



Increased malignancy incidence in IgE deficient patients not due to concomitant Common Variable Immunodeficiency

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ABSTRACT

Background: Immunoglobulin E (IgE) deficiency (<2.5 kU/L) has unclear clinical significance. Very little is known about the clinical characteristics of IgE deficiency in patients with Common Variable Immunodeficiency (CVID).

Objective: To evaluate the clinical and laboratory differences between patients with IgE deficiency and those with non-IgE deficiency with and without CVID diagnosis.

Methods: This is a retrospective study of adult patients who had total serum IgE levels measured at our facility from 2010 through 2015. Patients with IgE levels lower than 2.5 kU/L composed the IgE deficiency group. We used Clinical Looking Glass software to identify laboratory results and comorbid conditions including CVID and malignancy.

Results: The IgE levels were measured in 2,339 patients and 63 (2.7%) had IgE deficiency. Of those with IgE deficiency, 14 of 63 (22%) had CVID diagnosis compared with only 62 of 2,276 patients (2.7%) with non-IgE deficiency and CVID. A significantly higher rate of prior malignancy was found in patients with IgE deficiency (21 of 63, 33%) compared with those with non-IgE deficiency (197 of 2,276, 8.7%; $P = .001$; odds ratio 5.51, 95% confidence interval 3.07–9.88). Six of 14 patients with CVID and IgE deficiency (43%) had a prior malignancy diagnosis compared with 8 of 62 patients (13%) with CVID and non-IgE deficiency ($P = .009$; odds ratio 10.65, 95% confidence interval 1.79–63.19). In addition to the higher rate of malignancy, patients with CVID and IgE deficiency did not have more severe disease than those with CVID and non-IgE deficiency.

Conclusion: The rate of prior malignancy is significantly higher in patients with IgE deficiency than in those without IgE deficiency. Similarly, patients with CVID and IgE deficiency have a higher frequency of prior malignancy than those with CVID and non-IgE deficiency. However, patients with IgE deficiency have higher frequency of malignancy than patients with normal IgE levels even in the absence of CVID.

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Introduction

Immunoglobulin E (IgE) deficiency is characterized by total serum IgE levels lower than 2.5 kU/L. It has a prevalence of 1.2% to 10.5%,^{1–3} depending on the studied population. The clinical significance of IgE deficiency in humans is not fully understood. Mice with genetically determined IgE deficiency do not exhibit signs of any disease, so that normal life (at least in mice) appears to be possible in the absence of IgE.⁴ The clinical manifestations of patients with IgE deficiency range from none in previous reports⁵ to a higher prevalence of autoimmunity, respiratory infections, fatigue, and joint pain compared with individuals with normal IgE levels in some other studies.^{2,3} The longstanding debate between atopy and

risk of cancer led to different epidemiologic studies to assess this association, with inconsistent results. Lindelöf et al⁶ reported that the presence of atopy neither increased patients' risk of malignancy nor protected patients from malignancy, which was similar to the findings of other studies.^{7,8} In contrast, the overall risk of lymphoma was found to be significantly lower in subjects with high total serum IgE levels in a Spanish case-control study.⁹ Another European study found that high levels of IgE were associated with a low risk of chronic lymphocytic leukemia and possibly multiple myeloma.¹⁰ These studies primarily assessed the association between high levels of IgE and a possible protective role against malignancy, but there is not much published information regarding low levels of IgE and a possible increased risk of malignancy. However, one prospective study of incident cases of hematologic malignancies found much lower prediagnostic total IgE levels (<20 kU/L) among chronic lymphocytic leukemia and multiple myeloma cases compared with matched controls.¹¹ Recently, Magen et al² reported a higher prevalence of malignancy (17 of 158, 11%) in

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Table 1
Demographic Characteristics of Patients With IgE Deficiency and Non-IgE Deficiency

	IgE deficiency (n = 63)	Non-IgE deficiency (n = 2,276)	P value
Age (y), mean (SD)	51.85 (16.62)	47.79 (17.02)	.06
Women, %	74	77	.702
Race, %			
White	32	18	.005
African American	22	28	.325
Hispanic	9.5	15	.228
Asian	0	0.7	.491
Multiracial	1.5	1.9	.843
Declined or unknown	35	36	.862
Smoking status, %			
Never smoker	17.5	16.4	.829
Former smoker	3.2	7.3	.211
Current smoker	1.6	2.5	.631
Ordering disposition of IgE level by medical specialty, %			
Allergy and immunology	78	76 ^a	.79
Pulmonology	8	11 ^a	.52
Primary care	5	7 ^a	.56
Oncology	5	1 ^a	.13
Infectious disease	3	0 ^a	.07
Inpatient	2	3 ^a	.57

Abbreviation: IgE, immunoglobulin E.

^aA random sample of 100 patients with normal IgE levels was selected.

patients with IgE deficiency compared with patients with IgE levels higher than 2 kU/L (9 of 600, 1.5%). Therefore, very low levels of IgE might be associated with higher risk of malignancy, reflecting dysregulated antitumor immunity in this population, although the mechanism by which this might occur is not known.²

In contrast, patients with Common Variable Immunodeficiency (CVID) have a higher incidence of malignancy (9–13%).^{12–17} However, whether very low IgE levels in patients with CVID are associated with higher frequency of malignancy has never been fully assessed. The main objective of this study was to evaluate any clinical and laboratory differences between IgE deficiency and non-IgE deficiency seen in our population and secondarily to evaluate whether there was any association between malignancy and the combined presence of CVID and IgE deficiency.

Methods

Identifying Patients and Variables for Analysis

This was a retrospective study approved by the institutional review board of the Albert Einstein College of Medicine (Bronx, New York). All adult patients (≥ 18 years old) who had total IgE levels measured (Phadia, Uppsala, Sweden) from January 2010 through November 2015 at the Montefiore Medical Center (Bronx, New York) were identified using Clinical Looking Glass (CLG; Montefiore Medical Center), a software tool for analyzing electronic health record data. Patients who had total IgE levels lower than 2.5 kU/L composed the IgE deficiency group. Patients with total IgE levels of at least 2.5 kU/L composed the non-IgE deficiency group. For all patients included in the study, information about quantitative immunoglobulin levels (IgA, IgM, IgG), absolute eosinophil counts, parasite serologic results (*Strongyloides* IgG, *Trichinella* IgG, *Toxocara* IgG), vitamin D levels, and the presence of antinuclear antibody (ANA) and anti-thyroid peroxidase antibody (anti-TPO) was recorded. The closest values that were performed within 1 year from the date of total IgE level determination (index date) were included in the analysis for all laboratory tests mentioned earlier, except for parasite serologies, stool for ova and parasites, ANA, and anti-TPO. For these laboratory tests, the results of any measurements that were ever recorded were included. Sex, race (as reported in the electronic medical record), and age at the time of total IgE blood collection were noted. *International Classification of Diseases, Ninth Revision (ICD-9)* diagnoses of CVID, autoimmunity (systemic lupus erythematosus or rheumatoid arthritis), asthma, rhinitis, and any type of malignancy also were identified through CLG. In addition, a manual chart review of all patients with IgE deficiency was performed.

CVID in Patients With IgE Deficiency and Non-IgE Deficiency

Patients with IgE deficiency and those with non-IgE deficiency were further subdivided in 2 subgroups each based on whether they carried a CVID diagnosis. Of all patients who had a total IgE level measured, CLG software identified 88 patients who carried a physician diagnosis of CVID. A chart review was performed to confirm the CVID diagnosis based on the practice parameter for the

Table 2
Laboratory Characteristics and Associated Comorbidities in Patients With IgE Deficiency and Non-IgE Deficiency

	IgE deficiency (n = 63)	Non-IgE deficiency (n = 2,276)	P value
Laboratory results			
IgE level (kU/L), mean (SD)	0.95 (0.74)	370.51 (966.8)	<.001
Vitamin D level (ng/mL), mean (SD)	22.15 (10.56)	26.18 (12.43)	.13
Absolute eosinophil count (cells/ μ L), mean (SD)	0.22 (0.53)	0.24 (0.374)	.6
Positive ANA, n (%) ^a	7/31 (22.5)	213/917 (23)	.9
Positive anti-TPO, n (%) ^a	6/15 (40)	149/465 (32)	.5
Positive <i>Strongyloides</i> IgG, n (%) ^a	1/10 (1)	68/633 (10.7)	.9
Positive <i>Toxocara</i> IgG, n (%) ^a	0/3 (0)	5/84 (6)	.66
Positive <i>Trichinella</i> IgG, n (%) ^a	0/4 (0)	2/75 (2.7)	.74
Immunoglobulin levels (mg/dL), mean (SD) ^b			
IgA	122.91 (104.47)	255.96 (158.79)	.01
IgG	1,172 (533.5)	1,287.62 (476.5)	.15
IgM	141.6 (144.7)	107.15 (71.45)	.07
Comorbidities, %			
Malignancy	33	8.7	.001 ^c
SLE	0	0.7	.51
Rheumatoid arthritis	1.6	2.1	.79
Rhinitis	55.6	69.2	.021
Asthma	28.6	47.7	.003

Abbreviations: ANA, antinuclear antibody; Ig, immunoglobulin; SLE, systemic lupus erythematosus; TPO, thyroid peroxidase antibody.

^aPercentage out of number tested.^bIgA level was checked in 38 patients with IgE deficiency and 761 with non-IgE deficiency; IgG level was checked in 38 patients with IgE deficiency and 746 with non-IgE deficiency; and IgM level was checked in 38 patients with IgE deficiency and 751 with non-IgE deficiency.^cOdds ratio (5.51, 95% confidence interval 3.07–9.88) was adjusted for sex, age, and smoking status.

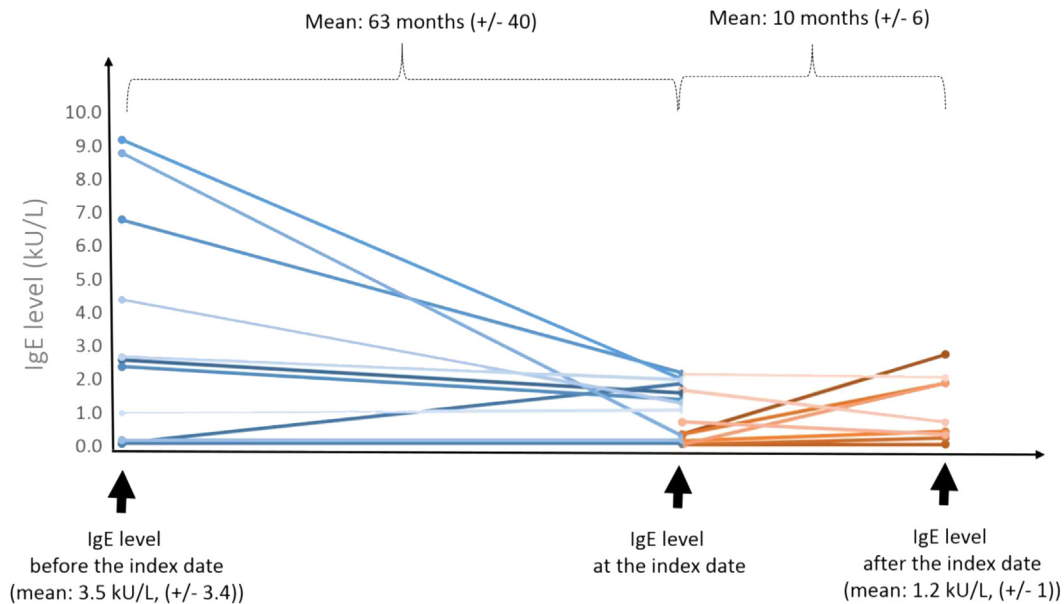


Figure 1. Additional immunoglobulin E (IgE) levels ordered before ($n = 11$) or after ($n = 9$) the index date included in the analysis.

diagnosis and management of primary immunodeficiency.¹⁸ Because of the retrospective nature of our study, laboratory data such as pretreatment immunoglobulin levels, response to vaccination, and lymphocyte subsets were not available for all patients (many patients had been on immunoglobulin replacement therapy for many years; other patients transferred their care from another medical facility while already on immunoglobulin replacement therapy). However, based on information found in the charts, 12 patients were removed from the analysis: 7 patients had mild asymptomatic hypogammaglobulinemia without requiring immunoglobulin supplementation, 1 patient had persistent hypogammaglobulinemia after rituxan infusion, 1 patient had delayed maturation of the immune system, 1 patient had only IgG subclass deficiency, and 2 patients did not have a CVID diagnosis in their charts.

A similar chart review was performed on 40 patients with a CVID diagnosis who did not have IgE levels measured. In total 76 patients with CVID who had IgE levels measured and 25 patients with CVID who did not have IgE levels measured were included in the final analysis. All patients with CVID included in the study were on immunoglobulin replacement therapy.

The presence of comorbid conditions such as bronchiectasis, autoimmunity (eg, autoimmune thrombocytopenia and autoimmune hemolytic anemia), neuropathy, and recurrent infections despite immunoglobulin replacement was noted for all patients with diagnosis of CVID.

Statistical Methods

Descriptive statistics were applied to all variables. Any missing laboratory results were interpreted as “missed data” and this was reflected in the proportion calculations, whereas any missing ICD-9 diagnosis was interpreted as “free of disease.” Continuous variables of nonparametric distribution were described as median and range, and parametrically distributed variables were presented as mean and SD. For the proposed variables, the 2-sample *t* test was performed to compare the mean levels between the 2 groups. The Mann-Whitney *U* test was used to test the null hypothesis that 2 samples of the same laboratory test have the same median or, alternatively, observations in one sample were larger than observations in the other. Multiple regression analyses were used to

calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) adjusted for age, sex, and smoking status. A *P* value less than 0.05 was considered statistically significant. Data were analyzed using Excel 2010 (Microsoft Inc, Redmond, Washington) and SPSS (IBM Corp, Armonk, New York).

Results

Demographics

From January 2010 through November 2015, 2,339 patients had total IgE levels measured and 63 patients (2.7%) were found to have IgE deficiency (<2.5 kU/L). Table 1 presents the demographics of all patients with IgE deficiency and those with non-IgE deficiency included in the analysis. Women were predominant in the 2 groups and Caucasian patients were more prevalent in the IgE deficiency group than in the non-IgE deficiency group. In patients with IgE deficiency, the IgE level had been ordered primarily by allergists (49 of 63, 78%; Table 1). IgE levels also were ordered by pulmonologists (5 of 63, 8%), primary care physicians (3 of 63, 5%), oncologists (3 of 63, 5%), and infectious disease physicians (2 of 63, 3%). To evaluate whether this pattern of ordering IgE levels was similar for patients without IgE deficiency, a chart review of a random sample of 100 patients with non-IgE deficiency showed that total serum IgE also was checked primarily by allergists (76 of 100, 76%), followed by pulmonologists (11 of 100, 11%), primary care physicians (7 of 100, 7%), and oncologists (1 of 100, 1%).

Table 3

Associated Immunodeficiencies in Patients With IgE Deficiency and Patients With Non-IgE Deficiency

	IgE deficiency ($n = 63$)	Non-IgE deficiency ($n = 2,276$)	<i>P</i> value
CVID, n (%)	14 (22)	62 (2.7)	$<.001$
IgM deficiency (<40 mg/dL), n (%) ^a	4/24 (17)	70/689 (10)	.3
IgA deficiency (<10 mg/dL), n (%) ^a	1/24 (4.2)	2/699 (0.3)	.004
T-cell immunodeficiency	3	No data	

Abbreviations: CVID, Common Variable Immunodeficiency; Ig, immunoglobulin.

^aPercentage of patients tested for each immunoglobulin and after excluding patients with diagnosis of CVID.

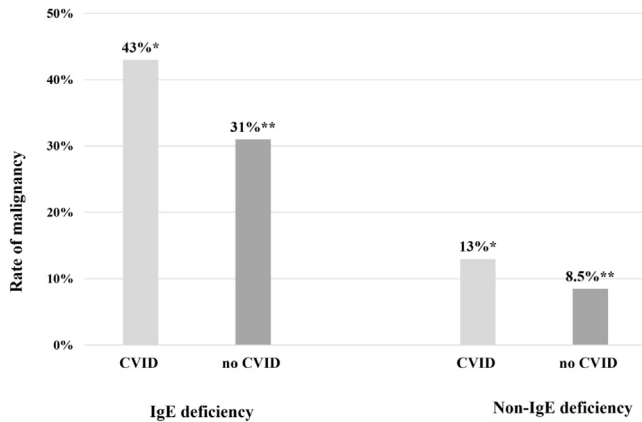


Figure 2. Rate of malignancy in patients with immunoglobulin E (IgE) deficiency and non-IgE deficiency based on Common Variable Immunodeficiency (CVID) diagnosis. *The rate of malignancy in patients with CVID and IgE deficiency ($n = 6$ of 14, 43%) was significantly higher than in patients with CVID and non-IgE deficiency ($n = 8$ of 62, 13%; $P = .009$; odds ratio 10.65, 95% confidence interval 1.79–63.19). **The rate of malignancy in patients with non-CVID and IgE deficiency ($n = 15$ of 49, 31%) was significantly higher than in patients with non-CVID and non-IgE deficiency ($n = 189$ of 2,214, 8.4%; $P = .001$, odds ratio 4.6, 95% confidence interval 2.35–8.97). Odds ratio was adjusted for sex, age, and smoking status.

Twenty patients with IgE deficiency had additional IgE levels measured before ($n = 11$) or after ($n = 9$) the index date included in the analysis. Before the index date, all patients had IgE levels below 10 kU/L and 6 of 11 patients had levels in the deficient range (Fig 1). After the index date, levels in all 9 patients remained below 2.5 kU/L.

Laboratory Characteristics

Laboratory characteristics of patients with IgE deficiency and those with non-IgE deficiency are listed in Table 2. The frequency of positive autoimmunity markers (positive ANA and anti-TPO results) was similar in the 2 groups. Although rates of positive parasite serologic results for each of the parasites included in the analysis appeared to be higher in patients with non-IgE deficiency, the difference was not statistically significant. A stool test for ova and parasites was performed in only a small number of patients with IgE deficiency ($n = 5$), so no analysis was performed using this variable. Patients with IgE deficiency had significantly lower IgA levels compared with those with non-IgE deficiency (122.91 vs 255.96; $P = .010$).

Associated Immunodeficiencies

Of 63 patients with IgE deficiency, 14 (22%) also had a CVID diagnosis compared with only 2.7% of patients (62 of 2,276) in the non-IgE deficiency group ($P < .001$; Table 3). Patients with CVID and IgE deficiency had lower IgE levels (mean 0.45 ± 0.5 kU/L) compared with patients without CVID and with IgE deficiency (mean 1.1 ± 0.7 kU/L; $P = .001$; data not shown). Other associated immunodeficiencies in the IgE deficiency group were IgM deficiency ($n = 4$), IgA deficiency ($n = 1$), and T-cell deficiency ($n = 3$).

Malignancy Rate and Other Associated Comorbidities

A significantly higher rate of malignancy was found in patients with IgE deficiency (21 of 63, 33%) compared with patients with non-IgE deficiency (197 of 2,276, 8.7%; $P < .001$; OR 5.51, 95% CI 3.07–9.88; Table 2). In all 21 patients with IgE deficiency and malignancy, the IgE level had been measured after the diagnosis of

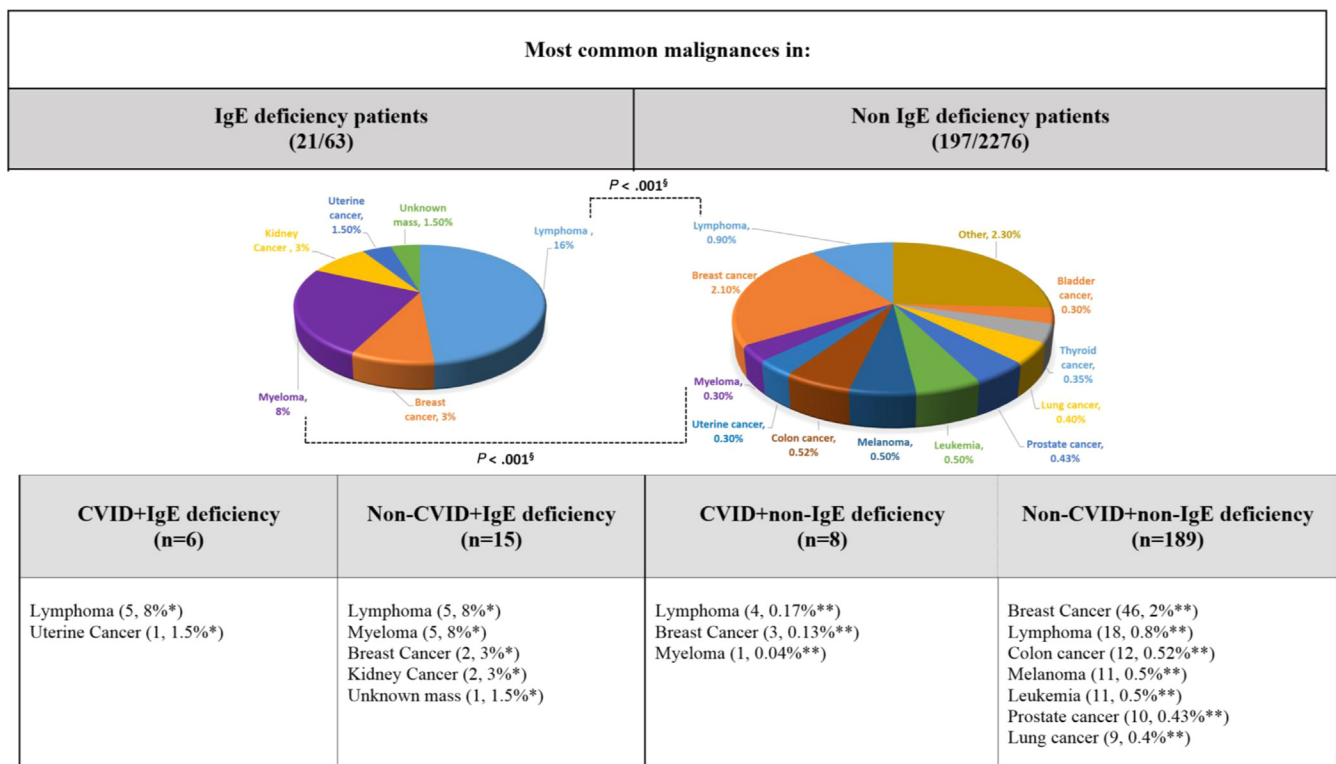


Figure 3. Rates of each type of malignancy in patients with immunoglobulin E (IgE) deficiency and non-IgE deficiency based on Common Variable Immunodeficiency (CVID) diagnosis. *Percentage of total patients with IgE deficiency. **Percentage of total patients with non-IgE deficiency. § Rates of lymphoma and myeloma remained significantly higher in the IgE deficiency group after patients with CVID were excluded. Other cancers were represented by oropharynx cancer, liver cancer, mediastinum cancer, vulvar cancer, testicular cancer, Kaposi sarcoma, brain tumor, bone cancer, orbit cancer, ovarian cancer, squamous cell carcinoma, stomach cancer, parotid cancer, mouth cancer, and tongue cancer.

Table 4

Clinical Characteristics of Patients With CVID With or Without IgE Deficiency

	CVID + IgE deficiency (n = 14)	CVID + no IgE deficiency (n = 62)	P value ^a	CVID, no IgE levels measured (n = 25)	P value ^b
Age (y), mean (SD)	49.71 (16.1)	53.03 (16.5)	.46	55 (15)	.3
Women, %	79	55	.103	68	.482
Race, %					
White	57	53	.791	40	.51
African American	7	0	.03	4	.1
Other or unknown	36	47	.45	56	.12
Autoimmune conditions, % ^c	43	32	.45	20	.128
Bronchiectasis, %	14	10	.61	16	.8
Neuropathy, %	21	16	.63	20	.9
Recurrent infections despite immunoglobulin replacement, %	21	18	.74	28	.65
Malignancy, %	43	13	.009	12	<.001
Immunoglobulin levels before starting replacement therapy, mean (SD) ^d					
IgG	413 (192)	492 (130)	.33	387 (202)	.26
IgA	28 (22)	82 (57)	.02	17 (27)	.79
IgM	33.6 (39)	58 (107)	.4	29 (29)	.21

Abbreviations: CVID, Common Variable Immunodeficiency; Ig, immunoglobulin.

^aCVID + IgE deficiency vs CVID + no IgE deficiency.^bCVID + IgE deficiency vs CVID and no IgE level performed.^cAutoimmune thrombocytopenia and autoimmune hemolytic anemia.^dInformation about pretreatment immunoglobulin levels were found in 7 patients from the CVID + IgE deficiency group, 24 patients from the CVID + no IgE deficiency group; and 10 patients from the CVID group in whom IgE level was not obtained.

neoplasm was made (mean 5.24 ± 3.68 years after cancer diagnosis). In 9 patients for whom there was information about the timing of the last chemotherapy and IgE testing, a mean of 8 ± 10 years elapsed between the 2 time points. One patient was on chemotherapy when the IgE level was checked.

We also reviewed the charts of a random sample of 100 patients with normal IgE levels and found that only 7 of 100 (7%) had a diagnosis of malignancy (data not shown). In 6 patients, the IgE levels were checked after diagnosis of malignancy was made (mean 7.3 ± 6.6 years). In 1 patient, the IgE level was measured 3 years before the diagnosis of multiple myeloma was made (178 kU/L).

In contrast, patients with non-IgE deficiency had higher rates of rhinitis and asthma diagnoses compared with those with IgE deficiency.

Rate of Malignancy in Patients With IgE Deficiency and Those With Non-IgE Deficiency Based on CVID Diagnosis

We found 14 patients with CVID and IgE deficiency and 62 with CVID and normal IgE levels.

Of the 14 patients with CVID and IgE deficiency, 6 (43%) had a diagnosis of malignancy compared with only 8 of 62 (13%) of those with CVID and no IgE deficiency ($P = .009$; OR 10.65, 95% CI 1.79–63.19; Fig 2). When excluding patients with CVID, the rate of cancer diagnosis remained increased in the IgE deficiency group (15 of 49, 31%) compared with the non-IgE deficiency group (189 of 2,214, 8.4%; $P = .001$, OR 4.6, 95% CI 2.35–8.97). The most common malignancy diagnoses in each subgroup are presented in Figure 3. Lymphoma and multiple myeloma were the most prevalent malignancies in patients with IgE deficiency.

Because patients with CVID and IgE deficiency were found to have a higher frequency of malignancy than patients with CVID without IgE deficiency, a chart review of all 76 patients with CVID was performed to evaluate whether the former group was sicker overall than the latter (Table 4). Patients with CVID and IgE deficiency did not have more severe disease (based on the presence of autoimmune conditions, bronchiectasis, neuropathy, and recurrent infections despite immunoglobulin replacement) compared with patients with CVID without IgE deficiency. However, pretreatment levels of IgA were lower in the CVID and IgE deficiency group.

As a comparison group, we reviewed the charts of 25 patients with CVID who did not have IgE levels measured. The demographic and clinical characteristics of patients with CVID with and without IgE deficiency were similar (Table 4). However, the rate of malignancy diagnosis was similar in patients with CVID without IgE deficiency (13%) and this comparison group (12%), but was significantly higher in patients with CVID and IgE deficiency (43%).

Data regarding the pre-immunoglobulin replacement therapy response to pneumococcal capsular polysaccharide vaccination were available for 21 patients with CVID (3 patients in CVID with IgE deficiency group and 18 in CVID without IgE deficiency group). All had an impaired response (concentration $>1.3 \mu\text{g/mL}$ in $<50\%$ of serotypes; data not shown).

Rate of Overall Malignancy Based on IgE Level

All patients included in the study were divided into 4 subgroups based on their IgE level (<2.5 [deficiency], 2.5–100, 100–1,000, and $\geq 1,000$ kU/L). The rate of malignancy diagnosis was the highest in patients with IgE deficiency but was significantly lower in all the other IgE groups (Fig 4). The malignancy rate was the same in patients with normal, high, or very high IgE levels.

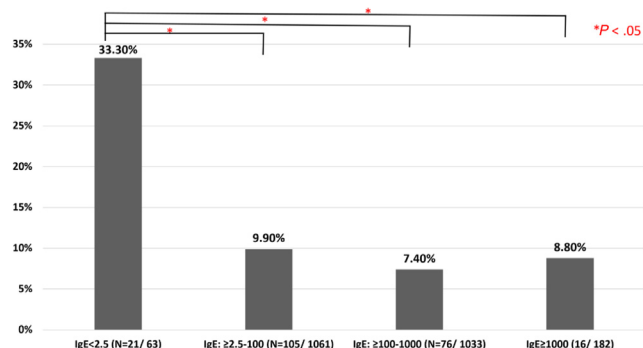


Figure 4. Proportion of malignancy in 4 subgroups of patients based on total serum immunoglobulin E (IgE) levels. N indicates number of patients diagnosed with malignancy divided by the total number of patients in each group.

Discussion

The objective of this study was to evaluate any clinical and laboratory differences between IgE deficiency and non-IgE deficiency based on CVID diagnosis.

We found a higher prevalence of overall malignancy in patients with IgE deficiency (33%, 21 of 63) compared with patients with IgE levels of at least 2.5 kU/L (8.6%, 197 of 2,276). Lymphoma and multiple myeloma were the most prevalent neoplasms in patients with very low IgE levels. Further sub-analysis showed that the higher prevalence of malignancy in patients with IgE deficiency was not due to an associated CVID diagnosis. Similarly, the risk of having a diagnosis of malignancy in patients with CVID was significantly higher in the IgE deficiency group compared with the non-IgE deficiency group, despite similar clinical characteristics.

Overall, the rate of malignancy in these patients with CVID was 18% (14 of 76), similar to what is reported in the literature.^{12–17} Although patients with CVID have a high rate of malignancy, the exact mechanism predisposing to cancer is not understood. Factors such as genetics, immune dysregulation, and chronic infections can increase susceptibility to malignancy in this population.^{19–21} In previous studies, inconsistent results have been reported for the link among atopy, IgE levels, and neoplasia in the general population.^{2,6–11} Data on any association between IgE levels and malignancy in patients with CVID are lacking. In our study, the rate of any type of malignancy was much higher in patients with CVID and associated IgE deficiency (43%, 6 of 14) compared with the rate of malignancy in patients with CVID and normal IgE levels (13%, 8 of 62; $P = .009$). Because of the retrospective nature of our study, we do not have information on all patients regarding immunoglobulin levels, response to vaccination, and lymphocyte subsets before immunoglobulin replacement therapy was initiated. These laboratory data would have been very helpful for characterizing the CVID phenotypes¹⁸ and for better evaluating any possible association among the severity of CVID, low IgE levels, and rates of cancer diagnosis. However, patients with CVID with and without IgE deficiency had similar clinical manifestations based on the presence of bronchiectasis, autoimmunity, neuropathy, and recurrent infections despite immunoglobulin replacement. Moreover, there was no difference in clinical presentation between patients with CVID and IgE deficiency and those with CVID who did not have IgE levels measured, except for the higher rate of malignancy diagnosis in the former group.

A prospective European study that enrolled 1,021 incident cases of B-cell non-Hodgkin lymphoma (diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia) and multiple myeloma and 1,021 matched controls with a mean follow-up time of 7 years found significantly lower prediagnostic total IgE levels (<20 kU/L) among chronic lymphocytic leukemia and multiple myeloma cases compared with matched controls.¹¹ In the same study, 40.4% of chronic lymphocytic leukemia cases diagnosed 3 years before and 16.3% of those diagnosed at least 5 years after the baseline total IgE was checked had IgE levels below the 10th percentile of control subjects.

One weakness of our study is that IgE levels were measured several years after the malignancy diagnosis and we do not have information about IgE levels before the cancer diagnosis. Another limitation is that IgE levels were measured mainly by allergy and immunology physicians and were not ordered as frequently by other subspecialists (selection bias). Nevertheless, very low IgE levels in these patients with a remote history of malignancy (who were not on chemotherapy at the time of IgE collection, which might have lowered IgE levels) suggest persistent immune dysregulation. It is not clear whether the immune dysregulation preceded the malignancy diagnosis and persisted or whether it developed after the malignancy.

Most large epidemiologic studies focusing on the link between IgE levels and malignancy risk are from European sites.^{6–11} However, one study explored cancer mortality in an 18 year-prospective cohort analysis of 1,102,247 US men and women who were free of cancer at baseline and found an inverse association between self-reported history of asthma and hay fever and overall cancer mortality.²² Unfortunately, IgE levels were not measured in this study. In our population, we found that the overall rate of malignancy was significantly higher in patients with IgE deficiency compared with those with IgE levels of at least 2.5 kU/L. In fact, the rate of malignancy was similar in subgroups of patients with normal (2.5–100 kU/L), high (100–1,000 kU/L), or very high ($\geq 1,000$ kU/L) IgE levels.

Although the role of IgE in tumor surveillance in humans is not completely understood, there are some experimental findings relevant to this question. IgE antibodies have been implicated in antibody-dependent cytotoxicity against tumor antigens in pancreatic²³ and ovarian²⁴ cancers. Interestingly, the effect of IgE-mediated cytotoxicity against pancreatic cancer cells was reversed by anti-IgE neutralizing antibody and IgE depletion.²³ In a nude-mouse model of ovarian cancer, injection of tumor-bearing mice with a chimeric IgE antibody against the folic acid receptor led to infiltration of monocytes into the tumors and prolonged survival of the mice.²⁴ Also, a potential antiprostata-specific antigen IgE was found to have in vitro antitumor protection against prostate cancer.²⁵ These findings suggest a role for IgE antibodies in fighting malignancies, although the exact mechanisms of IgE anti-tumor protection are not completely understood. It also has been suggested that persons with a history of atopic disorders might have enhanced immune function. Case-control studies have found that patients with asthma have significantly stronger natural killer cell activity against the leukemic cell line K-562²⁶ and patients with total serum IgE levels lower than 10 IU/mL have significantly weaker natural killer cell activity compared with those with IgE levels higher than 400 IU/mL.²⁷

In conclusion, we found that the rate of prior malignancy was higher in patients with IgE deficiency compared with patients with normal, high, or very high IgE levels. In our study, patients with IgE deficiency and CVID had higher frequency of prior malignancy compared with patients with CVID and normal IgE levels, but those with IgE deficiency had a higher frequency of malignancy even in the absence of CVID. We acknowledge the fact that unknown factors are contributing to the malignancy occurrence and that in our cohort the IgE levels were checked after the malignancy diagnosis was made. However, the results of this study, which are corroborated by previous findings,^{2,9–11,24,25} indicate a possible association of very low IgE levels with the development of neoplasia.

Prospective studies of patients with IgE deficiency with and without CVID are necessary to further document and evaluate the association between very low IgE levels and malignancy.

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