

Case Report

Late-onset amyloidosis cutis dyschromica: A rare case of progressive dyschromia caused by compound heterozygous *GPNMB* mutation

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ABSTRACT

Amyloidosis cutis dyschromica (ACD) is a rare form of primary cutaneous amyloidosis characterized by hypopigmented and hyperpigmented macules and patches without systemic involvement. Typically benign, ACD involves amyloid deposition in the papillary dermis. Mutations in the *glycoprotein nonmetastatic gene B* (*GPNMB*) gene, which is implicated in melanosome formation, as well as ultraviolet hypersensitivity and DNA repair defects, contribute to dyschromia. A 34-year-old female presented with a 10-year history of asymptomatic, mottled pigmented macules and patches on the upper and lower extremities. A skin biopsy showed widened dermal papillae containing eosinophilic amorphous deposits, highlighted in Congo red stain and cytokeratin 5/6 immunostaining, which confirmed the diagnosis. Furthermore, whole-exome sequencing identified a nonsense (Arg189Ter) and a missense variant (Cys425Ser) in *GPNMB*. It is essential for understanding the hereditary component and guiding counseling. Management primarily addresses cosmetic concerns. For this patient, strict photoprotection and oral antioxidants, such as vitamins C and E, were recommended.

Keywords: Amyloidosis cutis dyschromica, *Glycoprotein nonmetastatic gene B*, Primary cutaneous amyloidosis

INTRODUCTION

Amyloidosis cutis dyschromica (ACD) is a rare form of primary cutaneous amyloidosis, distinguished by diverse patterns of widespread skin dyschromia, mild pruritus, onset before puberty, and the deposition of amyloid in the subepidermal layer.^[1] Altogether 48 cases of ACD fulfilling each of the clinical and histological criteria described by Morishima^[2] were identified. In 37 cases, there was a positive family history; the remaining cases were sporadic. The mean age at diagnosis was 30 years, with a mean age of onset of 6 years (3–22 years). Males and females were affected with equal frequency. As seen in Table 1, most of the patients were of East Asian (Chinese/Hong Kong Chinese,^[3–12] Taiwanese^[13,14] and Japanese^[15]) or South East Asian ethnicity (Thai,^[16,17] Filipino,^[13,18,19] Indonesian^[20] and Sri Lankans^[21]). There are also reported cases in South Asia (Indian^[21–29] and Pakistani^[30–32]), in Middle East/West Asia (Iranians,^[33,34] Kuwaitis^[13]), and in North Africa (Libyans^[35]). Only five case reports of ACD have been published in Caucasian/European descent patients (Americans^[36,37] and Turkish^[38–40]). To date, there are 3 published cases of ACD in Filipino patients.^[13,18,19] Genetic factors and impaired DNA repair from UV light are suspected contributors to the etiology of ACD.^[38] Here, we describe a rare

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Table 1: Review of published case reports of amyloidosis cutis dyschromica across different countries.

Country	Case report title	Main author
China	Amyloidosis cutis dyschromica caused by compound heterozygous <i>GPNMB</i> mutations in a Chinese pedigree	Zhong <i>et al.</i> , ^[3]
	Case Report: Amyloidosis cutis dyschromica: Dermoscopy and reflectance confocal microscopy and gene mutation analysis of a Chinese pedigree	Wang <i>et al.</i> , ^[4]
	A homozygous <i>Y131X GPNMB</i> mutation in a Chinese family with amyloidosis cutis dyschromica	Wang <i>et al.</i> , ^[5]
	Amyloidosis cutis dyschromica cases caused by <i>GPNMB</i> mutations with different inheritance patterns	Qin <i>et al.</i> , ^[6]
	Amyloidosis cutis dyschromica due to homozygous variants of the <i>GPNMB</i> gene in a Chinese pedigree	Sha and Li, ^[7]
	Case of amyloidosis cutis dyschromica with palmoplantar keratoderma	Wang and Sun, ^[8]
	Case of amyloidosis cutis dyschromica with dermoscopy	Wang <i>et al.</i> , ^[9]
	Loss of <i>GPNMB</i> Causes Autosomal-Recessive Amyloidosis Cutis Dyschromica in Humans	Yang <i>et al.</i> , ^[12]
	Amyloidosis cutis dyschromica	Qiao <i>et al.</i> , ^[10]
	Amyloidosis cutis dyschromica in two female siblings: Cases report	Yang <i>et al.</i> , ^[11]
India	Dermoscopy of amyloidosis cutis dyschromica	Rane and Mahajan ^[21]
	Amyloidosis cutis dyschromica: A Rare subtype of primary cutaneous amyloidosis with dermoscopy	Priyadhashini <i>et al.</i> , ^[22]
	Amyloidosis cutis dyschromica, A rare subtype of primary cutaneous amyloidosis: case report and literature review	Sakhiya <i>et al.</i> , ^[24]
	Amyloidosis cutis dyschromica: A rare reticulate pigmentary dermatosis	Verma and Joshi, ^[25]
	Amyloidosis cutis dyschromica	Kurian <i>et al.</i> , ^[26]
	Amyloidosis cutis dyschromica: A rare pigmentary disorder	Garg <i>et al.</i> , ^[27]
	Amyloidosis cutis dyschromica in a patient with generalized morphea	Morales Callaghan <i>et al.</i> , ^[28]
	Amyloidosis cutis dyschromica in two siblings	Vijaikumar and Thappa, ^[29]
United States	A rare case of late-onset amyloidosis cutis dyschromica	Lau <i>et al.</i> , ^[36]
	Amyloidosis cutis dyschromica treated with acitretin: A case report	Hennessy <i>et al.</i> , ^[37]
Philippines	Amyloidosis cutis dyschromica in a 16-year-old Filipino girl: A case report	Bautista <i>et al.</i> , ^[18]
	Amyloidosis cutis dyschromica in two siblings and review of the epidemiology, clinical features, and management in 48 cases	Mahon <i>et al.</i> , ^[19]
Pakistan	Two missense mutations in <i>GPNMB</i> cause autosomal recessive amyloidosis cutis dyschromica in consanguineous Pakistani families	Rahman <i>et al.</i> , ^[30]
	Primary localized cutaneous amyloidosis affecting female individuals of a Pakistani pedigree	Bhojrul <i>et al.</i> , ^[31]
	Amyloidosis cutis dyschromica associated with atypical Parkinsonism, spasticity and motor weakness in a Pakistani female	Fernandes <i>et al.</i> , ^[32]
Thailand	Molecular basis and inheritance patterns of amyloidosis cutis dyschromica	Chiu <i>et al.</i> , ^[16]
	Familial amyloidosis cutis dyschromica: Six cases from three families	Choonhakarn and Wittayachanyapong, ^[17]
Iran	Amyloidosis cutis dyschromica: Report of 3 cases	Sepaskhah <i>et al.</i> , ^[33]
	Familial amyloidosis cutis dyschromica: A case report	Dehghani <i>et al.</i> , ^[34]
Kuwait/ Taiwan/ Philippines	Semidominant <i>GPNMB</i> mutations in amyloidosis cutis dyschromica	Onoufriadis <i>et al.</i> , ^[13]
Turkey	Late-onset amyloidosis cutis dyschromica: An unusual case	Kutlu <i>et al.</i> , ^[38]
	Association of amyloidosis cutis dyschromica and familial Mediterranean fever	Belli <i>et al.</i> , ^[39]
	Amyloidosis cutis dyschromica: A case treated with acitretin	Ozcan <i>et al.</i> , ^[40]

(Contd...)

Table 1: (Continued).

Country	Case report title	Main author
Libya (North Africa)	Amyloidosis cutis dyschromica, a rare cause of hyperpigmentation: A New case and literature review	Kuseyri <i>et al.</i> , ^[35]
Indonesia	Familial amyloidosis cutis dyschromica in three siblings: Report from Indonesia	Hermawan <i>et al.</i> , ^[20]
Sri Lanka	A rare type of primary cutaneous amyloidosis: Amyloidosis cutis dyschromica	N. P. Madarasingha ^[21]
Taiwan	Amyloidosis cutis dyschromica: Four cases from two families	Huang <i>et al.</i> , ^[14]
Japan	Amyloidosis cutis dyschromica. DNA repair reduction in the cellular response to UV light	Moriwaki <i>et al.</i> , ^[15]

GPNMB: Glycoprotein nonmetastatic gene B, UV: Ultraviolet

presentation of ACD demonstrating classic histopathologic features, but notably with late onset, localized presentation, and no familial history. Only 2 cases to date were published with late-onset ACD.^[36,38]

CASE REPORT

A 34-year-old female presented with a 10-year history of a few, asymptomatic, mottled hypopigmented and hyperpigmented macules on her upper extremities. Over time, these lesions increased in size and number, progressing into diffuse, hyperpigmented patches and mottled hypopigmented macules on both upper and lower extremities [Figure 1]. No systemic symptoms were present. Family members, including non-consanguineous parents, were not affected. Baseline laboratory examinations, including full blood count and biochemical tests, were unremarkable.

A skin punch biopsy in H&E stain revealed epidermal papillomatosis and widened dermal papillae containing eosinophilic amorphous deposits, confirming amyloid presence. Congo red stain and cytokeratin 5/6 immunostaining highlighted increased amyloid deposits, which confirmed the diagnosis of primary cutaneous amyloidosis [Figure 2]. Furthermore, peripheral blood specimens of both the patient and the mother were sent for genetic testing.

Whole exome sequencing identified two heterozygous variants in *GPNMB*. The first is a nonsense variant (c.565C>T, Arg189Ter) while the second is a missense variant (c.1238G>C, Cys413Ser). Sanger sequencing confirmed that the patient is a compound heterozygote for both mutations. Segregation analysis confirms the missense variant (c.1238G>C, Cys413Ser) was carried by the patient's mother [Figure 3].

DISCUSSION

Primary cutaneous amyloidosis refers to the extracellular deposition of amyloid material in previously normal skin without systemic involvement. The major variants of primary



Figure 1: Patient showing multiple, well-defined, mottled, hypopigmented macules surrounded by diffuse hyperpigmented patches on bilateral lower extremities.

cutaneous amyloidosis are macular and lichen.^[1] ACD, first described in 1970, is a rarely documented variant of cutaneous amyloidosis.^[2] Morishima described its features as the following: (i) dotted, reticular hyperpigmentation with hypopigmented macules distributed over nearly all of the body, (ii) no or little itch, (iii) onset before puberty, and (iv) focal amyloid deposition under the epidermis.^[2] The exact pathogenic mechanism of ACD is unknown; however, it is hypothesized that affected keratinocytes have an underlying genetic susceptibility to photodamage, causing defective DNA repair. Amyloid is then produced by these faulty keratinocytes that have undergone phagocytosis. The deposition of amyloid within the papillary dermis may cause stretching of the basement membrane and, therefore, a decrease in melanocyte density. As the disease is suspected to be familial, there are several genetic loci that are being studied for their relevance.^[18,40]

Mutations in the *GPNMB* are composed of 560 amino acids (GenBank: NP_0025011). It is a highly glycosylated type I transmembrane protein, and it was first isolated from weakly metastatic melanoma cells in 1995 as a regulator of tumor growth.^[41] It is highly expressed in melanocytes, is partially localized in melanosomes, lysosomes, and early endosomes.^[42] *GPNMB* was found to have critical roles in melanosome formation, autophagy/phagocytosis, clearance of apoptotic cell debris, and negative regulation of inflammation, which are associated with ACD.^[12] To

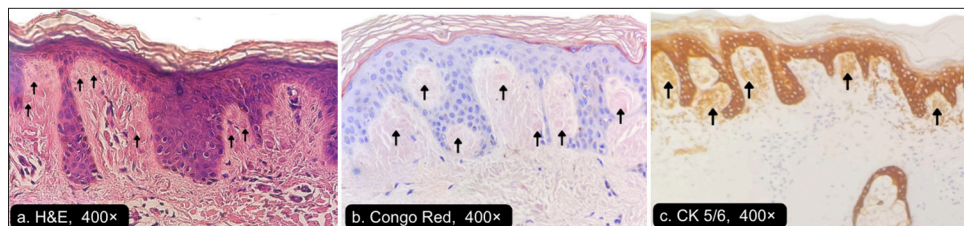


Figure 2: (a) Hematoxylin and eosin (H&E), 400 \times ; (b) Congo red, 400 \times ; (c) Cytokeratin (CK) 5/6, 400 \times . All images demonstrate eosinophilic, amorphous deposits consistent with amyloid deposition (black arrows).

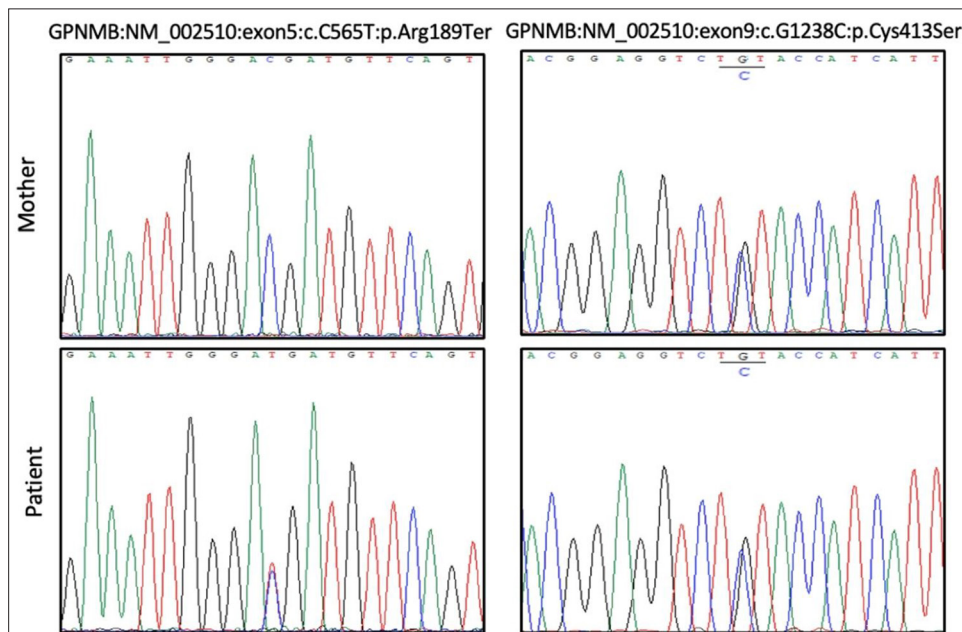


Figure 3: Sanger sequencing showing the presence of both *glycoprotein nonmetastatic gene B* variants. Segregation analysis confirms the missense variant (c.1238G>C, Cys413Ser) was carried by the patient's mother.

date, 12 *GPNMB* mutations have been identified in ACD. Most mutations are nonsense or frameshift mutations with only two documented missense mutations, p.Cys413Arg and p.Cys413Ser, located within the Kringle-like domain of *GPNMB*, 5 suggesting that this region may be critical for protein structure and function.^[16] Identifying a *GPNMB* mutation can help confirm the diagnosis of ACD, especially in atypical cases, and may guide genetic counseling for affected individuals and their families. Understanding the role of *GPNMB* in ACD pathogenesis might open avenues for potential targeted therapies, though current treatment remains supportive and symptomatic.

Different treatment modalities, including sunscreen, topical corticosteroids, keratolytics, dimethyl sulfoxide, capsaicin, CO₂ laser, and acitretin, have been used with varying degrees of effectiveness.^[38] Vitamin A derivatives, like acitretin, are used to treat ACD as they may repair the defective keratinization that allows keratinocytes to degenerate into amyloid.^[40]

CONCLUSION

ACD is an extremely rare condition, with most cases reported in East Asian populations, though sporadic reports exist worldwide. Understanding the clinical and histological features of ACD is critical for distinguishing it from other pigmentary disorders and for establishing an accurate diagnosis. Currently, there is no definitive treatment for ACD, and management focuses on symptomatic relief and aesthetic improvement. Further research into the genetic and molecular mechanisms underlying ACD is needed to better understand its etiology and develop targeted therapies.

Ethical approval: The Institutional Review Board has waived the ethical approval for this study. IRB ethical approval waiver number is 2026-08.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical

information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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