ELEVATION OF TOTAL SERUM IGE AS A PREDICTIVE BIOMARKER FOR RECURRENCE AND TREATMENT RESISTANCE IN NON-ATOPIC ADULT DERMATOMYCOSES

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Abstract: Dermatophytoses represent a major global health concern, with a rising occurrence of recurrent, persistent and treatment-resistant clinical chronic cases. Even though cell-mediated immunity (Th1/Th17) is the main mechanism accountable for clearing dermatophyte infections, the role of type I hypersensitivity-mediated humoral immune responses implicated in successful treatment setbacks has not been thoroughly or adequately investigated in clinical studies (Sardana et al., 2021; Woodfolk, 2005). This study presents the comprehensive evaluation of total serum Immunoglobulin E (IgE) as a predictive biomarker for the assessment of disease recurrence and identifying the host susceptibility factors in adult patients with active chronic dermatomycoses who do not present clinical signs of cutaneous atopy nor is it present in their medical history. This aids to provide a much thorough medical understanding of the immunological factors and mechanism that play a role in recurrent or persistent infections in individuals lacking obvious atopic skin diseases.
In this cross-sectional cohort study a total of 120 adult patients were included, all of which contained superficial dermophyte infections confirmed with both fungal cultures as well as direct potassium hydroxide (KOH). Patients were diagnosed with tinea cruris, tinea corporis and tinea pedis and divided into two clinical groups based on their disease course. Group A consisted of 60 patients with treatment-resistant infections, characterized by at least three episodes over the preceding 12 months despite appropriate medical antifungal treatment. Group B comprised of 60 patients experiencing their first episode of acute dermatophytosis. For the measurement of Total serum IgE. The chemiluminescent immunoassay (CLIA) was used with values below 100 IU/mL considered within the normal range. In order to minimize the confounding factors, patients that had conditions known to affect serum IgE levels were excluded such as; active atopic dermatitis, concurrent parasitic infections, allergic rhinitis.
An elevation in total serum IgE levels (> 100 IU/mL) was observed in 47 out of 60 patients (78.3%) with recurrent dermatophytosis (Group A), compared with solely 13 out of 60 patients in the acute infection group (Group B), thus presenting a statistically significant difference ($p < 0.0001$). Supporting this observation, the mean serum IgE concentration was markedly higher in Group A (584.2 ± 112.4 IU/mL) as opposed to Group B (112.6 ± 34.1IU/mL).
Trichophyton rubrum was, among the fungal species, the most frequently identified species, with 68.3% of positive cultures, followed by Trichophyton mentagrophytes (24.2%). ROC curve analysis identified 320 IU/mL as the optimal serum IgE cutoff for predicting recurrent treatment failure, achieving a sensitivity of 83.3%, a specificity of 88.3%, and an AUC of 0.912.
Subclinical elevation in the levels of total serum IgE among patients lacking atopic disease may reflect a subtle Th2-skewed immune profile that plays a role in the host immune responses and affects the effectiveness of fungal clearance. The incorporation of baseline serum IgE assessment in routine dermatological evaluation presents a very useful as well as necessary prognostic approach in identifying individuals that are most likely to have a recurrence in fungal infections and who need a more customized therapeutic approach.
Keywords: Dermatomycoses, Total Serum IgE, Fungal Recurrence, Treatment Resistance, Non-Atopic Dermatophytosis

1.INTRODUCTION

Superficial fungal infection resulting from dermatophyte species contributes to a growing challenge in clinical dermatology globally. Even though these infections have traditionally been viewed as localized and relatively easy to manage, recent epidemiological shifts suggest a rising incidence of chronic, persistent and recurrent superficial fungal infections. Many individuals suffering from tinea cruris, tinea corporis and tinea pedis

encounter repeated treatment setbacks and frequent recurrences regardless of receiving guidelines based oral and topical antifungal medications

During clinical examinations, these chronic lesions frequently appear with considerable disruption of the skin barriers, substantial hyperkeratotic changes and prominent inflammatory margins that spread outside the normal anatomical limits. Even though treatment failure is often linked to poor treatment adherence or fungal drug resistance, a significant percentage of recurrent cases occur among highly compliant patients infected with fully sensitive isolates. This observation points towards the suggestion that underlying host susceptibility factors may represent important driver to chronicity (Dogra & Uprety, 2016; Lohariwala & Gupta, 2025; Mahajan & Sahoo, 2016)

Even though total serum immunoglobulin E (IgE) is commonly evaluated in the assessment of allergic disorders, including atopic dermatitis, an increase in the IgE levels is also commonly detected in non-atopic patients with chronic dermatomycoses who lack a history of skin related atopic disease. Evaluation of baseline serum IgE may provide dermatologists with a readily available clinical marker for identifying susceptible patients at an early stage, thereby supporting a more individualized and long-term therapeutic approach

2.MATERIALS AND METHODS

This cross-sectional study was conducted with a total of 120 adult patients, all of whom have been diagnosed with active, superficial dermatomycoses, such as tinea pedis, tinea cruris, tinea corporis. This cohort was divided into two groups as follows;

Group A; The recurrent cohorts consisting of n = 60 adult patients with recurrent or chronic dermatophytosis, specified as having encountered at least three documented recurrent flares during the preceding 12 months regardless of the completion of the standard medical regimens of antifungal treatments.

Group B: The acute control cohort consisting of n = 60 adults' patients that have been admitted presenting their first episode of acute superficial dermatophyte infections and with no prior medical history of recurrent or chronic fungal disease

In order to provide a complete isolation for the association between the changes in the host serum IgE and the dermatophyte infections, very rigorous exclusion criteria were implemented. Potential patients were not accepted in the study in the event that they presented personal or family medical history of respiratory or cutaneous atopy such as asthma or allergic rhinitis. Furthermore, the exclusion criteria included active atopic dermatitis, helminthic infections, active parasitic underlying systemic immunosuppression or hepatic impairment.

To conduct the mycological assessment, for all patients regardless of their group, mycological confirmation was gathered through the collection of skin scraping from the active lesion edges and then divided for two complementary diagnostic procedures.

Subsequently, the gathered specimen was treated with a 10% Potassium Hydroxide (KOH) solution and then examined through the usage of light microscopy, the examination was carried out to confirm the presence of septate branching fungal hyphae. The scraped skin was inoculated into Sabouraud Dextrose Agar (SDA) supplemented with chloramphenicol and cycloheximide. The cultures were incubated at 28 °C for 21 days, during which period they were observed for microscopic characteristics and macroscopic colony morphology.

For the serum IgE measurement of the participant's venous blood samples were obtained at baseline. Then the serum was separated by means of centrifugation and total serum IgE concentrations were measured through the usage of Chemiluminescent Immunoassay (CLIA). The serum values that were below 100 IU/ml were considered within normal range, whilst the concentrations above 100IU/mL were considered elevated.

In order to perform a thorough statistical analysis, SPSS version 28.0 was incorporated, To assess the differences between the groups two-tailed independent samples t-tests were used, and the continuous quantitative variables were expressed as mean ± standard deviation SD. Furthermore, the categorical variables were examined using Pearson's Chi square. The Receiver Operating Characteristic (ROC) curve analysis was added in order to decide the optimal serum IgE threshold for predicting recurrent or chronic infection. In terms of sensitivity, diagnostic performance was assessed and the Area Under the Curve (AUC). A p-value lower than 0.05 was classified as significant

3.RESULTS

The overall study cohort comprised of 120 patients including 68 males (56.7%) and 52 females (43.3%) with a mean age 41.8 ± 12.3 years.. The demographic parameters were relatively well comparable between the two cohorts with no statically significant differences detected in age distribution (p=0.412) or gender ratio (p=0.580)

As far as the lesion distribution is concerned, tinea corporis was observed in 50 patients (41.7%), followed by tinea cruris in 40 patients (33.3%) and tinea pedis in 30 patients (25.0%). The distribution of the affected sites were consistent between Group A and Group B.

Mycological examination conducted through KOH microscopy resulted in positive findings in all 120 patients (100%). Meanwhile fungal culture demonstrated positive growth in 111 of the 120 cases (92.5%). The breakdown of isolates indicated that Trichophyton rubrum was the leading dermatophyte species accounting for 68.3% of positive cultures (n=82). Trichophyton mentagrophytes was identified in 24.2% of positive cultures (n=29), whereas Epidermophyton floccosum accounted for the remaining 7.5% (n=9). The distribution of isolated species presented no significant variation between Group A and Group B (p = 0.652) indicated that chronic recurrence was not notably associated with differences in the identified fungal species and may instead be related predominantly to host immunological factors.

Most importantly, in regard to serum IgE findings, the analysis of host humoral immune markers demonstrated significant disparities in serum IgE levels between the two groups.

Group A - Recurrent Cohort with n = 60; Elevated total serum IgE levels (>100 IU/mL) were identified in 47 of the 60 patients (78.3%). The remaining 13 patients (21.7%) had normal baseline IgE levels. The mean serum IgE concentrations in Group A was 584.2 ± 112.4 IU/mL.

Group B – Acute Control Cohort with n = 60; Elevated total serum IgE levels (>100 IU/mL) were detected in solely 13 out of 60 patients (21.7%). Whereas the majority of patients 47 individuals (78.3%) had serum IgE levels within normal range. The mean quantitative serum IgE concentration in Group B was 112.6 ± 34.1 IU/mL.

The difference in the proportion of elevated IgE between Group A (78.3%) and Group B (21.7%) was statistically noted $\chi^2 = 38.53, p < 0.0001$. Likewise, the difference in mean serum concentrations between the two groups 584.2 IU/mL vs. 112.6 IU/mL presented very strong statistical significance $t = 30.74, p < 0.0001$

To determine the predictive value of total serum IgE as a predictive biomarker for chronical fungal recurrence, a Receiver Operating Characteristic (ROC) curve analysis was carried out. The Area Under the Curve (AUC) was measured as 0.912 (95% CI: $0.858 - 0.966, p < 0.0001$, demonstrating excellent diagnostic accuracy.

The optimal decision threshold was established at 320 IU/mL. At this cutoff point baseline serum achieved the following diagnostic performance

- Sensitivity: $83.3%$
- Specificity: $88.3%$
- Positive Predictive Value (PPV): $87.7%$
- Negative Predictive Value (NPV): $84.1%$

4.DISCUSSION

The conclusions of this research study indicate a very strong clinical link between the subclinical elevation of total serum IgE and recurrent or chronic dermatophytosis infections in non-atopic adult individuals. The findings that 78.3% of patients in the Group A (Recurrent group) presented with increased levels of IgE, as opposed to 21.7% of patients in Group B (Acute control), presents a very distinct variation in host immune responses that might play a role in the susceptibility to the persistence of the fungal infections (Verma & Panda, 2023).

In the cases of patients that are non-atopic and present subclinical IgE elevations, the host immune signaling turns towards a Th2-predominant profile (Deng et al., 2023; Sardana et al., 2021). The secretion of Th2 cytokines, namely IL-4 and IL-13, induces B-cell class switching, resulting in IgE antibody production, while at the same time downregulating protective Th1/Th17 cellular immune response. Prior to circulating IgE antibodies cannot clearly eliminate fungal hyphae located within the outer cornified layers of the epidermis, this altered immune response could lead to inefficient fungal elimination,, thereby facilitating fungal persistence and subsequent disease recurrence (Monod & Feuermann, 2021).

The afore presented conclusions indicate the integration of pre-treatment total serum IgE assessment into standard dermatological evaluations for patients with prolonged or recurring dermatomycoses. A serum IgE concentration value above 320IU/mL could serve as preliminary prognostic marker of underlying increased risk and anticipated therapeutic failure. For healthcare professionals detecting an elevated IgE profile may support a more patient specific treatment approach (Gupta et al., 2020; Nenoff et al., 2022).

These strategies may consist of;

- Increased duration of initial antifungal treatment to promote complete fungal clearance.
- Implementing combined treatment approaches such as oral azoles or terbinafine administered together with topical keratolytics, including urea and ciclopirox.
- Introducing regular long-term maintenance treatment plans to reduce relapse in high-risk individuals

5.CONCLUSIONS

Total serum IgE levels were markedly increased in non-atopic patients with recurrent and chronic superficial dermatomycoses with an average concentraion of 584.2 ± 112.4 IU/mL, relative to the acute control group which had a mean concentration of 112.6 ± 34.1 IU/mL; $p < 0.0001$.

An initial serum IgE cutoff of 320 IU/mL was established as a useful threshold for detecting patients at a heightened risk of therapeutic failure and recurrent infection. ROC analysis indicated an Area Under the Curve (AUC = 0.912)with a diagnostic sensitivity of 83.3% and a diagnostic specificity of 88.3%. In addition, mild elevation in serum IgE may indicate a Th2-predominant immune shift that could compromise the protective cell-mediated fungal elimination. Consequently, serum IgE may present a very useful and vital prognostic marker that assists the identification of patients that are at a greater risk of recurrence and aid the medical staff to the development of more effective long-term treatment strategies.

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