

Clinical Significance of IgE in a Large Cohort of Patients with Moderate or Severe Chronic Graft-versus-Host Disease

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Chronic graft-versus-host disease (cGVHD) is a common complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and is associated with significant morbidity and mortality (1). It is characterized by immune dysregulation affecting multiple organs including skin, mouth, eyes, lungs, liver, gastrointestinal tract, joints and fascia, and genitals (1,2). Due to its complicated and multifactorial nature, half of patients fail first-line therapy and many fail at least one subsequent therapy. Better understanding of pathophysiology and prognostic markers is needed.

IgE has scarcely been investigated in allo-HSCT and has not been studied in cGVHD. It has been reported that patients with acute GVHD have elevated IgE compared to patients without acute GVHD (3). IgE has been studied in autoimmune disorders where total IgE and IgE autoantibodies have been shown to correlate with disease activity in systemic lupus, lupus nephritis, bullous pemphigoid (BP) and chronic idiopathic urticaria (CIU) (4). Furthermore, omalizumab, an IgE-receptor antibody, is an effective treatment for antihistamine-refractory CIU and BP and IgE blockade resulted in decreased interferon- α in cells cultured from patients with lupus (5). Given the role of IgE in autoimmune disorders, we hypothesize that IgE could be involved in the pathogenesis of cGVHD. We investigated the prevalence of elevated IgE and its significance in patients with moderate or severe cGVHD.

Patients were enrolled on the NIH cGVHD Natural History Study (NCT00092235) from 2004 to 2016. Patients (n=383) provided informed consent and underwent 1-week comprehensive multidisciplinary evaluation by several specialists and assessment using the NIH cGVHD diagnosis and staging system (6). Measurement of IgE only began in January 2012, so the first 283 patients enrolled before this time were excluded from analysis. Pediatric patients (n=33) and patients found to not have cGVHD or who failed to complete study evaluations (n=17) were also excluded. The final study population numbered 100 patients.

Patients were classified as having normal (≤ 90 IU/mL) or elevated IgE (> 90 IU/mL) based on the range of normal values reported by the NIH Clinical Center Department of Laboratory Medicine. We compared potential predictors of IgE and outcomes between these groups. Potential predictors of elevated IgE included demographic, transplant, and GVHD characteristics as well as an assortment of laboratory measures. Survival duration was calculated from date of evaluation until date of death or last follow-up by the Kaplan-Meier method and compared between groups using the log-rank test.

The patient population numbered 100 hematological malignancy patients with a median age of 51 years (range, 18–74) consisting of 61 male and 39 female patients (**Supplemental Table I**). 78 patients had severe and 19 moderate cGVHD. Median number of lines of prior systemic immunosuppressive therapy was 4 (range, 0–11) while 36 patients were receiving moderate and 43 high intensity immunosuppression (**Supplemental Table II**).

14/100 patients had elevated IgE and median IgE level in our population was 5.1IU/mL (range, 1-9106IU/mL) (**Supplemental Figure 1**). Patients with elevated IgE had significantly higher IgA (89.5 vs 36.5mg/dL, $p=0.00044$) and IgG (987.5 vs 532 mg/dL, $p=0.00015$) than patients with normal IgE. In addition, patients with elevated IgE had higher ALC (1.65 vs 0.86K/uL, $p=0.011$), AEC (0.16 vs 0.04K/uL, $p=0.04$), CD3+ cells (1035 vs 557 cells/ μ L, $p=0.014$), CD4+ cells (438 vs 250 cells/ μ L, $p=0.013$), CD8+ cells (558 vs 285 cells/ μ L, $p=0.011$), CD19+ cells (227 vs 35 cells/ μ L, $p=0.0083$), NK cells (200.5 vs 142 cells/ μ L, $p=0.024$), and IgM (71.5 vs 37mg/dL, $p=0.018$). Patients with elevated IgE also more frequently had history of asthma than patients with normal IgE (21.4% vs 3.5%, $p=0.035$). Lastly, patients with normal IgE were diagnosed with cGVHD more recently (28 vs. 45 months, $p=0.042$) (**Table I**). Elevated IgE was not associated with global or organ-specific measures of cGVHD severity or pulmonary function test measures.

Survival analysis found that all 14 patients with elevated IgE at evaluation were alive at median follow-up of 32 months (range, 7-56). 17/86 patients (20%) with normal IgE at evaluation had died. Moreover, all deaths occurred in patients with IgE<19IU/mL (**Supplemental Figure 2**).

We characterized the prevalence and potential importance of IgE in patients several years post-allo-HSCT diagnosed with moderate or severe cGVHD.

Associations of elevated IgE with higher levels of numerous immune cell subsets and immunoglobulins, largely within ranges of normal values, suggest that patients with elevated IgE have more robustly or extensively reconstituted immune systems. Patients with normal IgE often had immune cell subsets and immunoglobulins below ranges of normal values, indicating comparatively poorly reconstituted immune systems. We found that elevated IgE did not seem to affect any measures of cGVHD activity or severity. Acute phase reactants were not correlated with elevated IgE which suggests that elevated IgE is not driven by systemic inflammatory reaction.

Previous history of allergy was not associated with elevated IgE. However, patients with elevated IgE more frequently had history of asthma. It may be important to consider history of asthma and adjust accordingly in future analyses of IgE after allo-HSCT given the documented elevation and role of IgE in the pathogenesis and treatment of asthma.

We conducted this study in a clinically well-annotated population of patients with moderate or severe cGVHD, however this study did have some limitations. Patients evaluated before 2012 had to be excluded due to lack of IgE measurement. In addition, since the NIH natural history study is a cross sectional study, we were unable to track IgE over time to relate it to the activity of cGVHD. Finally, our population mostly contains patients with severe burden of cGVHD and does not reflect patients with less severe disease.

In summary, elevated IgE in cGVHD was associated with increased levels of multiple immune cell subsets and immunoglobulins suggesting that IgE may be a marker of more robust post-transplant immune reconstitution. Prior history of asthma was associated with elevated IgE, indicating that pre-transplant factors may still influence IgE even years after transplant. Importantly, elevated IgE was not associated with any global or organ-specific measures of cGVHD severity or activity or any acute phase reactants. These results suggest that in patients after allo-HSCT with cGVHD, elevated IgE is not a marker of disease or acute inflammation.

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Table I: Results of univariate analysis

Variable	Normal IgE N=86	Elevated IgE N=14	p-value
Time from transplant to consent (mo)	39 (10-295)	54 (13-223)	0.063
Time from transplant to cGVHD diagnosis (mo)	9 (1-261)	8 (2-142)	0.91
Time from diagnosis of cGVHD to consent (mo)	28 (1-265)	45 (11-204)	0.042
WBC	7.6 (2.2-17.1)	8.4 (2.9-13.7)	0.33
ANC	5.2 (0.7-15.2)	5.2 (0.9-9.1)	0.99
ALC	0.9 (<0.1-9.4)	1.7 (0.6-5.2)	0.011
AEC	0.04 (0-2.46)	0.16 (0-4)	0.04
CD3+	557 (64-6022)	1035 (235-2527)	0.014
CD4+	250 (33-1547)	438 (82-1663)	0.013
CD8+	285 (29-4833)	558 (127-1271)	0.011
CD19+	35 (0-6307)	227 (0-2094)	0.0083
NK	142 (4-624)	201 (93-436)	0.024
IgA	36.5 (5-194)	90 (22-481)	0.00044
IgG	532 (40-1939)	988 (443-1740)	0.00015
IgM	37 (5-376)	72 (22-239)	0.018
C3	136 (93-227)	134 (98-191)	0.36
C4	31 (13-64)	29 (19-47)	0.51
CRP	6.7 (0.4-77)	5.7 (1.1-54.7)	0.87
ESR	16.5 (2-113)	16 (8-69)	0.32
Platelets	239 (67-741)	262 (88-553)	0.32
Ferritin	230 (5-12827)	208 (16-2052)	0.42

In view of the large number of exploratory analyses performed to determine factors associated with normal IgE vs. elevated IgE, only $p < 0.005$ should be considered statistically significant while if $0.005 < p < 0.05$, the association reflects a strong trend. Abbreviations: AEC—absolute eosinophil count, ALC—absolute lymphocyte count, ANC—absolute neutrophil count, C3—complement component 3, C4—complement component 4, cGVHD—chronic graft-versus-host disease, CRP—C-reactive protein, ESR—eosinophil sedimentation rate, Ig—immunoglobulin, mo—months, NK—natural killer cells, WBC—white blood cells