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Clinical Report

Neonatal erythroderma and immunodysplasia: Overlap of cartilage-hair hypoplasia and Omenn syndrome

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ABSTRACT

Cartilage hair hypoplasia (CHH) syndrome (OMIM #250250) is a rare autosomal recessive metaphyseal dysplasia, characterized by disproportionate short stature, hypotrichosis and variable extra-skeletal manifestations, including immunodeficiency, anemia, intestinal diseases, and predisposition to malignancies.

CHH results from homozygous or compound heterozygous mutations in the *RMRP* gene on chromosome 9p13, which encodes an untranslated RNA component of mitochondrial RNA-processing endoribonuclease.

RMRP pathogenic variants can also lead to Omenn Syndrome (OS) (OMIM #603554), a systemic inflammatory condition displaying neonatal erythroderma and immunodeficiency.

This report highlights the genotypic and phenotypic overlap between CHH and OS, by presenting a newborn with skeletal dysplasia, immunodeficiency and neonatal onset erythroderma, carrying the homozygous NR_003051:n.35C > A variant in the RMRP gene.

1. Introduction

Cartilage Hair Hypoplasia (CHH) (OMIM #250250) is a rare autosomal recessive skeletal dysplasia due to mutations in the mitochondrial RNA-processing endoribonuclease gene (*RMRP*; MIM *157660), located on chromosome 9p13-p12 and encoding the RNA component of the RNase MRP (ribonuclease mitochondrial RNA processing) complex. This small nucleolar RNA (snoRNA) plays a key role in the cleavage of 5.8S rRNAfor ribosome assembly, in the processing of cyclin B mRNA, and interaction with the human telomerase catalytic subunit (hTERT) (Ridanpää et al., 2001; Hermanns et al., 2005; Maida et al., 2009). *RMRP* dysfunction impairs cell proliferation and differentiation, mostly affecting rapidly dividing cells such as lymphocytes and chondrocytes (Thiel et al., 2005; Vakkilainen et al., 2019a).

CHH has a broad phenotype, primarily characterized by disproportionate short stature with skeletal deformities, and hypotrichosis. Extra-skeletal manifestations range from variable degrees of immunodeficiency and bone marrow dysplasia to conditions such as Hirschsprung's disease (Rider et al., 2009; Kostjukovits et al., 2017; Mäkitie and Kaitila, 1993).

The clinical course and prognosis of CHH patients is mainly determined by the severity of immune dysfunction and by the increased risk of malignancies (Bordon et al., 2010; Ip et al., 2015).

Neonatal erythroderma (NE) is a rare condition defined as widespread redness and inflammation of the skin, covering at least 90 % of the body surface (Ott, 2019). Congenital ichthyoses, primary immunodeficiencies (PIDs), metabolic and genetic disorders, drug use and cutaneous infections are the main causes of NE (Al-Dhalimi, 2007; Pruszkowski et al., 2000). Erythroderma is one of the typical manifestations of Omenn syndrome (OS), an inflammatory condition characterized by skin manifestations, alopecia, chronic diarrhea, failure to thrive, lymphadenopathy, hepatosplenomegaly, and severe combined

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immunodeficiency (SCID). Rather than a distinct form of SCID, OS is an inflammatory phenotype that can be associated with genetically different SCIDs. Although OS is not caused by a defined genetic defect, the majority of OS cases reported to date are due to hypomorphic mutations in RAG1 (MIM*179615) and RAG2 (MIM*179616) genes, but mutations in other genes (ADA, IL2RG, IL7RA, DCLRE1C, CHD7, LIG4 and RMRP) are also reported (Dvorak et al., 2023).

To add further details to the knowledge of both the phenotypic spectrum of CHH and OS, we report on a newborn with skeletal dysplasia presenting impressive erythroderma at birth and carrying the homozygous *RMRP* c.35C > A pathogenic variant.

2. Clinical report

The proband is the third daughter of healthy consanguineous (second cousins) parents. Since the 19th week of gestation skeletal dysplasia was suspected because of micromelia (femur length: 23.5 mm; −2.84 DS) and a small thorax. Prenatal invasive diagnostic tests were refused by the parents.

The infant was born at 34weeks' gestation by caesarean section because of preterm labor and breech presentation. She needed resuscitation and admission to the Neonatal Intensive Care Unit for respiratory support. The Apgar score was 2, 7 and 8 at first, fifth and tenth minute, respectively.

At birth her auxological data were: weight 2130 g (38th centile; −0.30 DS), length 40 cm (<1st centile; −2.59 DS), and head circumference 33 cm (89th centile; 1.28 DS) (Villar et al., 2014).

The proband presented with rhizomelic limb shortening and striking cutaneous manifestations, including severe erythroderma and edematous skin (Fig. 1). Progressive hair and eyebrows loss became evident from the first week of life. Skeletal X-ray confirmed rhizomelia and dumbbell shaped femurs (Fig. 2). Congenital infections were excluded. She also developed hepatosplenomegaly and lymphadenopathy.

Furthermore, the infant developed anemia requiring blood transfusion, severe hypereosinophilia with normal IgE and progressive lymphopenia. On day 30 she presented multiple bacterial sepsis treated with antibiotics.

In the suspicion of immunodeficiency, a comprehensive immunological workup was performed (Table 1). Immunophenotype analysis revealed reduced lymphocyte T proliferation rate and absence of recent maturation stage T lymphocytes with expansion of the effector component. Additionally, B lymphocytes low levels, predominantly within the unswitched component, hypogammaglobulinemia were observed. Maternal engraftment was excluded. As a result, a diagnosis of T-B-NK + severe combined immunodeficiency (SCID) in a patient with clinical features of Omenn Syndrome (OS) was established.

Treatment with intravenous immunoglobulins, along with broad-spectrum antiviral, antibiotic, and antifungal prophylaxis were started. A haploidentical hematopoietic stem cell transplant was performed when the patient was two months old. Anyway, the child died at 20 months of age. Fig. 3 illustrates the child's growth trajectory during the first months of life.

Several genetic tests were performed: karyotype was 46 XX, normal, and genomic microarray analysis revealed no detectable copy number variations.

The next-generation panel for SCID identified NR 003051:n.35C > A as a homozygous pathogenic variant in the RMRP gene, confirming the diagnosis of OS in a patient affected by CHH. Parents were heterozygous for the same mutation. The NR 003051:n.35C > A RMRP pathogenic variant was submitted to ClinVar (SUB15583466).

3. Discussion

In this report, we describe a rare presentation of CHH with neonatal

Fig. 1. Erythrodermal and desquamative lesions (A). Hair hypoplasia with eyebrows and eyelashes involvement (B).

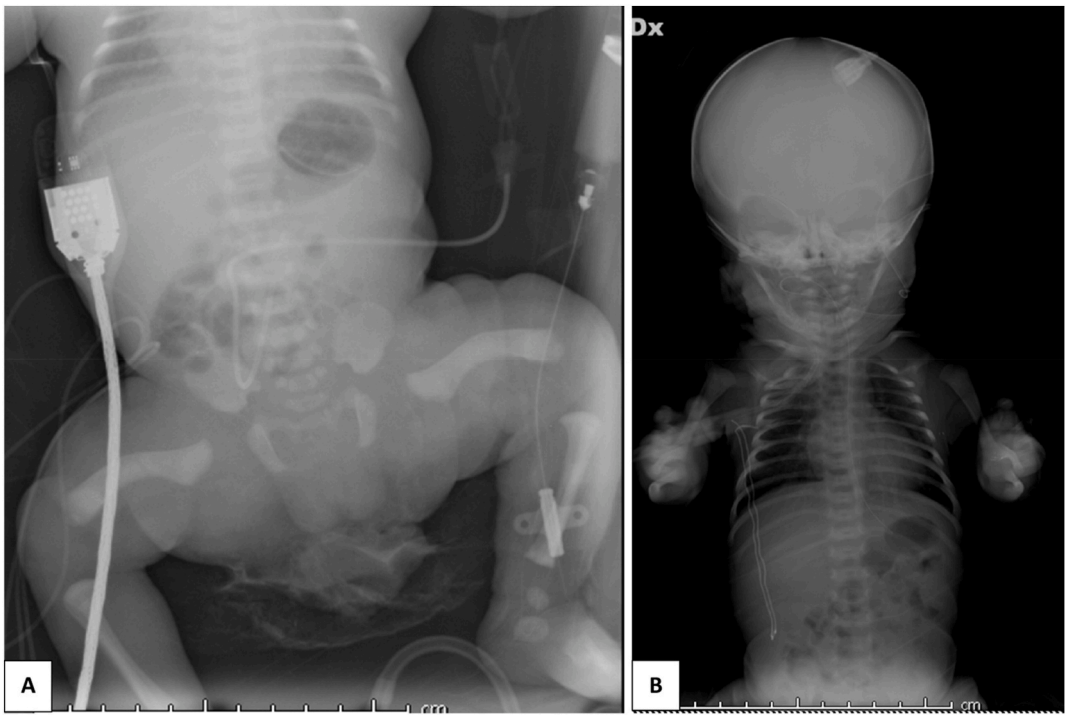

Fig. 2. A: at birth skeleton X-ray shows shortened long bones and dumbbell-shaped femurs. **2B**: Bell shaped thorax, with no spine nor skull anomalies.

Table 1
Humoral and cellular immunity tests.

Serum immunoglobulins (mg/dL)	Patient Values	Reference Values[b]
IgG	137	598–1672
IgA	1	0–5
IgM	43	5–15
IgE (UI/mL)	3	
Lymphocyte Subset	**Patient Values**	**Reference Values[b]**
$CD3^+$, cells per μL	1703	2908–5961
$CD3^+$ $CD4^+$, %	57.8	29.9–64.7
HLA antigen DR+	36.2	0.8–6.1
Naïve	0	68.8–91.7
Effector memory	85.6	1.5–8.3
$CD3^+CD8^+$, %	23.1	9.1–26.9
HLA antigen DR+	39.8	1.6–30.2
Naïve	0	37.9–90.7
Effector memory	81.9	1.3–27.2
$CD19^+$, %	4.1	11.2–33.2
$CD3^-CD56^+CD16^+$, cells per μL	130	273–1698
TRECs	213/mL	>32028/ml
KRECs	24215/mL	>93810/ml
Mitogenic responses[a]	**Patient vs control specimen**	
PHA	1.3 vs 1.8	
Anti-CD3	1.2 vs 2.3	

[a] Mitogenic responses are expressed as the stimulation index.
[b] Reference values are presented as 10th and 90th percentiles based on established values for infants 0–12 months old. Abbreviations: PHA = phytohemagglutinin; TRECs = T-cell receptor excision circles; KRECs = kappa-deleting recombination excision circles.

erythroderma and immunodeficiency.

The newborn exhibited typical features of CHH, including rhizomelic dwarfism, short tubular bones, metaphyseal dysplasia with widened and flared distal metaphyses, and mildly bowed femora, together withhair hypoplasia. Simultaneously, there were features such as erythroderma, SCID, hypereosinophilia, lymphadenopathy, and hepatosplenomegaly, which are part of the OS spectrum. Therefore, this clinical report highlights a significant phenotypic overlap between CHH and OS. However, the presence of skeletal dysplasia since the prenatal period, associated with a known *RMRP* homozygous pathogenic variant, led us to conclude that OS developed in this patient with genetically confirmed CHH (Ip et al., 2015; Lugli et al., 2021).

CHH is part of the broader CHH-anauxetic dysplasia (CHH-AD) and Supplementary Table 1 provides a comprehensive summary of its clinical and radiological features (Mäkitie et al., 1993). The immunological phenotype of CHH is highly variable, ranging from mild immunodeficiency to SCID, with some patients experiencing a progressive worsening of immunodeficiency over time (Vakkilainen et al., 2019b, 2020). Cell-mediated immunity is often impaired, with decreased lymphocyte proliferation responses in the majority of patients (Rider et al., 2009; Mäkitie and Kaitila, 1993; Vakkilainen et al., 2020; Mäkitie et al., 1995, 1998). Combined immunodeficiency has been reported in 24 % of individuals with CHH, with some of them presenting clinical features of OS (Vakkilainen et al., 2019b; Roifman et al., 2006).

OS represents a unique inflammatory phenotype that can be associated with various genetically diverse forms of SCID. It is characterized by severe immunodeficiency and features of immune dysregulation, such as early-onset erythroderma, hepatosplenomegaly, lymphadenopathy, alopecia, and chronic diarrhea (Omenn, 1965). Although most cases reported to date involve hypomorphic mutations in the RAG1 and RAG2 genes, OS is not caused by a single, well-defined genetic defect. Patients with OS associated with *RMRP* pathogenic variants have been previously reported, and their features are summarized in Table 2 (Dvorak et al., 2023; Greenberg-Kushnir et al., 2020).

In some of them, the diagnosis of CHH was delayed and was only recognized after the lack of catch-up growth following bone marrow transplantation (BMT) (Roifman et al., 2006).

Interestingly two patients presented OS without confirmed skeletal dysplasia, confirming the extreme phenotypic variability in patients with *RMRP* mutations (Kavadas et al., 2008).

Even if erythroderma was reported in all the patients with OS carrying *RMRP* mutations, to the best of our knowledge, the current patient is the first presenting erythroderma at birth.

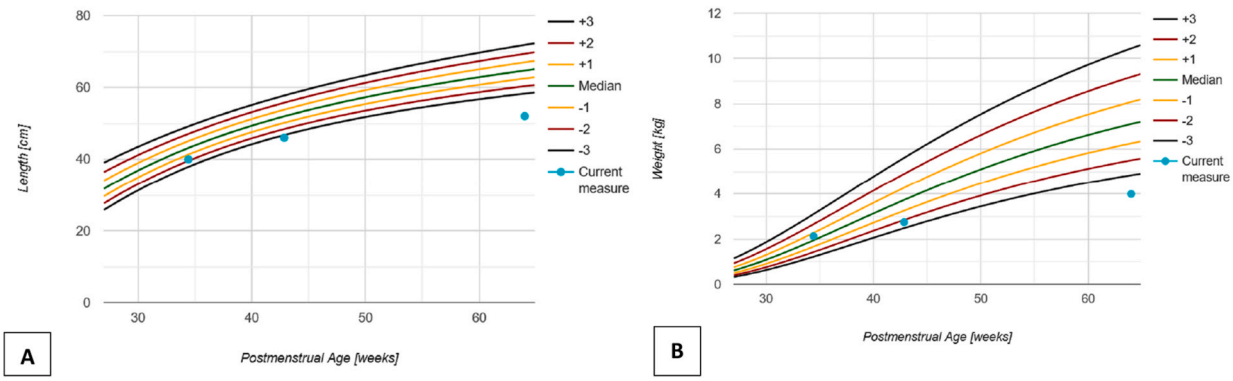

Fig. 3. Post-natal growth chart for length (3A) and weight (3B). INTERGROWTH-21ST Preterm Postnatal Growth Charts are used (Villar J 2015).

Table 2
Previously described patients with OS due to RMRP mutations, compared to our patient.

	Kavadas et al., 2008 (Kavadas et al., 2008)				Ip et al., 2015 (Ip et al., 2015)	Present paper
	Patient 1[b]	Patient 2[b]	Patient 3	Patient 4	Patient 5	Proband
General features						
Age (mo)	5	3	3.5	2.5	5	At birth
Sex	F	F	M	F	F	F
Gestational age	At term	At term	NR	NR	NR	34 + 3
Birth length cm (DS)	NR	NR	NR	NR	NR[a]	40 (−2.6)
Growth[a]						
Height percentile	<3rd	<3rd	<3rd	<3rd	≪0.4	<1st
Weight percentile	<3rd	<3rd	<3rd	<3rd	NR	38th
Clinical features						
Failure to thrive	+	+	+	+	+	NA
Absent or sparse hair	+	+	+	–	+	+
Short limbs	+	+			+	+
Erythroderma	Severe	Mild	Severe	Severe	Yes	Severe
Lymphadenopathy	+	+	+	+	+	-
Hepatomegaly	+	+	+	+	+	+
Splenomegaly	+	+	+	NR	+	+
Recurrent infections	+ *P. Jiroveci*	+ *P. Jiroveci*	+	+	–	Staphylococcus Aureus, Enterococcus Faecalis and Acinetobacter Baumanii sepsis
Protract/recurrent diarrhea	+	+	-	+	+	-
Immunodeficiency	T-/B-/NK + SCID Poor T-cell mitogenic response Oligoclonal expansion of lymphocyte T	T-/B-/NK- SCID Poor T-cell mitogenic response	T-/B-/NK + SCID Poor T-cell mitogenic response Oligoclonal expansion of lymphocyte T	T-/B-/NK + SCID Poor T-cell mitogenic response		T-/B-/NK + SCID Poor T-cell mitogenic response
CHH typical radiological findings	+	+	No evidence of metaphyseal dysplasia	No evidence of metaphyseal dysplasia	+	+
RMRP mutations						
Allele 1	TACTCTGTGAAGTACTCTG TGAAGCTGA at −10 (insertion)	ATCTGTG at −13 (insertion)	−25_-11dup	−25_-13dup	25_-11 dup	35 C > A
Allele 2	4 C > T	240 A > C	154 G > C	[b]5 T > C	4 C > T	35 C > A
Outcome	Alive and well 14 years after BMT	Alive and well 22 years after BMT	Alive and well 1.5 years after BMT	Alive and well 9 years after BMT	Alive and well 50 months after BMT	Died 20 months after BMT

at diagnosis.
firstly described by Roifman et al., 2006). ° Height persistently <3rd percentile after Bone Marrow Transplantation.
Disproportionate short stature at birth. **Abbreviations: BMT = Bone Marrow Transplantation, NR = Not reported; NA = Not applicable.**

The pre-natal suspicion of skeletal dysplasia and the short-limb dwarfism along with characteristic radiological findings at birth, strongly suggested the diagnosis of CHH early on.

From a genetic perspective, all previously described patients with OS and *RMRP* mutations were compound heterozygotes, with insertions or duplications in the promoter region on one allele and point mutations in the transcribed region, on the other.

As previously reported, mutations in the promoter region directly reduce *RMRP* RNA levels, and homozygous variants in this region are rarely reported, suggesting that the complete absence of *RMRP* is incompatible with life. In contrast, mutations in the transcribed region alter the RNA's secondary structure, leading to decreased stability or reduced enzymatic activity of the RNase MRP complex (Ridanpää et al., 2001; Kavadas et al., 2008; Tan et al., 2023; Vatanavicharn et al., 2010;

Mattijssen et al., 2010; Nakashima et al., 2007).

Our patient, carrying the homozygous NR 003051:n.35C > A RMRP variant in the transcribed region, is the first presenting OS with no alterations in the promoter region.

The homozygous NR 003051:n.35C > A mutation was first reported by Ip et al. in four South-Asian siblings. Among them, three presented with combined or severe combined immunodeficiency, while only two showed radiological features of skeletal dysplasia, underlining once again the high intra-familial phenotypic variability of *RMRP* mutations (Ip et al., 2015).

4. Conclusions

The unique clinical-instrumental phenotype (skeletal dysplasia with erythroderma, hyper-eosinophilia and SCID) associated with the homozygous NR 003051:n.35C > A pathogenic variant, lead us to the diagnosis of OS in a patient affected by CHH.

This report contributes to expanding the broad phenotypic spectrum of CHH disease, suggesting the potential of early skin involvement, particularly in case of severe immunodeficiency. Even if a certain overlap with OS and CHH has been already described, this case reinforces the link between these two conditions and suggests the importance of a comprehensive immunologic and genetic workup, including *RMRP* gene, in newborns presenting erythroderma.

CRediT authorship contribution statement

Anna Insalaco: Conceptualization, Data curation, Writing – original draft. **Cecilia Rossi:** Conceptualization, Investigation, Supervision, Validation, Visualization, Writing – review & editing. **Emma Bertucci:** Conceptualization, Investigation, Validation, Visualization, Writing – review & editing. **Chiara Fiorentini:** Conceptualization, Investigation, Validation, Visualization, Writing – review & editing. **Annarosa Soresina:** Investigation, Validation, Visualization, Writing – review & editing. **Silvia Giliani:** Investigation, Validation, Visualization, Writing – review & editing. **Fulvio Porta:** Investigation, Validation, Visualization, Writing – review & editing. **Alberto Berardi:** Conceptualization, Investigation, Supervision, Validation, Visualization, Writing – review & editing. **Licia Lugli:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2026.105069.

Data availability

The data that has been used is confidential.

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