

# Increased Malignancy Rate in Children With IgE Deficiency: A Single-center Experience

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**Background:** Immunoglobulin (Ig) E-deficient adults ( $\text{IgE} < 2.5 \text{ kU/L}$ ) have increased susceptibility for developing malignancy. We evaluated the association between IgE deficiency and cancer diagnosis in children (age younger than 18 y), compared with those non-IgE-deficient ( $\text{IgE} \geq 2.5 \text{ kU/L}$ ).

**Materials and Methods:** Information about malignancy diagnosis were compared between 4 cohorts of children who had IgE levels measured at our institution: IgE-deficient ( $\text{IgE} < 2.5 \text{ kU/L}$ ), normal IgE ( $2.5 < \text{IgE} \leq 100 \text{ kU/L}$ ), high IgE ( $100 \leq \text{IgE} < 1000 \text{ kU/L}$ ), very high IgE ( $\text{IgE} \geq 1000 \text{ kU/L}$ ).

**Results:** Overall, 94/4586 (2%) children had IgE deficiency. A significantly higher malignancy rate was found in IgE-deficient children (3/94, 3.2%) compared with non-IgE-deficient cohort (13/4492, 0.3%,  $P < 0.0001$ ). Analysis of the groups with different IgE levels revealed a significantly higher rate of cancer in IgE-deficient children (3.2%) compared with those with normal (0.5%; odds ratio [OR] = 7.84; 95% confidence interval [CI]: 1.94–31.61,  $P = 0.004$ ), high (0.2%; OR = 25.80; 95% CI: 4.94–134.54,  $P = 0.002$ ), and very high IgE levels (0.2%; OR = 42.17; 95% CI: 3.84–463.02,  $P < 0.0001$ ). All 3 IgE-deficient children had lymphoma. Malignancies in the other groups included lymphoma, leukemia, brain, liver, ovarian cancers.

**Conclusions:** Malignancy rate was higher in IgE-deficient children compared with those with normal, high, or very high IgE levels, supporting the hypothesis that IgE deficiency may be a marker for malignancy susceptibility in children. Larger, prospective studies are necessary to further evaluate this association.

**Key Words:** IgE deficiency, children, malignancy

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Although immunoglobulin (Ig) E is known to be primarily responsible for allergic disorders and for protection against parasites,<sup>1</sup> an accumulating body of evidence indicates that IgE is also involved in tumor surveillance.<sup>2–4</sup> Earlier epidemiological studies showed that the presence of an allergic disorder (eg, hay fever or asthma) was inversely associated with a cancer diagnosis<sup>5–9</sup> and more recent studies found that higher IgE levels (a signature of an increased allergic state) conferred protection from several types of malignancy, including chronic lymphocytic leukemia, multiple myeloma,<sup>10</sup>

or glioma.<sup>11</sup> Other studies showed that IgE levels  $> 100 \text{ kU/L}$  were associated with higher rates of survival in patients with multiple myeloma<sup>12</sup> and glioma.<sup>13</sup> The antitumor role of IgE is mediated through several different immunologic mechanisms including antibody-dependent mediated cytotoxicity, antibody-dependent mediated phagocytosis, and IgE-mediated cross-presentation of the tumor antigens by dendritic cells, resulting in generation of cytotoxic CD8<sup>+</sup> T lymphocytes.<sup>2–4</sup>

Consistent with the important role of IgE in protecting against malignancy development is the converse finding that IgE-deficient individuals have increased susceptibility to developing a malignancy. This has been shown in several retrospective studies<sup>14–16</sup> and 1 longitudinal/prospective<sup>17</sup> study of IgE-deficient individuals. However, most of these studies involved adults, and relatively little is known about the association between very low IgE levels and malignancy in children. One retrospective, matched case-control study describing 216 children and adults with IgE deficiency (defined as  $\text{IgE} < 2 \text{ kIU/L}$ ), found that IgE-deficient individuals age 12 years and older had a higher rate of malignancy diagnosis (11%) compared with those with  $\text{IgE} > 2 \text{ kIU/L}$  (1.5%,  $P < 0.001$ ).<sup>16</sup> However, the number of children (vs. adults) included in the study is unknown. The goal of the present study was to evaluate the association between IgE deficiency ( $\text{IgE} < 2.5 \text{ kU/mL}$ ) and malignancy diagnosis in children (age younger than 18 y) compared with those with non-IgE deficiency ( $\text{IgE} \geq 2.5 \text{ kU/mL}$ ).

## MATERIALS AND METHODS

### Subjects

This was a retrospective study approved by the Institutional Board Review of Albert Einstein College of Medicine in Bronx, NY. We utilized Clinical Looking Glass (a software tool that stores and analyzes electronic health record data) to identify children (age younger than 18 y) who had IgE levels measured (Phadia, Uppsala, Sweden) at Montefiore Medical Center between 2014 and 2017. Children who had IgE levels  $< 2.5 \text{ kU/L}$  comprised the IgE deficiency group. Non-IgE-deficient patients ( $\text{IgE} \geq 2.5 \text{ kU/L}$ ) were divided into 3 groups based on the total IgE level: normal IgE levels ( $2.5 < \text{IgE} \leq 100 \text{ kU/L}$ ); high IgE levels ( $100 \leq \text{IgE} < 1000 \text{ kU/L}$ ); and very high IgE levels (total  $\text{IgE} \geq 1000 \text{ kU/L}$ ). These cutoff levels were chosen based on prior studies performed in adult populations.<sup>14,15,17</sup>

For all patients included in the study, information about demographics (race, sex, age), quantitative Ig levels (IgA, IgM, and IgG), absolute eosinophil counts, International Classification of Diseases, Ninth or 10th Revision (ICD-9/10) diagnoses of common variable immunodeficiency (CVID), autoimmunity (systemic lupus erythematosus or rheumatoid arthritis), asthma, rhinitis, and any type of malignancy were also identified through Clinical

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Looking Glass. In addition, a manual chart review was performed for all patients with IgE deficiency and all patients with malignancy.

## Statistics

Data were analyzed using SPSS, version 24 (IBM Corp., Armonk, NY). Any missing laboratory results were interpreted as “missed data” and this was reflected in the proportion calculations, while any missing ICD-9/10 diagnoses were interpreted as “free of disease.” We used the 2-sample *t* test to compare the mean levels between 2 groups, while the Mann-Whitney *U* test was used to compare whether observations in 1 sample were larger than observations in the other. When we compared the median IgE levels between children with malignancy and children with no malignancy, an IgE level < 2 kU/L was coded as 1.99 kU/L for analysis purposes. We used binary logistic regression to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate for any associations between diagnosis of malignancy and total IgE level. Age, sex, and race were the variables with a tendency towards an association with a diagnosis of malignancy ( $P < 0.25$ ), so they were included into the final logistic regression model. A *P*-value < 0.05 was considered to be statistically significant.

## RESULTS

### Characteristics of Children Included in the Study

Between 2014 and 2017, IgE levels were measured in 4586 children and 94 (2%) had an IgE deficiency (IgE < 2.5 kU/L). The IgE-deficient group was younger compared with the non-IgE-deficient cohort ( $4.2 \pm 4.05$  vs.  $7.3 \pm 4.5$  y,  $P < 0.01$ ) and included more white children (10.6% vs. 4.4%,  $P = 0.04$ ) (Table 1). There were no significant differences in sex between the 2 groups.

To better characterize the cohort of children with IgE deficiency, we performed a chart review to evaluate what medical specialties ordered the IgE levels, as well as the reason for the test. In the IgE deficiency group, IgE levels had been ordered primarily by allergists (49.5%) and pulmonologists (20.4%) for evaluation of environmental allergies. This ordering pattern was similar to the non-IgE-deficient patients (Table 1).

Children with IgE deficiency had significantly lower levels of other Igs (IgG, IgA, and IgM) compared with non-IgE-deficient individuals, as well as lower absolute eosinophil counts. Rates of diagnoses of asthma and CVID were higher, while the rate of rhinitis was lower in IgE-deficient patients compared with those without IgE deficiency (Table 1).

### Children With IgE Deficiency Have Higher Rates of a Malignancy Diagnosis Compared With Non-IgE-deficient Patients

Overall, 16/4586 (0.35%) children had a diagnosis of malignancy. A significantly higher rate of malignancy diagnosis was found in patients with IgE deficiency (3/94, 3.2%) compared with non-IgE-deficient children (13/4492, 0.3%,  $P < 0.0001$ ) (Table 1).

The analysis of the groups with different IgE levels revealed a significantly higher rate of any type of malignancy in the IgE-deficient children (3/94, 3.2%) compared with those with normal (8/1775, 0.5%; OR = 7.84; 95% CI: 1.94–31.61,  $P = 0.004$ ), high (4/2059, 0.2%; OR = 25.80; 95% CI: 4.94–134.54,  $P = 0.002$ ), or very high IgE levels (1/658,

**TABLE 1.** Characteristics of IgE-deficient and Non-IgE-deficient Children Included in the Study

|                                                            | <b>IgE<br/>Deficiency<br/>(N = 94)</b> | <b>Non-IgE<br/>Deficiency<br/>(N = 4492)</b> | <b>P</b>           |
|------------------------------------------------------------|----------------------------------------|----------------------------------------------|--------------------|
| Age, mean (SD) (y)                                         | <b>4.194 (4.05)</b>                    | <b>7.31 (4.57)</b>                           | <b>&lt; 0.01</b>   |
| Female, n (%)                                              | 42 (44.7)                              | 2044 (45.5)                                  | 0.874              |
| Race (%)                                                   |                                        |                                              |                    |
| White                                                      | <b>10.6</b>                            | <b>4.4</b>                                   | <b>0.04</b>        |
| African American                                           | 20.2                                   | 24.6                                         | 0.325              |
| Hispanic                                                   | 37.2                                   | 38.8                                         | 0.758              |
| Other/unknown                                              | 31.9                                   | 32.1                                         | 0.416              |
| Ordering disposition of IgE level by medical specialty (%) |                                        |                                              |                    |
| Allergy and immunology                                     | 49.5                                   | 53.5*                                        | 0.67               |
| Pulmonology                                                | 20.4                                   | 27.3*                                        | 0.26               |
| Primary care                                               | 8.6                                    | 1*                                           | 0.03               |
| Inpatient                                                  | 6.5                                    | 7.1*                                         | 0.86               |
| Hematology                                                 | 1.1                                    | 0*                                           | 0.3                |
| Gastroenterology                                           | 10.8                                   | 4*                                           | 0.07               |
| Other/unknown                                              | 3.2                                    | 7*                                           | 0.23               |
| Laboratory results†                                        |                                        |                                              |                    |
| AEC, mean (SD) (cells/μL)                                  | <b>0.21 (0.27)</b>                     | <b>0.36 (0.49)</b>                           | <b>0.006</b>       |
| Immunoglobulin levels, mean (SD) (mg/dL)                   |                                        |                                              |                    |
| IgA                                                        | <b>83.7 (89.21)</b>                    | <b>139.24 (88.35)</b>                        | <b>&lt; 0.001</b>  |
| IgM                                                        | <b>85.75 (54.64)</b>                   | <b>108.89 (52.35)</b>                        | <b>0.014</b>       |
| IgG                                                        | <b>810.05 (413.60)</b>                 | <b>1116.46 (437.38)</b>                      | <b>&lt; 0.001</b>  |
| Associated comorbidities, n (%)                            |                                        |                                              |                    |
| Malignancy                                                 | <b>3 (3.2)</b>                         | <b>13 (0.3)</b>                              | <b>&lt; 0.0001</b> |
| Asthma                                                     | <b>70 (74.5)</b>                       | <b>2763 (61.5)</b>                           | <b>0.011</b>       |
| CVID                                                       | <b>2 (2.1)</b>                         | <b>12 (0.3)</b>                              | <b>0.001</b>       |
| Rheumatoid arthritis                                       | 0 (0)                                  | 2 (0)                                        | 0.838              |
| Rhinitis                                                   | <b>34 (36.2)</b>                       | <b>2843 (63.3)</b>                           | <b>&lt; 0.001</b>  |
| SLE                                                        | 0 (0)                                  | 5 (0.1)                                      | 0.746              |

Bold values indicate statistically significant ( $P < 0.05$ ).

\*Random sample of 100 non-IgE-deficient children.

†AEC was checked in 79 patients with IgE deficiency and 3370 patients with non-IgE deficiency; IgA level was checked in 41 patients with IgE deficiency and 798 with non-IgE deficiency; IgG level was checked in 34 patients with IgE deficiency and 530 patients with non-IgE deficiency; IgM level was checked in 33 patients with IgE deficiency and 506 patients with non-IgE deficiency.

AEC indicates absolute eosinophil count; CVID, common variable immunodeficiency; Ig, immunoglobulin; SLE, systemic lupus erythematosus.

0.2%; OR = 42.17; 95% CI: 3.84–463.02,  $P < 0.0001$ ) (Fig. 1). There was no difference in the rate of malignancy between children with normal, high, and very high IgE levels. None of the children with malignancy were on omalizumab (a monoclonal antibody used for the treatment of asthma and chronic idiopathic urticaria that binds free IgE) for which initial studies showed a numeric imbalance in malignancies in patients who received omalizumab (data not shown).<sup>18–20</sup>

### Characteristics of Children With IgE Deficiency and Malignancy

Table 2 shows the characteristics of children with malignancy. There was no difference between the 4 groups in age, race, or sex at the time of malignancy diagnosis. It is known that patients with CVID have higher rates of malignancy<sup>21</sup> and that very low IgE levels are found with high frequency in CVID individuals.<sup>22</sup> However, none of the children with a malignancy diagnosis in any of the groups carried a diagnosis of CVID. A subanalysis showed that the

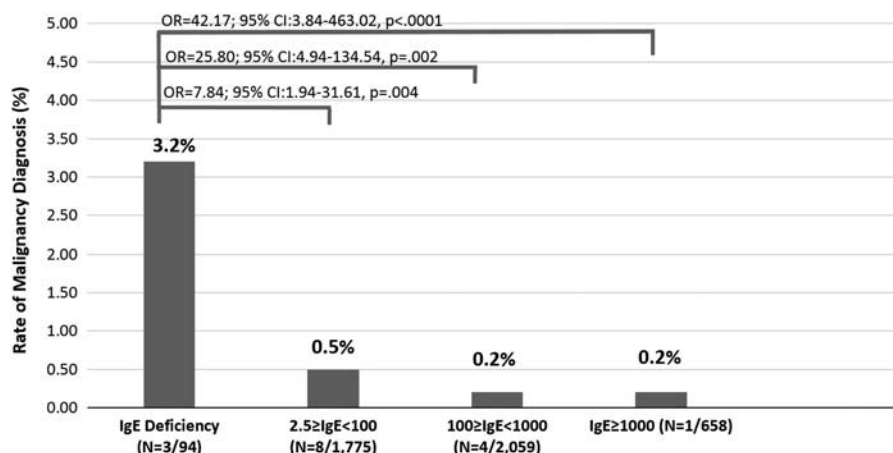


**FIGURE 1.** The rate of malignancy based on different IgE levels. CI indicates confidence interval; Ig, immunoglobulin; OR, odds ratio.

median IgE levels in the 16 patients with malignancy (42.5 kU/L, range: <2 to 3709 kU/L) was significantly lower than median IgE levels in children with no malignancy (324.2 kU/L, range: <2 to 5000 kU/L) (data not shown).

All 3 children with IgE deficiency and malignancy had lymphoma (100%) (2 children had diffuse large B-cell lymphoma, while in 1 patient, the type of lymphoma is unknown). Overall, the prevalence of lymphoma was significantly higher in IgE-deficient patients than in those with normal, high, and very high IgE levels (Table 2). Malignancies in the other IgE groups were varied and included lymphoma, leukemia, brain tumors, liver, and ovarian cancers.

A chart review was performed for all children with a malignancy diagnosis (N=16) to evaluate the relationship between IgE collection time and malignancy diagnosis. The majority of patients (14/16, 87.5%) had IgE levels checked after the malignancy diagnosis was made. On average, 20 ± 32 months elapsed between the diagnosis of malignancy and IgE collection time in IgE-deficient children, which was similar to the other groups (26 ± 36 mo in children with normal IgE levels, 2.5 ± 31 mo in those with high IgE levels, and 65 mo for the child with very high IgE levels,  $P > 0.5$ ).

Since the malignancy itself and the chemotherapeutic agents received as treatment for cancer may potentially affect the total IgE levels, we analyzed what cancer treatments the patients were on at the time of the IgE collection. Overall, 7/16 (43%) were on some type of chemotherapy at the time of IgE collection: 2/3 (66%) IgE-deficient patients, 3/8 (37.5%) children with normal IgE levels, and 2/4 (50%) children with high IgE levels.

## DISCUSSION

To the best of our knowledge, this is the first study evaluating the association between different IgE levels, IgE deficiency and the prevalence of malignancy in children. Our results indicate that the rate of malignancy diagnosis in children with IgE deficiency was 3.2%, a rate that was significantly higher than those with normal (0.5%), high (0.2%), or very high IgE levels (0.2%). These findings are similar to those reported in IgE-deficient adults<sup>14-16</sup> and serve to support the hypothesis that IgE is involved in tumor immune surveillance. Very low or absent IgE titers may be a risk factor for the development of malignancy both in children as well as adults.

In this study, all 3 IgE-deficient children with a diagnosis of malignancy had lymphoma. This finding is consistent with other previously published studies that demonstrated an inverse association between elevated IgE levels and lymphoma incidence. One study evaluating the association between prediagnostic total serum IgE levels and lymphoma risk showed that patients with intermediate (20 to 100 kU/L) and high (> 100 kU/L) total IgE levels had a lower risk of developing lymphoid neoplasms, compared with those with total IgE levels <20 kU/L.<sup>23</sup> Similarly, another case-control study found that the overall risk of lymphoma was significantly lower in patients with IgE levels in the high and middle tertiles, compared with those in the lowest tertile.<sup>24</sup> Another study evaluating the levels of IgG subclasses, IgA, IgM and IgE in patients with lymphoma and controls, found that IgG4 and IgE were lowest in patients with malignancy and that 37% of patients with B-cell non-Hodgkin lymphomas had IgE levels below the limit of detection (<5 IU/mL for the method used in that study), compared with 10% of control subjects ( $P < 0.0001$ ).<sup>25</sup> The same high rate of lymphoma diagnosis was also reported in adults with IgE deficiency compared with non-IgE-deficient individuals.<sup>14,16</sup> Interestingly, patient survival was significantly better in those with lymphomas that expressed the low-affinity IgE receptor, CD23, compared with patients with CD23-negative lymphomas,<sup>26,27</sup> suggesting that IgE binding to tumor cells might be involved in tumor inhibition or killing. We could not assess if there is any difference in malignancy outcomes in our cohort due to the small number of children included in the study. However, prospective studies on larger cohorts of patients with cancer and different IgE levels should help determine if there is any association between malignancy outcomes based on the IgE levels.

It is known that patients with CVID have a higher rate of lymphoma diagnosis,<sup>21</sup> and one recent study reported that IgE deficiency was a specific marker for CVID if there was a suspicion for primary humoral immunodeficiency.<sup>22</sup> It was, therefore, possible that the increased incidence of lymphoma found in our study was due to underlying CVID and not only to IgE deficiency. However, our analysis indicated that none of the children with a malignancy diagnosis in any of the IgE categories had associated CVID. More studies are necessary to evaluate the mechanisms of IgE deficiency. At this time, it is not known if IgE-deficient patients have very low IgE levels as part of an affected

**TABLE 2.** Characteristics of Children With Malignancy

|                                                                         | IgE Deficiency (N = 3)                                                                                                                                                         | 2.5 ≥ IgE < 100 (N = 8)                                                                                                                                                                                                                                                                                              | 100 ≥ IgE < 1000 (N = 4)                                                                                                                                                                                                | IgE ≥ 1000 (N = 1)                                                       |
|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Age at time of IgE collection, mean (SD) (y)                            | 8.40 (7.00)                                                                                                                                                                    | 7.77 (5.51)                                                                                                                                                                                                                                                                                                          | 8.5 (3.11)                                                                                                                                                                                                              | 17.0 (NA)                                                                |
| Age at time of malignancy diagnosis, mean (SD) (y)                      | 6.67 (8.08)                                                                                                                                                                    | 6.0 (5.26)                                                                                                                                                                                                                                                                                                           | 5.50 (2.65)                                                                                                                                                                                                             | 11.0 (NA)                                                                |
| Female, n (%)                                                           | 2 (66.7)                                                                                                                                                                       | 3 (37.5)                                                                                                                                                                                                                                                                                                             | 2 (50.0)                                                                                                                                                                                                                | 1 (100.0)                                                                |
| Race, n (%)                                                             |                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                         |                                                                          |
| White                                                                   | 1 (33.3)                                                                                                                                                                       | 2 (25.0)                                                                                                                                                                                                                                                                                                             | 2 (12.5)                                                                                                                                                                                                                | 0 (0)                                                                    |
| African American                                                        | 0 (0)                                                                                                                                                                          | 1 (12.5)                                                                                                                                                                                                                                                                                                             | 3 (18.8)                                                                                                                                                                                                                | 0 (0)                                                                    |
| Hispanic                                                                | 1 (33.3)                                                                                                                                                                       | 0 (30)                                                                                                                                                                                                                                                                                                               | 7 (43.8)                                                                                                                                                                                                                | 0 (0)                                                                    |
| Unknown/other                                                           | 1 (33.3)                                                                                                                                                                       | 3 (37.5)                                                                                                                                                                                                                                                                                                             | 4 (25)                                                                                                                                                                                                                  | 1 (100.0)                                                                |
| Laboratory results†                                                     |                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                         |                                                                          |
| AEC, mean (SD) (cells/μL)                                               | 0.2 (0.10)                                                                                                                                                                     | 0.26 (0.22)                                                                                                                                                                                                                                                                                                          | 0.23 (0.26)                                                                                                                                                                                                             | 0.5 (NA)                                                                 |
| Immunoglobulin levels, mean (SD) (mg/dL)                                |                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                         |                                                                          |
| IgA                                                                     | 72.5 (51.0)                                                                                                                                                                    | 181.00 (166.1)                                                                                                                                                                                                                                                                                                       | 96.7 (0)                                                                                                                                                                                                                | 321.00 (NA)                                                              |
| IgM                                                                     | 64.10 (23.4)                                                                                                                                                                   | 69.6 (56.0)                                                                                                                                                                                                                                                                                                          | 93.9 (0)                                                                                                                                                                                                                | 103.00 (NA)                                                              |
| IgG                                                                     | 651.00 (326.23)                                                                                                                                                                | 1374.6 (1163.1)                                                                                                                                                                                                                                                                                                      | NA                                                                                                                                                                                                                      | 2470.00 (NA)                                                             |
| CVID diagnosis, n (%)                                                   | 0 (0)                                                                                                                                                                          | 0 (0)                                                                                                                                                                                                                                                                                                                | 0 (0)                                                                                                                                                                                                                   | 0 (0)                                                                    |
| Time between IgE collection and diagnosis of malignancy, mean (SD) (mo) | 20 (32)                                                                                                                                                                        | 26 (36)                                                                                                                                                                                                                                                                                                              | 2.5 (31)                                                                                                                                                                                                                | 65 (NA)                                                                  |
| IgE level checked after malignancy diagnosis, n (%)                     | 2 (66.7)                                                                                                                                                                       | 7 (87.5)                                                                                                                                                                                                                                                                                                             | 4 (100.0)                                                                                                                                                                                                               | 1 (100.0)                                                                |
| Type of malignancy                                                      | Lymphoma (n = 3)*‡                                                                                                                                                             | Brain cancer (n = 3)<br>Leukemia (n = 2)<br>Liver cancer (n = 1)<br>Lymphoma (n = 1)*‡<br>Ovarian cancer (n = 1)                                                                                                                                                                                                     | Brain cancer (n = 2)<br>Leukemia (n = 1)<br>Lymphoma (n = 1)*‡                                                                                                                                                          | Liver cancer (n = 1)<br>Lymphoma (n = 0)*‡ (in the same patient)         |
| Chemotherapy status in relation to IgE collection time                  | 1 patient was not on any chemotherapeutics at the time of IgE collection<br>1 patient was on tacrolimus and mycophenolate mofetil<br>1 patient was on rapamycin and prednisone | 5 patients were not on any chemotherapeutics at the time of IgE collection<br>1 patient was on vincristine and carboplatin<br>1 patient was on methotrexate, dexamethasone, and mercaptopurine<br>1 patient was on CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone).<br>3 y prior, received rituximab | 2 patients were not on any chemotherapeutics at the time of IgE collection<br>1 patient was on vinblastine and prednisone at the time of IgE collection<br>1 patient was on dexamethasone at the time of IgE collection | 1 patient was not on any chemotherapeutics at the time of IgE collection |

†Eosinophil count was measured in 3 patients in IgE deficiency, 7 patients in 2.5 ≥ IgE < 100, 4 patients in 100 ≥ IgE < 1000; and 1 patients in IgE ≥ 1000; IgM level was measured in 3 patients in IgE deficiency, 4 patients in 2.5 ≥ IgE < 100, 1 patient in 100 ≥ IgE < 1000, 1 patient in IgE ≥ 1000; IgA level was measured in 3 patients in IgE deficiency, 6 patients in 2.5 ≥ IgE < 100, 1 patient in 100 ≥ IgE < 1000, and 1 patient in IgE ≥ 1000; IgG level was measured in 3 patients in IgE deficiency, 5 patients in 2.5 ≥ IgE < 100, 0 patients in 100 ≥ IgE < 1000, and 1 patient in IgE ≥ 1000.

‡IgE deficiency: diffuse large B-cell lymphoma, n = 2; unspecified = 1; normal IgE level: diffuse large B-cell lymphoma; high and very high IgE levels—the type of lymphoma is not specified.

AEC indicates absolute eosinophil count, CVID; common variable immunodeficiency, NA; not available.

\*P < 0.05.

immunomodulatory pathway which subsequently may result in higher rates and risk of malignancy, or if the very low serum IgE levels are a consequence of the malignancy.

One limitation of our study is that 2/3 children with IgE deficiency and malignancy had their IgE levels measured after the cancer diagnosis was made, making it difficult to distinguish if the very low IgE levels were caused by chemotherapy or if the IgE deficiency preceded the malignancy diagnosis. However, chart review of all children with a diagnosis of malignancy, indicated that the majority of patients (14/16, 87.5%) had their IgE levels checked after the diagnosis of malignancy was made, and 11 of these 14 children had normal IgE levels. Many of these children received chemotherapy treatment (Table 2) suggesting that chemotherapy itself does not cause IgE deficiency. At the time of IgE collection, 1 child with IgE deficiency was on tacrolimus and mycophenolate mophetil (MMF), while another patient was on rapamycin and prednisone.

There have been a number of small studies investigating the effect of chemotherapeutic drugs on IgE levels. Studies in asthmatic patients showed that corticosteroid treatment was associated with an increase in IgE levels over the duration of drug administration,<sup>28</sup> likely because of an increase in Th2 responses induced by the suppression of interferon- $\gamma$  production (which is known to inhibit Th2 differentiation).<sup>29</sup> Corticosteroid administration also induces interleukin-12 production which normally promotes a Th1 environment and enhances the expression of CD40 ligand on human lymphocytes, resulting in higher IgE levels.<sup>29,30</sup> Moreover, in our entire cohort of children with malignancy, 4 patients were on steroids at the time of IgE collection and were not IgE-deficient (Table 2). Data regarding how tacrolimus, rapamycin, or MMF may affect the IgE levels are limited. One study showed that the majority of children receiving tacrolimus immunosuppression after liver transplant had elevated total IgE levels, which was thought to be due to inhibition of the interleukin-2 activation of T cells and skewing of the immune response toward a Th2 response.<sup>31</sup> In contrast, one murine study found that rapamycin decreased plasma IgE levels in aged mice, but the effect in young mice was not assessed.<sup>32</sup> Another case report of a pediatric patient with liver transplantation-associated food allergy showed that addition of MMF to tacrolimus was associated with a decrease in food-specific IgE levels.<sup>33</sup> However, the fact that in at least 1 child, the IgE deficiency preceded the development of malignancy, supports the idea that IgE deficiency is related to the development of malignancy.

In conclusion, we have found that the rate of malignancy was higher in children with IgE deficiency compared with patients with normal, high, or very high IgE levels. We acknowledge the limitations of this study including that it is retrospective, the small number of children with malignancy and that there are potential confounding factors such as previous chemotherapy treatment before IgE measurement. Nevertheless, these findings are consistent with what has been reported in adults<sup>14–17</sup> and support the hypothesis that very low or absent IgE levels may be a marker for malignancy susceptibility not only in adults but also in children. How this finding could be used clinically remains to be established. Hopefully, the results of this small study will be used to generate larger and possibly prospective studies to better define the exact role of IgE in protection against tumor development in children.

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