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Original Article

Complete Blood Cell Count-Derived Inflammation Biomarkers in Patients with Xanthelasma Palpebrarum

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Abstract

Objectives: Xanthelasma palpebrarum (XP) is the most common type of cutaneous xanthoma, characterized by yellowish cutaneous plaques commonly located near the medial canthus of the eyelid. Although dyslipidemia significantly contributes to its development, inflammation is also believed to be another element in the pathogenesis, especially in normolipidemic patients. Recently, cell counts derived from complete blood counts have been identified as indicators of systemic inflammatory conditions and have also been under discussion concerning their relevance to ocular diseases. This study aimed to assess inflammation indices derived from complete blood cell counts (CBC) in XP patients with normal lipid levels.

Methods: Patients who had been referred to the oculoplasty department with the diagnosis of XP between January 2020 and January 2023 and age-matched control subjects were retrospectively reviewed. Patients who had abnormal lipid profiles and systemic diseases such as diabetes mellitus, hypertension, malignancy, cardiovascular diseases, systemic infections, and inflammatory diseases were not included in the study. CBC parameters were analyzed and compared between the groups.

Results: The study comprised 27 normolipidemic patients with XP and 27 age-matched healthy individuals as the control group. There were no statistically significant differences between the two groups in terms of age (p=0.143). The mean hemoglobin, neutrophil, monocyte, lymphocyte, platelet, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, systemic immune-inflammation index, and aggregate index of systemic inflammation values were higher in the patient group, but the differences were not statistically significant (p>0.05). The mean red cell distribution width and platelet-to-lymphocyte ratio appeared to be lower in the patient group compared to the control group; however, no significant differences were observed between the two groups (p=0.272, p=0.387, respectively).

Conclusion: This study might offer insights into the pathogenesis of XP, yet numerous questions remain unanswered, awaiting further investigation in future studies.

Keywords: Aggregate index of systemic inflammation, CBC-derived inflammation indices, monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, xanthelasma palpebrarum.

Introduction

Xanthelasma palpebrarum (XP) is the most common type of cutaneous xanthoma, characterized by yellowish cutaneous plaques, especially located near the medial canthus of the eyelid, predominantly occurring on the upper lid (1,2). The prevalence of XP is approximately 0.3% in men and 1.1% in women (1). Although the exact pathogenesis is not fully understood, XP represents the lipid accumulation within the histiocytic foam cells, typically found in the middle and su-

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perficial layers of the dermis, with associated fibrosis and inflammation (1,3). Hyperlipidemia, thyroid dysfunction, diabetes mellitus, inflammatory skin disorders, and allergic contact dermatitis are possible pathogenic triggers (4,5).

Inflammation is believed to be one component of the pathogenesis in patients with XP, contributing to the leakage of lipoproteins through dermal capillaries and subsequent engulfment by macrophages (6). In addition, the upregulation of inflammatory cells and mediators has been proposed to play a role in xanthelasma formation in the eyelid, like atherogenesis (7).

Reports also indicate that nearly half of the patients diagnosed with XP have hypercholesterolemia, suggesting that inherited or acquired dyslipidemias significantly contribute to its pathophysiology (1,3,8). However, many XP patients have normal lipid profiles (3). This raises the question: What components contribute to the pathogenesis in normolipidemic XP patients? This remains a controversial aspect, prompting ongoing debate and investigation.

Recently, complete blood cell count (CBC) parameters and their combinations have been identified as indicators of systemic vascular and inflammatory conditions (9-14). These markers have also been a subject of discussion concerning ocular diseases such as diabetic retinopathy, glaucoma, age-related macular degeneration, retinal vein occlusion, keratoconus, uveitis, and dry eye disease (15-20).

There have been limited studies systematically evaluating the inflammatory status of XP. Given this gap, the aim of the study was to evaluate the potential involvement of inflammation in normolipidemic XP patients. Specifically, it investigated whether there were any variations in inflammation biomarkers derived from CBC among these patients. To the best knowledge of the authors, the study marks the first attempt to assess the immune profile in normolipidemic XP patients.

Methods

Patients who had been referred to the oculoplasty department with the diagnosis of XP between January 2020 and January 2023 and age-matched control subjects were retrospectively reviewed. Patients who had abnormal lipid profiles and systemic diseases such as diabetes mellitus, hypertension, malignancy, cardiovascular diseases, systemic infections, and inflammatory diseases were not included in the study. The study protocol was approved by the institutional Ethics Committee (E1-23-3900) and adhered to the tenets of the Declaration of Helsinki.

Routine CBC parameters for the groups were analyzed. Hemoglobin (HG), red cell distribution width (RDW), neutrophil (N), monocyte (M), lymphocyte (L), platelet (P), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII) ((N × P/lymphocyte ratio), and the aggregate index of systemic inflammation (AISI) ((N × M × P)/L ratio) were compared between the two groups.

Statistical Analysis

The data distribution was assessed using the Kolmogorov-Smirnov test. Inflammatory markers were compared with the control group using various statistical tests: the Student's t-test for two numerical parametric independent groups, the dependent samples t-test for two numerical parametric dependent groups, the Mann–Whitney U-test for two numerical nonparametric independent groups, and the Wilcoxon test for two numerical nonparametric dependent groups. A value of $p \leq 0.05$ will be considered significant. All statistical analyses were performed using the SPSS 25.0 program (SPSS for Windows, version 25.0; SPSS, Inc., Chicago, IL, USA).

Results

A total of 27 normolipidemic XP patients and 27 age-matched healthy individuals as the control group were included in this retrospective study.

The mean age of normolipidemic XP patients was 49.03±8.05 years (34–67), while that of the control group was 52.25±7.87 years (39–69). There was no statistically significant difference in age between the two groups ($p=0.143$).

The mean Hg, N, M, L, P, NLR, MLR, SII, and AISI values were observed to be higher in the normolipidemic XP patients compared to the control group, yet these differences did not yield statistical significance ($p>0.05$). Conversely, the mean RDW and PLR values were lower in the normolipidemic XP patients than in the control group; however, these differences also did not reach statistical significance ($p=0.272$, $p=0.387$, respectively). Table 1 illustrates the comparison of laboratory parameters between the study groups.

Discussion

Recently, CBC parameters and their combinations have been identified as indicators of systemic vascular and inflammatory conditions (9-14).

Recently, CBC-derived indices, including NLR, MLR, PLR, SII, and AISI, have been used and proposed as prognostic indicators for evaluating systemic inflammatory status in several systemic diseases (9-14,21). These markers have also been under discussion concerning ocular diseases, such as diabetic retinopathy, glaucoma, age-related macular degeneration, retinal vein occlusion, keratoconus, uveitis, and dry eye disease (15-20). Indeed, SII holds an advantage as it incorporates three indices – Ns, Ls, and Ps – within its formula. This composite measure potentially allows for a simultaneous reflection of both inflammatory and immune states.

Table 1. Comparison of laboratory parameters between the study groups

	Normolipidemic XP group	Control group	p
HG (g/dL)	14.10±1.09	13.88±1.37	0.514
RDW (%)	13.39±1.02	13.69±0.98	0.272
Neutrophils ($\times 10^9$/L)	4.84±2.53	4.02±1.37	0.142
Monocytes ($\times 10^9$/L)	0.43±0.13	0.41±0.15	0.508
Lymphocytes ($\times 10^9$/L)	2.46±0.97	2.09±0.57	0.98
Platelets ($\times 10^9$/L)	270.51±75.33	262.03±44.62	0.617
NLR	2.25±1.92	2.01±0.71	0.549
MLR	5.84±1.96	5.53±1.72	0.545
PLR	121.72±55.53	133.34±41.23	0.387
SII	663.72±906.77	533.01±218.73	0.470
AISI	284.70±368.47	219.47±122.32	0.387

XP is the most common type of cutaneous xanthoma which is a benign periocular tumor characterized by yellowish cutaneous plaques, especially located near the medial canthus and more frequently on the upper lid (1,2). The prevalence of XP is approximately 0.3% in men and 1.1% in women (1). Lesions of XP tend to advance gradually, becoming more conspicuous over time and generally do not regress without treatment. While the precise pathogenesis is not entirely elucidated, XP involves the accumulation of lipids within the histiocytic foam cells typically found in the middle and superficial layers of the dermis, with associated fibrosis and inflammation (1,3). Hyperlipidemia, thyroid dysfunction, diabetes mellitus, inflammatory skin disorders, and allergic contact dermatitis are possible pathogenic triggers (4,5).

Reports suggest that approximately half of the patients diagnosed with XP have hypercholesterolemia (1,3). Consequently, congenital or acquired dyslipidemias are believed to significantly contribute to its pathophysiology (3,8). Indeed, the literature consistently confirms an association between xanthelasma and hyperlipidemia. Studies have demonstrated significantly higher total cholesterol and LDL levels in patients with xanthelasma when compared to control groups. (22,23). Decreased high-density lipoprotein (HDL) levels may also be associated with XP, even in normolipidemic patients, as a result of impaired cholesterol removal from the tissues (3,24). However, many XP patients exhibit normal lipid profiles. In normolipidemic XP patients, one aspect of the pathogenesis is believed to involve inflammation. This process involves the extravasation of lipoproteins through dermal capillary blood vessels, followed by the engulfment of these lipoproteins by macrophages (6). Analogous to atherogenesis, this process is thought to result from the upregulation of inflammatory cells and mediators within the eyelid tissue (7).

Experimentally, both xanthomas and atheromas share the same mechanisms of cholesterol storage, and it is well known that inflammation is a key process for atherosclerosis from its very beginning to plaque rupture (3).

Certainly, when examining literature related to inflammation in XP patients, a study revealed elevated NLR and PLR levels in XP patients (25). This particular study stands as the only one to date that utilized CBC-derived inflammation indices in XP patients. However, it is important to note that the patient group in this study included individuals with both hyperlipidemia and normolipidemia. When reviewing studies on CBC-derived inflammation indices, another notable study focused on gastric xanthelasmas. In this research, it was observed that N levels and NLR were notably higher while HDL levels were lower in patients with gastric xanthelasma compared to the control group ($p<0.05$) (26). In a histopathologic and immunohistochemical examination, XP specimens exhibited a notably more intense chronic lymphocytic infiltrate in comparison to control blepharoplasty tissues. This finding suggests the potential involvement of inflammation in XP (27). However, there was no recorded data pertaining to the lipid profile in this particular study. In a case report about a normolipidemic XP patient in conjunction with the development of Castleman's disease, the authors observed regression after removal of the tumor and resolution of inflammation. The authors emphasize the role of inflammation in lipid deposition and foam cell formation. In the study, the potential reversibility of the injury and the evidence pointing toward the necessity for further investigation into inflammation's role in lipid deposition were highlighted (28).

In this study, it was observed that NLR, MLR, SII, and AISI values, which serve as markers of systemic inflammation, were elevated in XP patients; however, they were not statistically significant.

The study bears several limitations. First, its retrospective design might impact the depth of analysis. Second, being a single-center study with a relatively small sample size might have affected the statistical significance of the findings. Third, using a single blood sample might not accurately predict the persistence of blood parameters over time. In addition, while the study group comprised normolipidemic patients, the HDL values were not known. Future studies may benefit from assessing HDL levels, as it could potentially contribute to understanding impaired cholesterol removal from tissues. Despite its limitations, the study rigorously adhered to strict inclusion and exclusion criteria, ensuring an appropriate study design and the observation of a very specific patient cohort. Notably, to the authors' knowledge, this study stands as the first attempt to evaluate the immune profile in normolipidemic XP patients.

The extent of inflammation's role in the pathophysiology of XP is not fully understood yet. Whether therapies targeting inflammation could potentially be useful in managing XP remains uncertain until further studies provide more definitive answers.

Conclusion

The present study revealed elevated NLR, MLR, SII, and AISI values in XP patients, suggesting systemic inflammation, though not reaching statistical significance. While this study offers insights into XP pathogenesis, many questions remain unanswered, awaiting further investigation in future studies.

Disclosures

Ethics Committee Approval: The study protocol was approved by the institutional Ethics Committee (E1-23-3900) and adhered to the tenets of the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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