Volume 3, Issue 5, May - 2025 **ISSN (E):** 2938-3811

THE SIGNIFICANCE OF CIRCULATING IMMUNE COMPLEXES AS PROINFLAMMATORY MARKERS IN CHILDREN WITH EPIDERMOLYSIS BULLOSA

A.A. Ismailova
T.U. Aripova
I.U. Khamraeva
Sh.Z. Khabibullaev
S.A. Ubaydullaev
N.F. Ruzimurodov
Institute of Immunology and Human Genomics,
Academy of Sciences of the Republic of Uzbekistan, Tashkent

Abstract
Systemic inflammation is a well-recognized aspect of epidermolysis bullosa (EB), yet many of the underlying immune mechanisms remain under active investigation. The aim of this study was to evaluate the diagnostic and prognostic significance of circulating immune complexes (CICs) of different molecular sizes in pediatric patients with EB.

Keywords: Epidermolysis bullosa, systemic inflammation, immunopathogenesis, pediatric dermatology.

Introduction

Materials and Methods

CICs of both high and low molecular weight were assessed in the sera of 42 children aged 2 to 12 years diagnosed with EB. The study population was hospitalized at the Republican Center of Dermatology, Ministry of Health, Uzbekistan, and blood samples were collected during the first two days of admission, prior to initiation of anti-inflammatory therapy.

Results

Analysis demonstrated a significant increase in CICs: large-molecular-weight CICs (3% PEG-precipitable) were elevated by a factor of 7.2, while small-molecular-weight CICs (4% PEG-precipitable) increased by a factor of 8.5 compared to healthy normative values. The ratio of large to small CICs (CIC3%/CIC4%) shifted from 1.1 in healthy controls to 1.7 in EB patients, indicating active systemic inflammation.

Conclusion

Elevated levels of CICs of varying molecular sizes in children with EB, particularly during disease exacerbation, may serve as sensitive biomarkers of ongoing systemic inflammation and immune dysregulation.

Web of Scientists and Scholars: Journal of Multidisciplinary Research

Relevance

Epidermolysis bullosa (EB) is a group of genetically determined skin disorders marked by extreme skin fragility, chronic wounds, and recurrent infections. While primarily considered a structural skin disorder, recent advances in immunodermatology have highlighted the role of systemic inflammation in the pathogenesis of EB, particularly in severe forms affecting children. Accumulating data from small, heterogeneous patient cohorts have shown that inflammatory mediators, including C-reactive protein and a range of cytokines, are elevated in EB, especially during disease flares. These insights have opened new therapeutic avenues involving anti-cytokine agents, although clinical trials remain ongoing. However, circulating immune complexes (CICs)—pathological aggregates of antigens and antibodies known to activate the complement system and contribute to tissue damage—have not yet been extensively studied in EB, especially in pediatric patients. These complexes are considered both indicators and mediators of immune activation in autoimmune diseases and chronic infections. Given their ability to deposit in tissues and provoke inflammation, and the known involvement of humoral immunity in EB, it is plausible that CICs may also contribute to the immune dysregulation observed in this disease. Understanding the distribution and magnitude of CICs, particularly their molecular sizes, could provide valuable insight into the immunopathogenesis of EB and offer additional biomarkers of disease activity.

Objective

The aim of this study was to assess the diagnostic and prognostic significance of circulating immune complexes of varying molecular sizes in children diagnosed with epidermolysis bullosa during the exacerbation phase of the disease.

Materials and Methods

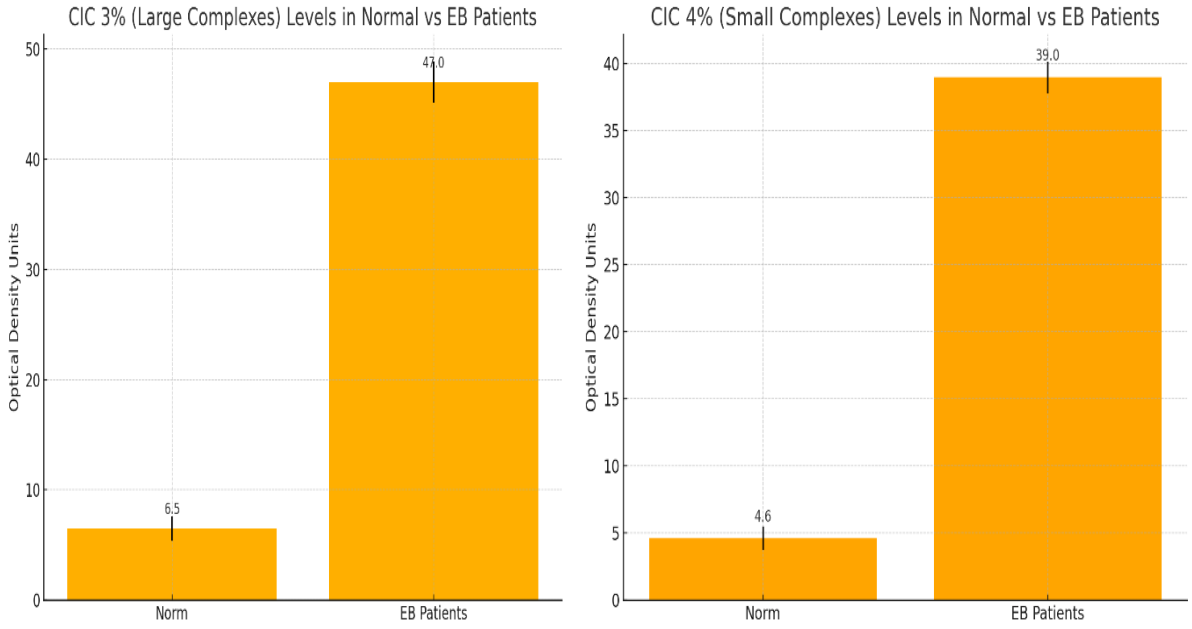
This study involved 42 children aged 2 to 12 years diagnosed with various clinical forms of epidermolysis bullosa and hospitalized at the Republican Center of Dermatology, Ministry of Health of Uzbekistan. Diagnosis was confirmed through clinical and genetic evaluation. Blood samples were collected during the first two days of hospitalization, prior to the initiation of anti-inflammatory or systemic therapy. Demographic and clinical analysis revealed a predominance of male patients (51.5%), most of whom were from rural areas (66.8%), with the largest age subgroup between 1 and 5 years. The majority of patients were diagnosed with the simplex form of EB (56.9%), while 34.1% had the dystrophic variant. Standard clinical and laboratory assessments were conducted, and additional immunological testing was performed using a spectrophotometric method for quantifying circulating immune complexes. Serum CIC levels were measured using polyethylene glycol (PEG) precipitation at two different concentrations: 3% for large complexes and 4% for small complexes. After dilution of 0.3 mL of serum in 0.9 mL borate buffer (pH 8.4), PEG solutions were added and samples incubated at room temperature. Optical density was measured at 450 nm using a 1 cm cuvette, and the resulting values were compared against normative data. Statistical analysis of CIC levels was conducted using Student's t-test to determine the significance of observed differences.

Results

Systemic inflammation was clinically confirmed in the majority of patients through markedly elevated levels of C-reactive protein, found in approximately 90% of the children. Further immunological assessment revealed significantly elevated levels of circulating immune complexes of both large (CIC 3%) and small (CIC 4%) molecular sizes in the EB group compared to healthy controls. The average concentration of large CICs in EB patients was 47 ± 1.9 OD units, whereas the normative value was 6.5 ± 1.12 OD units, corresponding to a 7.2-fold increase. The individual values ranged widely from 1 to 58 OD units, indicating considerable inter-patient variability likely associated with EB subtype and phase of disease (see Figure 1).

For small CICs, the average concentration in EB patients was 39 ± 1.2 OD units, with normative levels at 4.6 ± 0.88, representing an 8.5-fold increase. Values in this group ranged from 4 to 136 OD units, further reinforcing the presence of systemic immune activation. Notably, the elevation in small CICs was even more pronounced than in large CICs, consistent with literature suggesting that small, soluble immune complexes formed under antigen excess are more pathogenic due to their ability to deposit in tissues and evade clearance.

The ratio of large to small CICs (CIC3%/CIC4%) also revealed a significant shift. In healthy individuals, the ratio averaged 1.1, whereas in EB patients it increased to 1.7. This altered ratio reflects not only the absolute rise in CIC levels but also a shift in the balance of immune complex composition. This imbalance may be indicative of ongoing immune complex formation exceeding the capacity of clearance systems such as monocyte–macrophage pathways, especially under the stress of active skin injury and microbial colonization associated with EB.



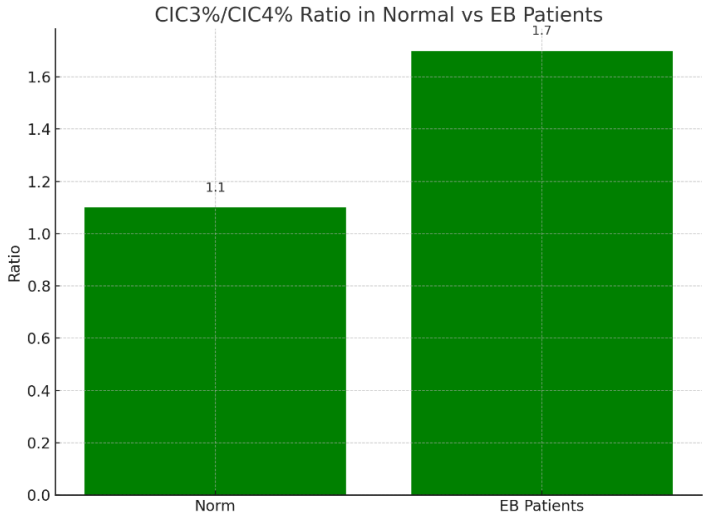


Figure 1. Comparative Immune Complex Assessment in Active Epidermolysis Bullosa and Normal Pediatric Serum

Taken together, these findings demonstrate a clear profile of humoral immune activation during EB exacerbations. The data suggest that both the absolute levels and proportions of CICs provide valuable insights into disease activity and systemic inflammatory burden in pediatric EB patients.

Discussion

The observed elevation of circulating immune complexes in children with EB underscores the broader immunological dysfunction associated with the disease. While previous research has primarily focused on cytokines as drivers of systemic inflammation in EB, this study highlights CICs as additional, potentially more stable indicators of ongoing immune activation. The significant increase in both large and small CICs suggests that the humoral immune system is actively involved during disease flares. Smaller CICs, which are more soluble and tend to accumulate in tissues under conditions of antigen excess, have been shown in other disorders to possess high pathogenic potential. Their persistence in circulation may reflect not only an intensified immune response but also a reduction in the efficacy of phagocytic clearance by monocytes and neutrophils, which is known to be impaired in chronic inflammatory conditions. The elevated CIC3%/CIC4% ratio observed in EB patients provides further evidence of this imbalance, supporting the hypothesis that CIC profiles could serve as surrogate markers for disease monitoring. Moreover, the presence of high CIC levels during exacerbation, and the possibility of their continued elevation during remission phases reported in the literature, suggest that CICs may also hold value in predicting the course of the disease or identifying subclinical inflammation. Further studies involving longitudinal data collection and correlation with clinical outcomes would be necessary to validate these observations and explore their utility in guiding therapeutic decisions.

Web of Scientists and Scholars: Journal of Multidisciplinary Research

Conclusion

This study demonstrates that circulating immune complexes of both large and small molecular sizes are significantly elevated in children with epidermolysis bullosa during periods of disease activity. The shift in the CIC3%/CIC4% ratio from 1.1 in healthy individuals to 1.7 in patients reflects a state of systemic inflammation and immunological imbalance. These findings support the relevance of CICs as potential biomarkers in the immunopathogenesis of EB and justify their inclusion in future diagnostic and prognostic assessments in clinical practice.

References

1. Reimer-Taschenbrecker A, Künstner A, Hirose M, Hübner S, Gewert S, Ibrahim S, et al. Predominance of Staphylococcus correlates with wound burden and disease activity in dystrophic epidermolysis bullosa: a prospective case-control study. J Invest Dermatol. 2022; 142: 2117–2127.e8.
2. Annicchiarico G, Morgese MG, Esposito S, Lopalco G, Lattarulo M, Tampoia M, et al. Proinflammatory cytokines and antiskin autoantibodies in patients with inherited epidermolysis bullosa. Medicine. 2015; 94:e1528.
3. Esposito S, Guez S, Orenti A, Tadini G, Scuvera G, Corti L, et al. Autoimmunity and cytokine imbalance in inherited epidermolysis bullosa. Int J Mol Sci. 2016; 17:1625.
4. Tampoia M, Abbracciavento L, Morrone M, Fumarulo R. IL-6/IL-10 ratio as a prognostic and predictive marker of the severity of inherited epidermolysis bullosa. Iran J Immunol. 2017; 14: 340–349.
5. Onoufriadis A, Proudfoot LE, Ainali C, Torre D, Papanikolaou M, Rayinda T, et al. Transcriptomic profiling of recessive dystrophic epidermolysis bullosa wounded skin highlights drug repurposing opportunities to improve wound healing. Exp Dermatol. 2022; 31: 420–426.
6. Nguyen HH, Shinkuma S, Hayashi R, Katsumi T, Nishiguchi T, Natsuga K, et al. New insight of itch mediators and proinflammatory cytokines in epidermolysis bullosa. J Cutan Immunol Allergy. 2022; 5: 78–87.
7. Odorisio T, Di Salvio M, Orecchia A, Di Zenzo G, Piccinni E, Cianfarani F, et al. Monozygotic twins discordant for recessive dystrophic epidermolysis bullosa phenotype highlight the role of TGF-β signalling in modifying disease severity. Hum Mol Genet. 2014; 23: 3907–3922.
8. Cianfarani F, De Domenico E, Nyström A, Mastroeni S, Abeni D, Baldini E, et al. Decorin counteracts disease progression in mice with recessive dystrophic epidermolysis bullosa. Matrix Biol. 2018; 81: 3–16.
9. Nyström A, Thriene K, Mittapalli V, Kern JS, Kiritsi D, Dengjel J, et al. Losartan ameliorates dystrophic epidermolysis bullosa and uncovers new disease mechanisms. EMBO Mol Med. 2015; 7: 1211–1228.
10. Papanikolaou M, Onoufriadis A, Mellerio JE, Nattkemper LA, Yosipovitch G, Steinhoff M, et al. Prevalence, pathophysiology and management of itch in epidermolysis bullosa. Br J Dermatol. 2021; 184: 816–825.

11. Shehadeh W, Sarig O, Bar J, Sprecher E, Samuelov L. Treatment of epidermolysis bullosa pruriginosa-associated pruritus with dupilumab. Br J Dermatol. 2020; 182: 1495–1497.
12. Clawson RC, Duran SF, Pariser RJ. Epidermolysis bullosa pruriginosa responding to dupilumab. JAAD Case Rep. 2021; 16: 69–71.
13. Wang Y, Zhou M, Zhang L, Zheng S, Hong Y, Gao X-H. Amelioration of dystrophic epidermolysis bullosa pruriginosa symptoms with dupilumab: a case report. Dermatol Ther. 2021; 34:e15130.
14. Reimer A, Hess M, Schwieger-Briel A, Kiritsi D, Schauer F, Schumann H, et al. Natural history of growth and anaemia in children with epidermolysis bullosa: a retrospective cohort study. Br J Dermatol. 2020; 182: 1437–1448.
15. Has C, Bauer JW, Bodemer C, Bolling MC, Bruckner-Tuderman L, Diem A, et al. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. Br J Dermatol. 2020; 183: 614–627.
16. Loh CCH, Kim J, Su JC, Daniel BS, Venugopal SS, Rhodes LM, et al. Development, reliability, and validity of a novel epidermolysis bullosa disease activity and scarring index (EBDASI). J Am Acad Dermatol. 2014; 70: 89–97.e1–13.
17. Morris V, Murphy LM, Rosenberg M, Rosenberg L, Holzer CE, Meyer WJ. Itch assessment scale for the pediatric burn survivor. J Burn Care Res. 2012; 33: 419–424.
18. Guide SV, Gonzalez ME, Bağcı IS, Agostini B, Chen H, Feeney G, et al. Trial of beremagene geperpavec (B-VEC) for dystrophic epidermolysis bullosa. N Engl J Med. 2022; 387: 2211–2219.
19. Eyerich K, Eyerich S. Immune response patterns in non-communicable inflammatory skin diseases. J Eur Acad Dermatol Venereol. 2018; 32: 692–703.
20. Haghighi Javid A, Li D, Technau-Hafsi K, Has C. Interleukin-17A immune pattern across genetic acantholytic and blistering disorders. Clin Exp Dermatol. 2023; 48: 518–523.

Web of Scientists and Scholars: Journal of Multidisciplinary Research