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Case report

Membranous aplasia cutis congenita: A rare case report highlighting clinical presentation, genetic insights, and the need for comprehensive evaluation

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ABSTRACT

Introduction: Membranous aplasia cutis congenita (MACC) is the most common clinical subtype of aplasia cutis congenita (ACC). It is typified by a localized skin lesion devoid of hair and features a membranous surface. While most MACC individuals do not present with concurrent abnormalities, it can sometimes co-occur with additional physical anomalies and various malformation syndromes. Moreover, the underlying causes of MACC remain elusive.

Case presentation: We describe a case of a 6-month-old female infant diagnosed with MACC. The patient presented with a midline skin lesion on the occipital scalp, characterized by a glistening surface and a hair collar sign. Dermoscopic examination revealed specific features, including translucency, telangiectasia, and hypertrichosis. The infant had a history of patent foramen ovale, and further examination uncovered an asymptomatic ventricular septal defect. Whole exome sequencing revealed 20 gene variants relevant to the clinical phenotype of the patient, suggesting a possible association with MACC.

Conclusion: MACC is a rare and underreported condition, primarily diagnosed based on its distinctive clinical features. It is imperative to emphasize the significance of thorough evaluations in MACC patients, encompassing developmental, cardiac, neurological, and genetic assessments to facilitate early detection and the exclusion of potentially life-threatening comorbidities. Importantly, genetic characterization, as demonstrated in this case, contributes to our understanding of MACC's etiology and highlights the need for further research in this field.

1. Introduction

Aplasia cutis congenita (ACC) is an uncommon and heterogeneous congenital skin disorder characterized by localized or generalized skin defects, primarily affecting the scalp [1,2]. Although ACC was first documented by Cordon et al., in 1767, its true incidence is likely underreported, with estimations of less than 0.03 % in newborns [3,4]. Histologically, patients with ACC lack normal skin structures, such as hair follicles, sebaceous glands, and sweat glands, along with a lack of collagen fibers in the dermis [4]. Diagnosing

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ACC in a neonate is typically straightforward, following the exclusion of obstetric trauma.

Nonetheless, given its association with other physical abnormalities or syndromes, accurately distinguishing between the various clinical subtypes of ACC is paramount for physicians to ensure comprehensive patient management and tailored treatment strategies. The classification system introduced by Frieden et al., in 1986 [1], based on affected areas, associated anomalies, and inheritance patterns, continues to serve as the foundation for categorizing ACC subtypes. A recent study by Sathishkumar et al. has further validated and refined this classification, highlighting the growing importance of incorporating genetic information into the diagnosis framework to further delineate ACC subtypes and predict associated conditions [5]. One of the most common subtypes of ACC, membranous aplasia cutis congenita (MACC), also known as bullous or cystic ACC, often presents as a flat lesion with a membranous or glistening surface [6,7]. Although several causative factors have been proposed, including intrauterine infections, trauma, placental infarcts, ectodermal dysplasia, chromosomal abnormalities, gene variants, and use of teratogenic substances, the exact etiology of MACC remains elusive [8–10]. Notably, there have been documented instances of ACC being inherited either in an autosomal dominant or recessive pattern and occasionally as an X-linked disorder [11,12]. Additionally, a study found that the BMS1 p.R930H variation in ACC patients is associated with p21-mediated cell cycle arrest, and skin morphogenesis [13]. Given the heterogeneity of this condition, additional research is needed to further elucidate the underlying genetic mechanisms. Herein, we present the case of a 6-month-old infant diagnosed with MACC and discuss the clinical and genetic findings.

2. Case presentation

A 6-month-old Chinese female infant presented to our outpatient department with a midline skin lesion on her posterior scalp. Initially, a scalp injury was considered in the differential diagnosis. However, the parents reported that the lesion had been present since birth and confirmed that there had been no history of trauma. The patient was born at term by unassisted vaginal delivery and had a history of patent foramen ovale (PFO) at birth. Notably, her mother had no history of viral infections, trauma, or exposure to teratogenic agents during pregnancy. Further dermatological examination revealed a single oval midline lesion measuring 0.6 × 0.7 cm in size and located in the occipital region. The skin defect presented with a glistening surface and was marked by the lack of hair and the presence of a hair collar sign (Fig. 1A). Dermoscopic examination of the lesion further revealed a translucent epidermis, telangiectasia, an absence of follicle orifices and hypertrichosis surrounding the lesion (Fig. 1B). Examination by a pediatrician revealed that the infant displayed normal development milestones, with the absence of spinal or limb deformities. Further X-ray imaging of the extremities corroborated with the above findings. Lung auscultation revealed clear breath sounds bilaterally and an absence of wheezing, rales, or rhonchi. There were no indications of anemia, cyanosis, or congestive heart failure. However, a grade 3 holosystolic murmur with the absence of a palpable thrill was detected at the lower left sternal border, with the second heart sound exhibiting a normal split and intensity. Given her history of PFO, an echocardiography was further conducted, revealing an asymptomatic ventricular septal defect (VSD). Based on the specific clinical manifestations, the infant was diagnosed with membranous aplasia cutis congenita. A comprehensive familial history revealed that the patient was the first case of MACC in the family, born to healthy and non-consanguineous parents. The patient is the only child affected by this condition. There is no known history of similar conditions among immediate or extended family members, including siblings, parents, grandparents, aunts, uncles, and cousins. Furthermore, the parents reported no other significant medical conditions or genetic disorders within the family lineage.

Due to the patient's tender age and the lack of adverse effects on her quality of life, invasive procedures such as biopsies were not considered. Instead, whole exome sequencing (WES) (KingMed Diagnostics, Guangzhou, China) using peripheral blood samples obtained from the infant and her parents was conducted to explore the possibility of genetic underpinnings for the child's condition. Primary analysis examined 78 genes associated with monogenic inherited diseases recommended by the American College of Medical Genetics (ACMG). Using genetic disease databases, including ClinVar, OMIM, HGMD, gnomAD, and population-scale sequencing databases, no pathogenic or likely pathogenic single nucleotide variants (SNV), small fragment insertion-deletion variants (Indel) or larger copy number variants (CNV) were detected. However, gene variations relevant to the clinical phenotype of the patient (using Human Phenotype Ontology (HPO) terms HP:0001655 Patent foramen ovale, HP:0001629 Ventricular septal defect, and HP:0011355 Localized skin lesion) revealed 20 gene variants that might be associated with the patient's condition (Table 1). Notably, these

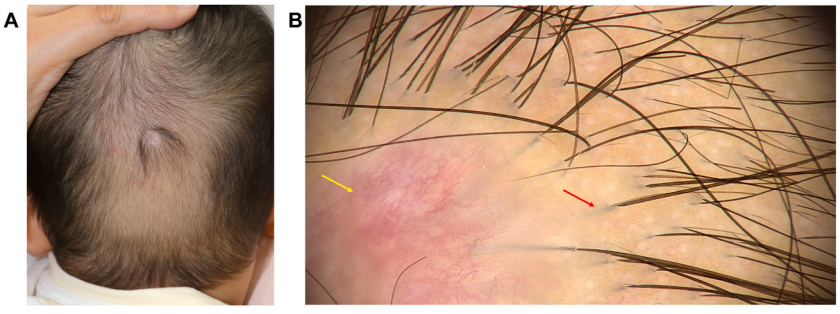

Fig. 1. Dermatological and dermoscopic examination of the midline scalp lesion. A. Clinical photograph shows a 0.6 × 0.7 cm oval lesion with a glistening surface, lacking hair, and displaying a distinct hair collar sign B. Dermoscopic analysis reveals a translucent epidermis and telangiectasia (yellow arrow), as well as an area of hypertrichosis (red arrow) surrounding the lesion.

Table 1
Gene variations relevant to the clinical phenotype of the patient.

Gene symbol	Chromosomal location (GRCh37) [a]	Transcript ID: Variant (amino acid variation)	Allele frequency [b]	ClinVar ID	Pathogenicity prediction [c]	OMIM disorder [d]	Mode of inheritance	Zygosity of the patient	Carriage status of parents [e]
MYOC	chr1: 171605642 (CM000663.1)	NM_000261.2: c.938C > T (p. Ser313Phe)	7.62E-4	NA	0.554	Glaucoma 1, open angle, A [MIM:137750]	AD	heterozygous	NA
APOB	chr2: 21228542 (CM000664.1)	NM_000384.3: c.11198C > T (p. Pro3733Leu)	NA	NA	0.248	Hypercholesterolemia, familial, 2 [MIM:144010] Hypobetalipoproteinemia, familial, 1 [MIM:615558]	AD/AR	heterozygous	NA
TBR1	chr2: 162273121 (CM000664.1)	NM_006593.4: c.200A > G (p. Asn67Ser)	5.44E-5	NA	0.344	Intellectual developmental disorder with autism and speech delay [MIM:606053]	AD	heterozygous	NA
COL12A1	chr6: 75812338 (CM000668.1)	NM_004370.6: c.8390A > G (p. Asn2797Ser)	2.93E-4	935024	0.231	Bethlem myopathy type 2 [MIM:616471] Ullrich congenital muscular dystrophy type 2 [MIM:616470]	AD/AR	heterozygous	NA
FIG4	chr6: 110110816 (CM000668.1)	NM_014845.5: c.2116G > A (p. Val706Ile)	6.15E-5	937457	0.075	Yunis-Varon syndrome [MIM:216340] Polymicrogyria, bilateral temporooccipital [MIM:612691] Amyotrophic lateral sclerosis 11 [MIM:612577] Charcot-marie-tooth disease, type 4J [MIM:611228]	AD/AR	heterozygous	NA
CFTR	chr7: 117188684 (CM000669.1)	NM_000492.4: c.1210-11T > G	2.02E-2	178713	NA	Cystic fibrosis [MIM:219700] Congenital bilateral absence of vas deferens [MIM:277180] Pancreatitis, hereditary [MIM:167800] Bronchiectasis with or without elevated sweat chloride 1 [MIM:211400]	AD/AR	heterozygous	NA
RP1L1	chr8: 10465140 (CM000670.1)	NM_178857.6: c.6468G > T (p. Glu2156Asp)	6.67E-4	NA	0.012	Occult macular dystrophy [MIM:613587] Retinitis pigmentosa 88 [MIM:618826]	AD/AR	heterozygous	NA
ZFHX4	chr8: 77617309 (CM000670.1)	NM_024721.5: c.986A > G (p. Lys329Arg)	8.90E-4	NA	0.305	Ptosis, hereditary congenital, 1 [MIM:178300]	AD	heterozygous	NA
PLEC	chr8: 144996766 (CM000670.1)	NM_000445.5: c.7412A > G (p. Asp2471Gly)	3.34E-4	NA	0.252	Epidermolysis bullosa simplex 5D, generalized intermediate, autosomal recessive [MIM:616487] Epidermolysis bullosa simplex 5B, with muscular dystrophy [MIM:226670] Epidermolysis bullosa simplex 5C, with pyloric atresia [MIM:612138]; Epidermolysis bullosa simplex 5A, Ogna type [MIM:131950] Muscular dystrophy, limb-girdle, autosomal recessive 17 [MIM:613723]	AD/AR	heterozygous	NA
ABCA1	chr9: 107599272 (CM000671.1)	NM_005502.4: c.1300G > A (p. Asp434Asn)	3.26E-4	NA	0.331	Tangier disease [MIM:205400] Hypoalphalipoproteinemia, primary, 1 [MIM:604091]	AD/AR	heterozygous	NA
RET	chr10: 43597858 (CM000672.1)	NM_020975.6: c.406G > A (p. Glu136Lys)	3.18E-4	216727	0.302	Hirschsprung disease, susceptibility to, 1 [MIM:142623] Multiple endocrine neoplasia, type IIA [MIM:171400] Familial medullary thyroid cancer [MIM:155240]	AD	heterozygous	NA

(*continued on next page*)

Table 1 (*continued*)

Gene symbol	Chromosomal location (GRCh37) [a]	Transcript ID: Variant (amino acid variation)	Allele frequency [b]	ClinVar ID	Pathogenicity prediction [c]	OMIM disorder [d]	Mode of inheritance	Zygosity of the patient	Carriage status of parents [e]
						Pheochromocytoma [MIM:171300] Multiple endocrine neoplasia type IIB [MIM:162300]			
EXT2	chr11: 44193187 (CM000673.1)	NM_207122.1: c.1200C > A (p. Phe400Leu)	1.14E-3	849654	0.76	Seizures, scoliosis, and macrocephaly/ microcephaly syndrome [MIM:616682] Multiple exostoses type II [MIM:133701]	AD/AR	heterozygous	NA
ATM	chr11: 108100002 (CM000673.1)	NM_000051.3: c.283C > A (p. Gln95Lys)	1.69E-3	181957	0.18	Ataxia-telangiectasia [MIM:208900] Breast cancer [MIM:114480]	AD/AR/SMu	heterozygous	NA
SLC37A4	chr11: 118895999 (CM000673.1)	NM_001164277.1: c.1025C > A (p. Ser342*)	NA	NA	NA	Glycogen storage disease Ib [MIM:232220] Congenital disorder of glycosylation, type IIw [MIM:619525] Glycogen storage disease Ic [MIM:232240]	AD/AR	heterozygous	NA
RAI1	chr17: 17697712 (CM000679.1)	NM_030665.4: c.1450G > A (p. Glu484Lys)	4.91E-4	NA	0.263	Smith-Magenis syndrome [MIM:182290]	AD	heterozygous	NA
NOTCH3	chr19: 15291062 (CM000681.1)	NM_000435.3: c.3148C > T (p. Arg1050Trp)	3.81E-4	NA	0.184	Lateral meningocele syndrome [MIM:130720] Myofibromatosis, infantile 2 [MIM:615293] Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy type 1 (CADASIL Type 1) [MIM:125310]	AD	heterozygous	NA
RYR1	chr19: 38995716 (CM000681.1)	NM_000540.3: c.8305G > A (p. Asp2769Asn)	2.66E-3	167619	0.316	Congenital myopathy 1A [MIM:117000] King-Denborough syndrome [MIM:619542] Malignant hyperthermia susceptibility 1 [MIM:145600] Congenital myopathy 1B, autosomal recessive [MIM:255320]	AD/AR	heterozygous	NA
APOE	chr19: 45409136 (CM000681.1)	NM_001302688.2: c.11G > A (p. Gly4Glu)	3.73E-3	NA	0.015	Alzheimer disease 2 [MIM:104310] Sea-blue histiocyte disease [MIM:269600] Alzheimer disease 3 [MIM:607822] Hyperlipoproteinemia, type III [MIM:617347] Lipoprotein glomerulopathy [MIM:611771] Macular degeneration, age-related, 1 [MIM:603075]	AD/AR	heterozygous	NA
JAG1	chr20: 10639284 (CM000682.1)	NM_000214.3: c.526G > A (p. Val176Ile)	4.73E-3	337758	0.301	Deafness, congenital heart defects, and posterior embryotoxon [MIM:617992] Charcot-Marie-Tooth disease, axonal, type 2HH [MIM:619574] Alagille syndrome 1 [MIM:118450] Tetralogy of Fallot [MIM:187500]	AD	heterozygous	NA
FLNA	chrX: 153583429 (CM000685.1)	NM_001456.3: c.4957G > A (p. Gly1653Ser)	1.26E-5	1194596	0.688	Otopalatodigital syndrome, type II [MIM:304120] Intestinal pseudoobstruction, neurona, chronic idiopathic, X-linked [MIM:300048] Cardiac valvular dysplasia, X-linked [MIM:314400] FG syndrome 2 [MIM:300321] Melnick-Needles syndrome [MIM:309350] Terminal osseous dysplasia [MIM:300244] Otopalatodigital syndrome, type I	XLD/XL/XLR	heterozygous	NA

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Table 1 (*continued*)

Gene symbol	Chromosomal location (GRCh37) [a]	Transcript ID: Variant (amino acid variation)	Allele frequency [b]	ClinVar ID	Pathogenicity prediction [c]	OMIM disorder [d]	Mode of inheritance	Zygosity of the patient	Carriage status of parents [e]
						[MIM:311300] Periventricular nodular Heterotopia 1 [MIM:300049] Frontometaphyseal dysplasia 1 [MIM:305620]			

Abbreviations: NA, not applicable; AD, autosomal dominant; AR, autosomal recessive; SMu, somatic mutation; XLD, X-linked dominant; XLR, X-linked recessive.

[a] Chromosomal location for genes in the GRCh37 human genome assembly were sourced from Ensembl (https://www.ensembl.org/index.html).

[b] The allele frequency was defined as the highest allele frequency of each population in the exome data set of the GnomAD database. More information can be found at https://gnomad.broadinstitute.org/.

[c] The numbers shown in the "pathogenicity prediction" column are the numerical results of the REVEL algorithm for predicting the pathogenicity of Missense Variants. The algorithm integrates 18 separate pathogenicity prediction results of 13 prediction tools, including SIFT、PolyPhen-2 and FATHMM v2.3, etc. For more details, please refer to PMID: 27666373.

[d] OMIM official website: https://www.omim.org/.

[e] The column of "carriage status of parents" only shows the information of the patient's parents who have undergone next-generation sequencing testing.

included variations in the *NOTCH3* gene (c.3148C > T, p. Arg1050Trp) and the *PLEC* gene (c.7412A > G, p. Asp2471Gly), which are discussed in detail in the discussion section for their potential clinical relevance.

Given the absence of ulceration, bleeding, or deeper tissue involvement in the scalp lesion, we recommended close monitoring. Regarding the VSD, the patient was referred to an experienced cardiologist who advised against immediate surgical intervention due to the infant's asymptomatic status. Instead, they suggested regular echocardiograms every six months to monitor the defect's size. Additionally, the parents were advised to schedule regular follow-up appointments at the pediatric department to monitor the child's development.

3. Discussion

The diagnosis of ACC and its clinical subtype, MACC is relatively straightforward, hinging mainly on the clinical presentation and dermoscopic examinations. ACC is associated with a plethora of disorders, requiring comprehensive patient assessment and tailored management strategies [14]. The Frieden classification system established decades ago, has served as a valuable tool for stratifying the subtypes of ACC but lacks specificity in terms of genetic information and subclassifications.

Diagnosing our patient's subtype presents a challenge due to its nuanced presentation. The solitary midline scalp lesion devoid of hair initially suggests Frieden's Type 1 ACC, which typically manifests as isolated lesions without associated anomalies. However, the absence of *BMS1* variation coupled with the discovery of a ventricular septal defect complicates this classification, prompting consideration of a broader syndromic presentation [13]. Adams-Oliver Syndrome (AOS), or Frieden's Type 2 ACC, emerges as a relevant consideration. AOS typically involves ACC affecting the scalp vertex along with limb defects. Notably, up to 20 % of AOS patients present with concurrent congenital heart defects (CHDs), including ventricular septal defects, pulmonary arterio-venous malformation, and tetralogy of Fallot [15–17]. Digilio et al. previously proposed that heterogeneity in the clinical presentation of AOS might include the association of CHD and ACC without limb defects [18]. Therefore, we believe that our patient might fall under a subclassification of Frieden's Type 2 ACC.

Notably, the pathogenesis of AOS is associated with genetic variations in six genes, namely, *DOCK6*, *ARHGAP31*, *RBPJ*, *EOGT*, *DLL4*, and *NOTCH1*, of which *NOTCH1* is the major contributor, underlying 10 % of AOS cases [19]. Although these variants were not identified in the present case, a missense gene variation in *NOTCH3*, c.3148C > T (p. Arg1050Trp) was detected. Similar to *NOTCH1*, *NOTCH3* is essential for stabilizing endothelial cell junctions [20] and has been shown to regulate neural stem cells in zebrafish models [21], suggesting conserved functions across different species. Moreover, *NOTCH3* is also expressed in hematopoietic progenitors and can partially substitute for *NOTCH1* in T cell lineage specification [22]. The Notch signaling pathway plays a crucial role in regulating cardiovascular development and homeostasis [23], with *NOTCH3* gene variants known to cause cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [24,25]. Nonetheless, further research is warranted to elucidate the specific role of *NOTCH3* variants in MACC and to determine any potential overlap with *NOTCH1*-related mechanisms.

In addition, our WES analysis also revealed a variation in the *PLEC* gene, specifically c.7412A > G (p. Asp2471Gly). Importantly, variation in the *PLEC* gene is associated with epidermolysis bullosa (EB) simplex [26,27]. According to the Friedan classification system, ACC associated with EB, also known as Bart syndrome, falls under type 6 ACC. However, our patient did not exhibit typical skin blisters usually found on the lower limbs or nail deformities associated with this syndrome. Therefore, establishing a direct link between the detected *PLEC* gene variation and the observed phenotype is challenging, requiring further in-depth analysis and follow-up time.

This single case study has several limitations that should be acknowledged. Our analysis primarily targeted clinically relevant genes, possibly leading to the oversight of variants in genes not typically linked to the observed phenotype, limiting our grasp of the genetic factors influencing MACC. Moreover, we did not undertake direct DNA sequencing validation, raising concerns about potential false positives within the WES data. Besides, additional genetic analyses, such as chromosomal arrays, were not conducted to assess structural variations. Therefore, future investigations should consider incorporating such analyses for a more comprehensive assessment of the genetic landscape associated with MACC.

4. Conclusions

Our case study underscores the importance of a multidisciplinary approach in diagnosing and managing MACC associated with congenital anomalies. WES allowed the identification of potential genetic contributors to MACC, including variations in genes like *NOTCH3* and *PLEC*. By emphasizing interdisciplinary collaboration and genetic testing, we can refine diagnostic algorithms and classifications to tailor management strategies for MACC. All in all, our findings contribute to advancing understanding and improving outcomes for affected individuals and their families.

Ethics statement

The patient's parents provided both verbal and written informed consent for the publication, which included the scientific use of clinical photographs. Assent was not obtained given the age of the patient.

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Authorship

Each of the listed authors satisfies the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) for this article, assumes responsibility for the overall integrity of the study, and has granted their consent for the publication of this manuscript.

CRediT authorship contribution statement

Qiu-Yun She: Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hui-ling Zhu:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Zhong-Rong Liu:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Wei-Ning Huang:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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