ADRENOLEUKODYSTROPHY: SHORT HAIR WITH TRICHOSCHISIS, HYPOTRICHOSIS OF THE EYEBROWS, AND ONYCHODYSTROPHY

Mun A.[1,2,3], Kobiljonova D.[1], Ibragimova L.[1], Mirsalikhova D.[1]
[1]Tashkent State Medical University, [2]National Children's Medical Center, [3]Central Asian University
Tashkent, Uzbekistan

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Abbreviations VLCFA = very long-chain fatty acids; X-ALD = X-linked adrenoleukodystrophy..

Case report. A 17-year-old female presented with progressive neurological deterioration and short, brittle hair since birth. Anthropometric parameters were within normal limits (weight 56.4 kg, height 156 cm, BMI 23.2 kg/m^2).

Dermatological examination revealed marked ectodermal abnormalities, including brittle and sparse hair consistent with trichoschisis, hypotrichosis of the eyebrows and eyelashes, and generalized onychodystrophy (Fig. 1, 2, 3). The skin appeared pale and thinned, with reduced turgor. No perifollicular erythema, scaling, or inflammatory changes were noted.

Dermoscopic examination, performed with a polarized dermoscope (DermLite DL5, ×20), highlighted characteristic hair shaft abnormalities. Numerous hairs exhibited a regular alternating pattern of elliptical nodes and constricted internodes, resulting in a moniliform appearance (Fig. 4). The nodes were uniformly spaced, thickened, and more pigmented, while the internodes appeared thinned, hypopigmented, and structurally fragile. Hair shaft fractures were consistently observed at the level of the internodes (Fig. 4). Additionally, several hairs showed distal fraying and longitudinal bifurcation, along with numerous short, broken shafts of varying lengths, consistent with increased fragility.

In addition to hair shaft abnormalities, dermoscopy identified focal areas of follicular hyperkeratosis. These appeared as yellowish, lobulated keratotic aggregates with a papillomatous or cauliflower-like morphology. The keratin masses were compact and adherent, partially enveloping adjacent hair shafts. The surrounding skin showed mild erythema and fine scaling, without evident vascular artifacts (Fig. 5).

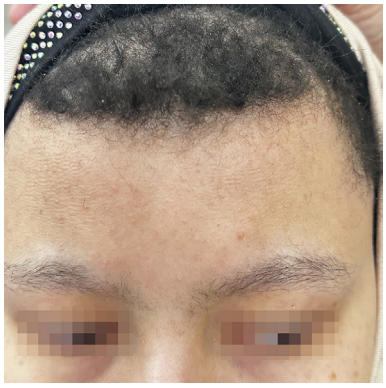

Fig. 1

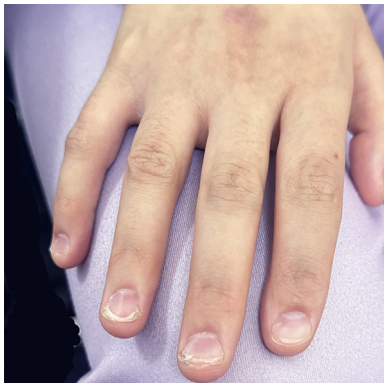

Fig. 2

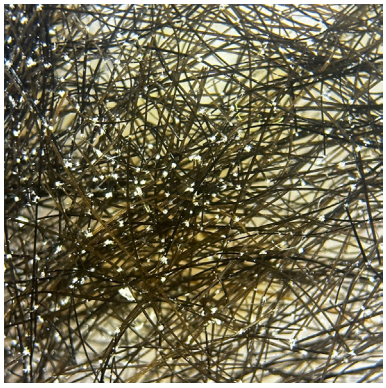

Fig. 3

Fig. 1, 2, 3: Adrenoleukodystrophy: short hair with trichoschisis, hypotrichosis of the eyebrows, and onychodystrophy.

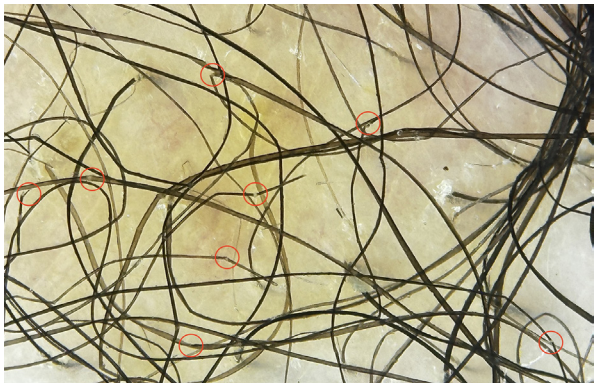

Fig. 4

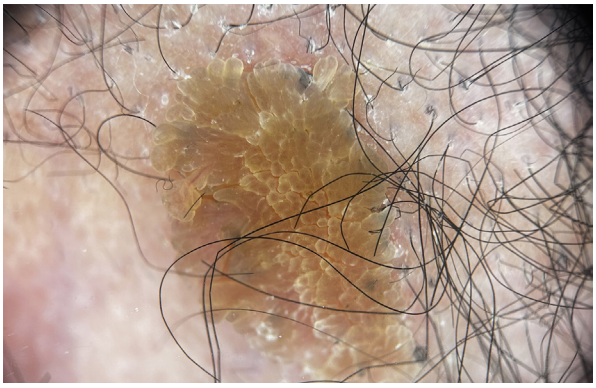

Fig. 5

Fig. 4, 5: Dermoscopy reveals hair shaft fractures (Fig. 4, red circle) and follicular keratosis (Fig. 5).

Neurological examination revealed progressive motor and cognitive decline, ataxic gait, postural instability, and loss of previously acquired skills. Cranial nerve assessment revealed bilateral optic disc atrophy. Deep tendon reflexes were increased, a finding compatible with upper motor neuron involvement. Brain MRI showed extensive leukoencephalopathy with diffuse white matter involvement affecting the parieto-temporo-occipital regions and the brainstem, findings consistent with a pattern of leukodystrophy.

Biochemical examinations revealed significantly elevated levels of very-long-chain fatty acids (VLCFAs), including an increase in C26:0 concentration and elevated C24:0/C22:0 and C26:0/C22:0 ratios, supporting the diagnosis of X-ALD.

Whole-exome sequencing (WES) identified: a homozygous pathogenic variant in the *ABCD1* gene (c.824G>A; p.Arg275Gln), classified as pathogenic according ACMG criteria and a homozygous variant of uncertain significance (VUS) in the *AARS1* gene (p.Asn604Thr).

The interpretation of the variants was performed according to ACMG guidelines, and the *ABCD1* variant was classified as pathogenic based on previously reported cases and functional relevance. The presence of a homozygous *ABCD1* variant in a female patient represents an unusual genetic scenario. Possible explanations of this finding include consanguinity, uniparental disomy, or skewed X-chromosome inactivation; however, parental genetic testing was not available, which limits further interpretation.

The final diagnosis was severe atypical X-linked adrenoleukodystrophy (ICD-10: E71.3), associated with a trichothiodystrophy-like phenotype potentially linked to the *AARS1* variant (ICD-10: L67.8).

The patient underwent long-term replacement therapy with hydrocortisone for primary adrenal insufficiency. Endocrine stabilization was achieved; however, no modifying effect on the neurological progression of the disease was observed. Management remained supportive and multidisciplinary, involving neurology, endocrinology, medical genetics, rehabilitation, and palliative care.

Discussion. This case describes a rare and severe presentation of X-linked adrenoleukodystrophy in a female patient with a homozygous variant of the *ABCD1* gene. Such presentations are extremely rare and may reflect unusual genetic mechanisms, including consanguinity or non-random X-chromosome inactivation. The clinical phenotype, which includes progressive leukodystrophy, elevated VLCFA levels, and characteristic neuroradiological findings, strongly supports the hypothesis of X-ALD as the primary diagnosis.

Dermoscopic findings of regularly spaced elliptical nodes with interposed constrictions and preferential breakage at the internodes are reminiscent of monilethrix. This is also supported by the uniformity of the beaded pattern combined with marked shaft fragility and the presence of short, broken hairs. These features reflect the underlying structural defect of the hair shaft, where periodic narrowing causes mechanical weakness, leading to fracture at the internodes. This explains the clinical picture characterized by short, brittle hair since birth, a distinctive feature of the condition.

The presence of follicular hyperkeratosis associated with characteristic hair shaft abnormalities further recalls the diagnosis of monilethrix, in which perifollicular keratinization disorders are frequently observed. This finding reflects abnormal follicular keratinization, which may contribute to altering the hair shaft and exacerbating clinical hair fragility.

However, the presence of marked ectodermal abnormalities, including brittle hair and generalized onychodystrophy, is atypical for X-ALD and prompted further genetic investigation. The identification of a concomitant homozygous variant of the *AARS1* gene, found in some cases of trichothiodystrophy, is consistent with a possible blended phenotype. While a causal link for the *AARS1* variant cannot be established, its phenotypic relevance remains plausible given the observed ectodermal manifestations. It is important to emphasize that the *AARS1* variant is currently classified as a variant of uncertain significance, and its pathogenic contribution cannot be definitively established. Therefore, its role must be interpreted with caution and within the context of clinical correlation.

Differential diagnosis included other inherited leukodystrophies, mitochondrial diseases, and ectodermal dysplasias. Specifically, mitochondrial encephalopathies and other peroxisomal disorders were considered due to overlapping neuroradiological features. However, the combination of markedly elevated VLCFA levels, characteristic MRI findings, and the identification of a pathogenic *ABCD1* variant strongly support the diagnosis of X-ALD.

Overall, this work highlights the emerging concept that complex phenotypes can result from multiple genetic conditions rather than a single unifying diagnosis.

Conclusion. This case demonstrates a rare and diagnostically complex presentation of severe X-ALD in a female patient with a concomitant AARS1 variant. While X-ALD explains the primary neurological phenotype, the ectodermal abnormalities suggest an additional genetic contribution. This report reinforces the need to consider blended phenotypes in complex multisystem disorders and underscores the clinical value of comprehensive genomic analysis.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Address to:
Dr. Andrey Mun
email: andrey_mun@yahoo.com

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