Original Article

Hypereosinophilic Syndrome Subtype Predicts Responsiveness to Glucocorticoids

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What is already known about this topic? Although small case series and one retrospective multicenter review suggest that steroid response is variable in hypereosinophilic syndrome (HES), this has not been examined systematically in a diverse group of subjects with HES evaluated in a uniform manner.

What does this article add to our knowledge? This article characterized the predictors of response to corticosteroids among groups of subjects with HES and may inform treatment decisions based on clinical HES subtype.

How does this study impact current management guidelines? There are no standardized guidelines for management of HES. Results of this study may inform decisions to initiate second-line therapy in certain HES subtypes or consideration of referral to tertiary centers with experience in HES.

BACKGROUND: Glucocorticoids (GCs) are considered first-line treatment for platelet-derived growth factor α (*PDGFRA*)-negative hypereosinophilic syndromes (HESs). Despite this, little is known about clinical predictors of GC responsiveness in HES.

OBJECTIVE: Knowledge of clinical and laboratory predictors of GC response before initiation of GC could lead to more rational selection of subjects with HES for whom earlier institution of second-line and alternative therapies would be appropriate.

METHODS: Response to GC, as defined by the reduction of the absolute eosinophil count to below 1000/mm^3 and control of symptoms, was assessed by a retrospective chart review of subjects with *PDGFRA*-negative HES evaluated on an institutional review board-approved protocol. Demographic, clinical, and laboratory parameters obtained before institution of GC, as well as final diagnosis, were evaluated to determine predictors of GC response. Proportional odds models were used for univariate and multivariate assessment of predictors with permutation adjusted *P* values to correct for multiple comparisons.

RESULTS: A total of 164 subjects with *PDGFRA*-negative HES were categorized according to GC response. Of them, 39% of the subjects responded to low dose (≤10 mg) prednisone, 9% did not respond to GC, and the remainder (52%) had variable responses to GC. The HES subtype diagnosis was the best predictor of response to GC with myeloid forms and lymphocytic variants of HES being the least responsive to GC.

CONCLUSIONS: In a large cohort of well-characterized subjects with HES, the odds of response to GC was predicted by HES subtype. Using this model, clinicians may more readily proceed to second-line agents in subjects with confirmed lymphocytic or myeloid forms of HES. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:190-5)

Key words: *Eosinophil; Hypereosinophilic syndrome; Glucocorticoid; Steroid-resistance; Prednisone*

Hypereosinophilic syndromes (HES) are a rare group of disorders characterized by marked peripheral and/or tissue eosinophilia resulting in clinical signs and symptoms. The clinical manifestations of HES are heterogeneous, and treatment algorithms vary depending on the clinical scenario.[1] Before the discovery of imatinib, the treatment of choice for platelet-derived growth factor (*PDGFR*)-associated HES,[2] glucocorticoids (GC) were considered first-line therapy for all patients with HES. Despite this, little is known about steroid responsiveness in different subgroups of patients with HES,[3] and few studies have explored the mechanisms underlying GC resistance in HES.[4]

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Abbreviations used
AEC- Absolute eosinophil count
EGPA- Eosinophilic granulomatosis with polyangiitis
GC- Glucocorticoid
HES- Hypereosinophilic syndrome
IHES- Idiopathic hypereosinophilic syndrome
LHES- Lymphocytic variant HES
MHES- Myeloid HES
MN- Myeloid neoplasm
PDGFRA- *Platelet-derived growth factor α*
SO-HES- Single-organ HES

The end organ manifestations of HES are extremely varied, ranging from bothersome symptoms, such as urticaria, myalgia, and fatigue, to disabling and/or life-threatening manifestations, such as mononeuritis multiplex, endomyocardial fibrosis, and stroke. Although the ultimate aim of HES therapy is to prevent these consequences, surrogate markers of disease activity have not been validated to date. That said, most experts use a combination of clinical symptoms and the peripheral blood absolute eosinophil count (AEC) to help guide therapeutic decisions.

Very few studies have evaluated predictors of response to the various medications used to treat HES.[5] Consequently, excluding the 10% to 20% of patients with HES with *PDGFR*-associated disease for whom imatinib is the treatment of choice, therapeutic interventions typically proceed in a stepwise fashion beginning with GCs.[1] Second-line GC-sparing agents are added if response to therapy is suboptimal or significant GC toxicity is observed. Because there is little consensus regarding GC dosing in the treatment of HES, the length of time before a second agent is added varies considerably. To begin to address this issue, we sought to identify predictors of response to GC using a well-characterized, consecutively recruited cohort of subjects with HES.

METHODS

Subject selection

Between 1993 and February 15, 2014, 330 subjects were evaluated on an institutional review board-approved protocol (NCT00001406) to study unexplained eosinophilia. All subjects signed informed consent before undergoing a complete evaluation, including medical history, physical examination, routine laboratory testing, electrocardiogram (EKG), echocardiogram, pulmonary function testing, and assessment of other end organ manifestations of eosinophilia as clinically indicated. HES was defined as AEC $\geq 1.5 \times 10^9$/L with signs and symptoms of organ or tissue involvement attributable to the eosinophilia or prominent tissue eosinophilia accompanied by peripheral eosinophilia (AEC greater than the upper limit of normal).[1] Subjects with HES with a secondary diagnosis known to cause eosinophilia, such as parasitic infection or drug hypersensitivity, and subjects with myeloid neoplasms (MN), including those associated with mutations in *PDGFRA*, were excluded (Figure 1). The remaining 259 subjects with confirmed HES had their electronic medical records and outside medical records screened for historical use of GC. Because this was a retrospective study, subjects were not treated with a standardized tapering schedule; however, charts were reviewed to identify those subjects treated with corticosteroids as a single agent followed by a taper (lasting from 2 weeks to several months) and for

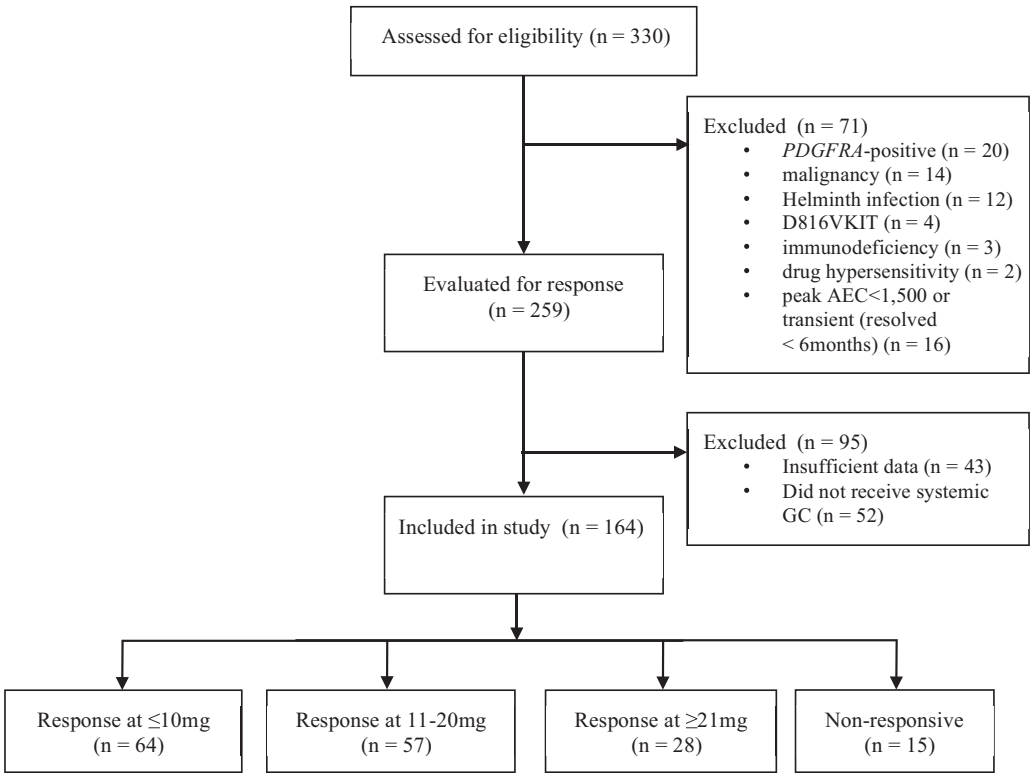

FIGURE 1. Consort diagram of subjects included in the study. *AEC*, Absolute eosinophil count; *GC*, glucocorticoid; *PDGFRA*, platelet-derived growth factor α.

TABLE I. Patient characteristics by dose category of prednisone

	Group 1 (≤10 mg) n = 64	Group 2 (11-20 mg) n = 57	Group 3 (≥21 mg) n = 28	Group 4 Nonresponders n = 15
Median minimally effective dose of prednisone in mg (range)	5 (1.5-10)	16 (11-20)	37.5 (21-80)	NA
Gender M/F	38M/26F	26M/31F	10M/18F	5M/10F
Race W/B/A/O/U	55/4/4/0/1	53/2/2/0/0	22/5/1/0/0	11/3/1/0/0
Median peak AEC (range)	4,164 (500-48,080)	7,900 (910-76,500)	4,824 (897-26,688)	11,237 (1,100-82,000)
Median age in years (range)	52.5 (2-85)	42 (4-84)	42 (14-63)	49 (16-70)
Median serum IgE level in unit (range)	164.5 (3.3-6,530)	277 (5-16,300)	214 (3.7-42,874)	93.2 (1.6-2,786)
Median serum B12 level in unit (range)	603.5 (227-3,914)	664 (293-5,055)	677 (201-1,312)	993 (205-2,583)
Median serum tryptase level in unit (range)	5.32 (0.99-18.4)	4.86 (0.99-28.1)	5.20 (1.22-16.5)	4.5 (1.7-25.3)
Median serum LDH in unit (range)	193 (115-409)	203 (90-435)	205 (115-695)	313 (100-587)
HES subtype				
IHES	38	26	15	6
HES/EGPA	15	18	5	0
LHES	5	8	8	3
MHES	0	0	0	5
SO-HES	6	5	0	1
Organ involvement				
Cardiac	9/64 (14%)	5/57 (9%)	4/28 (14%)	9/15 (50%)
Neurologic	12/64 (19%)	14/57 (25%)	9/28 (32%)	4/15 (27%)
Pulmonary	37/64 (58%)	39/57 (68%)	17/28 (61%)	10/15 (67%)
Gastrointestinal	22/64 (34%)	19/57 (33%)	12/28 (43%)	5/15 (33%)
Dermatologic	32/64 (50%)	36/57 (63%)	20/28 (71%)	9/15 (60%)
Sinus	24/64 (37.5%)	31/57 (54%)	16/28 (57%)	4/15 (27%)

A, Asian, *AEC*, absolute eosinophil count; *B*, black or African American; *HES/EGPA*, hypereosinophilic syndrome/eosinophilic granulomatosis with polyangiitis; *IHES*, idiopathic hypereosinophilic syndrome; *LDH*, lactose dehydrogenase; *LHES*, lymphocytic variant hypereosinophilic syndrome; *MHES*, myeloid hypereosinophilic syndrome; *O*, other; *SO-HES*, single-organ hypereosinophilic syndrome; *U*, unknown; *W*, white.

whom laboratory and clinical data were available before and during the taper to assess response to therapy (n = 164). Subjects initially treated with a starting dose of ≤40 mg of prednisone (or equivalent) were included if responsive; however, to classify a subject as a nonresponder, he or she had to have received >40 mg of prednisone equivalent for ≥1 week without response. Some subjects had their GC dose increased due to rising counts followed by additional attempts to taper; response to GC was defined as the minimum clinically effective dose at which AEC was below 1.0×10^9/L with concomitant improvement of symptoms or manifestations of organ disease after at least 1 week of treatment on a given dose. Two abstractors (P.K. and A.O.A.), trained to a standard for the definition of clinical response, reviewed the electronic and paper medical records. Daily equivalent prednisone doses were calculated for subjects taking other GC formulations. An average daily dose was calculated for subjects on alternate day dosing.

Categorization of response to GC

After abstraction of the data, subjects were grouped according to *a priori* dose-response categories based on the usual practice of practitioners taking care of these subjects. Subjects were considered to have a response to low-dose prednisone if they could be controlled on ≤10 mg of prednisone (group 1). These subjects were not typically treated with second-line agents, unless required due to GC comorbidities. Subjects whose eosinophil counts, disease manifestations, or symptoms required slightly higher doses of prednisone in the range of 11 to 20 mg (group 2) frequently required second-line eosinophil lowering therapies. Subjects requiring ≥21 mg prednisone (group 3) clinically differed from group 2 because the urgency of instituting second-line therapies was much greater to prevent progression of HES and/or prevent the significant side effects of longer term, high dose GC. Subjects who had no laboratory or clinical response to high dose prednisone given for at least 2 weeks (group 4) were considered nonresponders (Table I).

HES subtype categorization

During their clinical workup, subjects were diagnosed with one of the following HES clinical subtypes[1]: lymphocytic variant HES (LHES), myeloid HES (MHES), eosinophilic granulomatosis with polyangiitis (EGPA)/HES overlap, single-organ HES (SO-HES), or idiopathic HES (IHES). Subjects with LHES had an aberrant lymphocyte population demonstrated by flow cytometry[6] and/or T-cell receptor rearrangement by polymerase chain reaction. Subjects with clinical features of an MN,[7] but without confirmed cytogenetic or molecular abnormalities in the eosinophil lineage, were diagnosed with MHES. Subjects with HES and organ involvement typical of EGPA but without biopsy-proven vasculitis were classified as HES/EGPA overlap. Clinical features in this cohort included asthma, paranasal sinus involvement, nasal polyposis, pulmonary infiltrates, cardiomyopathy, and neuropathy with or without perivascular eosinophilia demonstrated by biopsy. Subjects with HES with clinical manifestations restricted to a single-organ system (ie, eosinophilic gastrointestinal disease, eosinophilic hepatitis, eosinophilic fasciitis, chronic eosinophilic pneumonia) were classified as SO-HES even though the organ involved varied between subjects. Finally, subjects with HES who did not fit any of the categories above were classified as IHES.

TABLE II. Predictors from the univariate proportional odds model

Predictor variable	N	Unadjusted *P* value*	Adjusted *P* value†
HES subtype	164	.012	<.001
LDH	146	.038	.156
Cardiac involvement	164	.058	.156
Serum vitamin B12	151	.083	.467
Dermatologic involvement	163	.089	.627
Peak absolute eosinophil count	153	.104	.627
Neurologic involvement	164	.189	.871
T-cell receptor rearrangement	161	.297	.918
IgE	159	.461	.982
Pulmonary involvement	164	.462	.982
Sinus involvement	160	.472	.982
Erythrocyte sedimentation rate	88	.59	.982
Pulmonary function testing	94	.666	.982
Gastrointestinal involvement	163	.685	.982
Serum tryptase	152	.974	.982

HES, Hypereosinophilic syndrome; *LDH*, lactose dehydrogenase.
*Generalized estimating equations score method, 2-sided.
†Permutation method adjusted for multiple comparisons, 2-sided.

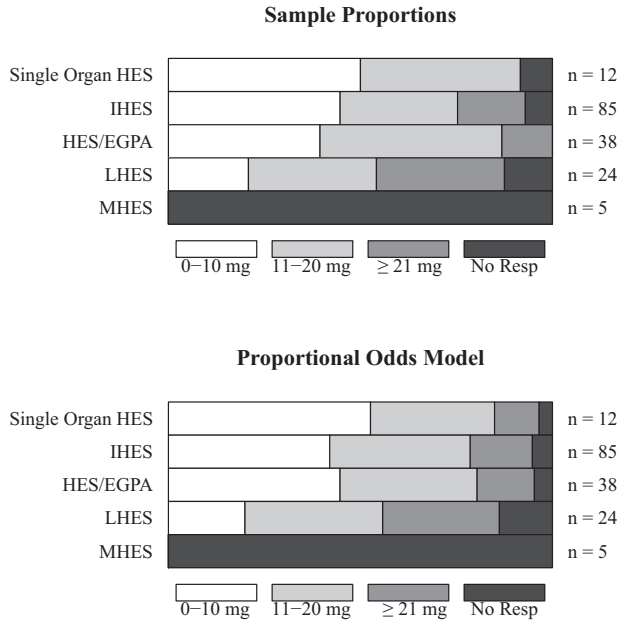

FIGURE 2. Graphical representation of sample and predicted proportions. Top: sample proportions for each response category (dose in mg) by HES subtype. Bottom: predicted proportions for each response category (dose in mg) by HES subtype from the proportional odds model. *EGPA*, Eosinophilic granulomatosis with polyangiitis; *HES*, hypereosinophilic syndrome, *IHES*, idiopathic hypereosinophilic syndrome; *LHES*, lymphocytic variant hypereosinophilic syndrome; *MHES*, myeloid hypereosinophilic syndrome.

Statistics and model building

Fifteen baseline predictor variables were measured (Table II) and fit using a univariate proportional odds model. All but 3 of the 15 variables had less than 8% missing, and we assumed missing to be completely at random. Inferences were made using Rao's score test with a sandwich estimator of variance, so that the inferences would be asymptotically valid whether or not the model was misspecified.[8] Because there was collinearity among the 15 predictors, and to adjust for multiple comparisons, a multiple comparison permutation adjustment method was used.[9] For models that did not converge, a more conservative estimate was utilized by moving a patient to the next response category to allow convergence. The best-fit univariate model used HES diagnosis to predict GC response, and we tested whether any additional predictors could be added to significantly improve fit using a permutation multiple comparison adjustment method.[9] Tests for association with demographic variables used Fisher's exact test (gender, race) and analysis of variance (age). R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria)[10] and SAS version 9.4 (SAS Institute, Cary, NC) were used for statistical analysis.

RESULTS

Most subjects with HES are steroid responsive

Overall, 90% (149/164) of subjects responded to GC (Figure 1). Among the 149 responders, 64 (43.0%) were controlled on ≤10 mg of prednisone equivalent (median 5 mg, range 1.5-10 mg) and 57 (38.3%) on 11 to 20 mg of prednisone equivalent (median 16 mg, range 11-20 mg). Only 28 (18.8%) of the responders required ≥21 mg of prednisone (median 37.5, range 21-80) to control AEC and symptoms. There were no significant differences between any of the groups with respect to demographics (Table I).

Fifteen baseline clinical and laboratory variables were selected for the predictive analysis based on their importance in defining clinical subtype and/or reports of association with GC response (Table II). We cannot exclude that the lack of association with GC response for the 2 variables with fewest observed values ("N"s denoted in Table II), erythrocyte sedimentation rate and pulmonary function testing, was not due to a smaller sample size. In the univariate analysis, HES subtype and elevated serum lactose dehydrogenase were significantly predictive of GC response. However, after correction for multiple comparisons, only HES subtype remained significantly predictive (Table II). To confirm that the model fit was appropriate, the observed and the predicted proportion of each of the 4 response values (dose) within each diagnosis group (HES subtype) were plotted (Figure 2) and show that the model fit mirrors the sample proportions very closely. No additional predictors improved the model fit when combined with HES subtype in the proportional odds model (all adjusted $P > .40$).

Subjects with MHES and LHES are less responsive to GC than other HES subtypes

To quantify the odds of response to GC in various subtypes of HES, odds ratios were defined using IHES as the reference (Table III). Because the odds of response for the MHES subtype did not converge (odds ratio = ∞), 1 MHES nonresponder was moved to the responsive category "≥21 mg" for analysis purposes to allow statistical convergence (Table III). Despite this change, the decreased response to GC in this clinical subtype remained significant. Subjects with HES/EGPA overlap and subjects with SO-HES did not have significantly different odds of response to GC when compared with subjects with IHES (1.12 [0.57-2.18],

TABLE III. Odds ratios of response to GC compared with IHES reference

Diagnosis group	Odds ratio = Odds (diagnosis group)/ Odds (HES)	Lower 95% confidence limit	Upper 95% confidence limit	Two-sided *P* value (testing for significant difference from HES)
IHES	Reference	–	–	–
HES/EGPA	1.12	0.57	2.18	.75
LHES	0.34	0.15	0.81	.015
MHES	0.013*	0.0013	0.118	.0001
SO-HES	1.54	0.50	4.67	.45

GC, Glucocorticoids; *HES/EGPA*, hypereosinophilic syndrome/eosinophilic granulomatosis with polyangiitis overlap; *IHES*, idiopathic hypereosinophilic syndrome; *LHES*, lymphocytic variant hypereosinophilic syndrome; *MHES*, myeloid hypereosinophilic syndrome; *SO-HES*, single-organ hypereosinophilic syndrome.
*One subject was moved from "nonresponsive" to "≥21 mg" to allow convergence.

$P = .75$, and 1.54 [0.50-4/67], $P = .45$, respectively). In contrast, subjects with LHES and MHES had significantly worse odds of response (0.34 [0.15-0.81], $P = .015$, and 0.013 [0.0013-0.118], $P = .0001$, respectively) when compared with IHES.

DISCUSSION

Heterogeneity of response to GC has been appreciated since the first descriptions of HES in the 1970s.[11,12] However, the inclusion of patients with *PDGFRA*-associated disease in these case series complicates the interpretation of GC response data, because this mutation is known to be GC resistant. In fact, in a large multicenter study of 188 subjects with HES,[3] 179 of whom were treated with GC, subjects with known *FIP1L1-PDGFRA* mutations accounted for 13 (65%) of the 20 nonresponders (Ogbogu et al, unpublished data, December 2009). In the present study, subjects with known mutations involving *PDGFRA* were excluded. Overall, 9% of *PDGFRA*-negative subjects with HES were found to be unresponsive to GC. This is similar to the findings in a recent series of 33 patients with IHES, in which 18% of subjects were GC resistant ($P = .13$, Fisher's exact test).[13]

Surprisingly, relatively few studies[14,15] have explored the potential mechanisms of GC resistance in subjects with HES. The selective absence of GC receptor expression on eosinophils was reported in a subset of GC-resistant patients with HES in 1989.[4] However, the clinical characteristics of many of the receptor-deficient patients in this cohort are suggestive of *PDGFRA*-positive disease (male gender, elevated serum B12, cardiac involvement). Thus, the broader applicability of the findings to *PDGFRA*-negative HES is uncertain. *In vitro* studies have focused on the reciprocal relationship between IL-5 and GC in regulating eosinophil apoptosis as a potential cause of GC resistance in HES,[14,15] although this has not been convincingly demonstrated *in vivo*. From a clinical standpoint, GC responsiveness has been associated with elevated IgE levels in several small studies,[12] but this relationship was not confirmed in 2 larger studies where *PDGFRA*-positive subjects were excluded.[3,13] Finally, although elevated serum thymus and activation regulated chemokine levels were more frequent in GC-responsive patients with HES in 2 studies,[3,16] measurement of this mediator is not standardized and its utility as a predictor of response remains unproven.

A major limitation of prior studies of GC responsiveness in HES has been the fact that the definition of "response" has not been universally applied. In the present study, statistical models were used to determine predictors of response to GC using a standard definition of response in a large cohort of subjects with *PDGFRA*-negative HES treated with GC. Predictors were chosen from data collected as part of a typical evaluation for HES and were based on available information on GC response from the literature. One limitation of this study was the retrospective design, which resulted in missing variables for some subjects. The lack of association with GC response for the variables with most missing values in the univariate testing may be related to the smaller sample size. The best-fit model with the available data showed that HES subtype was the most predictive of response to GC. Fortunately, the plausibility of the findings after correction for testing 15 predictors mirrors clinical experience in this disorder. A second limitation of the study was the potential for overfitting of the model because of the number of variables included in the model. We used a permutation multiple comparison procedure[9] to account for overfitting while considering issues of collinearity of abnormal laboratory values. Finally, we had to move 1 subject with MHES from the nonresponse category to a prednisone-response category to allow the model to converge. If anything, this suggests that the odds of response to GC in PDGFRA-negative MHES is even less than predicted in this model. In clinical practice, an HES subtype diagnosis is made using a combination of signs and symptoms in addition to individual laboratory parameters. It became apparent after the model was designed that these laboratory parameters became irrelevant once an HES subtype diagnosis was made.

In summary, our findings suggest that assignment of an HES subtype diagnosis is an important determinant of GC response in HES. Historically, patients with *PDGFRA* mutations have been described to be unresponsive to corticosteroids; however, a diagnosis of *PDGFRA*-negative MHES also predicts nonresponse to GC. For patients with LHES, initiation of second-line therapies may be useful early in the course of disease, because more than two thirds of the subjects with LHES in this retrospective cohort required moderate-to-high dose corticosteroids for disease control. Elucidation of the biologic reasons for the heterogeneity of response to GC could provide further insight into the etiology of different HES subtypes.

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