The epidemiology of pathologically confirmed clinically isolated aortitis: a North American population-based study

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Abstract

Objective

Clinically isolated aortitis (CIA) refers to inflammation of the aorta without signs of systemic vasculitis or infection. Population-based data on the epidemiology of CIA in North America is lacking. We aimed to investigate the epidemiology of pathologically confirmed CIA.

Methods

Residents of Olmsted County, Minnesota were screened for thoracic aortic aneurysm procedures with current procedural terminology codes between January 1, 2000, and December 31, 2021, using the resources of the Rochester Epidemiology Project. The medical records of all patients were manually reviewed. CIA was defined as histopathologically confirmed active aortitis diagnosed by evaluation of aortic tissue obtained during thoracic aortic aneurysm surgery in the absence of any infection, rheumatic disease, or systemic vasculitis. Incidence rates were age and sex adjusted to the 2020 United States total population.

Results

Eight incident cases of CIA were diagnosed during the study period; 6 (75%) of them were female. Median (IQR) age at diagnosis of CIA was 78.3 (70.2–78.9) years; all were diagnosed following ascending aortic aneurysm repair. The overall age and sex adjusted annual incidence rate of CIA was 8.9 (95% CI, 2.7–15.1) per 1,000,000 individuals over age 50 years. The median (IQR) duration of follow-up was 8.7 (1.2–12.0) years. The overall mortality compared to the age and sex matched general population did not differ (standardised mortality ratio: 1.58; 95% CI, 0.51–3.68).

Conclusion

This is the first population-based epidemiologic study of pathologically confirmed CIA in North America. CIA predominantly affects women in their eighth decade and is quite rare.

Key words

epidemiology, clinically isolated aortitis, population-based, vasculitis

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Introduction

Aortitis refers to inflammation of the aortic wall and can be broadly categorised into two groups: infectious and non-infectious (1). Non-infectious aortitis can be caused by a variety of systemic diseases, including giant cell arteritis (GCA), Takayasu's arteritis (TAK), and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (2).

Clinically isolated aortitis (CIA) refers to the detection of aortitis in the absence of any systemic disease or infection (3-5). The diagnosis of CIA generally relies on histopathological evaluation of aortic tissue obtained during thoracic aortic aneurysm surgery, making the diagnosis challenging. There is limited knowledge about the epidemiology and outcomes of CIA. Most of the previous studies were based on single-centre referral cohorts (6, 7). A recent transcriptomic study suggests that CIA might be a limited presentation of GCA (8).

To date, there is only one population-based study on CIA that was conducted in Europe (9) and epidemiology data in North America is lacking. The objectives of this study were to evaluate the epidemiology, clinical characteristics, and outcomes of patients with pathologically confirmed CIA in Olmsted County, Minnesota, between 2000–2021.

Materials and methods

In this population-based epidemiologic study, we screened all residents of Olmsted County, Minnesota for thoracic aortic aneurysm procedures with current procedural terminology (CPT) codes between January 1, 2000, and December 31, 2021, through the resources of the Rochester Epidemiology Project (REP). The REP is a records linkage system that enables researchers to access all medical information of the residents of Olmsted County through the inpatient, outpatient and emergency department visit records of all healthcare providers in Olmsted County. The features of the REP have been addressed elsewhere (10-12).

The medical records of all patients with at least one CPT code of interest were manually reviewed. Demographics, clinical, laboratory, histopathological, imaging, treatment, and outcome data of the patients with CIA were manually abstracted through December 31, 2021, last follow-up, or death. CIA was defined as histopathologically confirmed active aortitis diagnosed by evaluation of aortic tissue obtained during thoracic aortic aneurysm surgery in the absence of any infection, rheumatic disease, or systemic vasculitis.

All radiographic reports of the patients with CIA were manually reviewed. Incident vascular lesions were defined as new radiographic report of ectasia, aneurysm, dissection/intramural haematoma, non-atherosclerotic stenosis/occlusion in the aorta and/or any of its main branches at least 3 months after the index aortic surgery.

Descriptive statistics (mean with standard deviation [SD] and median with interquartile range [IQR]) were used to summarise patient characteristics. Sex-specific incidence rates were calculated using the number of incident cases as the numerator and population estimates from the REP census as the denominator for the subpopulation age ≥50 years. Incidence rates were age and sex adjusted to the 2020 United States total population. To compute 95% confidence intervals (95% CI) for incidence rates it was assumed that the number of incident cases followed a Poisson distribution. Mortality rates were estimated using the Kaplan-Meier method and were compared with expected mortality rates for persons of the same age, sex, and calendar year estimated using Minnesota population life tables. Statistical analyses were performed using SAS v. 9.4 (SAS Institute, Cary, NC, USA).

This study was approved by the Institutional Review Boards of the Mayo Clinic and Olmsted Medical Centre.

Results

A total of 232 patients with at least one CPT code for a thoracic aortic aneurysm procedure were identified. After chart review, 212 patients were found to have had thoracic aortic aneurysm/dissection surgery, and in 206 patients a histopathologic evaluation report of the aorta was available for review.

Thirteen patients were found to have histopathologic evidence of aortitis; 2 patients had infectious aortitis, 2 patients had underlying GCA, and 1 patient had polymyalgia rheumatica (PMR) (Fig. 1).

Eight incident cases of CIA were diagnosed during the study period; all were diagnosed following ascending aorta aneurysm repair. Demographics, baseline co-morbidities and pre-operative laboratory parameters are noted in Table I. Median (IQR) age at diagnosis was 78.3 (70.2–78.9) years. There were 6 (75%) females and 2 (25%) males. Median (IQR) duration of follow-up was 8.7 (1.2–12.0) years.

None of the patients met the 1990 or the 2022 ACR classification criteria for GCA.

The overall age and sex adjusted annual incidence rate of CIA was 8.9 (95% CI, 2.7–15.1) per 1,000,000 individuals over age 50 years with age adjusted rate of 12.7 (95% CI, 2.5–22.9) per 1,000,000 in females and 4.8 (95% CI, 0.0–11.4) per 1,000,000 in males.

Histopathological evaluation revealed giant cell aortitis in 7 (88%) patients and lymphoplasmacytic aortitis in 1 (13%) patient. Five (63%) patients were seen by a rheumatologist and 2 (25%) were treated with prednisone after the diagnosis of CIA with a median (IQR) starting dose of 35 (30–40) mg for a median (IQR) of 2.4 (1.6–3.2) years.

Most of the patients had cardiovascular signs and symptoms prior to the index aortic surgery (Supplementary Table S1). Five (63%) patients presented acutely to the emergency department prior to surgery; one had aortic dissection/contained rupture and died 6 days after the aortic surgery. Three (38%) underwent concomitant coronary artery bypass graft and ascending aortic aneurysm surgery.

In 4 (50%) patients, aortic dilatation was detected more than one year prior to the index aortic surgery (median [IQR] length of time between the detection of aortic dilatation and index aortic surgery was 4.83 [3.24–8.16] years). The mean (SD) diameter of the ascending aorta of the 7 patients at the time of index aortic surgery was 6.04 (0.56) cm based on computed tomography (in one patient size of the ascending aorta was not recorded).

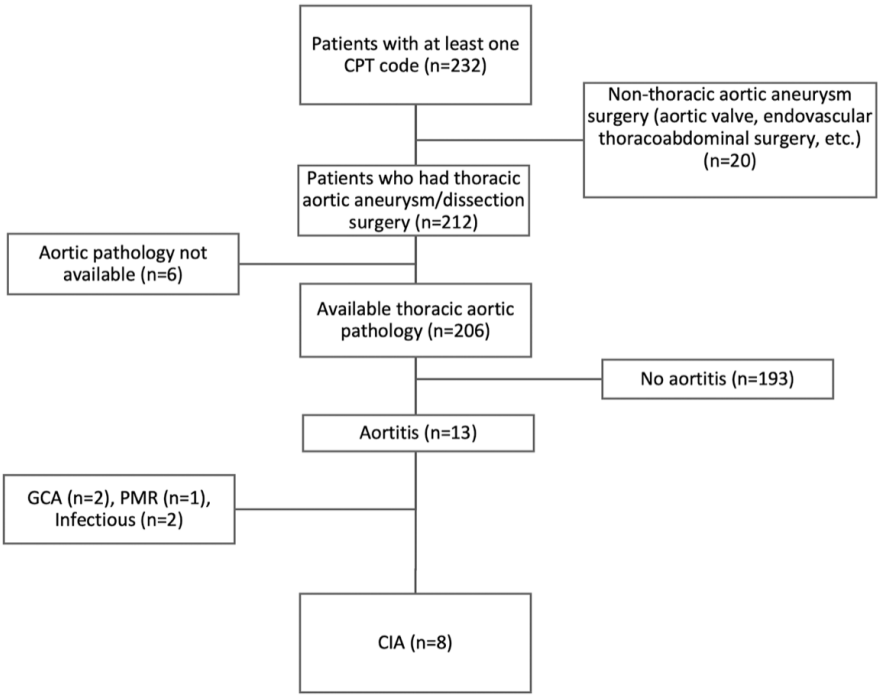

Fig. 1. Flowchart for the identification of the cohort.

None of the patients with CIA had signs or symptoms suggestive of systemic vasculitis. Available pre-operative inflammatory markers were not elevated. One patient had previous endovascular surgery for a descending thoracic aorta pseudoaneurysm.

Six (75%) patients (including those 2 patients treated with prednisone) had incident vascular lesions during the follow-up period; 4 with new aortic ectasia/aneurysm and new aortic branch lesions; 1 with new abdominal aorta aneurysm and 1 with new axillary artery ectasia. The median (IQR) length of time between the index aortic surgery and the detection of the first incident vascular lesion was 1.03 (0.88–2.17) years.

Of the 5 patients with incident aortic lesions, 2 had new thoraco-abdominal ectasia/aneurysm, 1 had new thoracic and 2 had abdominal ectasia/aneurysm. Two developed incident aortic dissection: one in the thoracic aorta and one in the abdominal aorta, extending to bilateral iliac arteries. One patient developed new bilateral subclavian stenoses and iliac artery ectasia.

Two patients required re-operation; one for an aortic arch aneurysm 16.4 years after the diagnosis of CIA and the other one required an aortic valve procedure 9.3 years after the diagnosis of CIA.

The survival rate of this cohort at 1, 5, and 10 years were 87.5% (95% CI, 67.3–100%), 62.5% (95% CI, 36.5–100%) and 46.9% (95% CI, 21.5–100%), respectively. Five patients died during follow-up. The overall mortality compared to the age and sex matched general population was not significantly increased with a standardised mortality ratio of 1.58 (95% CI, 0.51–3.68).

Discussion

This is the first population-based epidemiologic study of pathologically confirmed CIA in North America. CIA predominantly affects women over age 70 and is quite rare. Survival following a diagnosis of CIA in this small cohort was not significantly different from the general population.

The age and sex adjusted incidence rate of CIA per population has not been reported previously (13). A nationwide population-based cross-sectional study from Denmark reported 27 patients with idiopathic aortitis out of 37 patients with aortitis; however, histopathologic evaluation was avail-able for approximately 50% of the samples and incidence was not reported (9).

Table I. Characteristics of patients with incident CIA between 2000-2021 in Olmsted County, Minnesota, USA.

Characteristic*	Total (n=8)
Demographics	
Age at diagnosis, median (IQR) years	78.3 (70.2- 78.9)
Sex, female	6 (75)
Race, white	7 (88)
Duration of follow-up, median (IQR) years	8.7 (1.2- 12.0)
BMI Median (IQR) kg/m^2	26.7 (23.6- 33.1)
Smoking status, ever	4 (50)
Baseline co-morbidities**	
Diabetes mellitus	0 (0)
Hypertension	7 (88)
Hyperlipidaemia	5 (63)
Coronary artery disease	1 (13)
Cancer***	2 (25)
Chronic obstructive pulmonary disease	2 (25)
Chronic kidney disease	0 (0)
Pre-operative laboratory parameters	
Erythrocyte sedimentation rate median (IQR) (mm/hour)	25 (12- 26) (n=3)
C- reactive protein (mg/l)	5.4 (n=1)
Haemoglobin median (IQR) (g/dl)	12.8 (11.2- 13.5) (n=8)
White blood cell count median (IQR) (x 10^9/l)	8.4 (6.8- 10.1) (n=8)
Platelets median (IQR) (x 10^9/l)	231 (198.5- 251.5) (n=8)

*Except where indicated otherwise, values are the number (%) of patients.
**Co-morbidities that were diagnosed more than 1 year prior to the index aortic surgery.
***Both patients had breast cancer.

In this study, CIA was diagnosed in 8/13 (62%) of patients with aortitis and in 8/212 (4%) of patients who had thoracic aortic aneurysm surgery. These results are in line with the previously published studies (6, 14).

The demographic patterns of the patients with CIA, being predominantly white female over age 70, resembles patients with GCA. This finding along with the transcriptomic data may further support that CIA might be a smouldering or limited phenotype of GCA.

Currently, there is neither classification nor diagnostic criteria for CIA. According to the 2012 revised Chapel Hill Nomenclature, isolated aortitis was categorised as a single organ vasculitis with an emphasis on the lack of clarity regarding whether isolated aortitis is a limited expression of GCA or TAK (15). Previous studies have shown that, approximately 50% of the patients with CIA developed incident vascular lesions in the aorta or in its main branches during the follow-up period (6, 7). In our small cohort, 75% of patients developed incident vascular lesions. It is difficult to draw a conclusion because currently, there is no prospective study on CIA, and previous retrospective studies used different definitions.

In this study, we defined CIA as histopathologically confirmed active aortitis detected following aneurysm surgery; however, the frequency of radiographically confirmed aortitis was not evaluated. In a retrospective study of 32 patients with radiographically confirmed aortitis, 2 were considered as having idiopathic aortitis (16). The epidemiology of radiographically detected aortitis remains largely unknown. Ferfar *et al*. reported that in comparison to patients with GCA or TAK, patients with CIA had worse outcomes (17). It is still unknown whether the treatment of patients with CIA should be different from those with GCA or TAK and whether immunosuppressive agents could prevent the vascular complications of patients with CIA.

The population-based methodology of this study, which minimised referral bias, and the time span of more than two decades were its major strengths. The availability of histopathologic evaluation of almost all resected aorta specimen was one of the unique features of this work. The main limitation of this study was its retrospective design. Furthermore, our findings may not be generalisable to all patients with CIA, as we investigated only patients with pathologically proven CIA. Pathologically confirmed CIA could represent the severe form of CIA, as patients need to have enough aortic dilatation to undergo aortic surgery.

In conclusion, CIA is an orphan disease, and further research is required to truly understand the outcomes.

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