Revised Manuscript

A cohort study reveals myocarditis to be a rare and life-threatening presentation of large vessel vasculitis.

Katie Bechman[1], Deepa Gopalan[2], Petros Nihoyannopoulos[3], Justin C Mason[1]

[1]Rheumatology Department, [2]Department of Radiology, [3]Cardiology Unit, Imperial College Healthcare NHS Trust and Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK.

[1]katie.bechman@doctors.org.uk, [2]deepa.gopalan@imperial.nhs.uk
[3]p. nihoyannopoulos@imperial.ac.uk, [4]justin.mason@imperial.ac.uk

Introduction

The principle forms of large vessel vasculitis (LVV) in the adult are giant cell arteritis (GCA) and Takayasu arteritis (TA). TA is rare chronic granulomatous arteritis principally affecting the aorta and its major branches and typically presenting before the age of 40 years. Stenotic or occlusive lesions occur in >90% and may be associated with limb, internal organ and cerebral ischaemia, while aneurysms are reported in 10-25% of patients [1].

GCA is seen in patients >50 years of age and may affect the aorta and its branches, the superficial temporal arteries and not infrequently the vascular supply to the optic nerve, predisposing to anterior ischaemic optic neuropathy. Stenotic lesions of aortic branch arteries are less frequent than in TA and most commonly affect the axillary arteries. In contrast, aneurysmal dilatation of the thoracic aorta is more common in GCA than TA [2]. There are two overlapping clinical phenotypes in GCA; "classical" or cranial GCA presenting with headache, scalp tenderness, jaw claudication with or without visual disturbance, and a large-vessel, "systemic" phenotype characterized by aortitis and vasculitis affecting the subclavian and axillary arteries [3].

Cardiac involvement in LVV is a cause of morbidity and mortality, particularly in TA. Cardiac failure is seen most commonly secondary to uncontrolled arterial hypertension, or myocardial ischaemia consequent upon coronary arteritis or premature atherosclerosis. Aortic valve incompetence following ascending aortic dilatation, and pulmonary hypertension, represent other serious cardiovascular complications [4, 5]. However, inflammatory cardiomyopathy (cardiac dysfunction as a consequence of myocarditis), is rarely reported and principally in single case reports or in autopsy studies [6-9]. We therefore reviewed a large cohort of LVV patients to identify those patients presenting with cardiac failure secondary to myocarditis.

Methods

The Imperial College Healthcare NHS trust LVV database was retrospectively reviewed to identify patients with cardiac involvement at presentation. Amongst the cases identified, those presenting with cardiac failure were selected and the underlying cause determined. Next, patients with evidence for myocarditis at presentation were identified and the diagnosis, cardiac presentation, imaging studies and subsequent medical and surgical management were reviewed in detail. Laboratory measures were all performed as part of routine clinical care by the Imperial College pathology service using conventional methods.

Imaging techniques for these patients included conventional ^{18}F-Fluorodeoxyglucose positron emission tomography computerised tomography (^{18}F-FDG-PET-CT), aortic magnetic resonance angiography (MRA), coronary computerised tomographic angiography (CCTA) and transthoracic echocardiography (TTE). Those patients with suspected myocarditis were further investigated with cardiac magnetic resonance imaging (CMR) following the JACC White Paper criteria for the diagnosis of myocarditis [10]. CMR assessment of ventricular function was reproducible allowing identification, quantification and surveillance of functional abnormalities including estimation of left ventricular ejection fraction (LVEF). Myocardial oedema, a marker of inflammation in active disease was assessed using T2-sequences. A late gadolinium sequence was used as a marker of inflammatory tissue damage as evidenced by a “patchy”, non-ischemic pattern of enhancement.

All echocardiography studies were performed by accredited sonographers, with the subjects in the left lateral decubitus position, using a Philips iE33 system (Philips Medical Systems, Bothell, WA, USA), equipped with a phased-array transducer (5 to 1 MHz). An electrocardiogram was simultaneously recorded. Images were stored on a digital format for subsequent off-line review and frame-by-frame analysis using the ProSolv CardioVascular FujiFilm, Indianapolis, USA). Two-dimensional echocardiographic examination and colour Doppler data was performed according to the recommendations of the American Society of Echocardiography [11, 12] and the European Association of Echocardiography [13]. The following echocardiographic parameters were assessed: left ventricular (LV) end-systolic and end-diastolic diameters, LV wall thickness, LV fractional shortening, left atrial diameter, right ventricular function (eyeball estimation) regional wall motion abnormalities and LV ejection fraction. Pulsed Doppler of trans-mitral flow was recorded from the apical four chamber view, with the Doppler sample volume being placed at the level of the mitral valve leaflet tips in order to measure peak early (*E*) wave and atrial contraction (*A*) wave velocities and early filling deceleration time (DT).

Statistical analysis:

Data were grouped according to treatment stage and analysed using GraphPad Prism version 6.0. Differences between pre- and post- treatment LVEF were determined using a Mann Whitney test and a value of $p<0.05$ was considered significant.

Results

The LVV cohort included 139 patients with TA and 24 patients with GCA. Of this population, 16 patients presented with cardiac failure without a history of ischaemic coronary heart disease (Table 1). They included 14 (10%) with TA and 2 (8.3%) with GCA. Of note, all had ascending aortitis. Cardiovascular disease identified at presentation included aortic regurgitation (n=11), myocarditis (n=4), hypertensive cardiomyopathy secondary to renal artery stenosis (n=1). One patient with Takayasu presented with myocarditis and aortic regurgitation. The 4 patients with myocarditis represented 2.8% of the total LVV cohort and comprised 3 with TA and 1 with large vessel GCA. In addition to the immunosuppressive therapy described below, all patients received standard care for cardiac failure.

Case 1

The index case (No. 1, Table 1), a 22-year-old female of Indian descent presented with a 1 month history of chest pain, palpitations, paroxysmal nocturnal dyspnoea, left arm claudication and weight loss of 2.5 kg. Clinical examination revealed blood pressure of 190/95 mmHg in the right arm, absent left radial and brachial pulses and bilateral pleural effusions. CRP 38 g/L (normal <5), ESR 47 mm/hr, troponin 88 ng/L (<32 ng/L), BNP 165.3ng/L (<89 ng/L) and creatinine 115 mmol/L (55-110 μmol/L). Echocardiography revealed a dilated left ventricle, a left ventricular ejection fraction (LVEF) of 24%, anteroseptal regional wall motion abnormality and moderate functional mitral regurgitation, with normal right ventricle and pulmonary artery pressures.

Coronary CTA demonstrated non-obstructed coronary arteries. CMR revealed severe global systolic impairment of a dilated left ventricle, with ill-defined delayed enhancement in the anterolateral wall (Figure 1). MRA of the aorta revealed occluded left subclavian and right renal arteries, with significant proximal narrowing of the left renal artery. A diagnosis of TA complicated by myocarditis was made and prednisolone (0.5mg/kg/day) and intravenous cyclophosphamide (15mg/kg) monthly was commenced, alongside ovarian protection with leuprorelin, followed by cetrorelix. Serial echocardiography at 1, 2, 4 and 20 months revealed an improving LVEF of 36%, 41%, 49% and 58% respectively. Repeat CMR demonstrated complete resolution of myocarditis with remodelling of the left ventricle size and resolution of mitral regurgitation (Figure 1). Left renal artery angioplasty was successfully performed 6 months later.

Case 2

The second case (No. 2, Table 1), a 30 year-old UK born Pakistani female with newly diagnosed TA, presented to her local hospital with pulmonary oedema and a raised acute phase response (CRP 40g/L, ESR 68mm/hr). Echocardiography demonstrated a moderately dilated left ventricle with severe global hypokinesia and a LVEF of 20% with severe aortic regurgitation. CMR confirmed a dilated ascending aorta with an ill-defined focus of myocardial hyper-enhancement in the inferior and lateral walls, suggestive of myocarditis. Treatment with prednisolone (0.5mg/kg/day) and cyclophosphamide (15 mg/kg monthly) commenced. After 2 months an aortic valve replacement was performed. Histopathology revealed endomyocardial and subendocardial fibrosis, aortic wall intimal fibrosis with destruction of the media elastic layer, consistent with treated myocarditis. MRA demonstrated an occluded right vertebral artery, stenoses affecting the superior and inferior mesenteric arteries, bilateral renal artery stenosis and infra-renal aortic narrowing. Serial echocardiography at 1, 12 and 24 months revealed an improving LVEF of 27%, 38% and 44% respectively. These data suggest that the improvement in LVEF reflects not only the impact of immunosuppression but also a positive influence from aortic valve replacement.

Case 3

The third case (No 3, Table 1) a 25 year-old Caucasian female presented to her local hospital with acute pulmonary oedema. She was systemically unwell, with a marked acute phase response (CRP 75g/L, ESR >100mm/hr). An echocardiogram demonstrated a severely impaired left ventricle. CTA of the descending aorta demonstrated progressive narrowing to a calibre of only 7 mm at the level of the diaphragm. There were multiple stenoses affecting the renal arteries, coeliac axis and the superior mesenteric artery. CMR demonstrated a markedly dilated LV, with no myocardial scar or fibrosis and LVEF reduced to 20%. Perivascular soft tissue thickening and enhancement in the ascending and descending aorta was suggestive of aortitis. Oral prednisolone was commenced (0.75mg/kg/day). In light of concerns regarding fertility the patient declined cyclophosphamide and was therefore commenced on subcutaneous methotrexate (15mg/week). Despite therapy, she remained symptomatic with fevers and a persistent acute phase response. Intravenous tocilizumab (8mg/kg/monthly) was introduced with an excellent clinical and biochemical response. Subsequent CMR 2 months later demonstrated a normalised LV volume and function (LVEF 55%), while repeat echocardiography at 24 months revealed a LVEF of 65%.

The fourth case (No. 15, Table 1) a 62 year-old Caucasian male presented in acute pulmonary oedema. History revealed weight loss, night sweats and polymyalgic symptoms for 6 months. There were no symptoms of temporal arteritis and the temporal artery examination was normal. There was

no history or symptoms suggestive of an acute coronary syndrome or previous ischaemic heart disease and the ECG did not reveal a myocardial infarction. Further investigation revealed: CRP 230 g/L, ESR >100 mm/hr, troponin 32,490ng/L and an ^{18}FDG-PET-CT scan confirmed diffuse homogeneous uptake in the wall of the ascending aorta consistent with an active large vessel vasculitis complicated by myocarditis. Echocardiography demonstrated severely impaired systolic function with a LVEF of 31%. CMR revealed complex late gadolinium enhancement with both ischemic (subendocardial) and non-ischemic (myocardial and subepicardial) patterns. Based on serial imaging, the mid-wall enhancement in the septum and inferior wall transmural changes were more in keeping with a myocardial inflammatory process, while the lateral wall microvascular obstruction and anterior and anterolateral wall subendocardial enhancement was likely secondary to coronary artery disease (Figure 3). CTCA revealed atheroma in the left anterior and circumflex artery. However, the right coronary artery was unobstructed, a finding that supported that the inferior wall changes seen on CMR were secondary to myocarditis. Initial treatment included intravenous methylprednisolone (3 x 1 gram), oral prednisolone (1mg/kg/day) and cyclophosphamide (15 mg/kg). Importantly, follow-up CMR after 6 months immunosuppressive therapy revealed an increase in LVEF to 41% with resolution of the transmural enhancement seen in the inferior wall. At the 18 month follow-up LVEF had reached 47%. At this point, coronary angiography revealed significant disease (>60% stenosis) in the left anterior descending and circumflex artery, with an unaffected right coronary artery and a dominant right coronary perfusion system. In the absence of both symptoms and any demonstrable evidence of ischemia on first pass perfusion with adenosine, the Joint Cardiology-Cardiothoracic (JCC) multidisciplinary meeting decided against revascularisation.

Statistical analysis of changes in the LVEF in response to immunosuppressive treatment for each case is demonstrated in Figure 4. The mean LVEF at presentation was 23.75% ± 5.2, rising to 53.5% ± 9.8% ($p = 0.029$) at a median of 22 months (interquartile range 18.5-24) post-treatment.

Discussion

This cohort study demonstrates that inflammatory cardiomyopathy remains a rare, life-threatening and potentially reversible complication in LVV. Sixteen patients (11.5%) had cardiac failure at presentation, of whom 4 (2.8%) suffered overt cardiac dysfunction secondary to myocarditis. Cardiovascular disease remains a major cause of death in TA [1, 14], while in contrast cardiovascular mortality may not be significantly increased in GCA [15, 16]. Acute myocarditis is exceedingly rare in GCA, with only a handful of case studies reported [8, 17, 18]. In TA, cardiac mortality is commonly associated with heart failure, which has been attributed to the hemodynamic effects of ischaemic coronary artery disease, aortic regurgitation or systemic hypertension [3-5]. However, there are reports of left ventricular dysfunction in the absence of these haemodynamic factors, suggesting an inflammatory aetiology [14]. This hypothesis is supported by endomyocardial biopsy studies, which report a significant incidence of subclinical myocarditis in TA. The immunohistochemical analysis revealed myocardial infiltration by natural killer cells and γδ T lymphocytes, with associated release of the cytotoxic factor perforin [9, 19, 20].

Endomyocardial biopsy remains the gold standard for the diagnosis of myocarditis. However, its relative lack of sensitivity, combined with local factors including limited availability of experienced operators, equipment and cardiovascular pathology resources limit its use in some centres [21]. In addition, concern regarding procedure-related complications in those with severe inflammatory disease may influence access to endomyocardial biopsy. As a consequence, there is considerable interest in the role of non-invasive imaging modalities for the diagnosis of myocarditis [22, 23]. Combined CMR and Doppler echocardiography imaging represent sensitive non-invasive methods for early diagnosis and specific criteria have been proposed [10, 24].

The principle benefit of CMR is its superior tissue characterisation. Contemporaneous studies have demonstrated the clinical feasibility, high diagnostic accuracy and inter-observer consistency of CMR in supporting the diagnosis of myocarditis. CMR provides assessment of disease severity, risk stratification and prognosis [10, 21]. It may reveal signs of active disease including myocardial oedema, regional vasodilatation due to hyperaemia, and myocardial necrosis with subsequent fibrosis [10]. Three CMR image types revealing these abnormalities have been investigated in detail. T2-weighted sequences detect the high signal intensity of oedematous tissues in myocarditis. Early images following gadolinium administration demonstrate an increased volume of distribution into the intravascular and interstitial space, while late gadolinium enhancement reflects irreversible myocardial injury and is typically patchy in a non-ischemic distribution [24-26]. CMR sensitivity is

thought to be optimal within the first two weeks of symptom onset [10]. If 2 or more of the 3 tissue criteria are found then diagnostic accuracy reaches 78% [10]. Overall, this CMR protocol has been reported to confer a sensitivity of 76% and specificity of 95% for the detection of myocardial inflammation. [27, 28].

CMR is a rapidly evolving field and recent evidence shows that parametric methodology such as native T1 mapping can identify myocardial inflammation without the need for gadolinium [29]. Additional quantification of extracellular volumes of distribution (ECV) provides a measure of the extent of interstitial fibrosis [30]. Combining T1 mapping with LGE improves the diagnostic accuracy of CMR in detecting myocarditis to 91–96%. Add Luetkens However, clinical trials and consensus regarding methodology and diagnostic thresholds are now required before these techniques can be routinely incorporated in to clinical practice. Add Lagan et al 2017

The lack of T1 mapping and ECV data is an important limitation of our study. Although now available at our centre for selected patients, these sequences were not part of the protocol when the current cases presented. Indeed, such methodology is not yet available in many centres worldwide likely to encounter acute myocarditis. CMR was only performed in those with an abnormal echocardiogram or clinical suspicion of myocarditis. However, we suspect that subclinical myocarditis is relatively common, indeed our previous cross-sectional study of CMR in TA revealed late gadolinium enhancement indicating previously unrecognised myocardial injury in 27% of patients [14].

Initial follow-up imaging is determined by the individual case and typically occurs 4-6 weeks later. This allows evaluation of the response to treatment. Follow-up was principally guided by clinical, biochemical and imaging findings. Persistence of the tissue signs of inflammation or fibrosis may aid prognostication and risk stratification. However, in the setting of acute myocarditis with significant myocardial oedema, differentiation of inflammation and fibrosis is difficult. Thus serial imaging is helpful to assess resolution of oedema and identify the presence of persistent fibrosis.

Echocardiography proved an important component of the management. In the acute setting TTE determined cardiac valve function, chamber size and wall thickness. It also demonstrated regional wall abnormalities, estimated pulmonary artery pressures and quantified ventricular function and LVEF. Of note, strain echocardiography to determine circumferential and longitudinal strain imaging is a more sensitive means for detection of important prognostic functional changes than

TTE [31-33]. However, the predominant role for TTE is monitoring the response to treatment and for early detection of relapse [22].

Current guidelines [34] recommend combination therapy with prednisolone and cyclophosphamide for refractory LVV. This approach proved successful in myocarditis complicating TA and GCA, with a significant improvement in LVEF seen. Following six doses of cyclophosphamide (over 3-6 months) our practice is to switch to weekly oral methotrexate. Patients have monthly blood monitoring and undergo echocardiography initially after 1 month, repeated at 3 to 6 months intervals, with repeat MRA of the aorta at six months. However, the risk of infertility in young patients and enhanced cyclophosphamide toxicity in those over 65 years represents a significant disadvantage [35]. To mitigate this patient 1 received ovarian protection prior to each course of cyclophosphamide therapy. She has subsequently returned to regular menstruation with FSH and LH levels appropriate for her age. Patient 3 declined cyclophosphamide on account of the fertility risk and demonstrated an insufficient response to MTX. She was therefore prescribed biologic therapy in the form of tocilizumab (an anti-IL-6 monoclonal antibody). Although TNF-α and IL-6 receptor inhibition have been used successfully in the management of refractory TA [36, 37], the former is contraindicated in heart failure. Although a trial dedicated to myocarditis in LVV is unlikely, there remains an urgent need for prospective randomised trials of biologic agents in LVV *per se* [38]. Meanwhile, in light of the severity of inflammatory cardiomyopathy complicating LVV, we propose that IL-6 inhibition is considered early in the paradigm for those in whom cyclophosphamide is contraindicated or ineffective.

Conclusion.

Clinically significant myocarditis in LVV remains a rare life-threatening presentation. High-resolution non-invasive CMR imaging offers early detection and a diagnostic alternative when the current gold-standard myocardial biopsy is considered high risk. The sensitivity and sensitivity of CMR will be further improved as T1 mapping and ECV data become widely accessible. Treatment with cyclophosphamide and prednisolone is associated with resolution in myocardial enhancement and clinically important improvements in cardiac symptoms and LVEF.

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Table 1:

Patients with Takayasu or giant cell arteritis presenting with cardiac failure**.**

Figure 1:

A. Pre-treatment CMR showing a short axis slice at the level of the basal-mid ventricle which demonstrates an ill-defined delayed enhancement in the mid-myocardium anterolateral wall.

B. Post-treatment CMR in which the short axis slice at the basal-mid ventricle reveals resolution of the delayed enhancement in the mid-myocardium.

Figure 2:

A. Parasternal long-axis view showing a non-dilated LV with poor function pre-treatment with

B. Evidence for improvement following two years immunosuppression

Figure 3:

A. 2-chamber view from late gadolinium enhancement (LGE) sequence. Multiple foci of transmural enhancement along the inferior wall (block arrows) in the baseline study. Although the differentials include myocardial infarction as well as myocarditis, contemporaneous catheter angiography did not reveal any disease in the right coronary artery in a right dominant coronary system.

B. On serial follow-up there was reduction in the extent and severity of LGE along the inferior wall in keeping with improvement in the myocardial inflammation. The subendocardial LGE in the anterior wall (notched arrow) is an area of partial thickness myocardial infarction corresponding to the LAD territory disease on the catheter angiography. It does not show any significant change between the two examinations.

C. Short axis image of a T2W short tau inversion recovery (STIR) sequence that demonstrates a foci of high signal in the basal anterior wall and anteroseptum (arrows) in keeping with myocardial oedema.

Figure 4.

The left ventricular ejection fraction (LVEF) pre- and post-immunosuppressive therapy is shown. Differences were determined using a paired Student's t test, * = $p<0.05$.

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