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COMMENTARY

Hypergammaglobulinemia in Hidradenitis Suppurativa Patients: A New Emerging Association

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Abstract: Hypergammaglobulinemia is a sign of B cell and plasma cell hyperactivity marked by elevated levels of gamma globulins, proteins within the gamma fraction of serum electrophoresis, linked to diseases like acute hepatitis, Hodgkin's lymphoma, autoimmune conditions, and neoplasms. Monoclonal gammopathy of undetermined significance (MGUS) is found in 3.2% of individuals over 50 and 5.3% over 70 due to immunosenescence, the gradual immune decline influenced by chronic infections, malnutrition, hormonal dysregulation, and smoking. This retrospective, single-center observational study explored the association between hypergammaglobulinemia and Hidradenitis Suppurativa (HS) based on sex, age, disease severity (IHS4 score), and Adalimumab treatment. Sixty patients (54% women, 46% men, average age 47) were observed over 12 months. Hypergammaglobulinemia was found in 68% of patients, with the highest prevalence in the 15–29 age group (80%). It was also associated with increased disease severity, particularly in younger patients, who showed a reduced clinical response to Adalimumab (average HiSCR difference of 25%). While common inflammation markers like CRP and ESR remain essential for HS management, this study highlighted that hypergammaglobulinemia is more prevalent in younger patients with severe forms of HS. Unlike older patients, where immunosenescence can lead to more normal gamma globulin levels, younger patients demonstrated a strong link between chronic inflammation and disease. The findings suggest further investigation is needed to determine whether hypergammaglobulinemia is merely a marker or contributes to HS pathogenesis. If validated, hypergammaglobulinemia could be used to monitor disease progression and customize treatments. In conclusion, integrating immunological assessments into HS management could improve patient outcomes, particularly in younger demographics. With larger studies, hypergammaglobulinemia might be considered a predictive factor for HS, especially for severe or treatment-resistant cases.

Keywords: hidradenitis suppurativa, hypergammaglobulinemia, immunosenescence

Introduction

Hypergammaglobulinemia is an immunoproliferative disorder characterized by elevated levels of gamma globulins, proteins found in the gamma fraction of a serum electrophoretic trace. The increase in these proteins can be pathologically significant as it is associated with various diseases such as inflammatory conditions, cirrhosis, connective tissue diseases, acute hepatitis, mononucleosis, Hodgkin's lymphoma, malignant neoplasms, plasmacytoma, parasitic infections, Hashimoto's thyroiditis, burns, and sarcoidosis. Conversely, a decrease in their levels has been observed in immunosuppressive states such as AIDS, renal failure, Cushing's syndrome, and with the use of immunosuppressive drugs and steroids.[1,2] Monoclonal gammopathy of undetermined significance (MGUS) occurs in 3.2% of persons 50 years of age or older and in 5.3% of those 70 years of age or older.[2]

The higher prevalence in older age is justified by immunosenescence, which is the physiological and gradual deterioration of the immune system because of aging. It is a multifactorial condition associated with advancing age. The factors that predispose to this condition are primarily age but also include chronic viral infections that cause antigenic stimulation, malnutrition and undernutrition (particularly protein deficiency), dysregulation of various hormonal pathways, and smoking.[3]

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Materials and Methods

These concepts gave rise to our retrospective single-center, observational study designed to evaluate the potential association between hypergammaglobulinemia and hidradenitis suppurativa (HS) according to sex, age, disease severity according IHS4 score, and treatment with Adalimumab in HS patients. Hypergammaglobulinemia was evaluated by hematochemical tests. We evaluated the serum levels of IgG, IgM, and IgA in relation to disease severity, classified according to IHS4, at three-month intervals throughout the one-year study period. Only serum IgG levels, and not IgA or IgM, showed a significant correlation with severe IHS4. (Threshold values are detailed in Table 1)

Results

Sixty patients were recruited for the study, including 32 women (54%) and 28 men (46%), mean age 47 years, observation period was 12 months. Clinical features of patients and results of the study are reported in Table 1.

Forty-one patients had hypergammaglobulinemia (68%), and thirty-four patients (57%) were on Adalimumab therapy. The results were as follows: the age range most affected by hypergammaglobulinemia was the youngest age group, namely 15 to 29 years (80%), after which the prevalence decreased in higher age groups (Figure 1).

Correlation between IHS4 disease severity and frequency of hypergammaglobulinemia: disease severity was higher in the 15–29 age range, which is also the age range where hypergammaglobulinemia was more common (Figure 2). Finally, we observed a lower clinical response to Adalimumab therapy (mean 25% HiSCR difference) in young patients with HS and hypergammaglobulinemia compared to the rest of the study sample. The collected data were processed using GraphPad Prism software (GraphPad Inc., La Jolla, CA, USA). Paired *t*-test was used to compare data. P-value <0.05 with a 95% confidence interval was considered statistically significant in all analyses performed.

Discussion

Inflammation parameters commonly monitored in HS, such as CRP and ESR, remain fundamental for therapeutic management.[4,5] However, our study has shown that hypergammaglobulinemia is increasingly frequent in HS subjects, particularly in young patients with moderate to severe forms of the disease. Typically, in patients without HS, gamma globulins are more frequently elevated in the elderly population, contrary to our findings. This discrepancy may be due to physiological immunosenescence in elderly patients, which in this pathology can result in more normal gamma globulin levels compared to younger patients, where the link between chronic inflammation and the disease is not well controlled.[6–8]

Differently from the study conducted by Mintoff et al[6] where the authors conclude that Serum IgG behaves as a marker of severe HS disease, our study explored this correlation in practice, in particular we noted a characteristic age range and correlated therapeutic response with Adalimumab.

Table 1 Clinical Features of Patients with Results of the Study

Patients	60 32F (54%) 28M (46%) Mean age: 47
Cut off IgG Serum	0,00–17,00 g/dl
Hypergammaglobulinemia	41 Patients 34 during Adalimumab Therapy
Age range most affected by hypergammaglobulinemia	15–29 age range years
IHS4 severity and Hypergammaglobulinemia	Higher in the 15–29 age range
Response to Adalimumab therapy	25% HiSCR difference by patients without hypergammaglobulinemia

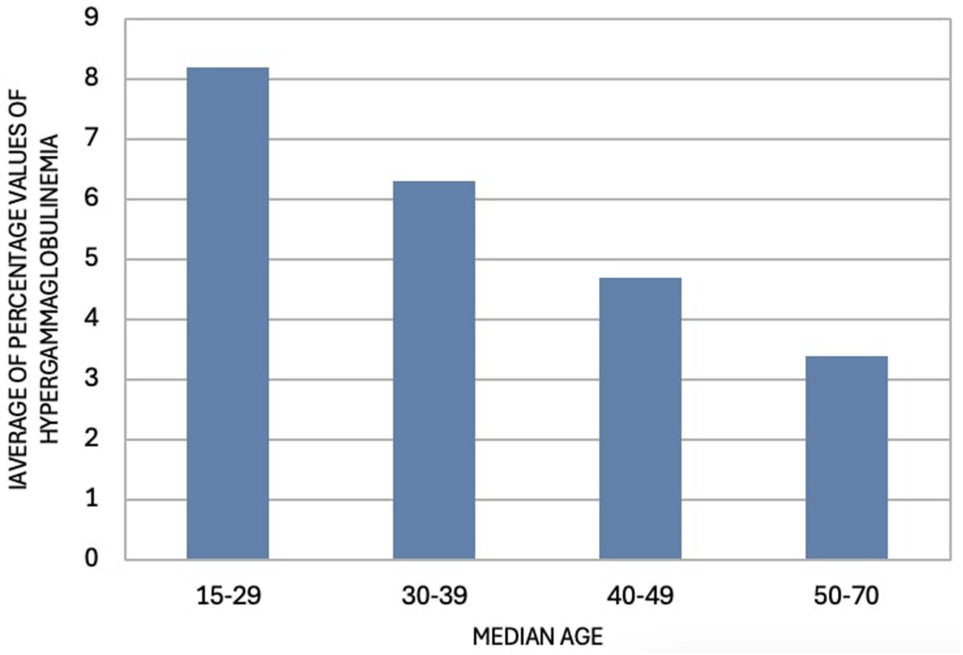

Figure 1 Average Percentages Of Gamma Globulin In Relation To Age Ranges Of All Patients.

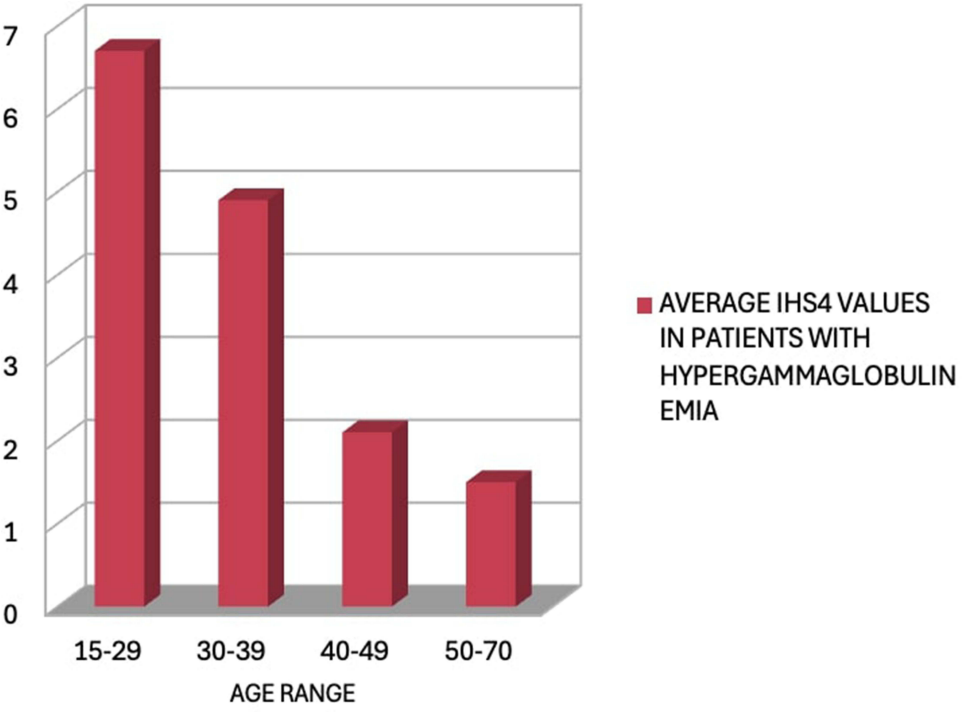

Figure 2 Average IHS4 Values.

We certainly agree with the authors with their findings that plasma cells and immunoglobulins may interact with the complement system, amplifying inflammation and contributing to the heavy inflammatory burden observed in HS.[6]

To expand on this conclusion, we could further explore the significance of these correlations and their potential implications for future research and clinical practice.

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Conclusion

Firstly, the correlation between young patients with HS (Hidradenitis Suppurativa) and hypergammaglobulinemia suggests that immune dysregulation might play a substantial role in the onset or exacerbation of HS in younger demographics. Future studies could investigate whether hypergammaglobulinemia is merely a biomarker associated with the disease or whether it contributes causally to HS pathogenesis. Understanding this relationship could help refine diagnostic criteria, making it possible to detect HS at earlier stages or identify at-risk individuals based on immune markers.

Secondly, the link between hypergammaglobulinemia and the severity of HS underscores the possibility that increased immunoglobulin levels could serve as an indicator of disease progression or severity. If future studies confirm this relationship, monitoring hypergammaglobulinemia levels could become a tool for assessing disease activity and tailoring treatments to individual patients' needs. Additionally, this could open avenues for therapeutic interventions targeting immune pathways, potentially reducing the severity or frequency of HS flares.[7–10]

In summary, these findings not only suggest directions for further investigation into immune markers in HS but also raise the possibility of integrating immunological assessments into the management of HS, especially among younger patients.

Therefore, with larger datasets encompassing more patients, hypergammaglobulinemia could potentially be considered as a predictive factor for HS, especially for more severe or treatment resistant disease.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author.

Ethics Statement

The study was conducted in accordance with the protocol and applicable ethical guidelines and principles derived from the 1964 Declaration of Helsinki. The study protocol was reviewed and approved by Local Ethic Committee University of Naples Federico II. Patients provided written informed consent before undergoing the specific study procedures.

Informed Consent

The patients gave the consent for publication.

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Disclosure

The authors declare no conflicts of interest in this work.

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