ISSN: 2476 - 2415

Research Article

International Journal of Clinical & Experimental Dermatology

Macular Amyloidosis, A Type of Pigmentation in Atopic Dermatitis that is Pathogenically Related

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Submitted: 2024, Apr 05; **Accepted**: 2024, May 15; **Published**: 2024, Nov 13

Citation: Balighi, K., Nikzad, R., Daneshpazhooh, M., Ansari, M. S. (2024). Macular Amyloidosis, A Type of Pigmentation in Atopic Dermatitis that is Pathogenically Related. *Int J Clin Expl Dermatol, 9*(2), 01-04.

Abstract

Background

Macular amyloidosis (MA) is a chronic pruritic skin condition characterized by hyperpigmentation, primarily affecting the back and extensor surfaces of the extremities. The exact etiology remains unknown; however, genetic and environmental factors, such as chronic friction, appear to play a role. An association between atopic dermatitis and cutaneous amyloidosis has been reported.

Methods

This study evaluates the prevalence of atopy in 40 patients diagnosed with MA.

Results

Atopic dermatitis, asthma, and allergic rhinitis were observed in 20%, 8%, and 20% of patients, respectively. A positive family history of atopy was noted in 90% of patients. Pruritus was significantly more severe in patients with atopic dermatitis (p-value = 0.003).

Conclusions

We recommend considering both personal and family histories of atopy when assessing patients with MA.

Keywords: Atopic Dermatitis, Cutaneous Amyloidosis, Familial Amyloidosis, Hyperpigmentation, Pigmentation Disorders

1. Introduction

Macular amyloidosis (MA) is a form of primary localized cutaneous amyloidosis, characterized by hyperpigmentation predominantly affecting the upper back and extensor surfaces of the extremities, often exhibiting a rippled pattern [1]. Individuals from South America, Asia, and the Middle East are more frequently affected [2]. The pathogenesis remains elusive, although chronic friction, viral infections, environmental factors, and genetic predisposition have been proposed as potential etiological factors [1]. Pruritic skin conditions, such as atopic dermatitis (AD), with prolonged scratching behavior may contribute to the development of MA [3]. Additionally, mutations in the genes encoding oncostatin M receptor β (OSMRβ) or the alpha subunit of the interleukin (IL)-31 receptor underlie certain familial cases of MA [2,4]. This study aims to evaluate the prevalence of atopic dermatitis, asthma, and allergic rhinitis in patients with MA.

2. Methods

In this cross-sectional study, we included all patients diagnosed with MA who were referred to the outpatient clinic. Diagnosis was clinically established by an expert dermatologist based on the characteristic morphology and location of lesions. After explaining the study protocols and obtaining informed written consent, we recorded demographic data, family history of MA, lesion location and morphology, severity of pruritus (assessed via a visual analogue scale), and personal and family histories of atopic dermatitis (based on Hanifin and Rajka criteria), asthma, and allergic rhinitis. Serum levels of immunoglobulin E (IgE) and blood eosinophilia were analyzed in all patients. Statistical analysis was performed using SPSS version 24 software, considering a p-value of 0.05 as significant. Continuous variables were reported as mean ± standard deviation, while categorical variables were expressed as frequency (percentage). The chi-squared test and Fisher's exact

test were utilized to assess the relationships between categorical variables, and Student's t-test was employed to compare means of two quantitative groups. The Research Ethics Committee approved this study (ethics code: 1396.2877).

3. Results

Forty patients participated in this study, with ages ranging from 21 to 64 years and a mean age of 43 ± 12.7 years. Eighty percent (32) of the patients were female, and 20% (8) were male. The most common anatomical locations were the shoulder and interscapular region, with only one location involved in 40% (16) of patients. A positive family history of MA was noted in only 10% (4) of patients. The severity of pruritus was measured using the visual analogue scale, resulting in a mean score of 6.1 ± 2.3, with the most frequently reported score being 5 (25%). All patients experienced some degree of pruritus, and the majority reported moderate pruritus, with 80% (32) scoring 5 or higher. A personal history of atopy was reported in 18 patients, with 8 (20%) having atopic dermatitis, 2 (5%) having asthma, and 8 (20%) having allergic rhinitis.

A positive family history of atopy was observed in 90% (36) of patients, with 15% (6) having atopic dermatitis, 30% (12) having asthma, and 45% (18) having allergic rhinitis. IgE levels and blood eosinophil counts were measured in 28 patients, as others declined the tests.

Elevated IgE levels were found in 10 (35.7%) individuals, with a mean IgE level of 704.14 ± 983.11 IU/ml. No eosinophilia was detected in any patient. The mean pruritus score in patients with atopic dermatitis was 8.25 ± 2.18, significantly higher than in other patients (p-value = 0.003). A higher mean IgE level was observed in patients with atopic dermatitis; however, this difference was not statistically significant (1394.25 ± 1182.12 IU/ml vs. 725.97 ± 428.1 IU/ml, p-value = 0.14).

No association was found between the number of sites involved in MA and the severity of pruritus or the history of atopic dermatitis.

Gender	**Count (percent)**
Male	8 (20%)
Female	32 (80%)
Location	
Shoulder	24 (60%)
Interscapular	24 (60%)
Neck	10 (25%)
Face	10 (25%)
Clavicle	6 (15%)
Lower back	6 (15%)
Lower extremity	4 (10%)
Upper extremity	2 (5%)
Upper back	2 (5%)
Pruritus score	
1-2	2 (5%)
3-4	6 (15%)
5-6	18 (45%)
7-8	8 (20%)
9-10	6 (15%)
Hanifin and Rajka diagnostic criteria	
Major criteria	
Pruritus	40 (100%)
Flexural lichenification or linearity	-
Chronic or chronically relapsing dermatitis	18 (45%)
Personal history of atopy	14 (35%)
Family history of atopy	36 (90%)
Minor criteria	
Xerosis	34 (85%)

Keratosis pilaris	4 (10%)
Ichthyosis	2 (5%)
Early age of onset	2 (5%)
Facial pallor or erythema	2 (5%)
Food intolerance	12 (30%)
Itch when sweating	24 (60%)

Table 1: Demographic Data, Location of Lesion, Pruritus Score and Atopic Dermatitis Diagnostic Criteria Prevalence

4. Discussion

MA is a prevalent skin condition in Middle Eastern countries [4]. Diagnosis can typically be made clinically based on characteristic skin lesions and locations, often accompanied by pruritus. In cases with uncertainty, histopathological examination should be considered [5]. Our patients refused to undergo a biopsy because of their typicallesions, leading to a diagnosis made purely on clinical grounds. Our findings align with previous studies, indicating a higher prevalence in females and in individuals during their fourth and fifth decades of life [1,4,6]. While pruritus is a common complaint, it is important to note that 10-40% of patients may not experience it [1,4]. In our study, all patients reported some degree of pruritus, with 80% (32) of patients declared scores of 5 and more. In a study by Jowkar et al. pruritus reported in 86% of patients, and 32% experienced severe pruritus [1].

The association between atopic dermatitis (AD) and primary cutaneous amyloidosis (CA) has been documented in the literature [7,8]. In 1970, Shanon first reported 9 cases with atopy-related conditions (seven cases of asthma, one of rhinitis, and one of allergic conjunctivitis) associated with cutaneous amyloidosis, with seven out of nine patients having a positive family history [9]. A large population-based study in Taiwan demonstrated a significant relationship between an earlier age of onset and CA related to AD, with 38% of patients having a positive history of other atopic conditions [2]. Similarly, a study from Singapore revealed that AD was significantly more prevalent among patients with CA, both in sporadic and familial cases. However, no association was found between pruritus in CA and AD in that study [4]. Our data indicate that patients with atopic dermatitis experienced more severe pruritus associated with MA. Additionally, there is a report of MA developing in an atopic patient following aeroallergen immunotherapy at the injection site [10].

Scratching behaviour, physical trauma, and barrier impairment in patients with AD lead to keratinocyte apoptosis. This process results in degenerated keratin peptides that are converted into amyloid fibrils by dermal fibroblasts and macrophages [7, 8]. AD is a chronic skin condition mediated by Th2 cells, with pruritus being a significant feature. Interleukin (IL)-31, produced by Th2 cells, is known to be a pruritogenic cytokine. Intradermal injection of IL-31 into mice induces severe pruritus, and long-term administration can lead to dermatitis. IL-31 expression is prevalent in atopic dermatitis lesions, particularly following exposure to staphylococcal superantigens. Components of the heterodimeric receptor complex, such as IL-31 receptor A (IL-31RA) and oncostatin M receptor (OSMR), are involved in the signaling pathways that mediate IL-31-induced pruritus [11]. Mutations in the genes encoding these proteins are implicated in certain familial cases of CA. These findings suggest that IL-31 may play a role in the pathogenesis of both CA and AD, indicating a potential association between the two conditions.

In our study, a family history of MA was observed in only 10% of patients, while personal and family histories of atopy were positive in 45% and 90% of patients, respectively. We propose that atopy should be considered an etiological factor in the development of MA in both familial and sporadic cases. Post-inflammatory hyperpigmentation (PIH) is another common cause of skin pigmentation. Various inflammatory condition, such as dermatitis, can lead to PIH; however, symmetric distribution, involvement of the back, rippling pattern, and accompanied pruritus in MA can differentiate these conditions [12]. In response to inflammation, melanogenesis is induced by prostaglandins, leukotrienes, and cytokines in PIH, resulting in epidermal or dermal pigmentation. Histopathological examination typically reveals increased epidermal melanin, melanophages, and perivascular lymphocytic infiltration [13]. In contrast, MA is characterized by the deposition of amorphous material in dermal papillae, with occasional pigment incontinence [14]. Other causes of dermal hyperpigmentation include lichen planus pigmentosus (LPP) and erythema dyschromicum perstans (EDP). LPP typically affects sun-exposed and intertriginous areas, while EDP usually involves the trunk. These conditions can be differentiated from MA based on discrete lesions, the pattern of involvement, lack of pruritus, and distinct histopathological findings. Similar histological features, such as melanophages and subtle interface changes, may be seen in both conditions [15]. Thus, MA differs from other pigmentation causes in terms of pathogenesis and histology. The association between MA and AD appears to be independent of the development of PIH following AD or other inflammatory processes, with IL-31 potentially playing a pathogenic role in both disorders. MA is challenging to treat and significantly impacts patients' quality of life and self-esteem. Prevention is preferable to treatment; therefore, controlling pruritus in patients with AD, a predisposing factor, may help prevent the further development of MA. Emerging biologic treatments, such as dupilumab, may effectively manage AD, consequently preventing MA, particularly in patients with a positive family history.

This study has several limitations, including a small sample size and the absence of a control group. Further investigations are

warranted to evaluate the association between atopy and cutaneous amyloidosis.

5. Statements

5.1. Statement of Ethics

This study approved by the Research Ethics Committee of the Tehran University of Medical Sciences (ethics code: IR.TUMS.MEDICINE.REC.1396.2877)

We have obtained the written informed consent of all patients or their parents to participate in this study.

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