Incidence, prevalence and mortality on chronic periaortitis: a population-based study

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Abstract

Objective

To evaluate the epidemiology, presentation and outcomes of patients with chronic periaortitis from 1998 through 2018.

Methods

An inception cohort of patients with incident chronic periaortitis from January 1, 1998 through December 31, 2018, in Olmsted County, Minnesota was identified based on comprehensive individual medical record review utilising the Rochester Epidemiology Project medical record linkage system. Inclusion required radiographic and/or histologic confirmation of periarterial soft tissue thickening around at least part of the infra-renal abdominal aorta or the common iliac arteries. Data were collected on demographic characteristics, clinical presentation, renal and radiographic outcomes, and mortality. Incidence rates were age and sex adjusted to the 2010 United States white population.

Results

Eleven incident cases of chronic periaortitis were identified during the study period. Average age at diagnosis was 61.8±13.4 years. The cohort included 9 men (82%) and 2 women (18%). Age- and sex-adjusted incidence rates per 100,000 population were 0.26 for females, 1.56 for males and 0.87 overall. Overall prevalence on January 1, 2015 was 8.98 per 100,000 population. Median (IQR) length of follow-up was 10.1 (2.5, 13.8) years. Overall mortality was similar to the expected age, sex, and calendar estimates of the Minnesota population with standardised mortality ratio (95% CI) for the entire cohort 2.07 (0.67, 4.84).

Conclusion

This study reports the first epidemiologic data on chronic periaortitis in the United States. In this cohort of patients with chronic periaortitis, men were 4 times more commonly affected than women. Mortality was not increased compared to the general population.

Key words

periaortitis, incidence, prevalence, epidemiology

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Received on July 20, 2021; accepted in revised form on January 4, 2022.

Funding: this study was made possible by the generosity of the Audrey M. Nelson Rheumatology Career Development award and through use of the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG034676, and Grant Number UL1 TR002377 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing interests: none declared.

Introduction

Chronic periaortitis (CP) includes a spectrum of rare diseases characterised by fibro-inflammatory periarterial soft tissue thickening with a predilection for the infra-renal abdominal aorta and iliac arteries (1). The aetiologies of periaortitis are varied and have been attributed to medications, infections, malignancy, radiation, and surgery, though most remain idiopathic (2). CP can manifest in either an aneurysmal or non-aneurysmal form. The latter, commonly referred to as idiopathic retroperitoneal fibrosis (iRPF), can be either isolated or associated with systemic autoimmunity and has been reported in psoriatic arthritis (3), rheumatoid arthritis (4, 5), systemic lupus erythematosus (6, 7), anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (8, 9), and more recently in the systemic inflammatory condition, immunoglobulin G4 (IgG4)-related disease (10). Due to its rarity, only two epidemiologic studies have been completed evaluating the incidence of iRPF, both in Europe (11, 12). To date, no North American epidemiologic studies have been performed evaluating the constellation of rare conditions making up the spectrum of CP. The purpose of this study was to evaluate the incidence, prevalence, and mortality of CP in a well-defined population in the United States.

Methods

Data source and study population

Through the resources of the Rochester Epidemiology Project, the population of Olmsted County Minnesota, in which resides the city of Rochester, is well-suited for the investigation of the epidemiology of CP because comprehensive and complete medical records for all residents seeking medical care for more than six decades are available. A record linkage system allows ready access to the medical records from all health care providers for the local population, including Mayo Clinic and Olmsted Medical Center and their affiliated hospitals, as well as nursing homes and a few private practitioners. The potential use of this data system for use in population-based studies has been previously described (13). This system ensures virtually complete ascertainment of all clinical recognised cases of CP in the residents of Olmsted County.

Approval for this study was obtained from the Mayo Clinic (IRB# 18-006486) and Olmsted Medical Center (IRB# 026-OMC-20) institutional review boards. The need for informed consent was reviewed and waived.

Study design

A cohort containing Olmsted County residents diagnosed as having CP from January 1, 1998 through December 31, 2018 was identified. International Classification of Disease Ninth (ICD-9) or Tenth (ICD-10) revision coding was used for patient screening. Each ICD code is mapped to a singular disease term, often with multiple inclusion terms which refer to associated conditions which are considered as 'synonyms.' Given neither iRPF, nor CP have a singular descriptive disease term in either ICD-9 or ICD-10, synonym description codes for iRPF and CP were utilised. The diagnostic codes used for screening purposes were composed from a review of 400 individual referral cases of iRPF/CP sent to our institution between 1996-2016. All of the referral patients had at least one of the following codes used at one point in their evaluation: ICD-9 593.3 (stricture of ureter), 593.4 (other ureteric obstruction not elsewhere classified), 789.39 (abdominal or pelvic swelling, mass, or lump, other specified site) and ICD-10 codes N13.5 (crossing vessel and stricture of ureter without hydronephrosis), R19.09 (other intra-abdominal or pelvic swelling, mass and lump), K68.9 (other disorders of retroperitoneum). The medical records of all patients in the Rochester Epidemiology Project with at least one of the aforementioned codes during the specified time frame were manually reviewed.

Study definitions

All patients defined as having CP required the presence of radiographic and/or histopathologic confirmation of an inflammatory process demonstrated by peri-arterial soft tissue thickening, affecting at least part of the infra-renal abdominal aorta or the common iliac

arteries. The following patients were excluded: (1) patients with radiographic features of inflammation isolated to the arterial wall (intima, media or adventitia) without associated peri-adventitial soft tissue thickening [*i.e.* aortitis] (2) patients with retroperitoneal adenopathy or malignant tissue that resulted in the entrapment of the ureters, aorta, or inferior vena cava, without defined concomitant peri-arterial soft tissue thickening, (3) patients with retroperitoneal soft tissue thickening that did not include peri-arterial (aorta and/or iliac artery) involvement (for example isolated soft tissue thickening in the renal hilum, ureter, pelvis, etc.)

Definitions for CP and its subsets were adapted from nomenclature proposed by Palmisano and Vaglio (1). The following categories were utilised: (1) isolated, (2) associated with systemic autoimmune disease (3) IgG4-related, (4) secondary. Patients were listed as having CP associated with systemic autoimmune disease were required to have a defined diagnosed systemic autoimmune condition known at the time of CP diagnosis or for which the autoimmune disease was diagnosed concomitantly with the identification of CP. Patients with IgG4-related CP were defined as having both evidence of CP and fulfilment of the 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease (14). The aetiology was determined to be secondary if one of the following was present and felt to have contributed to the development of the periarterial soft tissue thickening: medications (methysergide, ergot alkaloids), infection (histoplasmosis, tuberculosis, actinomyces), malignancy (biopsy confirmed), abdominopelvic radiation. Patients that did not fulfil one of the aforementioned subsets were considered isolated. Each category was further differentiated based on the presence or absence of aneurysm at the time of diagnosis.

Renal function staging at baseline and follow-up were defined based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines for classification and stratification of chronic kidney disease (15). Outcomes of the peri-aortic/peri-iliac soft tissue thickening were categorised as (1) worsened, (2) unchanged (3) improved but not resolved and (4) resolved; the latter only considered if previously documented peri-aortic/peri-iliac soft tissue thickening was no longer detected radiographically.

Statistical analyses

Descriptive statistics (means, percentages, etc.) were used to summarise the data. Age- and sex-specific incidence rates were calculated by using the number of incident cases as the numerator and population counts from the REP census for adults (age ≥18 years) as the denominator. Overall incidence rates were age and/or age/sex adjusted to the 2010 white population of the United States. The point prevalence of CP was determined using the number of prevalent cases on January 1, 2015 as the numerator and the Olmsted County population based on the REP census on January 1, 2015 as the denominator. To compute 95% confidence intervals (CIs) for incidence and prevalence rates, it was assumed that the number of incident cases followed a Poisson distribution. Trends in incidence rates were examined using Poisson regression methods, with smoothing splines for age and calendar year.

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 estimates using Minnesota population life tables. The standardised mortality ratio (SMR) was estimated as the ratio of the observed and expected number of deaths. The 95% CIs for the SMR were calculated assuming that the expected rates are fixed and the observed rates follow a Poisson distribution. Statistical analyses were performed using SAS v. 9.4 (SAS Institute, Cary, North Carolina, USA) and R v. 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The initial search strategy yielded 1,702 potential subjects based on ICD coding database retrieval. Following direct medical chart review, only 17 subjects were found to have confirmatory evidence of CP by radiology and/or histopathology. Six subjects were excluded from incidence rate analysis because 3 subjects were non-residents of Olmsted County on the date of diagnosis and 3 subjects had a diagnosis date outside of the study period. The resulting cohort therefore included 11 subjects.

The subset of CP was determined to be isolated, non-aneurysmal CP in 3 subjects (27%) and isolated, aneurysmal CP in 3 subjects (27%) (Fig. 1). Two subjects (18%) were determined to have non-aneurysmal CP associated with autoimmune disease; one with eosinophilic granulomatosis with polyangiitis and the other with seropositive rheumatoid arthritis. Three subjects (27%) with CP had associated malignancy with the aetiologies including Erdheim-Chester Disease, follicular non-Hodgkin lymphoma, and prostatic adenocarcinoma with metastasis. None of the subjects in the cohort met classification criteria for IgG4-related disease.

Overall, the age and sex adjusted total annual incidence rate (95% CI) of CP in adults from 1998-2018 was 0.87 (0.36, 1.39) per 100,000 population with age adjusted rate in females of 0.26 (0.00, 0.63) and 1.56 (0.53, 2.59) in males, per 100,000 population. Prevalence rates were calculated on January 1, 2015. The age- and sex-adjusted prevalence rate (95% CI) of CP in adults on January 1, 2015 was 8.98 (1.78, 16.19) per 100,000 population. The age-adjusted prevalence rate for females was 6.20 (0.00, 14.80) and 12.84 (0.18, 25.51) in males, per 100,000 population.

The baseline presentation features, demographics and co-morbidities of the cohort are noted in Table I. Mean (±SD) age at diagnosis was 61.8 (±13.4) years. There was a male predominance with 9 (82%) males and 2 (18%) females. No patient had a history of tuberculosis or histoplasmosis. None of the 11 patients had a prior reported exposure to methysergide, ergotamines, methyldopa, pergolide or asbestos. Five patients had prior abdominal surgeries before onset of CP, 4 with appendectomy, and 1 bilateral inguinal hernia repair.

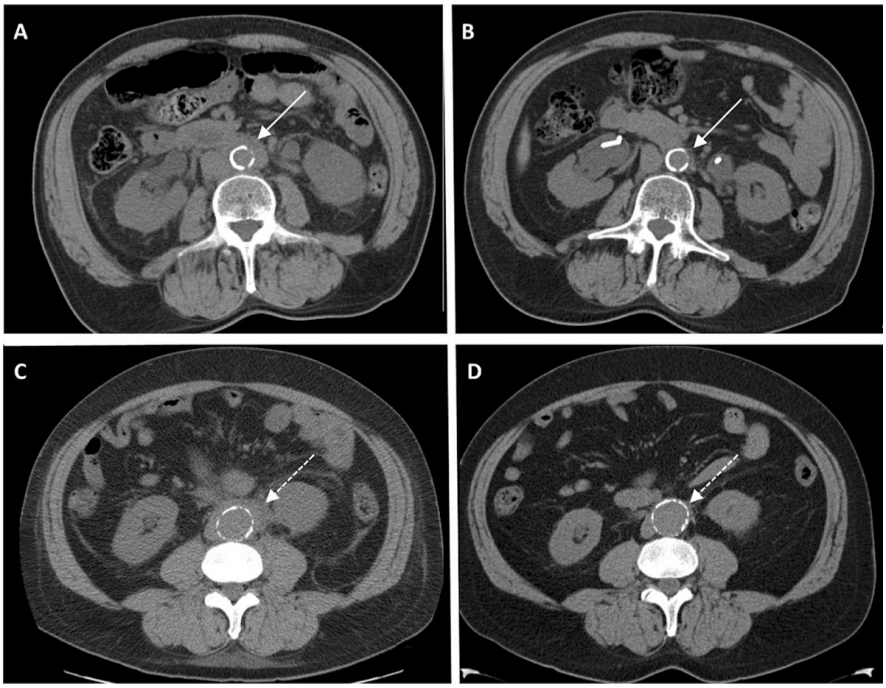

Fig. 1. Cross-sectional non-contrast computed tomography imaging demonstrating initial and follow-up imaging in representative patients with non-aneurysmal, isolated chronic periaortitis (panel A: before, panel B: after treatment) and aneurysmal, isolated chronic periaortitis (panel C: before; panel D: after treatment).

Table I. Demographic characteristics and presentation features of patients diagnosed with incident chronic periaortitis from 1998-2018 in Olmsted County, Minnesota.

Characteristic, n (%)	Total (n=11)
Demographics	
Age at diagnosis, years*	61.8 ± 13.4
Sex, male	9 (82)
Race, white	11 (100)
Length of follow-up, years¥	10.1 (2.5, 13.8)
Baseline presentation features	
Back pain	4 (36)
Abdomino-pelvic pain	6 (55)
Flank pain	2 (18)
Reduced urine output	3 (27)
Anorexia	4 (36)
Wt loss >5lbs	1 (9)
Nausea	3 (27)
Vomiting	2 (18)
Baseline co-morbidities	
Diabetes mellitus	2 (18)
Hypertension	8 (73)
Coronary artery disease	2 (18)
Rheumatic disease	4 (36)
Hypothyroidism	1 (9)
Smoking status	
Never	4 (36)
Former	4 (36)
Current	3 (27)
Baseline laboratory parameters	
Creatinine, mg/dL*	2.7 ± 3.4
Haemoglobin, g/dL*	12.3 ± 2.0
Sedimentation rate, mm/hr*	67.5 ± 24.6
C-reactive protein, mg/L*	29.2 ± 36.2

*mean ± SD, ¥median (IQR).

The most common presenting symptom was pain with 55% (6/11) reporting abdomino-pelvic pain, 36% (4/11) back pain, and 18% (2/11) flank pain. Obstructive uropathy was present in 73% (8/11) of subjects as evidenced by hydronephrosis on radiographic imaging: 3 (27%) unilateral left, 1 (9%) unilateral right, 4 (36%) bilateral. The mean (± SD) creatinine at presentation was 2.7 (± 3.4) mg/dL. Renal function stage at initial diagnosis was stage 2 in 2 (18%), stage 3a in 5 (45%), stage 3b in 1 (9%), stage 4 in 1 (9%) and stage 5 in 2 (18%). One of the stage 5 patients required temporary dialysis at diagnosis. Ureteral stenting was required at diagnosis in seven patients, unilateral left in 2, unilateral right in 1 and bilateral in 4. All 11 patients received prednisone at time of diagnosis with a median (IQR) dose of 40 (30, 60) mg/day. Additional non-glucocorticoid therapeutics were used in 10 patients with the total number of patients receiving each treatment as follows: methotrexate (n=7), rituximab (n=2), hydroxychloroquine (n=3), abatacept (n=1), mycophenolate (n=1), azathioprine (n=1), tocilizumab (n=1), cyclophosphamide (n=1), anakinra (n=1), tamoxifen (n=1).

Renal function stage at last follow-up declined in 2 patients (stage 2 to 3b, 3a to 3b), remained the same in 3 patients and improved in 6 patients. Among those with improvement, the two patients with Stage 5 at diagnosis both improved to Stage 3a. Mean (± SD) creatinine at last follow-up was 1.2 (± 0.2) mg/dL. Among the seven patients requiring baseline indwelling ureteral stent placement only two required ongoing ureteral stenting at last follow up. None of the four patients without ureteral stenting at diagnosis progressed to require stenting during the follow-up period. No patient underwent ureterolysis surgery in this cohort.

Among patients that did not have an autoimmune disease diagnosed prior to or at the time of CP diagnosis, two patients subsequently developed chronic seronegative rheumatoid arthritis during follow-up requiring ongoing immunosuppression. Besides the three patients found to have malignancy at the time of CP diagnosis, no additional patients were diagnosed with malignancy during the study period.

At the date of last follow-up, seven patients were able to discontinue prednisone and remain off. The four patients remaining on prednisone included the two patients with autoimmune disease (rheumatoid and eosinophilic granulomatosis with polyangiitis) at baseline and the two patients that developed seronegative rheumatoid arthritis during follow up. Five patients remained on disease modifying agents at date of last visit. Three patients were receiving methotrexate (two rheumatoid arthritis, one eosinophilic granulomatosis with polyangiitis). One patient with rheumatoid arthritis was receiving maintenance rituximab. The patient with Erdheim-Chester disease was receiving anakinra.

The periarterial soft tissue thickening at last follow-up had increased in size/thickness in 1 (9%), unchanged in 2 (18%), decreased in size but did not resolve in 6 (55%), and fully resolved in 2 (18%). No new locations of peri-arterial soft tissue thickening developed during follow-up. The single patient

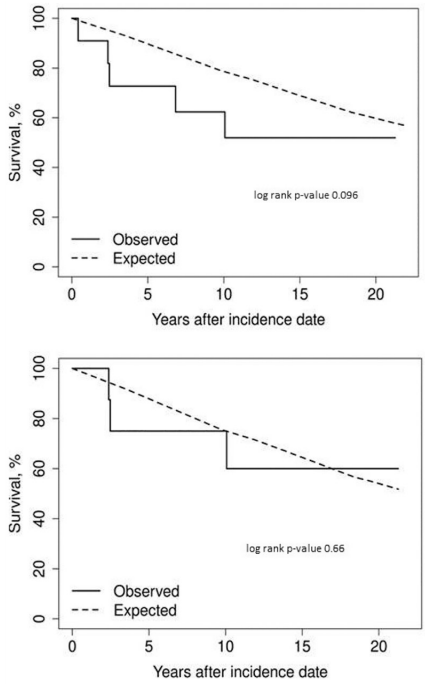

Fig. 2. Survival of patients with chronic periaortitis (solid line) for the entire cohort (upper panel) and chronic periaortitis excluding malignancy (lower panel) compared to the expected survival (dotted line) based on the same age, sex, and calendar year estimates using Minnesota population life tables.

with worsening had initial improvement but then redeveloped peri-aortic soft tissue thickening at the previously affected area after therapy discontinuation, thus requiring reinitiation of immunosuppression. Among patients with non-aneurysmal CP, none of the observed CP locations subsequently became aneurysmal. Of those with baseline aneurysmal CP, one had no change in growth while 2 had increase in growth (34 mm to 36 mm; 48 mm to 52 mm, respectively); neither of which required endovascular or surgical intervention.

For all patients with CP the 2, 5 and 10 year survival rates (95% CI) were 91 (75, 100), 73 (51, 100) and 62 (39, 100), respectively with an overall standardised mortality ratio (95% CI) for the entire cohort of 2.07 (0.67, 4.84) [Figure 2, upper panel]. When the 3 patients with malignancy were excluded, the 2, 5, and 10 year survival rates (95% CI) were 100 (100, 100), 75 (50, 100), and 75 (50, 100) with a standardised mortality ratio (95% CI) of 1.28 (0.26, 3.75) (Fig. 2, lower panel).

Discussion

CP includes a spectrum of clinical subsets and nomenclature regarding these entities is challenging due to lack of established consensus. It has been proposed to separate patients into those with secondary causes due to infections, malignancies, medications, radiation, etc. from those with so-called idiopathic forms (16). Among the idiopathic forms of CP, further subgrouping of isolated, IgG4-related, and associated with autoimmune disease has been suggested (1). Additional further differentiation has also been advocated based on the presence or absence of aneurysm at the time of diagnosis with the former often referred to as inflammatory abdominal aortic aneurysm (2). As such there remains a large degree of variability in reported CP cohorts with some excluding cases observed in the context of aortic aneurysm (17, 18) while others include both aneurysmal and non-aneurysmal CP under the terminology of iRPF (11, 12, 19). Furthermore, while few cohorts include CP detected in a patient with recent or current diagnosis of malignancy (20-22), the majority of studies exclude such patients (11, 12, 17, 18, 23), resulting in a lack of information evaluating secondary forms of CP. Given the lack of epidemiologic data on the clinical subsets of CP, we decided to include all patients in this cohort that demonstrated evidence of definitive peri-arterial soft tissue thickening of the infra-renal abdominal aorta and/or iliac arteries.

Our study reports the first epidemiologic data on CP subsets in the United States between 1998-2018, identifying an age- and sex-adjusted overall incidence of 0.87 and prevalence on January 1, 2015 of 8.98 per 100,000 population in Olmsted County, Minnesota. To date, only two additional studies have evaluated the epidemiology of CP. A Finnish study by Uibu and colleagues reported an incidence of 0.10 and prevalence of 1.38 per 100,000 person years in their catchment area (11). A Dutch study by van Bommel *et al*. identified a higher incidence with 1.3 per 100,000 inhabitants (12). While each study excluded cases with associated diagnosis of malignancy, both studies included patients with periaortitis associated with baseline aortic aneurysm/dilatation, which accounted for 23% of the Dutch cohort (12). Our cohort noted similar percentage of cases with aneurysmal CP, with 27% (3/11) of cases having baseline aortic or iliac artery aneurysm associated with the peri-arterial inflammatory process.

Auto-immune disease and chronic inflammatory conditions have been associated with CP, but the aetiopathogenic role of these conditions in the development of CP is not well understood. In our cohort 2/11 (18%) of the cases had associated auto-immune disease; one with eosinophilic granulomatosis with polyangiitis and the other with rheumatoid arthritis. Concurrent autoimmune disease has been reported similarly in other cohorts with frequencies of 15-24% (12, 18, 19, 24). Experts have proposed that the presence and frequency of varied autoimmune diseases observed in association with CP raises the suspicion that CP likely results from a systemic immune dysregulation for which the pathogenesis is multifactorial (16). Further research in this area is needed.

The inclusion of patients with malignancy in our cohort (3/11, 27%) was necessary to understand the epidemiology of secondary causes of CP. Importantly, inclusion of such patients only occurred if they had definitive radiographic features indicative of CP prior to initiation of chemotherapy or radiation. No patient had direct infiltration of the periaortic space by solid tumour or entrapment of the ureters or the aortocaval vessels by adenopathy. We feel these secondary CP patients are important to report as they identify a subset with radiologic findings similar to cases with idiopathic forms of CP and highlight that biopsy is necessary in such times to differentiate. In the patient with Erdheim-Chester, biopsy of the periaortic and perinephric tissue resulted in diagnosis. The patient with prostate adenocarcinoma and the patient with non-Hodgkin's lymphoma had mildly enlarged lymph nodes in the aortoiliac region which were non-contiguous with the periaortic thickening. Biopsy of aorto-iliac lymph nodes con-

firmed malignancy but biopsy of the periaortic thickening was not undertaken in either case. As such it is presumed the periaortic soft tissue was reactive but presence of malignant cells in this space cannot be excluded. Given periaortitis was observed prior to initiation of chemotherapy or radiation in these patients, the periaortic tissue was not considered to be due treatment effect. Due to a paucity of studies describing secondary cases of CP observed in the context of malignancy (20, 22, 25), more reports will need to include this information before comparisons in diagnosis and outcome can be made.

The current study reaffirms several findings that have been observed in similar reports including a mean diagnosis age in the 5th-6th decade of life, a male predominance, and the most common presentation features being nonspecific pain in the low back, abdomen, and flank (11, 12, 17-20). Importantly, this study also highlights that while a high proportion of patients present with obstructive uropathy requiring ureteral stent placement, prompt initiation of medical therapy and ureteral patency interventions result in the majority of patients improving renal function during follow-up. Renal decline requiring dialysis was not observed. Analogous findings have been reported by van Bommel *et al*. with only 1 of 24 patients requiring long-term dialysis (19). Mortality in CP is not well-defined. Van Bommel *et al*. reported a mortality of 8% with a median follow-up duration of 55 months. Kermani *et al*. noted 6% of patients died during follow-up with a mean time from diagnosis to death of 3.2±3.1 years. Our study is the first to report mortality of CP compared to similar age, sex, and calendar year population estimates. Notably, mortality of CP was not increased, even with inclusion of secondary CP due to malignancy. Confirmation of this finding in larger cohorts will be required.

Glucocorticoids have been a mainstay and recommended first-line agent in the management of CP (16), as was observed in our cohort. Additional treatments are often employed but remain highly variable because of the lack of well-designed studies to provide guidance on treatment. The provider rationale for which additional therapy was employed was not universally available and therefore could not be commented on. Due to the limited cohort size and retrospective nature, we were not able to compare outcomes based on therapeutics received. Nevertheless, it is reassuring that overall 55% of patients had decrease in soft tissue size and 18% with resolution of the peri-arterial soft tissue mass. Similar radiographic outcomes have been reported in comparable cohorts with the majority having periaortic mass reduction (54-67%) and complete regression noted in 9-13% (18, 19). Outcomes in the current study focused on reduction of peri-aortic soft tissue thickening on computed tomography; however, recent studies have found that multimodality imaging with positron emission tomography integrated with magnetic resonance imaging (PET-MRI) provides additional detail regarding imaging-based disease activity monitoring in both aortitis and peri-aortitis (26, 27). Evaluation of larger cohorts using similar prospective multi-modality imaging assessments will be critical for understanding iRF/CP.

In addition to improvement in the peri-aortic soft tissue thickening, it is notable that development of subsequent aortic aneurysm among patients without baseline aneurysm was not seen. Adjunct therapy was variably employed but all patients received glucocorticoids. It is uncertain if exposure to glucocorticoids is protective against aneurysmal conversion or if patients with iRPF/CP without baseline aneurysm have an inherently low likelihood to develop subsequent aneurysm. Prospective randomised studies with long-term follow-up are needed to evaluate which treatment options are optimal among patients with CP.

The major strengths of this study include that it is a population-based study with long-term follow-up. The comprehensive record linkage system allows capture of nearly all cases of CP in the community with verification by direct medical chart review, minimising misclassification. This study, however, must also be interpreted in the context of its limitations. First of all is the retrospective design and its inherent limitations of information restricted to that which is documented in the medical record. Second, the population of Olmsted County, Minnesota is predominantly white and therefore may not be generalisable to all patient populations affected by CP. Third, given there is not a current diagnosis code specific to CP it is possible that despite use of multiple available synonym codes, we may have overlooked patients not identified in our database search. Although we recognise that different providers and institutions may use alternative coding for patients with CP, we feel that the utilisation of diagnostic codes that were observed among a large population of referral patients to our institution over the span of three decades notably reduces the possibility of under-recognition. Nevertheless, given the rarity of this condition, it will be imperative for future revisions of the International Classification of Disease to develop standardised and distinct diagnosis coding to provide the opportunity to more readily research this uncommon condition across population databases.

In conclusion, we report the first epidemiologic study of CP in the United States with an age- and sex-adjusted overall incidence of 0.87 and prevalence on January 1, 2015 of 8.98 per 100,000 population in Olmsted County, Minnesota. In our cohort, radiographic improvement occurred in the majority and renal outcomes were generally favourable. Overall mortality was not different from that of the general population.

Acknowledgements

The authors thank Dr Audrey M. Nelson, emeritus Professor of Medicine, Division of Rheumatology, Mayo Clinic, Rochester, Minnesota, USA for the financial support of early rheumatology investigators through her Career Development Award. In addition, the authors thank and acknowledge Dr Harvinder Luthra, emeritus Professor of Medicine, Division of Rheumatology, Mayo Clinic, Rochester, Minnesota, USA for his four decades of expertise

in the diagnosis and management of patients with retroperitoneal fibrosis/chronic periaortitis prior to his retirement in 2014.

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