosing spondylitis (7), and infections (especially syphilis (8) and tuberculosis (9)). In a significant fraction of cases, aortitis is diagnosed in patients with no history or clinical symptoms of a systemic disease (10–12). This type of aortitis is referred to as 'idiopathic aortitis' (IA). Isolated aortitis (IsA), a subtype of IA, is a single organ vasculitis diagnosed when detailed imaging of aortic branch vessels does not reveal abnormalities (11,13).

IA is presently a poorly defined entity with no specific pathological or clinical criteria for its classification or diagnosis. Furthermore, the term 'idiopathic aortitis' is used loosely for a variety of clinical settings, including cases that are classified as specific types of large vessel vasculitis (GCA or Tak) upon review of clinical history (12), and the terms 'isolated' and 'idiopathic aortitis' are often used interchangeably (10,11). All of the present knowledge about IA comes from retrospective series of cases with pathologically identified aortitis (10–12). The largest of these series come from the Mayo Clinic (an older series of 45 cases of aortitis, 21 of which are classified as idiopathic (10), and a more recent series of 64 patients with 52 cases of IA (11)) and Cleveland Clinic (an older series of 52 cases of aortitis, 36 of which were classified as idiopathic (12) and a recent yet unpublished report of 196 cases, with 129 cases of IA (14)). Since no guidelines exist to direct the initial workup, treatment, and subsequent monitoring of

these patients, great case-to-case variability is observed underlining the need for a more systematic approach to this emerging condition.

This review was conducted to determine: 1) the frequency of idiopathic aortitis amongst aortic specimens at The Ottawa Hospital over a 10 year period; 2) the clinical, biochemical, and radiographic characteristics of idiopathic aortitis; 3) the approach to work-up, treatment and follow-up taken by the treating physicians; and 4) long-term outcomes.

Methods:

All cases of aortitis diagnosed on pathologic review of specimens of heart or aorta between January 1, 2003 and July 31, 2013 at The Ottawa Hospital were identified by reviewing the pathology database and searching the following terms: 'aorta', 'aortic', and 'aortitis'. Charts of all identified cases were reviewed for demographics, clinical information, as well as available laboratory investigations and imaging at baseline and follow-up.

Cases were classified as 1) infectious aortitis, 2) secondary aortitis (SA) associated with a systemic vasculitis or another inflammatory condition, and 3) IA. Cases of IA where detailed imaging of aortic branch vessels did not reveal abnormalities were further classified as IsA. Cases in group 3 (IA and IsA) constitute the focus of this study.

Descriptive statistics were used to summarize the outcomes using Microsoft Office Excel 2011. SPSS software (version 23) was used for logistic regression analyses.

This project was approved by the Ottawa Health Science Network Research Ethics Board (OHSN-REB, protocol #: 20130549).

Results:

Study group

Six hundred and eighty two aortic specimen were analyzed during the study period. Forty seven cases of aortitis were identified, giving the incidence of aortitis in aortic specimen of 6.9%. Seven cases (14% of aortitis) were infectious. Of the 40 cases of non-infectious aortitis, 32 (80% of non-infectious and 68% of all aortitis) were idiopathic (IA) and 8 (20% of non-infectious and 17% of all aortitis) were associated with a systemic condition (SA) (Figure 1). The systemic conditions associated with SA were isolated polymyalgia rheumatica (PMR), Takayasu's arteritis, and RA (n=1 for each), and 5 GCA (3 isolated, 1 in combination with PMR, and 1 with RA). In 3 cases classified as SA the associated systemic condition was diagnosed within 1 year following the diagnosis of aortitis. Out of the 32 cases of IA, 6 could be further classified as IsA. Incidence of non-infectious aortitis in our cohort is 5.9%, incidence of IA is 4.7% and incidence of IsA is 0.9%. Mean age of patients with IA was 63.8 years (range 17-83), and 18/32 (56.3%) were female (Table 1).

Characteristics at the time of diagnosis of aortitis

Baseline characteristics of patients with idiopathic aortitis are presented in Table 1. The majority of patients with IA presented with either aneurysm-related symptoms such as chest pain and dyspnea (n=12, 38%) or incidentally discovered aneurysm on imaging or echocardiography (n=14, 44%). Other presentations included abdominal pain, weakness and lower extremity claudication. Presentation was unknown in 3 (9%) patients.

Out of 13 IA patients with at least one of ESR or CRP measured, 10 had significant elevation (>30) of ESR, CRP, or both (see Table 1 for further details).

Imaging findings

Computed tomography (CT) was the most common modality for preoperative imaging of IA, having been used in 25/32 (78%) of patients with IA. Of the remaining patients, 5 were assessed with echocardiography and imaging modality was not documented for 2.

Out of 23 IA-related aneurysms, all but one involved the ascending aorta: 6 were limited to ascending aorta and the rest had variable degree of proximal and distal extension (with 2 spanning the whole length of aorta from ascending to abdominal); one aneurysm was limited to aortic arch. Nine IA patients did not have aneurysms but had their aortitis diagnosed on pathology of the specimen from aortic valve-related surgery or coronary artery bypass grafting.

Twenty-one out of 32 patients (66%) with IA had complete imaging of aortic branch vessels. Branch vessel lesions were found in 15/21 (71%) of imaged patients, and additional aortic lesions were found in 3 (2 of whom also had branch vessel involvement) (see Table 2).

Treatment of aortitis

Twelve out of 32 patients (38%) with non-infectious aortitis received treatment with glucocorticoids post-operatively, including 2/6 patients with IsA. Significant variability was observed both in the initial doses of prednisone (starting dose ranged between 20 and 100 mg/day) and in the duration of treatment (ranging from 2.5 weeks to greater than 9 years, with definitive stop date only known for 3 patients).

Three patients with IA received additional immunosuppressive agents between 5 months and 8 years after diagnosis of aortitis. One patient was diagnosed with RA at the time of treatment with methotrexate, 8 years after diagnosis of IA, and in 2 patients the reason for use of methotrexate is unknown.

Logistic regression analysis was performed to identify predictors of treatment in patients with IA. Out of age, sex, presence of cardiovascular risk factors, presence of additional radiographic lesions on baseline imaging and having a significantly elevated inflammatory marker (ESR and/or CRP >30), the latter was the only factor that significantly predicted treatment status in both univariate and multivariate analyses. Having elevated inflammatory markers increased the odds ratio for treatment with glucocorticoids by 7.9 and 21.4 in the 2 types of analyses, respectively (significance <0.05).

Outcomes on follow-up

Mean follow-up duration was 47.5 months (range1-123 months) in patients with IA.

CT and echocardiography were the most common modalities used for follow-up imaging of IA, having been used in 23 and 10 patients respectively (some patients were studied with more than one imaging modality). A minority of patients had further imaging with magnetic resonance angiography (MRA), conventional aortography, and positron emission tomography (PET).

Twelve out of 32 (38%) patients with IA had complete imaging of branch vessels at least once during follow-up. Table 2 details the number and location of additional aortic and branch lesions in IA patients. New lesions were found in 5/12 (42%) patients 3 months to 8 years

following surgery, and none of the patients with new lesions at follow-up were initially classified as IsA.

Development of additional radiographic lesions at follow-up in patients with IA did not differ significantly by treatment status. Out of the 12 patients who had complete follow-up imaging, half received post-operative glucocorticoids; 3 of the treated and 2 of the untreated patients developed delayed lesions. Notably, 10/12 imaged patients with IA, and all 5 patients with new lesions, had additional branch lesions at the time of diagnosis of IA.

Logistic regression analyses did not identify significant predictors for development of delayed radiographic lesions. Presence of additional radiographic abnormalities at the time of diagnosis of aortitis was identified as a strong (and the only) predictor of having complete follow-up imaging; having additional radiographic abnormalities at baseline increased the odds ratio of having complete follow-up imaging by a factor of 9.3 (univariate logistic regression model).

Three patients with IA had additional surgeries during the follow-up period: 2 patients required endovascular stenting of the thoracic aorta at the site of initial surgery 2 and 4 months after their original aortic surgeries, and the patient with IsA who had 2 distinct aortic lesions underwent open thoracoabdominal aneurysm repair 31 months after the original aortic surgery.

Three patients were diagnosed with a systemic condition within one year of diagnosis of aortitis (2 GCA and 1 Takayasu's), and these were classified as cases of SA. Two patients were diagnosed with a new systemic condition during follow-up – 1 with cutaneous lupus erythematosus 6.2 years following surgery and 1 with RA 8 years following surgery. Given the

length of time between diagnoses of aortitis and new systemic conditions, these patients were analyzed as cases of IA. Neither of these patients had IsA as their initial diagnosis. One patient with IA (later diagnosed with cutaneous lupus erythematosus) was reported deceased from a high-grade myelodysplastic syndrome.

Discussion:

We identified 32 cases of IA, 6 of which were further classified as IsA. Additional aortic or branch vessel lesions were found in 16/21 (76%) imaged patients with IA at baseline, and 12/32 patients (38%) with IA received perioperative treatment with glucocorticoids. During the mean follow-up duration of 47.5 months, 5 out of 12 imaged patients (42%) developed new radiographic lesions, 3 required additional vascular surgery, and 2 received diagnosis of a systemic condition.

The incidence of aortitis amongst aortic specimens in our cohort is 6.9% and the incidence of IA is 4.7%, comparable to incidences of 2-9% described in published retrospective series (10–12,15,16). The majority of cases of aortitis in our cohort were idiopathic, consistent with the existing literature (3,11,12). Median age of our IA cohort was 64 years, also within the reported range of 63-71 years in studies from 2000-2014 (10–12,14). We observed roughly equal gender distribution (56% female), similar to findings by Liang et al (50%) (11); in contrast, a number of previous reports highlight female predominance in cases of IA (12,14), which is the opposite of the male predominance typically observed in cases of idiopathic non-inflammatory abdominal aortic aneurysms. Aortic aneurysms associated with IA were limited to the thoracic aorta in 91% of cases in our study, comparable to those seen by Rojo-Leva (12) and Miller (10)

(96% in each) and those reported for aortitis associated with systemic conditions including GCA (1,17,19), RA (10,18), and SLE (6).

Thirty eight percent of our patients with IA were treated with glucocorticoids, which is slightly higher than the range of 9-34% reported in previous studies (10–12,14). This may be the result of increase in treatment with increased recognition of IA over time. Studies with lower rates of treatment, including those by Rojo et al (21%) (12) and Miller et al (9%) (10) reviewed cases of IA dating back to 1977 and 1985, respectively, whereas the oldest cases included in our cohort were from 2003.

Sixty six percent of our IA patients had complete imaging of aortic branch vessels, with additional lesions found at baseline in 76% of imaged patients. Liang et al reported a similar rate of baseline radiographic lesions of 72% in their cohort of non-infectious aortitis with imaging rate of 89% (11). In our study only 12/32 (38%) patients with IA had complete follow-up imaging, and 5/12 (42%) were found to have developed new aortic or branch lesions. This incidence of delayed radiographic lesions is similar to 44.6% reported in the study by Clifford (14), where routine follow-up imaging was performed on all patients. Notably, we found presence of additional radiographic lesions at the time of diagnosis of aortitis to be strongly predictive of having complete follow-up imaging. While tendency to follow-up patients with existing radiographic abnormalities seems to be intuitive, evidence and guidelines regarding appropriate follow-up of patients with IA are lacking resulting in great variability.

Interestingly, the only variable that predicted treatment with glucocorticoids in this study was having a significantly elevated ESR or CRP (>30 for either) at the time of diagnosis of aortitis. Notably, only 3 of 13 tested patients in our study had normal inflammatory markers,

while many previous studies report relatively normal inflammatory markers in most patients with IA (11,20). This suggests the possibility of confounding by indication, with inflammatory markers being tested preferentially in patients suspected to have systemic inflammation and considered for treatment. In view of current lack of guidelines regarding which patients need to be treated, or evidence that treatment changes outcomes altogether (21), the approach of treating patients with evidence of systemic inflammation seems reasonable.

Our study is primarily limited by its retrospective design and the relatively small size of the cohort. In view of the relatively recent recognition of IA as an entity and its rarity, all currently available literature on this condition is retrospective. This paper describes the first Canadian cohort with IA reported to date. We present detailed descriptions of clinical, laboratory, and radiographic findings both at baseline and at follow-up, and additionally review corticosteroid and immunosuppressive therapies used to treat patients with IA.

No consensus exists regarding the appropriate way to work-up, treat, and follow patients with IA, resulting in great variability of approaches both between and within reported studies. Studying such heterogeneous populations in turn makes it difficult to draw conclusions with regard to the optimal strategy for managing this rare condition. Larger, prospective and systematic studies are required to address unanswered clinical questions regarding idiopathic and isolated aortitis.

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Tables:

Table 1. Baseline characteristics of patients with idiopathic aortitis

Clinical features	**Number (%) (out of 32)**
Age, mean in years (range)	63.8 (17-83)
Sex, female	18 (56%)
Smoking status	
At/prior to diagnosis	22 (69%)
Never	4 (13%)
Unknown	6 (19%)
Comorbidities at diagnosis	
Hypertension	20 (63%)
Dyslipidemia	14 (44%)
CAD	14 (44%)
CVA/TIA	5 (16%)
Diabetes mellitus	4 (13%)
Chronic renal failure	2 (6%)
Medications at diagnosis	
ASA	31 (97%)
Other antiplatelet	3 (9%)
ACE inhibitor/ARB	18 (56%)
Beta-blocker	27 (84%)
Statin	12 (38%)
$\geq$1 antihypertensive	30 (94%)
Inflammatory markers	
Number with measured ESR/CRP	12/9
ESR (mm/hr), mean (range)	41.0 (5-75)
CRP (mg/L) , mean (range)	82.8 (6.6-179)
Presence of additional radiographic lesions, out of 21 fully imaged patients	16/21 (76%)
Additional aortic lesions	3/21 (14%)
Additional branch lesions	15/21 (71%)

CAD, coronary artery disease; CVA, cerebrovascular accident; TIA, transient ischemic attack; ASA, acetylsalicylic acid; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

Table 2. Additional aortic or aortic branch lesions in patients with idiopathic aortitis (total 32 patients)

Location	**Before or at diagnosis of aortitis**	**Delayed (3 months-8 years post-op)**
Aorta or branches (total)	16 patients with additional lesions at diagnosis	5 patients with additional lesions at follow-up
Additional aortic lesions	3 patients (1 isolated and 2 with additional branch lesions) 1 AAA 1 residual Type B dissection 1 distal abdominal aortic stenosis	3 patients (all with additional branch lesions) 2 AAA 1 increased aortic wall thickness
Additional branch lesions	15 out of 21 imaged patients 5 carotid stenosis < 50% 11 arch branch dilatations in 7 pts 5 right innominate 2 carotid 3 subclavian 1 all vessels; spont. resolution 1 arch branch thickening 1 left internal carotid artery occlusion 2 iliac stenoses 2 dissections 1 common iliac 1 left subclavian	5 out of 12 imaged patients 3 arch branch dilatations in 3 pts 1 right innominate 1 carotid 1 subclavian 1 left common iliac artery dissection 1 left common iliac artery aneurysm

AAA, abdominal aortic aneurysm

Figure legends:

Figure 1. All cases of aortitis identified on pathologic review of surgical specimen

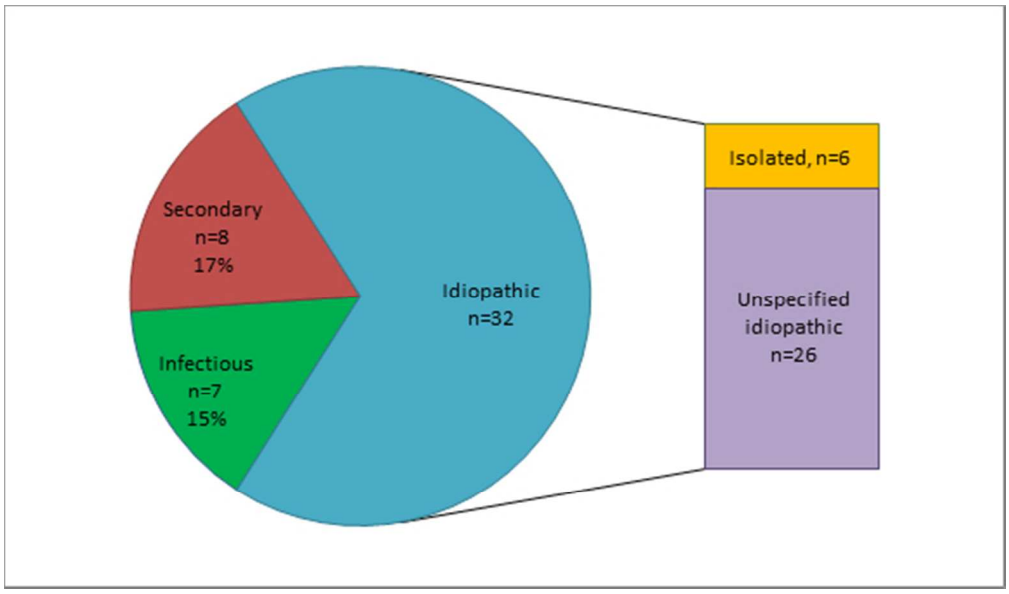

Figure 1. All cases of aortitis identified on pathologic review of surgical specimen