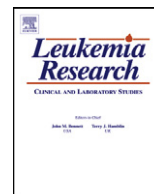




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Mortality in hypereosinophilic syndrome: 19 years of experience at Mayo Clinic with a review of the literature

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ABSTRACT

Background: Information in the literature regarding causes of mortality in patients with hypereosinophilic syndrome (HES) is limited.

Methods: This was a retrospective review of the morbidities and causes of death in HES patients at Mayo Clinic.

Results: Overall, out of the 247 diagnosed HES patients, 23 died during the 19 years that this review encompassed. The cause of death was identified in 15 patients (65%): cardiac dysfunction in 5 (33%), infection in 3 (20%), unrelated malignancy in 3 (20%), thromboembolic phenomena in 2 (13%), and vascular disease in 2 (13%).

Conclusion: Targeted monitoring of the at-risk end organs, combined with early treatment, may have the ability to improve survival and reduce morbidity in HES patients.

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1. Introduction

Hypereosinophilic syndrome (HES) encompasses a diverse group of disorders characterized by serum eosinophil levels of $1.5 \times 10^9/L$ or higher for 6 months or longer, lack of evidence of secondary causes, and eosinophilic organ involvement [1]. One of the observed limitations of this definition is the requirement of elevated eosinophil levels $1.5 \times 10^9/L$ or higher for 6 months or longer. Prompt diagnosis and treatment are required before 6 months have passed to prevent potentially serious end-organ damage. New diagnostic criteria have been proposed to address this limitation [2,3]. The proposed new definition of HES includes eosinophil levels higher than $1.5 \times 10^9/L$ on at least two occasions separated by at least 4 weeks (excluding cases where urgent therapy is required) and evidence of eosinophil-related organ damage [3]. Similar to previous definitions, HES can be divided into primary (neoplastic) HES, secondary HES, and idiopathic HES [3]. The severity of eosinophilia has been divided arbitrarily into mild (0.5 – $1.5 \times 10^9/L$), moderate (1.5 – $5.0 \times 10^9/L$), and severe

($>5.0 \times 10^9/L$) [4,5]. There is no absolute threshold for eosinophilia treatment; organ damage may occur at varying eosinophil levels in different patients although the reason for this remains unknown. Some experts recommend an absolute eosinophil count of $2.0 \times 10^9/L$ or higher as an indication for treatment initiation in the absence of organ damage [6].

Hypereosinophilia of undetermined clinical significance (HE_{US}), the term used to describe marked and persistent blood eosinophilia or tissue eosinophilia and/or marked deposition of eosinophil proteins in tissues, may not, in some patients, be associated with clinical manifestations. HE_{US} patients have no underlying neoplastic or non-neoplastic disease to explain the hypereosinophilia nor do they have detectable organ dysfunction. However, with the development of organ damage attributed to eosinophil infiltration and/or degranulation, it is then appropriate to apply the term “hypereosinophilic syndrome” [3].

Survival in HES has improved over time. One study of 57 HES patients published in 1975 demonstrated an average survival of approximately 9 months from the time of diagnosis [1]. A study of 40 patients from 1989 reported a 5-year survival rate of 80% [7]. There are no recent reports of survival data in the literature.

Only isolated case reports are available in the literature regarding specific causes of mortality in HES patients. Frequently reported causes of death include cardiac dysfunction, thromboembolic disease, neurologic dysfunction, and infection. We reviewed causes of mortality in HES patients seen at Mayo Clinic. We also examined causes of morbidity in these same patients.

Abbreviations: FIP1L1-PDGFR α , Fip1-like 1-platelet-derived growth factor receptor α fusion gene; HES, hypereosinophilic syndrome; MBP, major basic protein.

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2. Materials and methods

With approval from the Mayo Clinic Institutional Review Board in accordance with federal regulations, we performed a systematic retrospective medical record review and death certificate analysis of all patients who received a diagnosis of HES at Mayo Clinic in Rochester, MN, from January 1, 1990, through December 31, 2008. In particular, we examined the clinical history, treatment, outcome, and causes of morbidity and mortality in these patients. This review did not seek to determine the incidence of death in HES but rather to report causes of mortality and the associated organ systems affected in those patients that died.

In total, 247 medical records of patients who received a diagnosis of HES were reviewed. Overall, 23 of these patients received a diagnosis of HES and had died. All of the deceased patients included in this review met criteria for the diagnosis of HES [1]. In each case, the patients underwent a comprehensive assessment to rule out secondary causes of eosinophilia including evaluation for parasitic infections; CT scans of the chest, abdomen and pelvis to rule out malignancy, and bone marrow biopsy to rule out myeloproliferative disease. Many of the patients underwent peripheral blood leukemia/lymphoma phenotypic analysis by flow cytometry and T-cell receptor gene mutation analysis. If information regarding the cause of mortality was not available in the patient's medical record, the office of vital records in the patient's home state was contacted to determine the cause of death. Altogether, the cause of death in 15 of the 23 patients was determined by the above methods. In the remaining 8 patients, the cause of death is not known. In the majority of cases, organ involvement was determined via histologic analysis or imaging modalities. In some cases, organ involvement was determined by a physician's clinical diagnosis.

To identify previous medical literature regarding causes of morbidity and mortality in HES patients, we performed a PubMed search with the subject headings *hypereosinophilic syndrome*, *mortality*, and *death*. Literature published through May 2010 was reviewed.

3. Results

Sixteen patients (70%) were men and 7 (30%) were women. The average age at death was 60 years (range, 27–85 years; 59 years in men, 63 years in women). The mean absolute peak eosinophil level for all 23 patients was $15.1 \times 10^9/L$ (range, $1.6\text{--}100.2 \times 10^9/L$). The mean peak eosinophil levels were $11.3 \times 10^9/L$ (range, $1.6\text{--}30.0 \times 10^9/L$) in men and $23.8 \times 10^9/L$ (range, $2.2\text{--}100.2 \times 10^9/L$) in women. Interleukin-5 levels were measured in 4 patients and were elevated in 2 (mean, 36.6 pg/mL; range, 11.5–61.76 pg/mL, normal <7.8 pg/mL). Immunoglobulin E levels were measured in 12 patients and elevated in 9 (mean, 2279 kU/L; range, 44–3247 kU/L, reference range mean, 13.2 kU/L). Four of the 23 patients were tested for the Fip1-like 1-platelet-derived growth factor receptor α fusion gene (FIP1L1-PDGFR α), and all 4 had negative results. Of the 23 patients, 3 underwent T-cell receptor gene mutation analyses which were found to be negative.

Corticosteroids, hydroxyurea and interferon-alpha were the most common treatment modalities used with treatment rates of 96% (22/23), 61% (14/23), and 30% (7/23) respectively. Other medications utilized included vincristine (4 patients), cladribine (2), imatinib mesylate (2), cyclosporin (1), mepolizumab (1) and intravenous gamma-globulin (1).

In the 23 patients who died, HES affected the following organ systems in order of decreasing frequency: cardiovascular in 18 (78%), neurologic in 10 (43%), dermatologic in 9 (39%), pulmonary in 6 (26%), and gastrointestinal in 1 (4%). When comparing organ involvement on the basis of sex, 14 men (88%) vs. 4 women (57%) had cardiovascular involvement, 8 men (50%) vs. 2 women (29%) had neurologic involvement, 5 men (31%) vs. 4 women (57%) had dermatologic involvement, 4 men (25%) vs. 2 women (29%) had pulmonary involvement, and 1 man (6%) vs. no women had gastrointestinal tract involvement. 18 (78%) of the 23 patients had at least 2 organs affected.

The cause of death was identified in 15 patients (65%), 12 men and 3 women. Death was attributed to cardiac dysfunction (complete heart block, eosinophilic myocarditis, cardiomyopathy and sudden cardiac death) in 5 (33%), infection in 3 (20%), unrelated malignancy in 3 (20%), thromboembolic phenomena in 2 (13%), and vascular disease in 2 (13%) (Table 1). Of the 23 patients, 14 (61%) had a history of nicotine dependence.

Table 1
Causes of death by system in 15 hypereosinophilic syndrome patients.

Cause of death	Peak eosinophils within 4 months of death	No. (%)
Cardiac dysfunction		5 (33)
^a Complete heart block	Unknown	
^a Eosinophilic myocarditis	$4.96 \times 10^9/L$	
^a Eosinophilic myocarditis/ischemic cardiomyopathy	Unknown	
^a Sudden cardiac death	$5.10 \times 10^9/L$	
^a Cardiomyopathy	Unknown	
Infection		3 (20)
Pneumonia	Unknown	
Cellulitis	Unknown	
Salmonella bacteremia	Unknown	
Malignancy		3 (20)
Multiple myeloma	Unknown	
Lung cancer, patient #1	$0.31 \times 10^9/L$	
Lung cancer, patient #2	$1.45 \times 10^9/L$	
Thromboembolic phenomena		2 (13)
^a Multiple embolic infarcts	$9.0 \times 10^9/L$	
^a Pulmonary embolism	$3.23 \times 10^9/L$	
Vascular disease		2 (13)
Pulmonary vasculitis	Unknown	
Arteriosclerotic vascular disease	Unknown	

^a Death presumed secondary to hypereosinophilic syndrome.

The literature review yielded the cause of death in 21 HES patients, as described in case reports listed and summarized in Tables 2 and 3.

4. Discussion

HES treatment has evolved during the 19 years of this study period. Conventional therapies such as corticosteroids and hydroxyurea are commonly used in HES treatment. Corticosteroids have

Table 2
Cause of death in 21 hypereosinophilic syndrome patients reported in the literature.

Source	Cause of death
Cheung et al. [8] Kanamori et al. [9]	Spontaneous liver rupture Leptomenigeal disease and cerebral eosinophilic mass lesion
Grigoryan et al. [10] Carnero-Alcazar et al. [11] Sato et al. [12]	Cerebral arteriolar thromboembolism Myocardial fibrosis Multiple occlusive coronary thrombi and right ventricular thrombus
Chou et al. [13]	Cerebral spinal fluid infiltration by eosinophils
Chao et al. [14]	Ventricular fibrillation secondary to ventricular thrombus and endomyocardial fibrosis
Arima et al. [15] Salanitri [16] Anghel et al. [17]	Intracerebral hemorrhage Septicemia Cerebral hemorrhage during an episode of sepsis
Corradi et al. [18]	Heart failure with sudden arrhythmic death
Leiferman and Gleich [19] Scheinfeld [20]	Intracerebral hemorrhage Diffuse cerebral edema with uncal and tonsillar herniation
Gudmundsson et al. [21] Ault et al. [22] Noguchi et al. [23] Johnston and Woodcock [24] Rauch et al. [25]	Severe aortic insufficiency Pneumococcal sepsis Septic shock Acute aortic thrombosis Myocardial infarction secondary to an occlusive thrombus
Egesten et al. [26] Zientek et al. [27] Myers [28]	Cardiac mural thrombi Anoxic brain injury Pneumonia

Table 3

Cause of death by system in 21 hypereosinophilic syndrome patients reported in the literature.

Organ system	No. (%)
Cardiac/thromboembolic	9 (43)
Cerebral arteriolar thromboembolism	
Myocardial fibrosis	
Multiple occlusive coronary thrombi and right ventricular thrombus	
Ventricular fibrillation secondary to ventricular thrombus and endomyocardial fibrosis	
Heart failure with sudden arrhythmic death	
Severe aortic insufficiency	
Acute aortic thrombosis	
Myocardial infarction secondary to an occlusive thrombus	
Cardiac mural thrombi	
Neurologic	7 (33)
Leptomeningeal disease and cerebral eosinophilic mass lesion	
Cerebral spinal fluid infiltration by eosinophils	
Intracerebral hemorrhage (2)	
Cerebral hemorrhage during an episode of sepsis	
Diffuse cerebral edema with uncal and tonsillar herniation	
Anoxic brain injury	
Infection	4 (19)
Septicemia	
Pneumococcal sepsis	
Septic shock	
Pneumonia	
Other	(5)
Spontaneous liver rupture	

remained first-line treatment for many *FIP1L1*-*PDGFRA*-negative HES patients [29,30]. Chemotherapeutic agents are sometimes used as second- or third-line treatment strategies [30,31]. Potential steroid-sparing agents such as interferon alfa were first introduced around 1990 [32]. Interferon alpha has the capability to induce remission and reverse end-organ damage in some cases [33–35].

Recent advances in HES diagnosis and classification have affected treatment. For example, imatinib mesylate is now first-line therapy for *FIP1L1*-*PDGFRA*-positive disease [30], dramatically changing the prognosis in this disease variant [22,36,37]. Investigational drugs such as mepolizumab (anti-interleukin 5) and alemtuzumab (anti-CD52) represent agents with specific therapeutic targets. In general, directed therapy has the potential of minimizing adverse effects compared with traditional, less specific immunosuppressants. It is likely that these advances in treatment modalities have positively affected HES mortality as evidenced by improved survival with HES over time [1,7].

Activated eosinophils cause tissue damage by a variety of mechanisms. Eosinophilic granule proteins exert pro-inflammatory effects via the release of toxic granule proteins and preformed inflammatory mediators. Activation of nearby inflammatory cells also leads to direct cytotoxic cell damage [38]. Major basic protein (MBP), one of the more potent eosinophilic granule proteins, causes damage by increasing vascular permeability, activating complement, and triggering surrounding cells such as basophils and mast cells. MBP also stimulates tissue remodeling which may lead to fibrosis [39]. Eosinophilic granules predispose to thrombosis by acting as platelet agonists and reducing the anti-coagulant actions of heparin and tryptase [39,40]. Furthermore, MBP has been shown to decrease the generation of activated protein C by inhibition of thrombomodulin. This combination of cell damage with resultant organ system dysfunction and increased thrombotic potential in HES patients may lead to death, as reported in certain patients in this series.

Compared with specific organ involvement reported in the literature, this report of 23 HES fatalities showed a lower percentage of

dermatologic (39% vs. 69% historically), pulmonary (26% vs. 44% historically), and gastrointestinal tract (4% vs. 38% historically) involvement. Interestingly, the percentage of cardiac involvement was higher in this study (78% vs. 20% historically) [41], but mortality itself from cardiac disease was lower than previously reported [42]. The reason for the lower mortality from cardiac disease is unclear, although it may be attributable to earlier diagnosis and therapy or more effective therapy. Additionally, the marked decrease in HES gastrointestinal tract involvement may reflect the increased awareness, diagnosis, and treatment of eosinophilic gastrointestinal tract diseases as single-organ eosinophilic disorders [43,44], rather than being considered as manifestations of HES itself. In this series, 18 (78%) of the 23 patients were found to have at least 2 organ systems involved, indicating that multi-organ disease may be a potential indicator of more severe disease and may possibly be a risk factor for fatal disease.

A recent multicenter study involving 188 HES patients reported a mean peak absolute eosinophil count of $6.6 \times 10^9/L$ [41], which contrasts markedly with the mean peak absolute eosinophil count, $15.1 \times 10^9/L$, in our cohort of deceased HES patients. Previous studies have reported that the degree of eosinophilia was unrelated to the development of cardiac disease [45]. No reports have correlated the specific level of eosinophilia with end-organ damage. However, this study raises the possibility that higher eosinophil counts may be associated with higher mortality from diverse causes.

In the past, HES was thought to occur in men at a much higher rate than in women [1]. More recent studies have reported a male-to-female ratio of 11:8 [41]. Of the 23 patients in our study who died, more than twice as many were men (ratio of 16:7), suggesting that male sex is a risk factor for fatal disease. This may be a reflection of the higher prevalence of *FIP1L1*-*PDGFRA* in the male population; however, we were unable to document this in our small series as many of our patients died before standard testing was available. This mutation was generally thought to be associated with a higher severity of disease before therapy with imatinib mesylate was available [46,47]. Further distinguishing features of myeloid HES may include elevated serum vitamin B12, anemia, thrombocytopenia, hepatomegaly, splenomegaly, myelofibrosis, or hypercellular bone marrow [46,48,49].

This series includes numerous previously unreported and apparently unrelated causes of death, including multiple myeloma, pulmonary vasculitis, and salmonella bacteremia. No malignancy-related deaths could be found in previous literature (vs. 20% in the current series). In comparison with the causes of death reported in the literature, we found no neurologic-related mortality (vs. 33%) and similar infectious-related mortality (20% vs. 19%) (Tables 2 and 3). These differences may reflect the improved ability to diagnose and effectively treat HES before irreversible organ damage or other complications have occurred.

There is a paucity of information in the literature regarding causes of death in HES patients. To our knowledge, this is the first series on HES-related mortality in more than 30 years. On the basis of our findings it would seem prudent for physicians caring for HES patients to continue to carefully monitor for cardiac involvement, infectious complications, and the development of malignancies in their patients. Knowledge of the organ system-related causes of mortality in HES is important to the physician caring for these patients. Close monitoring, specifically, of the at-risk end organs, combined with early treatment, may have the ability to improve survival and reduce morbidity in HES patients. As our expanding knowledge of the pathophysiology and genetic factors of this condition increases, the opportunity for the development of targeted therapies will also increase and survival in HES patients will likely continue to improve over time.

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Conflict of interest statement

The authors have nothing to disclose.

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