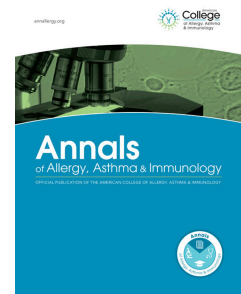


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Higher rates of malignancy in IgE deficient patients with negative immediate hypersensitivity skin tests

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Higher rates of malignancy in IgE deficient patients with negative immediate hypersensitivity skin tests

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Given the known role of tissue-bound IgE in anti-tumor immunity [1], and new data showing that IgE deficient patients (IgE<2.5 kU/L) have significantly higher rates and risk of developing malignancy [2-4], we investigated whether the presence of skin test reactivity (reflecting the presence of skin mast cell-bound IgE) was associated with malignancy diagnoses in IgE deficient patients presenting for evaluation of environmental allergy-like symptoms. In clinical practice, an aeroallergen skin testing diagnostic regimen consists of skin prick tests (SPT) and intradermal skin tests (IDST). [5] A positive skin test is initiated by the crosslinking of skin mast cell-bound specific IgE by injected allergen, with subsequent mast cell degranulation and is the only currently clinically available test assessing the presence of tissue-bound IgE.

Forty-seven (47) patients with selective IgE deficiency (no diagnosis of common variable immunodeficiency after chart review) were evaluated between 2014-2019 in our Allergy Clinics for asthma and/or rhinitis and had environmental skin tests done (trees, grass, and weed pollens, dog and cat epithelia, mouse and rat dander, cockroach, dust mites, mixed feathers and mixed molds (Greer Laboratories, Inc., Lenoir, NC)). Skin prick testing were performed in all patients. An IDST was done if the SPT was negative to any specific allergen but the physician strongly suspected that the symptoms are likely in relation to environmental allergies. At least one positive skin test was found in 33/47 (70.2%) patients, comprising the “skin test positive” group. Fourteen (14) patients had negative testing after full sets of SPT and IDST were done and comprised the group with “completely negative skin tests” Chart reviews were performed to identify those with a documented diagnosis of any type of malignancy. We used binary logistic regression to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of having a diagnosis of malignancy in patients with at least one positive skin test compared with those with

completely negative skin tests. Covariates included in the logistic regression were age, gender, smoking status and race. A p -value <0.05 was considered statistically significant. Since this was a pilot study, no power calculation was performed.

Patients included in the study were predominantly female (87.2%), of African-American or Hispanic origin (68.1%), with a mean age of 52.5 years (± 15.4). Overall, 8/47 (17%) of the IgE deficient patients had a malignancy diagnosis. The rate of a malignancy diagnosis was significantly higher in IgE deficient patients with completely negative skin tests (6/14, 42.9%), compared with those with at least one positive test (2/33, 6.1%, $p=0.007$, OR=34.86, 95% CI: 2.67-453.6) (Figure 1). Three patients had their IgE levels checked before the cancer diagnosis was made (mean elapsed time-29.6 $\pm$ 16.5 months) and five had IgE measured after the malignancy was diagnosed (mean elapsed time-86.4 $\pm$ 51.3 months). The types of cancers found in this cohort were: skin squamous cell carcinoma (treated surgically), squamous cervical cancer (cold knife cone resection), renal cell carcinoma (received kidney transplant 7 years prior to IgE collection; was on mycophenolate mofetil, prednisone and tacrolimus at the time of IgE test), breast cancer (treated 14 years prior at another institution), follicular thyroid cancer (treated surgically and with radioactive iodine therapy), endometrial adenocarcinoma (treated surgically), adenocarcinoma of rectum (treated with 5-fluorouracil and radiation therapy until 3 years prior to IgE collection, followed by diverting loop ileostomy), chronic lymphocytic leukemia (not requiring treatment so far). Other serum immunoglobulin levels were available in 6/8 patients with malignancy and were within normal range. (data not shown)

To the best of our knowledge, this is the first study indicating that in IgE deficient patients, having a positive immediate hypersensitivity skin test reaction might influence the susceptibility for developing a malignancy. These findings are consistent with the hypothesis that tissue-bound IgE plays an important role in tumor surveillance, [1, 6, 7] something that does not appear to be widely appreciated by the scientific or medical community.

In clinical practice, the only way to currently assess the existence of tissue bound-IgE is by eliciting positive immediate hypersensitivity skin test reactions with specific allergens. In our study, despite having very low serum IgE levels, a large proportion of IgE deficient patients had positive skin tests, indicating the presence of tissue bound-IgE. While some IgE deficient patients produce enough IgE to prime mast cells, others either produce no IgE at all or produce IgE in amounts that are too small to prime the cells, and these comprise the IgE deficient individuals with completely negative skin tests. In this study, those IgE deficient patients with absent cell-bound IgE had the highest likelihood of having an associated malignancy diagnosis, adding to the existing evidence that tissue-bound IgE is involved in local anti-tumor activity. [6, 8]. Utilizing skin tests to detect the presence of bound-IgE might therefore be a useful tool for predicting which IgE deficient individuals have the highest risk for developing a malignancy. Unfortunately, immediate type hypersensitivity skin testing will only detect mast cell bound-IgE in atopic individuals. A more accurate method for measuring tissue-bound IgE in both atopic and non-atopic individuals would be to use anti-human IgE for quantitative skin testing [9], or to directly assess bound-IgE in appropriately stained skin biopsy specimens.

Although our findings are based on a small retrospective study, the results of this pilot study could be used to design larger prospective studies. Another limitation is that the majority of cancer patients had their IgE levels checked after the malignancy diagnosis was made, so we

cannot be sure if the deficiency was intrinsic or whether it was caused by the malignancy or by subsequent treatment. However, one previous prospective study did find that IgE deficiency preceded the malignancy diagnosis. [4] In addition, other serum immunoglobulin levels were normal in all IgE-deficient cancer patients who had levels checked after the malignancy treatment. Finally, although using IDST raises the possibility of irritant reactions, IDST are generally performed when SPT to aeroallergens are negative despite a convincing clinical history [5]. Moreover, identifying the group of patients with completely negative skin tests after full sets of skin tests were performed, is a strength of this study.

In conclusion, this is the first study indicating that IgE deficient patients with absent serum and mast cell bound IgE have the highest risk for cancer diagnosis. Larger studies are needed to more definitively evaluate if immediate hypersensitivity skin test hyperreactivity could be used as a predictor for malignancy susceptibility in IgE deficient individuals.

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Figure 1. Rate of malignancy diagnosis in IgE deficient individuals, based on immediate hypersensitivity skin testing results

*model adjusted for age, race, gender and smoking status

