Cardiopulmonary involvement in Takayasu's arteritis

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ABSTRACT

Objective. *To evaluate cardiopulmonary (CP) involvement in patients with Takayasu's arteritis (TAK) and assess the impact on disease outcomes.*

Methods. *A retrospective cohort of patients with newly diagnosed TAK from 1984 to 2009 was assembled. Demographics, baseline disease characteristics, relapse events, surgeries and mortality were abstracted from direct medical record review. Angiograms, advanced imaging and cardiac studies were reviewed for evidence of CP involvement. Cox models with time-dependent covariates were used to assess the association between CP involvement and outcomes.*

Results. *A total of 124 patients with TAK were identified. Forty-five (36%) patients had at least one objective CP abnormality observed within 6 months of TAK diagnosis. Age at diagnosis was higher in those with CP involvement than those without (34.6 vs 30.1 yrs; p=0.04). Baseline characteristics and symptoms were similar, except shortness of breath, which was more frequently observed at TAK diagnosis in patients with CP involvement compared to those without (53% vs 21%; p=0.001). Composite CP involvement was not associated with risk of first surgery [Hazard ratio (95% CI): 1.21 (0.64-2.30); p=0.56]. However, pulmonary hypertension (PH) on echocardiogram was significantly associated with risk of first surgery [HR (95% CI): 12.9 (1.86-89.14); p=0.01]. CP involvement was not significantly associated with mortality [HR (95% CI): 2.51 (0.45-14.02); p=0.29].*

Conclusion. *Cardiopulmonary abnormalities in TAK are common at the time of initial presentation. In this population, the presence of PH predicted a 13-fold increased risk for vascular or valvular surgery. In this cohort, the presence of CP involvement did not increase mortality.*

Introduction

Takayasu arteritis (TAK) is a systemic vasculitis of unknown aetiology, primarily affecting the proximal aorta and its main branches. Granulomatous inflammation presents within the adventitia and media results in arterial stenosis/occlusion or aneurysmal dilatation of the large vessels. Since identification of TAK can be delayed due to the non-specific nature of presenting symptoms, vascular damage is often present at time of diagnosis. Large-vessel ischaemic complications are a major cause of morbidity and require surgical or endovascular correction in over half of the cases (1). Although recent cohorts have demonstrated 10-year survival rates of 90–97% (1, 2), the primary determinants of mortality across populations continue to be due to cardiopulmonary (CP) sequelae.

The development of CP pathology over the course of follow-up has been well-documented and includes the following entities: valvular regurgitation, pulmonary hypertension (PH), heart failure, and direct inflammatory involvement of the coronary and pulmonary arteries. CP pathology may be asymptomatic early on, and subtle symptoms may be overshadowed by other disease manifestations at the time of diagnosis. Therefore, these conditions may not be discovered until later in the disease course or at autopsy (3-6). Consequently, few cohorts have evaluated the presence of CP involvement near the time of diagnosis (7-9) and its impact on future outcomes is relatively unknown. The goal of this study was to characterise the patterns of CP involvement present within 6 months of TAK diagnosis in a large-single institution cohort and determine its effect on patient outcome during long-term follow-up.

Patients and methods

The study population comprised of a previously described cohort of patients

Table I. Definitions of cardiopulmonary involvement.

Feature of CP Involvement	Data regarded as a positive finding
Pulmonary arterial vasculitis	Presence of aneurysm, stenosis, occlusion or dilation in main or segmental pulmonary arteries by advanced imaging (MRA, CTA, conventional angiogram)
Coronary artery vasculitis	Presence of aneurysm, stenosis (greater than 70%), occlusion or dilation of coronary arteries by advanced imaging (MRA, CTA, conventional angiogram)
Left ventricular dysfunction	Echocardiographic findings of ejection fraction <=50%, diastolic dysfunction >=grade 2
Left ventricular enlargement	Echocardiographic findings of diastolic diameter >=50 mm, systolic diameter >=35 mm
Valvular dysfunction	Echocardiographic findings of moderate or severe valvular regurgitation (tricuspid, pulmonic, mitral, aortic
Pulmonary hypertension	Echocardiographic findings of right ventricular systolic pressure >=40 mmHg
Left ventricular regional wall motion abnormality	Echocardiographic findings of hypokinesis, akinesis, dyskinesia or aneurysm of left ventricular base, mid cavity or apex
Electrocardiogram abnormality	Tracings consistent with left ventricular hypertrophy, right ventricular hypertrophy, left axis deviation, right axis deviation, atrial arrhythmia (atrial fibrillation, atrial flutter, atrial tachycardia), right bundle branch block, left bundle branch block or left anterior fascicular block
Cardiac perfusion defect	Any perfusion defect noted on cardiac nuclear uptake studies

with newly diagnosed TAK evaluated at the Mayo Clinic in Rochester, Minnesota, from January 1, 1984, through December 31, 2009 (1). The study was approved by the Institutional Review Board at the Mayo Clinic.

Data were gathered from direct medical record review by a physician abstractor using a preformatted questionnaire. Information collected included demographic information, baseline disease characteristics, laboratory values at first visit (or before treatment if available) and disease activity. All angiograms (invasive and non-invasive) evaluating coronary and pulmonary vasculature as well as echocardiograms, cardiac nuclear uptake studies and electrocardiograms (ECG) were evaluated for objective evidence of CP abnormalities. To be considered as part of the initial disease process, CP findings needed to be documented within 6 months of initial TAK presentation. Charts were further reviewed to identify relapse events, cardiovascular and valvular surgeries and mortality during follow-up. Only patients with greater than one year of follow-up were included in the analysis of relapse and surgery event outcomes.

For purposes of this study, CP involvement was defined as the presence of one or more of the features described in Table I. Patients with a history of, or abnormalities resulting from, atherosclerotic coronary artery disease were excluded from analysis.

Statistical analysis

Descriptive statistics were used to summarise the data. Continuous data were presented as mean (SD) or median [interquartile range (IQR); 25th percentile, 75th percentile] and categorical variables as percentages. The Wilcoxon rank-sum test was used to analyse continuous variables and the chi-square test was used for categorical variables. Kaplan-Meier methods were used to estimate the rate of developing outcome (*i.e.* time to first event) and predictors of outcome were examined using Cox proportional hazard models. Analyses were performed using SAS v. 9.3 (SAS Institute, Cary, NC, USA).

Results

Cohort

A total of 126 newly diagnosed cases of TAK were identified. Two patients were excluded due to a concomitant diagnosis of atherosclerotic coronary artery disease during the study period. Among the remaining 124 patients with TAK, 92 had at least one study evaluating for objective evidence of CP involvement. The number of patients with at least one study present for the following modalities included 48 patients with angiographies (invasive and/or non-invasive) evaluating the pulmonary vasculature, 27 coronary angiograms, 60 echocardiograms, 63 ECGs and 8 cardiac nuclear uptake studies. Seventy-seven of these patients had greater than one year of documented follow-up (median: 5.5 years; IQR: 2.9–8.8 years) and were included in the relapse and surgery event sub-analyses (1).

Baseline characteristics

The total cohort consisted of 113 (91%) females and 11 males with a mean age of 31.5 (±10.5) years. Fifty patients (40%) had evidence of systemic hypertension, 22 of which were due to renal artery stenosis. The most frequently observed Hata angiographic classification was type V (57%) followed by type I (20%).

Cardiopulmonary involvement

Thirty-two patients (26%) did not have available results of cardiopulmonary studies performed within the first six months of initial presentation beyond the diagnostic angiography used to confirm TAK diagnosis. Among the remaining 92 patients evaluated with additional cardiopulmonary studies, 45 (49%) patients were identified as having at least one objective CP abnormality while 47 (51%) patients did not demonstrate evidence of CP involvement. Comparison of baseline characteristics based on the presence or absence of CP involvement is shown in Table II. Patients with CP involvement were older (34.6 *vs*. 30.1 years, p=0.04) and more frequently had symptoms of shortness of breath noted at the time of diagnosis (53% *vs*. 21%, p=0.001).

Frequency and distribution of cardiopulmonary involvement

Among the 45 patients with at least one objective CP abnormality observed within 6 months of TAK diagnosis, nine had direct evidence of pulmonary vasculitis on angiography. The most common pulmonary segment involved

Table II. Baseline characteristics of patients with Takayasu arteritis based on presence or absence of cardiopulmonary involvement.

Characteristic, n (%)	CP (+) (n=45)	CP (-) (n=47)	*p*-value
Age at diagnosis, year[a]	34.6 (±10.6)	30.1 (±10.2)	0.04
Female	40 (89)	42 (89)	0.94
ESR, mm/h[b]	19.0 (5.0-114.0)	26.0 (3.0-153.0)	0.41
CRP, mg/L[b]	12.8 (2.9-81.0)	50.3 (1.0-201.0)	0.14
Hata type V	18 (51)	24 (54)	0.59
Shortness of breath	24 (53)	10 (21)	0.001
Syncope	5 (11)	3 (6)	0.42
Cough	12 (27)	8 (17)	0.26
Palpitations	11 (24)	6 (13)	0.15
Chest pain	21 (47)	15 (32)	0.15
Hypertension	21 (47)	17 (36)	0.31
Renal artery stenosis	9 (20)	14 (30)	0.28
Initial steroid dose, mg[a]	60 (±17.2)	57.1 (±15.1)	0.39

[a]mean (±SD); [b]median (interquartile range); CP: cardiopulmonary; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

was the right main pulmonary artery (n=7). Coronary arteritis was observed in 3 patients. Thirteen patients had persistent abnormalities (9 left axis deviation, 4 right axis deviation) on EKG. Cardiac nuclear uptake imaging identified regional wall motion abnormalities in three patients. Functional abnormalities detected by echocardiography were present in 35 (28%) patients, as described in Table III.

Outcomes

Seventy-seven patients had ≥1 year of follow-up. During this time, 31 patients had at least one clinical TAK relapse event. The presence of CP involvement at diagnosis was not predictive of relapse. Forty-four (58% by 5 years after diagnosis) patients had one or more cardiovascular surgeries or endovascular procedures during follow-up. Although composite CP involvement was not predictive, patients with PH observed within 6 months of diagnosis had a near thirteen-fold increased risk of surgery during the follow-up period (hazard ratio [HR] 12.87; 95% confidence interval [CI] 1.86 - 89.14, *p*=0.010). All seven PH patients underwent a surgical procedure, which included aortic valve replacement (n=2), coronary artery bypass (n=1), septal ablation (n=1), pulmonary artery angioplasty (n=1), and aortic root and hemiarch replacement (n=2).

Seven patients died during follow-up. Causes of death were mesenteric ischaemic complications (n=1), ruptured aortic aneurysm (n=1), heart failure (n=1) and unknown (n=4). The presence of composite CP involvement was not significantly associated with an increase in mortality (HR: 2.51; 95% CI: 0.45-14.02; *p*=0.29).

Table III. Distribution of abnormalities observed on echocardiography.

Involvement	n
≥1 Cardiopulmonary abnormality	45
Left ventricular enlargement	17
Left atrial enlargement	17
Pulmonary hypertension	7
Moderate aortic valve regurgitation	6
Severe aortic valve regurgitation	4
Left ventricular systolic heart failure	4

Discussion

This report constitutes the largest North-American cohort of patients with TAK evaluated for objective CP involvement at or near diagnosis. Evidence of CP abnormalities was common and observed in over 36% of all patients (49% of those tested).

The predilection of TAK to affect the aorta and its main branches leads to frequent involvement of the CP structures and vessels. Less well known, however, is the timing of these CP abnormalities in relation to disease onset. Small autopsy studies evaluating patients with end-stage fibrotic disease have noted histologically significant coronary lesions in 9–19% and pulmonary arteritis in 20% of cases (4-6). Advances in invasive and non-invasive angiography techniques have allowed for earlier evaluation of non-aortic vascular abnormalities; however, the frequency of identified involvement and the timing of radiographic evaluation have notably varied among studied populations. Indeed, angiographic findings of coronary artery lesions have ranged from 8–53% (2, 10-20) and pulmonary artery lesions from 5–70% (2, 3, 10, 14, 16-18, 20-22) among different cohorts.

In the current study coronary and pulmonary artery abnormalities were observed in a minority of cases. The majority of studies evaluating coronary arteries have not differentiated between atherosclerotic lesions and coronary arteritis. One possible explanation for less frequent coronary artery involvement in the current study is the exclusion of patients with prevalent or incident atherosclerotic CAD. With advancement of age an independent risk factor for cardiovascular disease (23), and older age of disease-onset (*i.e.*, >40 years) associated with higher frequency of coronary lesions, the younger mean age of disease-onset in the current cohort may additionally contribute to a lower total number of observed lesions (24). Progression of pulmonary arterial abnormalities has also been observed in patients over the course of disease (22); therefore, the current focus on identifying arterial lesions at or near diagnosis in this study may underestimate future development of pulmonary artery abnormalities as has been described later in the course of illness.

Despite the relatively low frequency of observed clinically significant coronary stenoses, congestive heart failure remains a major cause of death among patients with TAK (6, 9, 25). Incorporation of myocardial perfusion scanning in patients with TAK has demonstrated that microcirculatory dysfunction likely plays a larger role in the development of myocardial damage than lesions of the larger epicardial coronary arteries. Comarmond et al. evaluated 25 patients with TAK using Thallium-201 myocardial perfusion scanning and found 84% had abnormal perfusion studies (26). Only 2 of 11 patients with abnormal scans had coronary stenoses on angi-

ography. Hashimoto and colleagues observed similar findings among 38 women with TAK of which 20 (53%) had abnormal stress myocardial scintigraphy, 2 of which had angiographically significant stenosis (27). In the current study, myocardial perfusion scans were performed in only 8 patients. Of these 8 patients, 50% demonstrated abnormal myocardial perfusion despite normal coronary angiography. Geometric and hypertrophic remodelling due to pressure overload from systemic hypertension, aortic stenosis and aortic valve regurgitation are suggested as the main pathophysiologic causes for these findings (26, 27). However, histologically confirmed myocardial inflammation has also been observed in such cases (9).

Aortic regurgitation resulting from proximal aortic root dilation occurs often in patients with TAK. Evidence of moderate regurgitation has been observed in 11–33% (10, 15, 21, 24) of patients while severe regurgitation is noted less frequently in 6-11% (12, 21) over the course of disease. Comparable rates of moderate/severe aortic regurgitation were seen in the current study. Clinically significant pulmonary hypertension can result from aortic regurgitation as well as pulmonary arteritis, aortic stenosis and left heart disease. Isolated pulmonary vasculitis causing PH is uncommon. Among 48 patients with TAK and PH investigated by Wang and colleagues, 36 had evidence of pulmonary arteritis, of which only 7 had isolated pulmonary vasculitis (28). The remainder had evidence of additional aortic or proximal branch stenoses. Of the 12 patients with PH without pulmonary arteritis, aortic regurgitation was present in 75%. Although in the current study a lower number of patients with pulmonary arteritis was observed, aortic regurgitation similarly was the major contributing factor among patients with PH without associated pulmonary arteritis.

Limited information is available regarding the impact of baseline CP complications on long-term outcomes in patients with TAK. While some cohorts have identified moderate/severe aortic regurgitation as a risk factor for increased mortality (19, 25, 29), few studies have evaluated the presence of baseline CP involvement on predicting risk of future surgery. In the current study, composite CP involvement was not associated with increased risk of surgery, relapse, or mortality. However, the presence of PH within 6 months of diagnosis was associated with a near 13-fold increased risk of future endovascular or surgical event. Such findings suggest that specific CP abnormalities, rather than the aggregate, may provide greater predictive capacity in evaluation of patients with TAK and should be further evaluated in prospective studies.

CP symptoms in TAK are frequent but non-specific. As such, respiratory symptoms are frequently overshadowed by other symptoms of systemic disease (28) while clinically silent findings of pulmonary artery involvement and PH progress, leading to gradual development of congestive heart failure (30). Shortness of breath, in the current study, was found more frequently among patients with CP involvement compared to those without evidence of CP abnormalities. This finding is in keeping with other studies noting dyspnea to be an indicator of underlying CP dysfunction (12, 28, 30). Beyond recommendations for obtaining baseline large arterial imaging, consensus guidelines on the diagnosis and management of TAK provide little guidance on evaluation for CP dysfunction (31, 32). Given the frequency and type of observed CP abnormalities, adjunct transthoracic echocardiography, particularly in patients with symptoms of dyspnea, is a reasonable screening modality at the time of TAK diagnosis to detect the presence of CP disease before irreversible pathophysiologic changes occur. Further studies evaluating baseline and surveillance echocardiography are needed to determine its clinical utility in patients with TAK.

Strengths of this study include the size of this large single-institution cohort as well as long-term follow-up for outcome assessment. In addition, restricting identification of CP abnormalities to within 6 months of diagnosis allows for assessment of these features at baseline on future outcomes of interest. Nevertheless, this study must be interpreted in light of limitations inherent to its retrospective design, including missing data. Investigations performed were at the discretion of the treating physicians and therefore did not include all study modalities in each patient. Additionally, treatment was not standardised so there is insufficient information to know if medical treatment impacts outcome among patients with or without CP abnormalities. Furthermore, the definition of PH was based on non-invasive echocardiographic estimates rather than right heart catheterisation haemodynamic pressures. Nevertheless, transthoracic echocardiography has been shown as a reliable non-invasive method of detecting PH (33) and is advocated as the initial screening and subsequent monitoring modality for patients with concern for PH because of its safety, availability, ease of use, and cost-effectiveness (34).

In conclusion, CP involvement in TAK is common and can be identified in at least one-third of patients within 6 months of diagnosis. Given patients with evidence of CP abnormalities may be asymptomatic a heightened suspicion for additional evaluation is needed. Patients with TAK presenting with evidence of PH within 6 months of diagnosis demonstrate a high likelihood of requiring surgery, therefore close monitoring of such cases is suggested. Further studies investigating the prevalence of CP involvement at diagnosis are needed. Prospective studies identifying the impact of immunosuppressive and cardiovascular drug therapy on CP involvement and disease outcomes in patients with TAK should be undertaken.

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