SHORT COMMUNICATION

Familial Amyloidosis Cutis Dyschromica with *GPNMB* mutation: A Case Report and Literature Review

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Primary localized cutaneous amyloidosis (PLCA) is a chronic dermatologic condition characterized by keratinocyte dysfunction and deposition of amyloid material within the skin (1). The main morphological variants of primary localized cutaneous amyloidosis (PLCA) include lichen, macular, and nodular types. A rare subtype, amyloidosis cutis dyschromica (ACD), presents exclusively with cutaneous features, including symmetrical hypopigmented macules encircled by reticulated and macular hyperpigmentation (2, 3). Familial ACD, a hereditary form of PLCA, affects both sexes and typically presents before puberty (1, 2).

Although PLCA has been reported globally, familial cases are particularly rare and are more frequently observed in Asia and South America (4, 5). Herein, we report a case of autosomal-recessive ACD in a Thai patient with a confirmed *GPNMB* mutation, along with a review of the relevant literature.

CASE REPORT

A 21-year-old Thai woman presented with a 10-year history of progressive skin dyschromia accompanied by chronic pruritus. She reported no family history of similar dermatological symptoms. Dermatological examination revealed numerous small hypopigmented macules surrounded by hyperpigmented areas on the back, posterior aspect of the left forearm, both legs, and the dorsal surfaces of the hands with sparing of the palms, soles, and face (**Fig. 1**). There were no signs of systemic involvement.

A skin biopsy from the leg revealed globular, amorphous eosinophilic deposits in the papillary dermis on haematoxylin and eosin (H&E) staining. These deposits were accompanied by melanophages and pigmentary incontinence. Congo red staining demonstrated amyloid deposits in the papillary dermis and focally beneath the dermoepidermal junction (DEJ). Under polarized microscopy, subtle apple-green birefringence was observed (**Fig. 2**), supporting a diagnosis of cutaneous amyloidosis.

After obtaining written informed consent, genomic DNA was extracted from peripheral blood using the QIAamp DNA Blood Mini Kit (https://www.qiagen.com/). The coding regions and flanking intronic sequences of the *GPNMB* gene were amplified by PCR and sequenced bidirectionally using Sanger sequencing. Sequence analysis using Sequencher® software (https://www.genecodes.com/) and *in silico* pathogenicity prediction tools identified a homozygous pathogenic variant, c.565C>T (chr7:23299622 C>T, p.Arg189*, NM_002510.3), as depicted in Fig. S1. This result confirmed the diagnosis of autosomal-recessive ACD due to a *GPNMB* mutation. The patient was treated with acitretin 10 mg daily along with 10% lactic acid cream and sun protection for 1 year, with a moderate clinical response.

DISCUSSION

Familial amyloidosis cutis dyschromica (ACD) is a rare inherited disorder characterized by cutaneous amyloid deposition and gradually progressive pigmentary

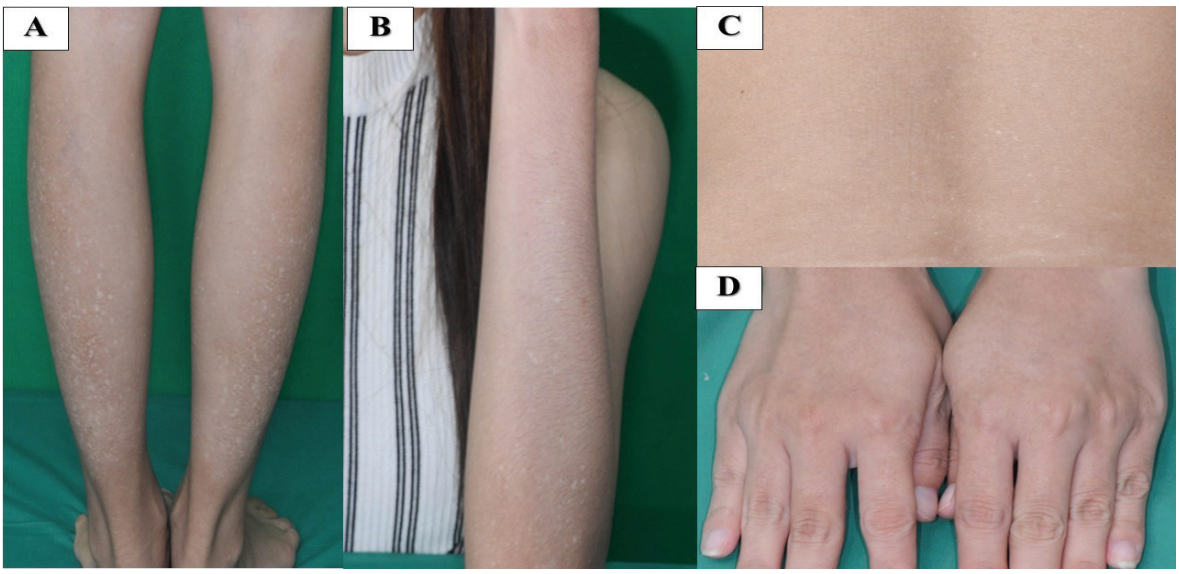

Fig. 1. Clinical presentation showing multiple hypopigmented macules surrounded by hyperpigmentation on the (A) legs, (B) left forearm, (C) back, and (D) dorsal hands.

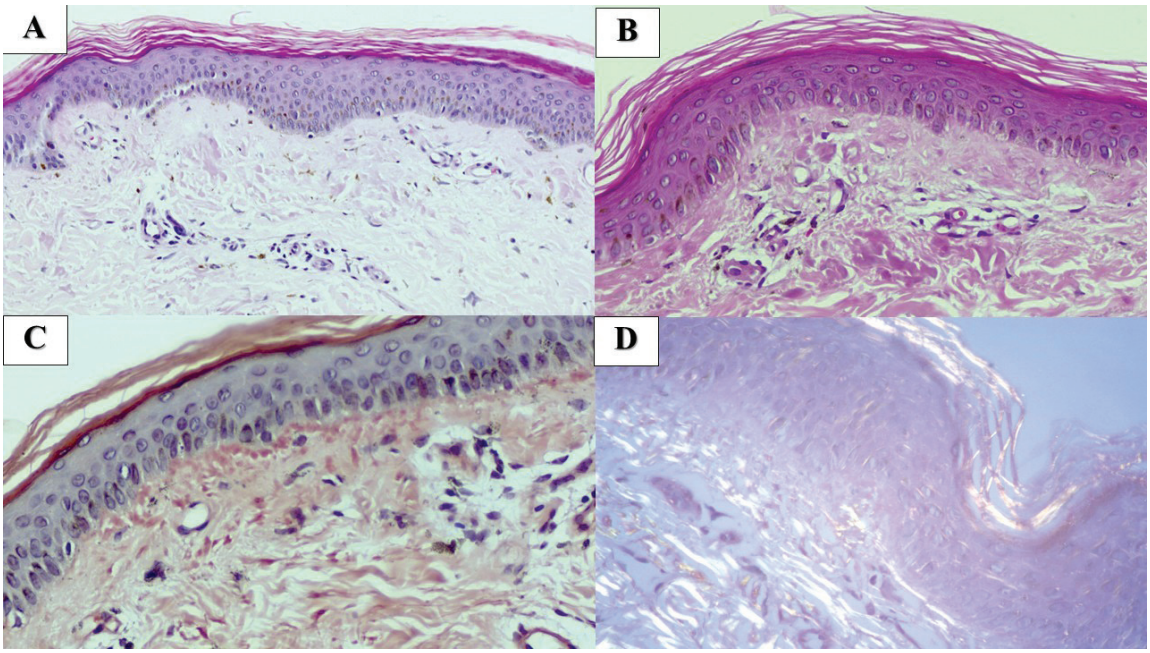

Fig. 2. Histopathology of a skin biopsy revealing amorphous eosinophilic deposits and melanophages in the papillary dermis (H&E, original magnification: 20× (A), 40× (B)). Congo red staining demonstrates focal amyloid deposition at the dermoepidermal junction and papillary dermis (40× (C)), with subtle apple-green birefringence under polarized light (D).

changes. Mutations in the *GPNMB* gene have been identified as a causative factor in autosomal-recessive ACD. *GPNMB* encodes a transmembrane glycoprotein predominantly expressed in melanocytes, where it plays a critical role in melanosome formation and melanin biosynthesis. *GPNMB* mutations may disrupt keratinocyte homeostasis by enhancing inflammation, impairing melanocyte–keratinocyte interactions, and altering stress responses – ultimately leading to keratinocyte degeneration and amyloid deposition in ACD. Notably, GPNMB is not a structural component of amyloid; rather, the amyloid material originates from degenerated keratinocytes (1, 2, 6–8). In our patient, the homozygous nonsense mutation c.565C>T (p.Arg189*) in *GPNMB* leads to a premature stop codon, resulting in a truncated, nonfunctional protein. This variant has been previously reported in patients with ACD (5). Qin et al. also described ACD patients harbouring this mutation with similar clinical features (6). Histopathological findings in this case were consistent with PLCA, demonstrating eosinophilic globular deposits in the papillary dermis. The observed melanophages and pigmentary incontinence likely account for the hyperpigmentation. Congo red staining revealed amyloid deposits localized at the dermoepidermal junction (DEJ) and papillary dermis, with subtle green birefringence under polarized light. No amyloid components deposit in the deeper layer of the dermis and blood vessels. This pattern was associated with keratin-amyloid material, distinguishable from immunoglobulin amyloid components in the reticular layer of the dermis and vessels displaying plasma cell growth in the nodular form (9).

The absence of papules or plaques and abnormal reticulated pigmented macules in familial ACD are the primary distinguishing features from macular and lichen amyloidosis (1). In this patient, the lesions were located on the extremities and back, sparing the face, palms, and soles – findings consistent with the typical distribution seen in ACD (8). The differential diagnosis includes dyschromatosis universalis hereditaria (DUH) and xeroderma pigmentosum (XP) (1). To elucidate, DUH exhibits irregular distributions of hyper- and hypopigmented macules, and pigmentation changes are attributed to basal layer melanin variations, which differentiates familial ACD from histological findings. Genetic alterations in DUH encompass *ABCB6*, *SASH1*, *KITLG*, and *PER3*, which are distinct from those associated with familial ACD (10). XP is characterized by photosensitivity and freckling in sun-exposed areas and nonspecific findings from skin biopsies can be found (1, 11). Hence, clinical manifestations, histological findings, and genetic findings can be discerned from these disorders. Notably, studies revealed the 34βE12 cytokeratin marker was a cost-effectiveness marker for detecting keratin-amyloid material (12).

Additional mutations in *IL6*, *IL31*, and *OSMR* have been implicated in PLCA pathogenesis through modulation of keratinocyte proliferation and apoptosis via the JAK-STAT, PI3K/Akt, and MAPK signalling pathways (13, 14). A summary of previous reports of *GPNMB*-related ACD is provided in **Table I**. While a number of mutations have been described, no consistent genotype–phenotype correlation has been established (13). No recent data support a correlation between ethnicity and

Table I. Summary of reported cases of amyloidosis cutis dyschromica with identified *GPNMB* mutations, including genotype, clinical features, and treatment response

Author, year	Number of sampling patients	Country	Sex (male/female)	Detailed mutation	Zygosity (homozygosity/heterozygosity) (*n*)	Clinical manifestation	Locations	Treatment and response (*n*)
Onoufriadis, 2019 (15)	16	Kuwait	9 (2/7)	c.700+5G>T	7/2	Hypopigmented macules surrounded by hyperpigmentation	Back and trunk	NA
		Philippines	4 (2/2)	c.1238G>C	3/1	Hypopigmented macules surrounded by hyperpigmentation, multiple hyperpigmented macules	Limb	
		Taiwan	3 (2/1)	c.565C>T	1/2	Hypopigmented macules surrounded by hyperpigmentation	Limb	
				c.1056delT	1/2			
Qin, 2021 (6)	19	China	19 (8/11)	c.935delA, c.969 T>A, c.393 T>G, c.565C>T, c.1056delT, c.1238 G>C	NA	Hyperpigmented and hypopigmented macules, lichenification, bullae	Back, face, limbs, and trunk	NA
Wang, 2021 (3)	1	China	1(1/0)	c.393T>G, c.719_720delTG	NA	Hypo- and hyperpigmented spots	Back, limbs, abdomen, neck, and palmoplantar regions	NA
Yang, 2018 (8)	9	Taiwan	9(5/4)	c.296del	0/1	Symmetrical hypo -and hyperpigmented spots and patches, bullous, and xerotic eczema	Face, neck, trunk, limbs, hands, and feet without palm and sole	Oral acitretin (mild improvement) (1)
				c.390G>A	0/1			
				c.565C>T	8/1			
				c.660T>G	0/5			
				c.719_720del	0/1			
				c.877_880del	0/1			
				c.1056del	0/1			
				c.1461T>C	1/2			

NA: not applicable.

clinical presentation, highlighting the need for further studies. This patient showed a moderate response to acitretin and sun protection; however, no consistently effective treatment for ACD exists, and management remains symptomatic with variable outcomes. Further prospective and mechanistic studies are needed to clarify the underlying molecular mechanisms and clinical variability in ACD.

The authors have no conflicts of interest to declare.

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