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Serum IgE in the clinical features and disease outcomes of anti-interferon-γ autoantibodies syndrome

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Abstract

Background Anti-interferon-γ autoantibodies (AIGAs) syndrome is a recently recognized adult-onset immunodeficiency syndrome. Serum Immunoglobulin E (IgE) is increased in AIGAs syndrome, but the role of serum IgE levels in the clinical features and disease outcomes of AIGAs syndrome is not clear.

Methods We retrospectively enrolled 163 patients diagnosed AIGAs syndrome with serum IgE examined at baseline from 2021 to 2024 and compared the clinical features between Group A (serum IgE level ≤ 212 IU/mL) and Group B (serum IgE level > 212 IU/mL). Multivariable Cox regression method was used to explore the risk factors associated with disease outcomes.

Results 163 patients were included in this study, of whom 97 patients were in Group A (serum IgE level ≤ 212 IU/mL) and 66 patients in Group B (serum IgE level > 212 IU/mL). Group B showed higher number of infectious episodes, elevated levels of erythrocyte sedimentation rate (ESR), CD3 + T cells, immunoglobulin G (IgG), IgA, and globulins (GLB), shorter progression-free survival (PFS), and increased exacerbation numbers.

Group B exhibited a higher incidence of fatigue, dyspnea, loss of appetite, rash, moist rales, hepatomegaly, and splenomegaly. Skin, bone marrow and spleen involvements were more common in Group B. IgE demonstrated correlations with IgG, GLB, Albumin (ALB), Eosinophils (EOS), IgG4, and ESR. During the follow-up, Group B exhibiting higher number of exacerbations compared to Group A ($P < 0.0001$). Multivariable Cox regression analysis revealed that High AIGAs titers (hazard ratio [HR], 2.418, 95% confidence interval [CI]1.037–5.642, $P = 0.041$), WBC > 22.52×10^9cells/L (HR2.199, 95%CI1.194–4.050, $P = 0.012$) were independent risk factors of disease exacerbation. Glucocorticoid treatment was commonly used in patients with AIGAs syndrome who had elevated IgE levels and skin involvement, demonstrating efficacy in improving condition.

Conclusions Elevated serum IgE levels are associated with more severe clinical features in AIGAs syndrome, including increased infectious episodes, elevated inflammatory markers/immune markers, and multi-organ involvement, particularly skin. IgE serves as a marker of skin involvement and may indicate a potential response to glucocorticoid treatment.

Keywords Anti-interferon-γ autoantibodies syndrome, IgE, Clinical features, Outcomes, Skin involvement, Glucocorticoid treatment

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Background

Anti-interferon (IFN)-γ autoantibodies (AIGAs) syndrome is a type of adult-onset immunodeficiency syndrome characterized by elevated neutralizing AIGAs [1]. These autoantibodies disrupt the binding of IFN-γ to its receptors, inhibiting the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway and the phosphorylation of STAT-1 [2]. This impairment compromises IFN-γ–mediated immunity, leading to multiple opportunistic infections, including *non-tuberculous mycobacteria* (NTM), *Talaromyces marneffei* (TM), *tuberculosis* (TB), *Salmonella species*, and *herpes zoster virus* [3–5]. The combination of immunosuppression and chronic recurrent infections imposes a severe disease burden on patients.

Since the first case of AIGAs in a Filipino patient with disseminated infection was reported in 2004 [6], numerous cases have been documented worldwide, with the majority originating from Southeast Asia [3, 7–9]. Guangxi, located in southern China, is a high-incidence area. We have conducted extensive research to deepen our understanding of TM infection and AIGAs syndrome [10, 11].

AIGAs syndrome is a multisystem disorder affecting multiple organs, including the lungs, lymph nodes, skin, bones, and blood [5, 9]. Patients with this syndrome often exhibit elevated levels of immunoglobulin E (IgE), especially those presenting with skin lesions [12]. The clinical immunological features of AIGAs syndrome, marked by elevated erythrocyte sedimentation rate (ESR), globulin (GLB), IgG, IgE, and IgG4 levels, have been reported [11]. Previous studies have suggested that IgE and IgG autoantibodies were associated with various autoimmune diseases [13–15]. Patients with autoimmune diseases, such as systemic lupus erythematosus (SLE), have been reported to exhibit double-stranded DNA (dsDNA)-specific IgE, which can activate interferon pathways, potentially exacerbating autoimmune responses [16]. Although elevated IgE levels are observed in some AIGAs syndrome patients, the specific role of serum IgE in the syndrome remains unclear.

This retrospective analysis provided a comprehensive examination of the role of serum IgE in the clinical characteristics and disease outcomes of patients with AIGAs syndrome.

Methods

Study design and participants

This retrospective study was based on a prospective cohort study conducted at the First Affiliated Hospital of Guangxi Medical University from January 2021 to July 2024. Inclusion criteria required patients to have a confirmed diagnosis of AIGAs syndrome with baseline serum IgE level measurement. Exclusion criteria included a history of HIV infection or acquired immune deficiency syndrome (AIDS), as well as the absence of baseline serum IgE measurement. Based on baseline serum IgE levels, patients were categorized into two groups: Group A (serum IgE level ≤ 212 IU/mL) and Group B (serum IgE level > 212 IU/mL).

The study was approved by the Research Ethics Commission of The First Affiliated Hospital of Guangxi Medical University (IRB Protocol Number: 2024-S497-01) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants provided written informed consent. Clinical trial number: not applicable.

Data collection

Demographic and clinical data were collected January 2021 to July 2024. Plasma samples for detecting AIGAs were collected at specific time points (initial diagnosis; followed up at regular visits of 1, 3, 6, 9 months, and 1 year). Data of outcomes were collected at various times during the visits.

Detection of AIGAs

AIGAs levels in plasma samples were measured using indirect ELISA and Western blot (WB) analysis as previously described [11]. All samples were tested at first thaw. Each sample was analyzed at 3 dilutions (1:100, 1:500, 1:2500).

WB analysis assessed AIGAs' neutralizing effect on the STAT1 pathway. THP-1 cells differentiated into macrophages with Phorbol 12-myristate 13-acetate (PMA), mimicking the human immune context. Serum from patients was pre-incubated with IFN-γ to mimic the physiological response. WB revealed that AIGAs positivity correlated with STAT1 pathway inhibition, evident by diminished p-STAT1 signals on Polyvinylidene Fluoride (PVDF) membranes. In contrast, AIGAs-negative samples exhibited normal p-STAT1 expression. Protein signal intensity was quantified utilizing Image J.

Definitions

Diagnostic criteria for AIGAs syndrome: patients diagnosed with NTM, TM and other bacterial and fungal opportunistic infections, determined positive AIGAs by indirect ELISA method, and WB verified the neutralization of AIGAs and its impact on downstream pathways.

Disseminated infection was defined as the involvement of two or more non-adjacent organ systems, while limited infection was defined as the involvement of only one.

The principal outcomes of AIGAs-positive patients were grouped into four categories: cured (no reappearance of infection for at least 6 months post-treatment,

negative AIGAs result in ELISA testing, and confirmed without neutralizing ability by WB), improvement (symptoms amelioration post-treatment), exacerbation (symptoms that deteriorate following treatment may necessitate hospitalization for further management), and death. Progression-free survival (PFS) was defined as the time from the diagnosis of the disease to the occurrence of the first exacerbation. Exacerbation, PFS, and overall survival (OS) were recorded during the follow-up period.

Statistical analysis

The baseline IgE cut-off value of 212 IU/mL was calculated using the Maxstat algorithm [17]. Normally distributed quantitative variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median (interquartile range, IQR). Characteristics were compared between the different groups using t-test, ANOVA, chi-square test, fisher's exact test, and non-parametric test. Correlation analysis between IgE levels and other variables was conducted using Spearman correlation analysis. The Cox proportional hazards regression model was used to assess factors influencing disease exacerbation. For factors that exhibited statistical significance in the univariable Cox regression analysis, we employed the "glmnet" package in R to perform lasso regression for variable selection. Subsequently, we utilized the "survival" package to conduct a multivariable Cox regression analysis to explore the combined effects of these factors on the disease exacerbation in patients with AIGAs syndrome.

Statistical analysis and graph generation were conducted using SPSS (Version 26.0), R language (Version 4.3.2), and GraphPad Prism (Version 9). A two-tailed P value less than 0.05 was considered statistically significant.

Results

Baseline features of the patients enrolled in this study

A total of 163 patients with AIGAs syndrome were eligible for the study. Patients were stratified into Group A (serum IgE ≤ 212 IU/mL, $n=97$) and Group B (serum IgE > 212 IU/mL, $n=66$) based on their baseline serum IgE levels. For the 97 patients in Group A, 41patients experienced exacerbations, 7 patients died, and 1 patient cured. For the 66 patients in Group B, 42 patients experienced exacerbations, 11 patients died, and 1 patient cured. Furthermore, 63 of the 163 patients had been followed up for more than 1 year, and were regularly monitored for AIGAs titer and immune indices at predetermined time points (0, 1, 3, 6, 9, and 12 months). The flowchart of the study is presented in Fig. 1. The population distribution of AIGAs titers and IgE levels in Groups A and B is illustrated in Fig. 2.

Differences in clinical features between Group A and Group B

The demographic and laboratory data of Group A and Group B are showed in Table 1. The mean age of disease onset was 54.99 ± 12.71 years in Group A and 55.00 ± 12.30 years in Group B. Group B had a significantly higher number of infectious episodes than Group A ($P=0.010$, Table 1). No significant differences were observed in gender, age, Body Mass Index (BMI), or geographic residence. Additionally, there were no differences between the two groups regarding allergic diseases, underlying diseases, and disseminated infections (Table 1). A comparison of laboratory data between Group A and Group B revealed that Group B exhibited elevated levels of erythrocyte sedimentation rate (ESR), CD3 + T cells, immunoglobulin G (IgG), IgA, and globulins (GLB) ($P<0.05$, Table 1). Additionally, Group B showed lower levels in albumin (ALB), and cholesterol esterase (CHE) ($P<0.05$, Table 1).

In comparing the symptoms and signs, Group B exhibited a higher incidence of fatigue, dyspnea, loss of appetite, enlarged superficial lymph nodes, rash, moist rales, hepatomegaly, and splenomegaly ($P<0.05$, Table 2). Regarding the involved organs, skin, bone marrow and spleen involvements were more common in Group B ($P<0.05$, Table 2).

Using Spearman's correlation analysis, we found that serum IgE levels were positively correlated with serum IgG levels (r = 0.3702, $P<0.001$, Fig. 3A). Serum IgE levels also showed a positive correlation with GLB levels (r = 0.2479, $P<0.001$, Fig. 3B). Conversely, serum IgE levels were negatively correlated with ALB levels (r = -0.1787, $P=0.0229$, Fig. 3C). Additionally, serum IgE levels showed a positive correlation with eosinophilic granulocyte (EOS) levels (r = 0.1609, $P=0.0408$, Fig. 3D) and serum IgG4 levels (r = 0.2495, $P=0.0164$, Fig. 3E). Furthermore, serum IgE levels demonstrated a positive correlation with ESR (r = 0.1651, $P=0.0375$, Fig. 3F). A stronger correlation was observed between serum IgE levels and the ratio of serum IgG, GLB, and IgG4 levels compared to other indices.

Serum IgE during the follow-up period

Of the 63 patients who underwent regular follow-up visits at 0, 1, 3, 6, 9, and 12 months, IgE levels decreased as the condition improved (Fig. 4). Concurrently, the levels of White Blood Cell (WBC), Neutrophils (Neu), EOS, ESR, IgG, IgG4, and GLB decreased, ALB increased (Fig. 4). During the follow-up, the proportion of patients with high AIGAs titers (1:2500) decreased, while the proportion of those with lower titers (1:100, 1:500) increased (Fig. 4).

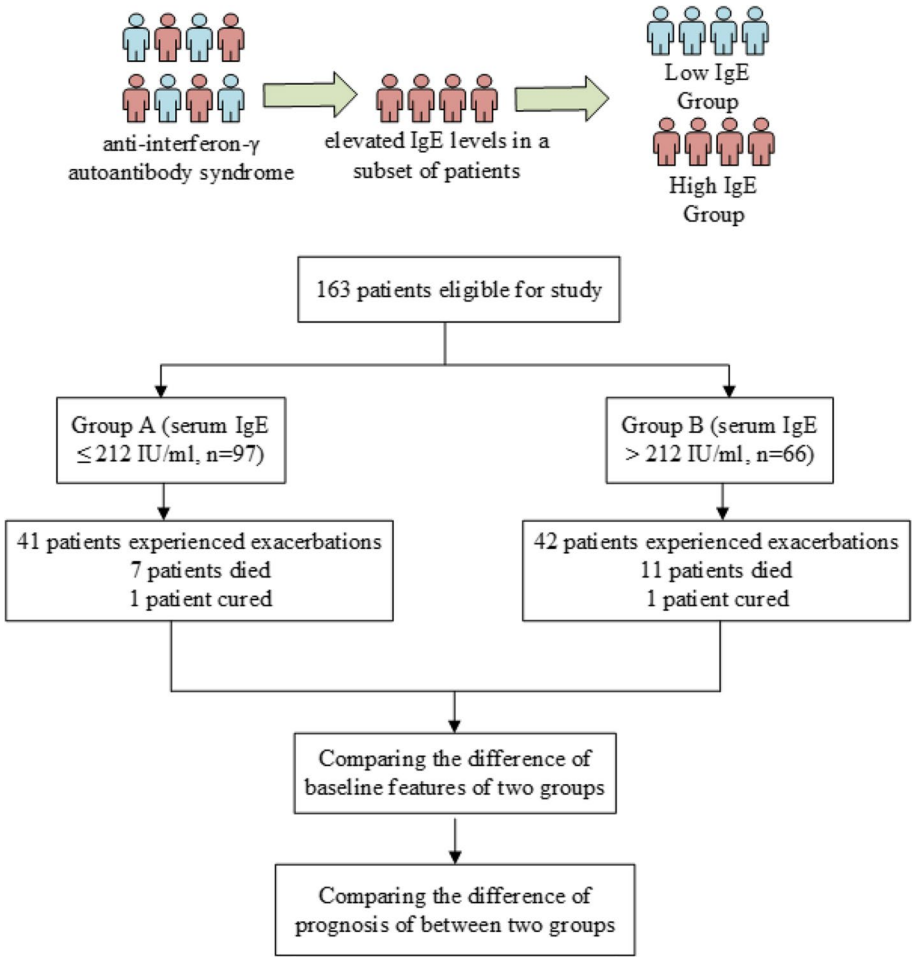

Fig. 1 The flowchart of the study

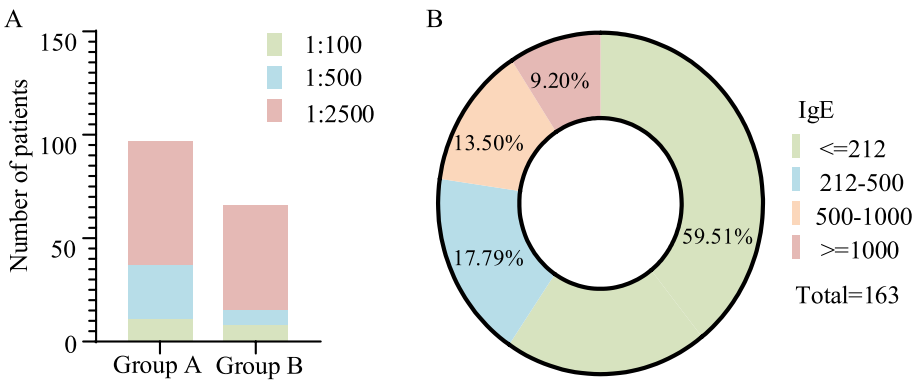

Fig. 2 Population distribution of AIGAs titers (**A**) and population distribution of serum IgE levels (**B**)

Relationship between serum IgE levels and clinical outcomes

During the follow-up, the frequency of disease exacerbations in AIGAs syndrome was documented, with the Group B exhibiting a significantly higher number of exacerbations compared to the Group A ($P < 0.0001$, Fig. 5). The average number of exacerbations was 1.30 and 2.86 in Group A and Group B. Monofactor Cox regression

Table 1 Comparison of demographic and laboratory data between Group A (serum IgE ≤ 212 IU/mL) and Group B (serum IgE > 212 IU/mL)

Variables	Group A (*n* = 97)	Group B (*n* = 66)	*P* value
General characteristics			
Gender, male *n* (%)	51(52.6)	40(60.6)	0.405
Average age (years)	54.99 ± 12.71	55.00 ± 12.30	0.717
BMI (kg/m^2)	21.48 ± 2.89	21.24 ± 3.21	0.542
Underlying diseases, yes *n* (%)	48(49.5)	27(40.9)	0.366
Allergy disease, yes *n* (%)	3(42.9)	4(57.1)	0.442*
Residence, rural *n* (%)	61(62.9)	48(72.7)	0.156
No. of infective pathogens	4(2–5)	5(3–7)	0.010
Disseminated infection, yes *n* (%)	84(86.6)	60(90.9)	0.294
Laboratory data			
AIGAs titers			0.157
1: 100 n (%)	11(11.3)	8(12.1)	
1: 500 n (%)	26(26.8)	7(10.6)	
1: 2500 n (%)	60(61.9)	51(77.3)	
WBC (x10^{9}cells/L)	12.64(8.84–16.41)	15.43(10.26–19.51)	0.054
Neu (x10^{9}cells/L)	9.20(5.33–13.09)	11.10(7.08–16.14)	0.059
Lym (x10^{9}cells/L)	1.86 ± 0.99	1.87 ± 0.87	0.976
Eos (x10^{9}cells/L)	0.26(0.11–0.57)	0.41(0.13–1.04)	0.094
Mon (x10^{9}cells/L)	0.74(0.52–0.93)	0.78(0.57–1.24)	0.231
Hb (g/L)	108.00 ± 21.13	93.54 ± 25.32	0.068
CRP (mg/L)	83.54 ± 59.23	100.58 ± 67.69	0.100
ESR (mm/h)	69.76 ± 30.77	85.00 ± 36.39	0.009
SF (μg/L)	517.93(239.49–1063.64)	855.96(441.01–1514.89)	0.067
CD3$^+$T cells (%)	67.31(58.38–71.82)	69.93(60.73–78.90)	0.037
CD4$^+$T cells (%)	34.92 ± 10.06	36.84 ± 10.69	0.280
CD8$^+$ T cells (%)	27.39 ± 10.17	29.24 ± 9.25	0.261
NK cells (%)	18.56 ± 8.36	15.65 ± 9.25	0.110
B cells (%)	11.75(7.47–15.90)	9.45(5.42–14.77)	0.137
IgG (g/L)	18.36(14.73–23.57)	24.56(18.95–34.09)	< 0.001
IgA (g/L)	1.13(0.70–1.61)	2.85(2.08–3.62)	0.021
IgM (g/L)	1.07(0.72–1.55)	2.39(1.66–3.02)	0.889
IgG4 (g/L)	1.29(0.51–2.19)	1.53(0.92–2.97)	0.101
GLB (g/L)	39.60(35.02–45.85)	44.75(37.35–52.97)	0.009
ALB (g/L)	32.75 ± 5.81	30.36 ± 6.75	0.035
CHE(U/L)	5119.50(3662.00–7161.50)	3767.00(2257.50–5986.00)	0.002
D-Dimer(mg/L)	442.00(235.00–902.00)	695.00(270.00–1214.00)	0.067

* Fisher's exact test

analysis identified 20 exacerbating risk factors and 3 exacerbating protective factors (Table 3).

We performed lasso regression to select influential factors with statistically significant differences from the results of the univariable Cox regression analysis. Ten factors were included in the model: High AIGAs titers, Dyspnea, Nausea, Dry rales, Fungal co-infection, WBC > 22.52 × 10^{9}cells/L, Neu > 19.02 × 10^{9}cells/L, IgE > 212 IU/mL, ALB > 36.1 g/L, CHE > 4739U/L. We then conducted a multivariable Cox regression analysis with these factors. After adjusting for other factors, High AIGAs titers (hazard ratio [HR], 2.418, 95% confidence interval [CI]1.037–5.642, $P = 0.041$), WBC > 22.52 × 10^{9}cells/L (HR2.199, 95%CI1.194–4.050, $P = 0.012$) were independent risk factors of disease exacerbation in patients with AIGAs syndrome (Table 4).

The median time of PFS for the Group A was 18 months, whereas the Group B was 9 months. Group B had a higher risk of exacerbation compared to the Group A (HR1.613; 95% CI: 1.032–2.522), which was

Table 2 Comparison of symptoms, signs and involved organs between Group A (serum IgE ≤ 212 IU/mL) and Group B(serum IgE > 212 IU/mL)

Variables	Group A (*n* = 97)	Group B (*n* = 66)	*P* value
Symptoms, *n* (%)			
Fever	58(59.8)	49(74.2)	0.057
Chilly	30(30.9)	21(31.8)	0.904
Cough	83(85.6)	53(80.3)	0.373
Expectoration	70(72.2)	48(72.7)	0.937
Hemoptysis	10(10.6)	6(3.1)	1.000*
Weight loss	34(35.1)	33(50.0)	0.057
Fatigue	28(28.9)	35(53.0)	0.001
Dyspnea	25(25.8)	36(54.5)	< 0.001
Loss of appetite	26(26.8)	30(45.5)	0.014
Nausea	5(5.2)	6(9.1)	0.355*
Chest tightness	15(15.5)	16(24.2)	0.222*
Chest pain	27(27.8)	14(21.2)	0.339
Bone or joint pain	18(18.6)	13(19.7)	0.842*
Headache	20(20.6)	12(18.2)	0.841*
Signs, *n* (%)			
Enlarged superficial lymph nodes	62(63.9)	54(81.8)	0.013
Anemic appearance	21(21.6)	18(27.3)	0.457
Moist rales	13(13.4)	21(31.8)	0.005*
Dry rales	3(3.1)	1(1.5)	0.648*
Pleural effusion	6(6.2)	5(7.6)	0.758*
Rash	15(15.5)	26(39.4)	0.001
Skin abscesses	9(9.3)	7(10.6)	0.794*
Hepatomegaly	2(2.1)	12(18.2)	< 0.001*
Splenomegaly	3(3.1)	9(13.6)	0.015*
Involved organs, *n*(%)			
Lung involvement	94(96.9)	62(93.9)	0.442*
Lymph nodes involvement	83(85.6)	61(92.4)	0.181
Bone involvement	50(51.5)	31(47.0)	0.566
Skin involvement	25(25.8)	30(45.5)	0.009
Bone marrow	2(2.1)	7(10.6)	0.032*
Bloodstream infection	14(14.4)	15(22.7)	0.212*
Pleura	14(14.4)	10(15.2)	1.000*
Soft tissue	6(6.2)	6(9.1)	0.549*
Liver	3(3.1)	8(12.1)	0.051*
Spleen	6(6.2)	12(18.2)	0.022*

* Fisher's exact test

statistically significant ($P = 0.024$, Fig. 6A). And there was no significant difference of OS ($P = 0.195$, HR1.842, 95%CI 0.729–4.654, Fig. 6B). Comparing of co-infections, treatment, and outcomes between Group A and Group B, there were more commonly used glucocorticoids and anti-tuberculosis therapy, and higher numbers of patients experienced exacerbations in the Group B ($P < 0.05$, Supplementary Table S1), other co-infections and treatment methods, disease course, and outcome had no significant difference (Supplementary Table S1).

Glucocorticoids reduce IgE levels and improve skin lesions

In our study, we observed that skin involvement was prevalent among patients in the high IgE group. A comparative analysis of clinical characteristics revealed that patients with skin involvement exhibited significantly higher levels of WBC, Neu, Eos, serum ferritin (SF), IgE and D-dimer ($P < 0.05$, Supplementary Table S2) compared to those without skin involvement.

Glucocorticoid treatment has shown efficacy in patients with AIGAs syndrome, particularly those presenting with

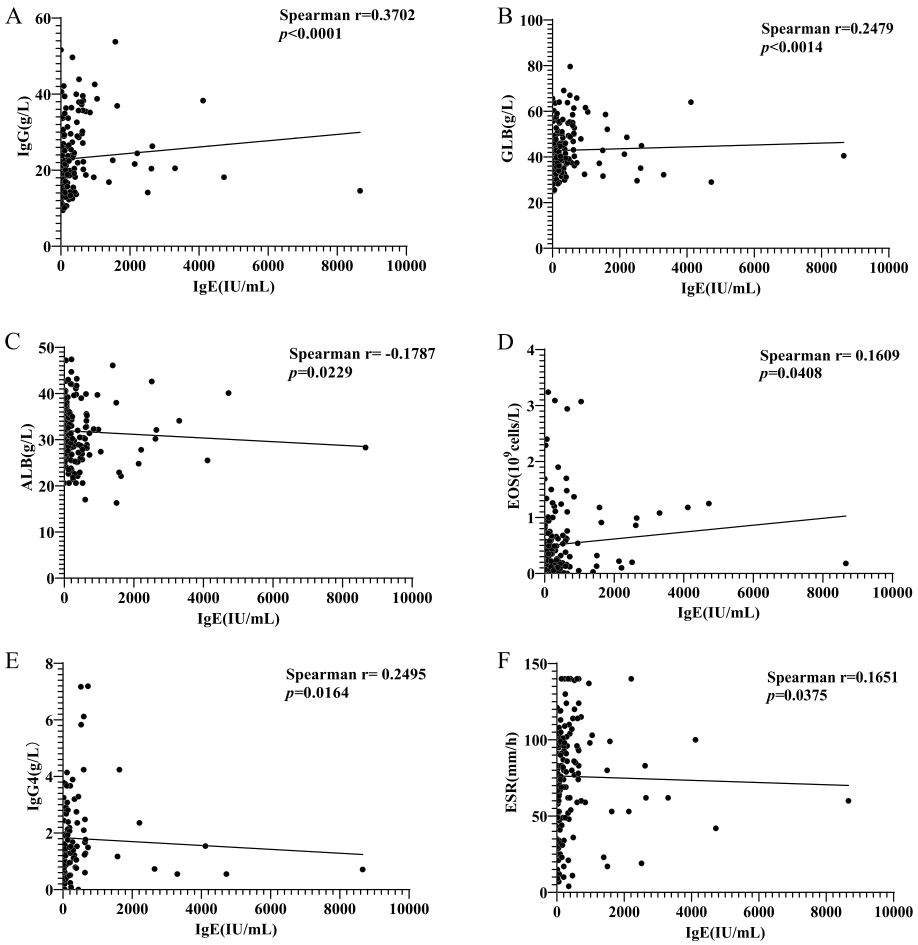

Fig. 3 Spearman Correlations of baseline serum IgE with IgG(**A**), GLB(**B**), ALB(**C**), EOS(**D**), IgG4(E), and ESR(F). The correlation between serum IgE levels and the ratio of serum IgG, GLB, and IgG4 levels was stronger than with other indices. ($p < 0.05$ indicates statistical significance)

elevated IgE levels and skin lesions (Fig. 7). One patient with AIGAs syndrome and elevated IgE levels, who also presented with Sweet's syndrome, experienced significant improvement in skin lesion symptoms following glucocorticoid treatment (Supplementary Fig. 1, Supplementary Fig. 2). For 25 patients with high serum IgE levels (> 212 IU/mL), clinical markers were assessed before and after glucocorticoid treatment. Glucocorticoid therapy led to significant reductions in Neu, CRP, ESR, IgG, IgA, IgG4, IgE, and GLB, alongside increases in lymphocytes (Lym) and ALB (Supplementary Table S3).

Discussion

This study conducted a retrospective analysis to investigate the role of serum IgE in AIGAs syndrome and further delineated its clinical features and outcomes. Elevated serum IgE levels are associated with more severe clinical features in AIGAs syndrome, including increased infectious episodes, elevated inflammatory markers/immune markers, and multi-organ involvement, particularly skin. IgE serves as a marker of skin involvement and may indicate a potential response to glucocorticoid treatment.

Elevated serum IgE was observed in some patients with AIGAs syndrome, this is consistent with the previous studies [11, 12]. As we know, elevated IgE is commonly associated with allergies, infections, and other diseases. However, in this study, we observed that there were few allergic diseases or underlying diseases typically associated with elevated IgE levels. This suggests that IgE may not exert its effects through their role in allergies, but rather through autoimmune mechanisms. In terms of infecting pathogens, including TM, NTM, and Aspergillus, no significant differences were observed. IgE autoantibodies was reported to be associated with some autoimmune diseases, such as Systemic Lupus Erythematosus (SLE) [16], autoimmune bullous diseases [18], rheumatoid arthritis [19], suggesting a similar phenomenon may occur in AIGAs syndrome. These conditions may be accompanied by an abnormal response of the

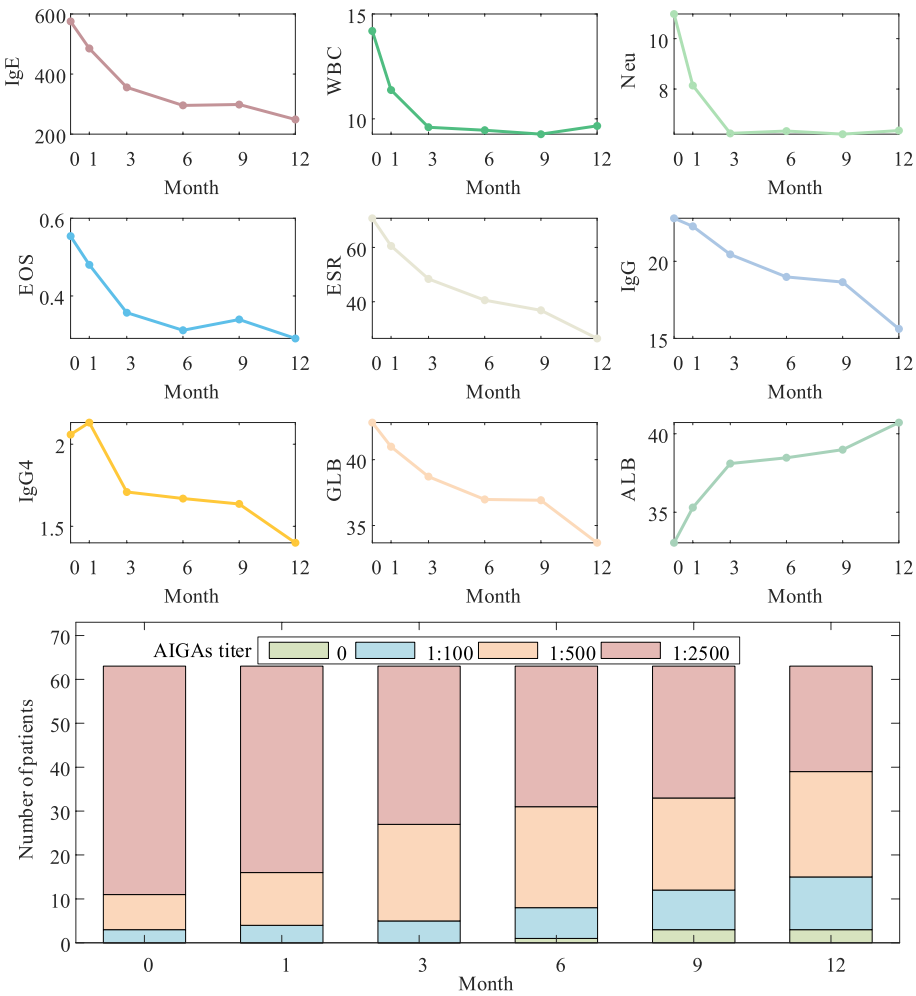

Fig. 4 The changes of IgE, WBC, Neu, EOS, ESR, IgG, IgG4, GLB, ALB, and AIGAs titers during the follow-up

immune system, resulting in elevated levels of IgE. At follow up, as the condition improved, IgE, along with WBC, Neu, EOS, ESR, IgG, and IgG4, decreased in parallel with the reduction of AIGAs, consistent with previous study [11]. Through correlation analysis, we found that IgE was more strongly correlated with IgG, IgG4, and GLB, with a weaker correlation than with EOS, ESR, and ALB. AIGAs belong to the IgG-type autoantibodies, which include subclasses IgG1, IgG3, and IgG4 [20], whereas IgE-type autoantibodies may play a pathogenic role in certain conditions leading to disease exacerbation or skin lesions.

In AIGAs syndrome, the presence of neutralizing AIGAs results in the blockage of IFN-γ signaling, which in turn affects macrophage immune function, allowing intracellular pathogens to survive and multiply leading to severe disseminated infections [21]. AIGAs are IgG-type autoantibodies. The most prevalent autoantibody isotype in serum is IgG. In autoimmune diseases, there is an IgG1/IgE isotype switch in B cells, which is regulated by cytokines and the nature of the antigen itself [22, 23]. Recent research has expanded the roles of IgE from allergies to autoimmune diseases. The mechanisms by which IgE autoantibodies contribute to these diseases may include the following: IgE autoantibodies have the capacity to bind to self-antigens and accumulate within tissues, thereby inducing modifications in structural cells and triggering inflammation. This inflammatory response is mediated not only via the activation of basophils and mast cells but also through innovative pathways, such as the stimulation of IFN secretion by plasmacytoid dendritic cells (pDCs), which, in addition to other effects, can facilitate the differentiation of plasma cells [14, 24]. The presence of these autoantibodies is linked to the maintenance of autoimmune processes, as self-reactive IgE antibodies foster adaptive immune responses directed against self-antigens through the activation of both T-cells and B-cells [25, 26]. This cascade leads to the production of autoantibodies and exacerbation of

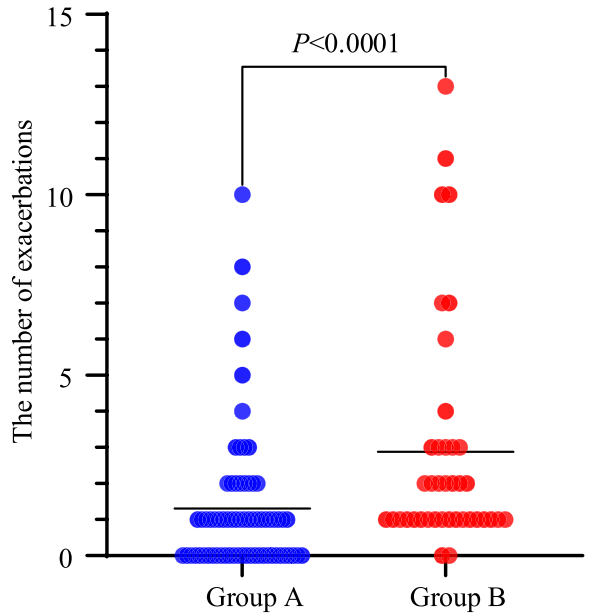

Fig. 5 Comparison of the number of exacerbations between Group A and Group B

Table 3 Univariable cox regression analysis of factors associated with disease exacerbation in patients with AIGAs syndrome

Variables	HR	95% confidence interval (CI)	*P* value
High AIGAs titers	5.168	2.376–11.239	< 0.001
Dyspnea	1.878	1.206–2.923	0.005
Chest tightness	1.892	1.114–3.214	0.018
Nausea	3.106	1.593–6.056	0.001
Hepatomegaly	2.494	1.266–4.915	0.008
Dry rales	3.583	1.304–9.844	0.013
Moist rales	1.755	1.072–2.872	0.025
Pleural effusion	2.132	1.024–4.438	0.043
Enlarged superficial lymph nodes	1.720	1.005–2.942	0.048
Skin involvement	2.104	1.351–3.277	0.001
Bloodstream infection	1.712	1.038–2.823	0.035
Spleen	1.883	1.054–3.365	0.032
Disseminated infection, yes *n* (%)	3.076	0.969–9.767	0.057
Fungal co-infection	2.149	1.291–3.577	0.003
WBC > 22.52×10^9cells/L	2.550	1.539–4.225	< 0.001
Neu > 19.02×10^9cells/L	2.892	1.738–4.812	< 0.001
Hb > 93.5 g/L	0.570	0.366–0.899	0.013
EOS > 0.27×10^9cells/L	1.858	1.165–2.964	0.009
IgG > 22.97 g/L	1.824	1.155–2.880	0.01
GLB > 56.4 g/L	2.185	1.223–3.905	0.008
IgE > 212 IU/mL	1.558	1.002–2.424	0.049
ALB > 36.1 g/L	0.421	0.217–0.818	0.011
CHE > 4739U/L	0.565	0.351–0.907	0.018

Table 4 Multivariable cox regression analysis of factors associated with disease exacerbation in patients with AIGAs syndrome

Variables	HR	95% confidence interval (CI)	*P* value
High AIGAs titers	2.418	1.037–5.642	0.041
Dyspnea	1.257	0.723–2.187	0.417
Nausea	1.314	0.467–3.698	0.605
Dry rales	3.424	0.859–13.646	0.081
Fungal co-infection	1.314	0.729–2.370	0.364
WBC > 22.52×10^9cells/L	2.199	1.194–4.050	0.012
Neu > 19.02×10^9cells/L	1.194	0.575–2.476	0.635
IgE > 212 IU/mL	1.527	0.907–2.569	0.111
ALB > 36.1 g/L	0.584	0.239–1.432	0.240
CHE > 4739U/L	0.789	0.436–1.425	0.431

autoimmune diseases. In summary, IgE and IgG autoantibodies (AIGAs) may synergize to the pathogenesis or progression of AIGAs syndrome. Therefore, it is interesting to further investigate IgE autoantibodies, which may shed light on pathogenesis of AIGAs syndrome in future studies.

In this study, patients with higher baseline IgE levels exhibited elevated inflammatory and immune markers, a greater number of symptoms, and a higher propensity for disease exacerbation and multi-organ involvement, suggesting more complex and severe disease conditions. Our previous studies have suggested the effectiveness of glucocorticoids, especially in the subtype of high AIGAs titers with immune damage as suggested in liang et al. [11, 12, 27]. Skin involvement is extremely common in AIGAs patients with elevated IgE levels. Despite undergoing anti-infectious treatment, these patients often continue to exhibit skin lesions, and pathological and microbiological examinations of the skin fail to identify any significant infectious agents, suggests that the skin involvement may be immunologically mediated. Such skin involvement can usually be alleviated with glucocorticoids, highlighting the potential role of immunological factors in the pathogenesis of skin manifestations in these patients. Reactive dermatoses, such as Sweet's syndrome in AIGAs syndrome, have been effectively treated with glucocorticoids in previous studies [28, 29]. As a common immunomodulatory agent, glucocorticoids can stabilize cell membranes, mitigate immune inflammatory responses, and maintain organismal homeostasis [30–32]. Glucocorticoids was effective in reducing IgE and improved disease condition in AIGAs syndrome. Additionally, given that IgE levels are elevated in some AIGAs patients with skin lesions, anti-IgE monoclonal antibodies, such as omalizumab, may reduce autoreactive IgE

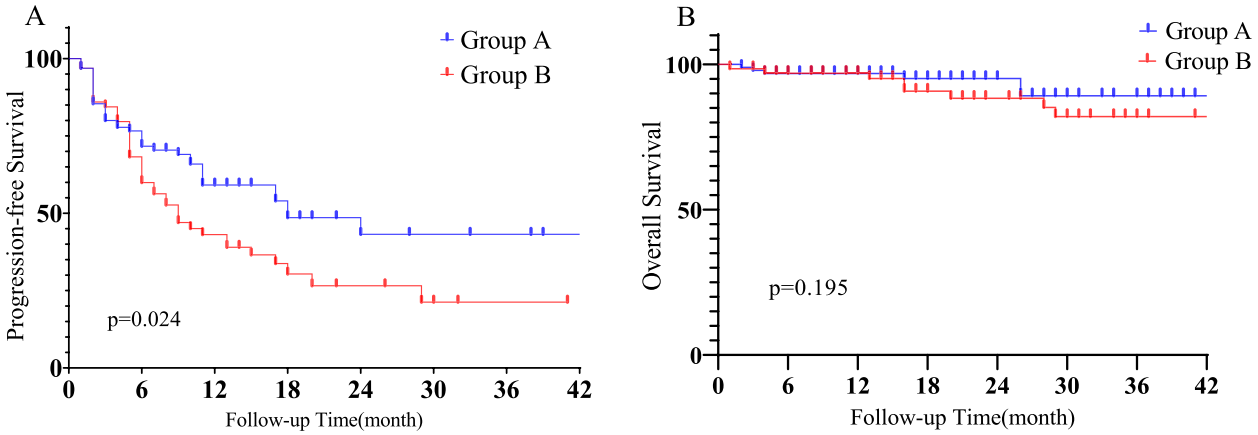

Fig. 6 Kaplan–Meier Curves for PFS(**A**) and OS(**B**) in the Group A and Group B

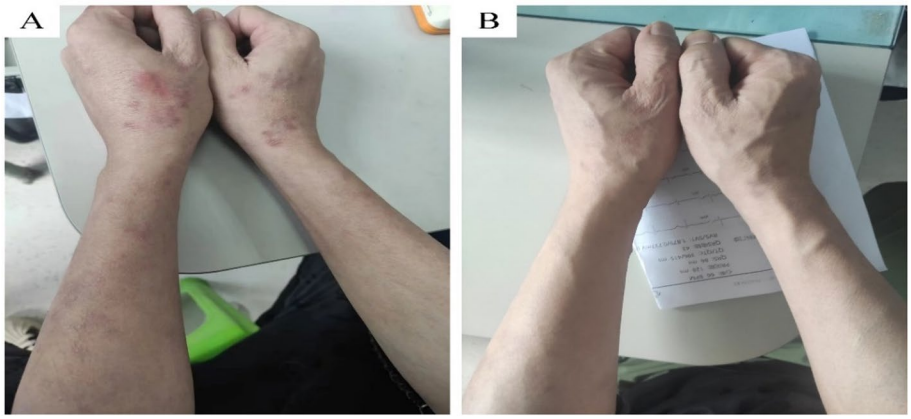

Fig. 7 Comparison of skin lesions before (**A**) and after (**B**) glucocorticoid treatment in a patient with AIGAs syndrome and elevated IgE

levels in the management of AIGAs syndrome. Further investigation is needed to explore the specific mechanisms of glucocorticoids, to determine the optimal duration of treatment or to develop new agents.

Our results indicated that high titers of AIGAs, high levels of WBC counts were risk factors of disease exacerbation. The correlation between AIGAs and disease severity and exacerbation has been confirmed [11, 33]. Elevated levels of AIGAs along with disseminated infections, predict a higher likelihood of disease exacerbation in AIGAs patients. Elevated IgE levels were found to be significant in univariate Cox regression analysis, not an independent risk factor for disease exacerbation, potentially due to collinearity with other markers, such as AIGAs. It is possible that the effects of IgE are indirectly associated through AIGAs, or confounding factors may be present, despite our efforts to reduce multicollinearity using lasso regression. Furthermore, disease exacerbation is a complex process likely influenced by the interplay of multiple factors. IgE may exert its effects through various mechanisms in the body, including direct involvement in immune responses and modulation of inflammatory cell activity.

This study, with a large number of cases, provides a comprehensive analysis of the role of circulating IgE in AIGAs syndrome, which will benefit to enhance clinical recognition and offers insights for further investigation into the pathogenesis. However, this study has some limitations. First, it was a retrospective study. Second, we did not conduct further analyses of atopy IgE. Lastly, there were no additional experimental studies investigating the mechanisms of IgE autoantibodies. Therefore, prospective studies and further experiments on the relationship between IgE and AIGAs are essential for extrapolating the findings.

Conclusions

Elevated serum IgE levels are associated with more severe clinical features in AIGAs syndrome, including increased infectious episodes, elevated inflammatory markers/immune markers, and multi-organ involvement, particularly skin. IgE serves as a marker of skin involvement and may indicate a potential response to glucocorticoid treatment.

Abbreviations

AIGAs	Anti-interferon-γ autoantibodies
IgE	Immunoglobulin E
IgG	Immunoglobulin G
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
IgA	Immunoglobulin A
IgM	Immunoglobulin M
IgG4	Immunoglobulin G4
GLB	Globulins
WBC	White Blood Cell
SF	Serum Ferritin
CHE	Cholesterol esterase
BMI	Body Mass Index
PFS	Progression-free survival
OS	Overall survival
ALB	Albumin
EOS	Eosinophils
IFN-γ	Interferon-γ
NTM	*Non-tuberculous mycobacteria*
TM	*Talaromyces marneffei*
TB	*Tuberculosis*
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12865-025-00696-6.

Supplementary Material 1: Supplementary Table S1. Comparison of Co-infections, Treatment, and Outcomes between Group A (IgE ≤ 212 IU/mL) and Group B (IgE > 212 IU/mL). Supplementary Table S2. Comparison of Clinical Characteristics in Patients with and without Skin Involvement. Supplementary Table S3. Comparison of laboratory data before and after glucocorticoid treatment of AIGAs syndrome with Serum IgE>212 IU/mL.

Supplementary Material 2: Supplementary Figure 1. Comparison of skin lesions before (A) and after (B) glucocorticoid treatment in a patient with AIGAs syndrome and elevated IgE levels who also presented with Sweet's syndrome. Supplementary Figure 2. Photomicrograph of a skin lesion from a patient with AIGAs syndrome and elevated IgE levels, presenting with Sweet's syndrome. The image showed a dense infiltration of neutrophils, histiocytes, and lymphocytes in the epidermal and upper dermal layers. Necrosis and parakeratosis of the epithelium were seen. (hematoxylin-eosin; before glucocorticoid treatment).

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Authors contributions

Z.H designed the study and had full responsibility for the facticity of data. H.L, S. L, X. L, and X. H conducted the experiments and collected data. N.C and Q.Y managed data extraction and analyses. N.C contributed to manuscript writing. All authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University.
All of the patients provided written informed consent for enrollment in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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