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CLINICAL FEATURE
ORIGINAL RESEARCH



Hypereosinophilic syndrome: endomyocardial biopsy versus echocardiography to diagnose cardiac involvement

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ABSTRACT

Objective: To compare echocardiograms and endomyocardial biopsies to diagnose cardiac involvement in hypereosinophilic syndrome.

Methods: We examined the agreement between echocardiography and endomyocardial biopsies to detect cardiac involvement in hypereosinophilic syndrome by reviewing cases identified as hypereosinophilia or hypereosinophilic syndrome in Mayo Clinic databases from January 1978 through June 2009. Single-organ cases of eosinophilia such as eosinophilic fasciitis and eosinophilic gastroenteritis were excluded. We recorded echocardiogram and endomyocardial biopsy results including biopsy staining for eosinophil granule major basic protein (if performed). Clinical and laboratory features documented included presenting symptom(s), maximum total eosinophil count, dose of prednisone (if any) and eosinophil count at the time of endomyocardial biopsy, cardiac enzymes, serum tryptase level, electrocardiogram result, the result of testing for the FIP1L1-PDGFR fusion gene, complications associated with the biopsy procedures and available follow-up information.

Results: From a total of 387 patients' records screened 288 met the criteria for hypereosinophilic syndrome and of these 240 had echocardiograms. Among these patients there were 138 normal echocardiograms, 67 had echocardiograms without findings of hypereosinophilic syndrome but with one or more other abnormalities, and 35 had echocardiograms with findings consistent with hypereosinophilic syndrome. Twenty-five patients from this group of 35 patients had both echocardiogram and endomyocardial biopsy. In 15 patients there was agreement between both endomyocardial biopsy and echocardiography as to the presence ($n = 7$) or absence ($n = 8$) for findings of cardiac involvement. In 10 of 25 patients test results diverged: 3 patients with positive echocardiographic changes did not have confirmatory findings by endomyocardial biopsy and seven patients with positive biopsy findings had echocardiograms without findings of hypereosinophilic syndrome.

Conclusions: Echocardiograms and endomyocardial biopsies agree for presence or absence of cardiac involvement 60% of the time. Endomyocardial biopsy detected cardiac involvement in 7 patients in whom the echocardiogram was negative for findings of hypereosinophilic syndrome.

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restrictive cardiomyopathy

1. Introduction

The hostile effects of hypereosinophilia on the cardiovascular system have been well known for decades [1–5]. Cardiovascular damage may occur in patients with untreated hypereosinophilic syndrome (HES) or in eosinophilic leukemias with the *FIP1L1-PDGFR* fusion gene, but it is not unique to these conditions [6]. Myocardial damage has also been observed in disorders in which hypereosinophilia occurs secondary to other problems such as filariasis [7,8], trichinosis [9], carcinomas [10], lymphomas [11], administration of granulocyte-macrophage colony-stimulating factor [12], drug reactions [13], and others.

The reported frequency of cardiovascular involvement in HES varies widely. A 1982 report from the National Institutes of Health described 27 of 50 cases (54%) with cardiovascular involvement [14], whereas a more recent multicenter summary reported that 9 of 188 (4.7%) had cardiac manifestations

at presentation [15]. The reasons for this discrepancy are not completely clear; however, possible explanations include earlier diagnosis and more effective treatment of eosinophilia because of an enhanced appreciation of the morbidity and mortality associated with a substantially elevated eosinophil level. In addition to management of hypereosinophilia, control of the clinical sequelae of hypereosinophilia-induced endomyocardial disease may require surgical intervention such as valve replacement, endocardectomy, or even cardiac transplantation [16–19].

Echocardiography is a valuable noninvasive technique to assess for the presence and degree of cardiac involvement in HES [20]. Endomyocardial biopsy is a second method to assess possible cardiac involvement in HES and has been considered the gold standard for this purpose. Each of these methods has its advantages and drawbacks. For example, endomyocardial biopsy is invasive, and obtaining an adequate biopsy sample may be difficult especially in the presence of endocardial fibrosis.

Although the growing importance of cardiac magnetic resonance imaging (MRI) in the diagnosis, monitoring, and prognostic stratification of cardiomyopathies should not be overlooked and can reduce the need for invasive endomyocardial biopsies in patients with HES, it may not be possible to perform this procedure on all patients [21,22]. Absolute contraindications to cardiac MRI are well known and include patients with a cardiac pacemaker or defibrillator and those who have metal-containing implants such as deep brain stimulators or other metallic foreign bodies.

Remarkably, there have been no head-to-head comparisons of echocardiography and endomyocardial biopsy reported in a large series of HES patients. Here, we examined the results of these two techniques, when both were performed on the same patient, to identify cardiac involvement in HES with the aim to determine the agreement between these procedures.

2. Materials and methods

This study was approved by the Mayo Clinic Institutional Review Board. Patients with a diagnosis of hypereosinophilia or HES at Mayo Clinic (Rochester, MN, USA) from January 1978 through June 2009 were identified through institutional electronic databases. This retrospective study was considered to be exempt under 45 CFR 46.101, item 4 and therefore no informed consent was necessary. The selected medical records were reviewed closely to confirm the diagnosis of HES according to criteria for HES 'in place' at the time of their diagnosis. Because patient accrual ended in 2009, the criteria as originally established by Chusid et al. [23] were used throughout. Although it is recognized that more recent criteria have subsequently been proposed by Simon et al. [24] and Valent et al. [6], it was felt to be appropriate to utilize HES diagnostic criteria employed by physicians at the times the patients were actually evaluated during these years rather than to second guess their clinical judgments by employing the more recent criteria.

We identified patients with HES who had undergone both echocardiography and endomyocardial biopsy at Mayo Clinic and determined the agreement between these tests in detecting cardiac involvement. Echocardiographic criteria utilized to diagnose HES cardiac involvement in these patients have been published [25,26]. The echocardiographic diagnosis of eosinophilic heart disease was based on the review by a level 3 echocardiography-trained cardiologist requiring definitive evidence of cardiac involvement with (1) endomyocardial plaques, (2) evidence of endocardial thickening of the inflow areas/atrioventricular valves, and/or (3) thrombotic-fibrotic obliteration of the ventricular apices. Findings of unexplained atrial enlargement or diastolic function abnormalities were supportive but not diagnostic in isolation. Myocardial enhancement echocardiography was used when available. Echocardiography and biopsy were obtained at the discretion of physicians providing care to these patients, in the context of clinical and laboratory findings suggestive of HES. We additionally recorded the presenting symptom(s), maximum total eosinophil count, dose of prednisone (if any), and eosinophil count at the time of endomyocardial biopsy, creatine phosphokinase and/or troponin values, serum tryptase,

electrocardiogram, the result of testing for the *FIP1L1-PDGFR* fusion gene, any complications associated with the biopsy procedures, and any available follow-up information on individual patients. In addition to routine hematoxylin and eosin (H&E) staining, some of the cardiac biopsies had also been stained for the presence of eosinophil major basic protein (MBP) and these results are given as well.

3. Results

Of 387 patients listed with a diagnosis of hypereosinophilia or HES, we eliminated those with 'single-organ' eosinophilic conditions such as eosinophilic gastroenteritis and eosinophilic esophagitis, hypereosinophilia associated with drug reactions, lung cancer, rheumatoid arthritis, systemic mastocytosis, immune complex disease, eosinophilia-myalgia syndrome, eosinophilic pneumonia, atopic dermatitis, episodic angioedema with eosinophilia syndrome, eosinophilic granulomatosis with polyangiitis, and identifiable secondary eosinophilias. After exclusion of these patients, 288 patients remained, and 240 of these had had an echocardiogram. Thirty-five patients had findings consistent with HES, and, of these, 25 patients were identified who additionally underwent endomyocardial biopsy at Mayo Clinic. Additionally, 138 of the 240 patients had normal echocardiograms and 67 patients had one or more abnormal findings on echocardiogram that were not characteristic of HES (Figure 1). Representative examples of the latter findings included left and/or right ventricular enlargement, decreased global cardiac function, mild valvular regurgitation, the presence of valve replacements, regional wall motion abnormalities, (bi)atrial enlargement, and others.

Table 1 summarizes clinical and laboratory findings, including age, sex, presenting symptom(s), biopsy side, maximal eosinophil count, prednisone use, and eosinophil count at the time of biopsy. There were 17 male and 8 female patients who had both procedures. The age at presentation ranged from 26 to 81 years for males and 27 to 71 years for females. Testing for the *FIP1L1-PDGFR* fusion gene was negative in four patients and was not done in 21 patients. Creatine phosphokinase or troponin tests were done only sporadically, and no valid comparison between groups was possible for these tests. Serum tryptase levels were determined in seven patients. In five of these patients, the result was normal; however, for two patients, patient 15 (biopsy and echocardiogram negative) and patient 23 (biopsy positive and echocardiogram negative), the levels were increased at 41.4 and 16.5 ng/mL, respectively (reference range <11.5 ng/mL).

Positive findings of HES by echocardiogram were confirmed by positive endomyocardial biopsy findings in seven patients. In two of these patients, the use of echo contrast aided in delineation of the extent of involvement on echocardiogram. Lack of echocardiogram findings of HES was confirmed by a negative endomyocardial biopsy in eight patients. Positive findings by echocardiogram were not confirmed by biopsy in three patients, and in seven patients, a negative echocardiogram was associated with a positive biopsy. Unexpected findings on echocardiograms were Shone syndrome (bicuspid aortic valve with mild atrioventricular regurgitation, parachute mitral valve, and supra-valvular mitral ring)

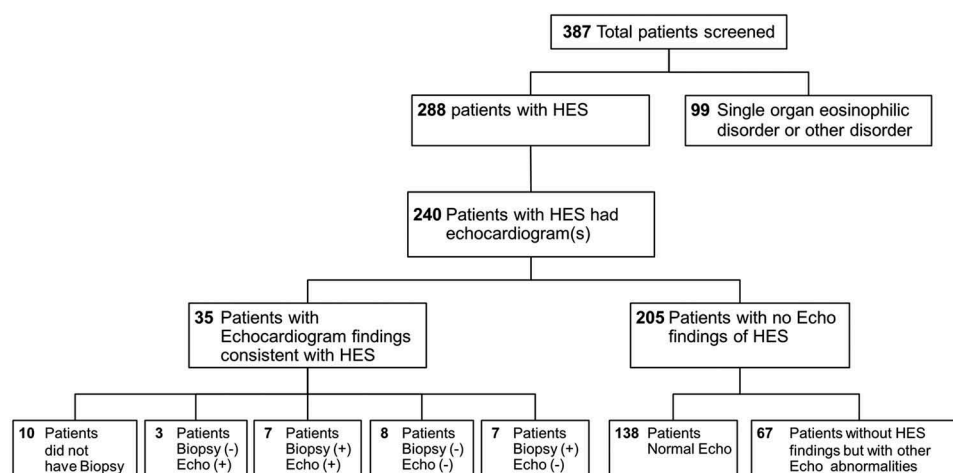


Figure 1. Patients screened for hypereosinophilic syndrome who ultimately underwent both echocardiogram and endomyocardial biopsy.

in one patient and both Lambl's excrescences involving the mitral valve and a bicuspid aortic valve in one patient. Three patients, 2 in 1997, 10 in 1998, and 23 in 2015, underwent cardiac MRI. For patient 2, the MRI, taken early in the patient's clinical course, showed a 3–5-mm-thick rind-like area of higher signal and signal enhancement on T2 and post-contrast images involving the apical portion of the left ventricle. This finding was felt to be consistent with an infiltrative process involving the endocardium. The MRI of patient 10 showed poorly defined filling defects in the left ventricle corresponding to the masses seen on echocardiogram as well as generalized left ventricle hypokinesis. For patient 23, the MRI, taken 12 years after the diagnosis of HES, was normal. Echocardiogram and cardiac MRI images appear in [Figure 2](#).

Endomyocardial biopsies were generally done either shortly after or within weeks to several months of the echocardiogram; however, in several referred patients, eosinophilia had been present for years before their presentation at our clinic. This fact delayed endomyocardial biopsy in these patients with the longest interval between the diagnosis of hypereosinophilia and biopsy having occurred for patient 10 (56 months) and patient 12 (55 months). Eleven patients were taking prednisone when biopsied. The dose ranged from 10 mg every other day to 60 mg/day in divided doses. Patient 3 was additionally taking hydroxyurea. Of the 14 patients with positive biopsies, 6 patients were taking prednisone and 1 was taking, additionally, hydroxyurea. Thirteen patients were not taking prednisone when biopsied. Patient 16 had discontinued interferon alpha 2B 3 weeks before biopsy, and patient 22 had recently begun imatinib mesylate. It could not be determined whether or not one patient (patient 1) was taking prednisone. Left ventricular endomyocardial biopsy was performed on 5 patients, and right ventricular biopsy was performed on 20 patients. Four of the five left ventricular biopsies were positive for findings of eosinophilic cardiomyopathy. The remaining patient (patient 13 in the table) who had a negative left ventricular biopsy also had a negative echocardiogram. Positive biopsy findings among our patients included one or more of the following: interstitial eosinophil infiltration, the presence of organizing mural

thrombi, the presence of particles/granules from degranulating eosinophils, and myocardial thickening/fibrosis. Staining for eosinophil MBP was additionally performed on eight biopsies with positive staining on four biopsies, negative staining on three biopsies, and one biopsy showing very limited staining in two small areas at the endo/myocardial interface. The H&E staining of this latter biopsy was negative for eosinophil infiltration. Representative biopsy findings with immunofluorescent staining for eosinophil MBP and H&E are shown in [Figure 3](#).

One nonfatal complication of biopsy occurred in this series. Patient 4 experienced cardiac perforation and tamponade. There were no predominant electrocardiographic findings among our patients and no acute changes associated with the biopsy procedure.

Eight patients have died 1–16 years after their initial HES diagnoses. Four patients were still alive (2015 or later) after intervals ranging from 8 to 13 years. Thirteen patients were not seen again after intervals ranging from less than 1 year (generally a single consultative visit) to 6 years.

4. Discussion

The increasing presence of implantable devices may necessitate reliance on non-MRI imaging in individual cases of HES in the future, and, in fact, the majority of the patient accruals for this study predated the regular use of cardiac MRI. Two of the patients had cardiac pacemakers in place and three other patients underwent cardiac MRI. Despite the introduction of cardiac MRI imaging, combined use of echocardiograms, endomyocardial biopsies, and cardiac MRI to evaluate eosinophilic individuals may be necessary [27]. In one reported case of a patient with eosinophilia and elevated cardiac enzymes, echocardiogram and MRI were nondiagnostic, and only the endomyocardial biopsy confirmed the underlying diagnosis of eosinophilic myocarditis [28]. The presenting complaints among these patients were quite diverse. Patients who had negative endomyocardial biopsy more commonly presented with dermatological complaints (erythroderma, mucosal

Table 1. Hematologic, echocardiographic, and endomyocardial biopsy findings in hypereosinophilic syndrome.

Patient	Echocardiogram and biopsy results	Age at time of biopsy	Sex	Presenting symptom(s)	Biopsy side	Maximum eosinophil count	Prednisone dose (P) at time of biopsy	Eosinophil count at time of biopsy
						Reference range 0.05–0.5 × 10 ⁹ /L	Reference range 0.05–0.5 × 10 ⁹ /L	
Biopsy negative, echo positive for HES-3 patients								
1		81	M	Dyspnea	RV	5.07	Not recorded	3.28
2		75	M	Dyspnea, wheezing	RV	3.44	No	1.31
3		71	F	Fatigue	RV	5.53	20 mg/day	5.53
Both biopsy and echo positive for HES-7 patients								
4		36	M	Abdominal pain	RV	18.774	20 mg/day (+) hydroxyurea	14.109
5		42	M	Cough; Dyspnea	RV	8.833	No	4.782
6		65	M	Cardiomyopathy, dyspnea	LV	3.543	No	3.543
7		27	F	Neck/shoulder pain	RV	0.110 ^a	No	0.030
8		64	F	Dyspnea	RV	0.07 ^b	20 mg TID	0.07
9		32	F	Cough, wheezing	RV	3.24	15 mg QID	0
10		40	M	DVT, PE	LV	3.13	20 mg BID	0.400
Biopsy and echo negative for HES-8 patients								
11		41	M	Cough	RV	7.794	No	7.794
12		32	M	Erythroderma	RV	7.871	10 mg QOD	7.871
13		28	M	Mucosal lesions	LV	17.024	10 mg/day	7.384
14		38	M	Recurrent syncope	RV	9.80	No	8.151
15		51	M	Cough	RV	4.80	30 mg BID	0.01
16		57	M	Pruritic rash	RV	2.62	No	0.62
17		47	M	Pulmonary hypertension	RV	1.49	No	1.32
18		55	F	Exfoliative dermatitis	RV	4.29	No	0.819
Biopsy positive and echo negative 7 patients								
19		65	M	Cough	LV	23.179	No	1.759
20		66	F	Fatigue	RV	2.502	No	1.247
21		45	M	Fatigue, malaise	RV	11.51	No	4.36
22		46	M	Asthma	RV	8.07	No	1.08
23		52	F	Change in bowel habits	RV	10.73	10 mg/day	8.55
24		46	F	Chest pain, shortness of breath	LV	4.45	10 mg/day	0
25		51	M	Chest pain, Shortness of breath	RV	28	12 mg/day	0.15

^aOutside reports of 10–30% eosinophils on four occasions.^bWhile taking prednisone.

Echo: echocardiography; F: female; LV: left ventricle; M: male; DVT: deep vein thrombosis; PE: pulmonary embolism; RV: right ventricle; QID: four times daily; TID: three times daily; BID: twice daily; QOD: every other day; P: prednisone.

lesions, rash, and exfoliative dermatitis), whereas biopsy-positive patients more commonly presented with other cardiopulmonary complaints such as cardiomyopathy, deep vein thrombosis/pulmonary embolism, chest pain/shortness of breath, or asthma (Table 1).

Echocardiographic findings consistent with HES, and reported in our patients, included endocardial thickening, fibrothrombotic obliteration of ventricular apices, and valvular regurgitation from restricted motion of the posterior mitral

valve leaflet [29]. In addition, Doppler and hemodynamic studies in HES patients may show features of restrictive cardiomyopathy and endomyocardial fibrosis [30], and minor criteria can include findings such as restrictive flow pattern across mitral or tricuspid valves, diastolic opening of the pulmonary valve, diffuse thickening of the anterior mitral valve leaflet, enlarged atrium with normal-sized ventricle, enhanced M-movement of the interventricular septum, and enhanced density of the moderator band [31].

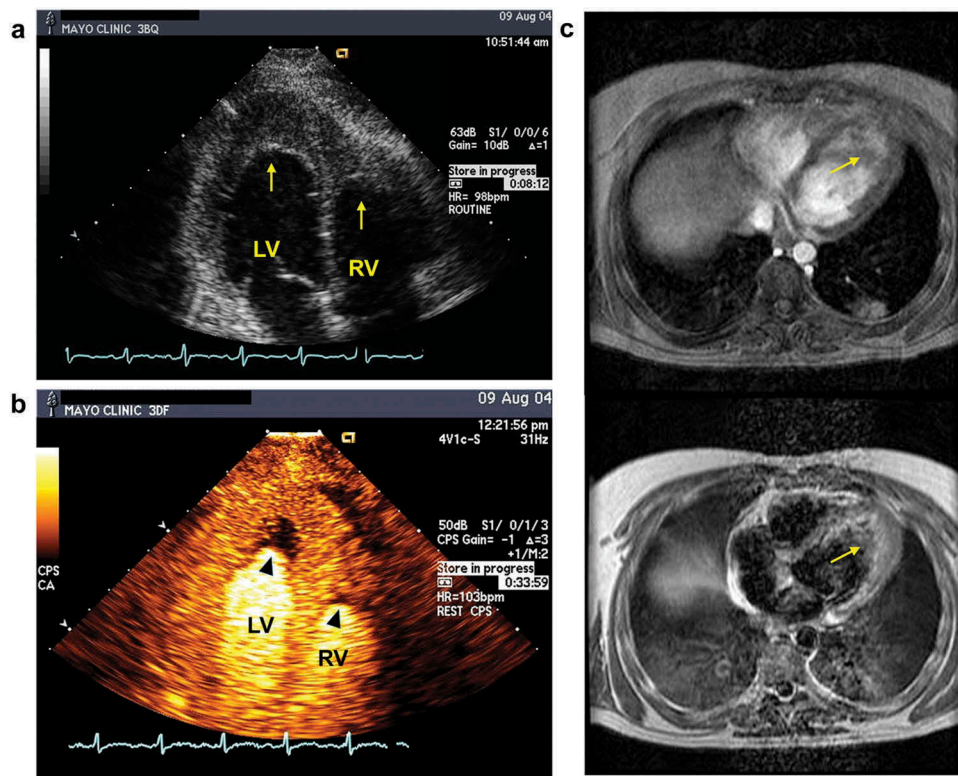


Figure 2. (a,b) Echocardiogram: Transthoracic echocardiography (a) in a 27 year old female demonstrates thrombotic-fibrotic obliteration of the apices of the left (LV) and right ventricles (RV) (arrows). Transthoracic echocardiography with myocardial enhancement imaging with intravenous echo contrast (b) clearly demonstrates the component of apical obliteration by non-perfusing thrombus which appears black (arrows). Endomyocardial biopsy confirmed eosinophilic endomyocardial disease. (c) Cardiac MRI: Cardiac MRI demonstrates evidence of left ventricular apical thrombotic material (arrows) in a 41 year old male with eosinophilic heart disease.

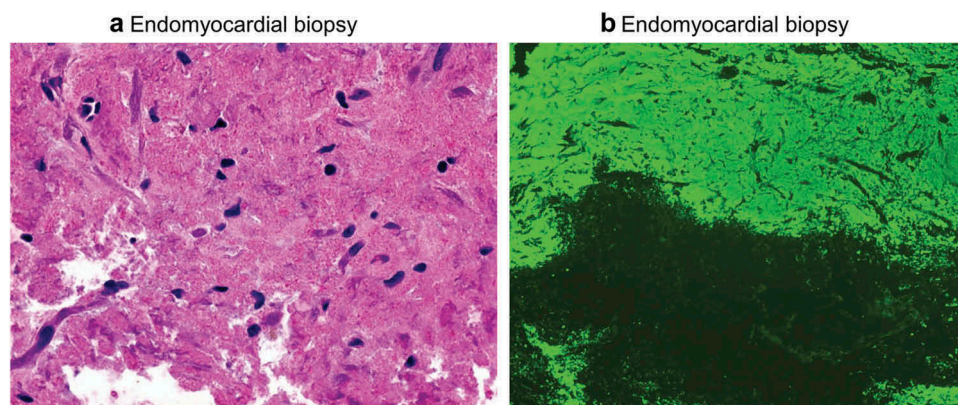


Figure 3. (a,b) Eosinophilic myocarditis in hypereosinophilic syndrome, from a right ventricular endomyocardial biopsy in a 27-year-old woman. (a) Endomyocardial biopsy showing extensive degranulation of eosinophils (small red dots), without intact eosinophils (Hematoxylin-eosin, originally x150). (b) Endomyocardial biopsy showing extensive extracellular deposition of eosinophil major basic protein (MBP). (Immunofluorescent stain using anti-MBP, originally x160).

Right ventricular endomyocardial biopsy, often considered to be the gold standard for the diagnosis of cardiac involvement in HES, has been used for this purpose for about 30 years [1]. Here, we additionally report the results of left ventricular biopsy for five patients. In this subset of our patients, positive findings of HES were present in four patients. The invasive endomyocardial biopsy procedure does have drawbacks and may be most valuable in diagnosing early cardiac involvement because fibrous tissue and superimposed thrombi may prevent acquisition of an adequate tissue

specimen in late-stage disease [32]. Endomyocardial biopsy also may lack sensitivity as the eosinophilic infiltration can be focal [33]. In the present series, one patient experienced a nonfatal, though serious, complication of the biopsy procedure.

The data presented here constitute a retrospective review of HES cases seen at one tertiary referral center and could possibly have included patients with disease more severe than what is commonly found with HES. Follow-up was limited in many cases. There was no consistent reporting of creatine

phosphokinase or troponin levels. It is problematic to make general statements about response to treatment(s) or clinical outcomes among these cases because many patients were lost to follow-up or had only a single consultative appointment. At least 8 of the 25 patients are known to have died during the years this study encompassed, and 1 patient remains alive following cardiac transplantation. Several other patients were already elderly at the time of their evaluation.

During the years of patient accrual, advances in treatment for HES occurred as did improvement in the instrumentation for performing echocardiography. Nonuniform care of these patients during this period may have transpired because of possible discrepancies in the rapidity with which these advances were applied in practice. In addition, *FIP1L1-PDGFR* fusion gene analysis was possible on only a limited number of patients because this test was not available until the latter years of patient accrual. Similarly, only a minority of patients had measurement of serum tryptase.

Imaging techniques have matured over the time span of this study. The routine use of myocardial enhancement echocardiography likely would improve the sensitivity for the detection of eosinophilic heart disease. Cardiac MRI may also have a higher sensitivity than non-contrast echocardiography, and its comparison to endomyocardial biopsy warrants further investigation. However, cardiac MRI is not always available. Access remains challenging outside of major institutions and imaging is challenging in the setting of metallic implants. Cardiac MRI may be possible in selected patients with implanted cardiac devices [34] although when the ferromagnetic material is in the field of view, cardiac MRI imaging artifacts are common often rendering studies nondiagnostic. HES patients with older pacemakers, implantable cardioverter defibrillators, retained leads, and other metallic implants will continue to depend on echocardiography with or without endomyocardial biopsy to assess their cardiac status. Therefore, an appreciation of the benefits, risks, and accuracy of these procedures is important.

5. Conclusions

In this retrospective study, the first to compare echocardiography and endomyocardial biopsy to detect cardiac involvement in HES, we found agreement between these tests 60% of the time. Our findings suggest that in HES patients suspected of having cardiac involvement, endomyocardial biopsy is superior to echocardiography. In our cohort of 25 patients reviewed (1978–2009) who had undergone both procedures, 7 patients with a negative echocardiogram were found by endomyocardial biopsy to have evidence for HES involving the heart.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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