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Letter

Hyperpigmentation and atrophy in folds as cutaneous manifestation in a case of mitochondrial myopathy

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Abstract

Mitochondrial myopathies are inborn metabolism defect diseases manifested by symptoms reflecting failure of the final step in the mitochondrial respiratory chain. Clinical expression of these conditions can vary widely, but typically includes organ systems with a high energy demand, such as striated muscle, myocardium, and nervous and liver tissues. In contrast, cutaneous manifestations are rare and are non-specific, most commonly presenting as pigmentation disorders. In this case report, we present a case of Alpers syndrome accompanied by hyperpigmentation and atrophy in skin folds.

Introduction

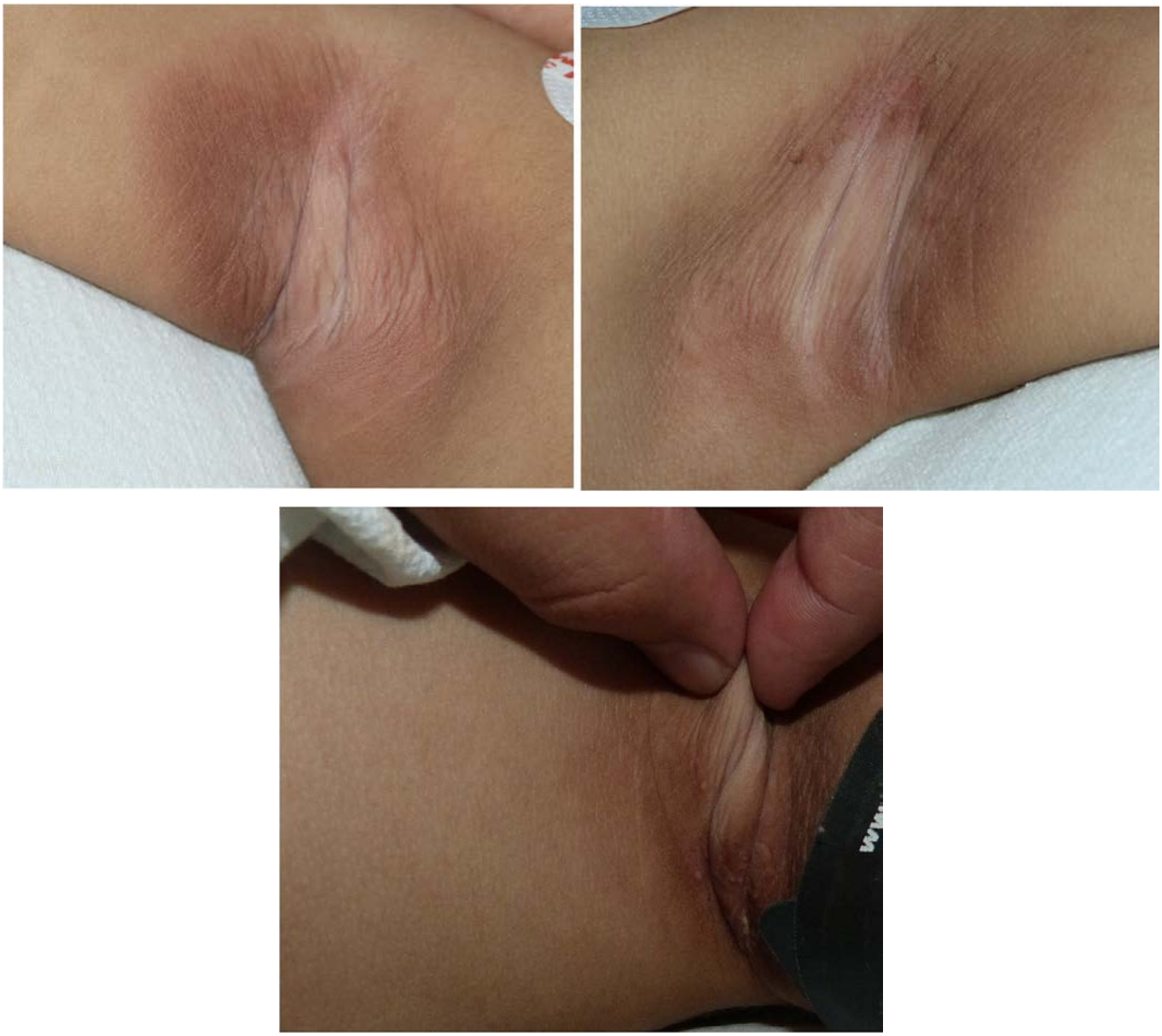
Mitochondrial myopathies are a heterogeneous group of inherited or acquired diseases resulting from a failure in the mitochondrial respiratory chain [1]. Primary mitochondriopathies are the most common of metabolic birth defects, with an incidence of 13 cases per 100,000 inhabitants [2,3]. Mutations in mitochondria and nuclear DNA encoding any of the 13 oxidative phosphorylation enzymes within the mitochondrial respiratory chain can manifest as a variety of clinical syndromes [4]. Such mutations can lead to failures in energy production, abnormal metabolism of carbohydrates and lipids, and elevated blood lactate. These clinical findings frequently lack diagnostic specificity. Therefore, dynamic testing is needed to demonstrate an abnormality in energy production [5].

The phenotypic expression of inherited mitochondrial-DNA mutations depends on the proportion of unaffected DNA within tissues, which changes with each new conception [1]. Therefore, mitochondrial dysfunction syndromes can be passed down in divergent inheritance patterns and thus affect any organ or system, presenting as many symptoms or groups of symptoms [6]. However, the clinical manifestations of these conditions will be more apparent in tissues with a high metabolic demand [7], such as the muscular and the nervous systems [6]. As a result, a progressive multisystemic disorder affecting the central or peripheral nervous system, striated muscle, or heart is a strong indicator of a mitochondriopathy. The prognosis in these cases is poor and patients die at an early age owing to cardiac and neuromuscular respiratory complications. The diagnosis is ultimately based on clinical suspicion supported by evidence from physical examination and biochemical, morphologic, and genetic test results [4].

Cutaneous manifestations of mitochondrial myopathies are nonspecific and their precise frequency is unknown [8]. Pearson syndrome manifests with sideroblastic anemia and exocrine pancreatic dysfunction, accompanied by cervical symmetric lipomas [9] and Ekbom Syndrome is accompanied by poikiloderma in exposed areas in addition to hereditary ataxia, myoclonic epilepsy, and neuropathy [10]. In this paper we present a particular pattern of hyperpigmentation and skin atrophy in skin folds in a patient with Alpers syndrome.

Case synopsis

A 10-month-old boy with a normal perinatal history was born to healthy parents without consanguinity. The parents had a previous child (female) who died during her first year from complications of Alpers syndrome. Our patient's condition began with neurodevelopmental regression at six months of age, such as loss of head control and paralysis of the sixth cranial nerve. Owing to respiratory dysfunction, our patient was hospitalized with pneumonia at seven months of age, at which time a muscle biopsy for morphologic and dynamic studies of energy metabolism revealed "ragged red fibers". As the patient also showed a rapidly progressing polydystrophy, morphologic alterations of skeletal muscle, psychomotor regression with microcephaly, and hepatocellular dysfunction, he was diagnosed with Alpers syndrome and treatment with coenzyme Q, pyridoxine, and carnitine was begun. Three months later, he was hospitalized for pyelonephritis complicated by respiratory failure, quadriplegia, and stupor secondary to hypoxia. During this episode, a bilateral and symmetrical disseminated skin eruption affecting armpits, groin, and dorsum of the foot was noticed, characterized by hyperpigmented macules with hypochromic centers, confluent over the dorsal portion of the ankles (Figure 1). The consistency of the skin was lax and atrophic. There was no history of previous dermatitis nor topical steroid therapy on affected surfaces No clinical changes were observed in hair, nails, or mucous membranes. After two weeks of intensive care support, the patient died owing to respiratory complications.



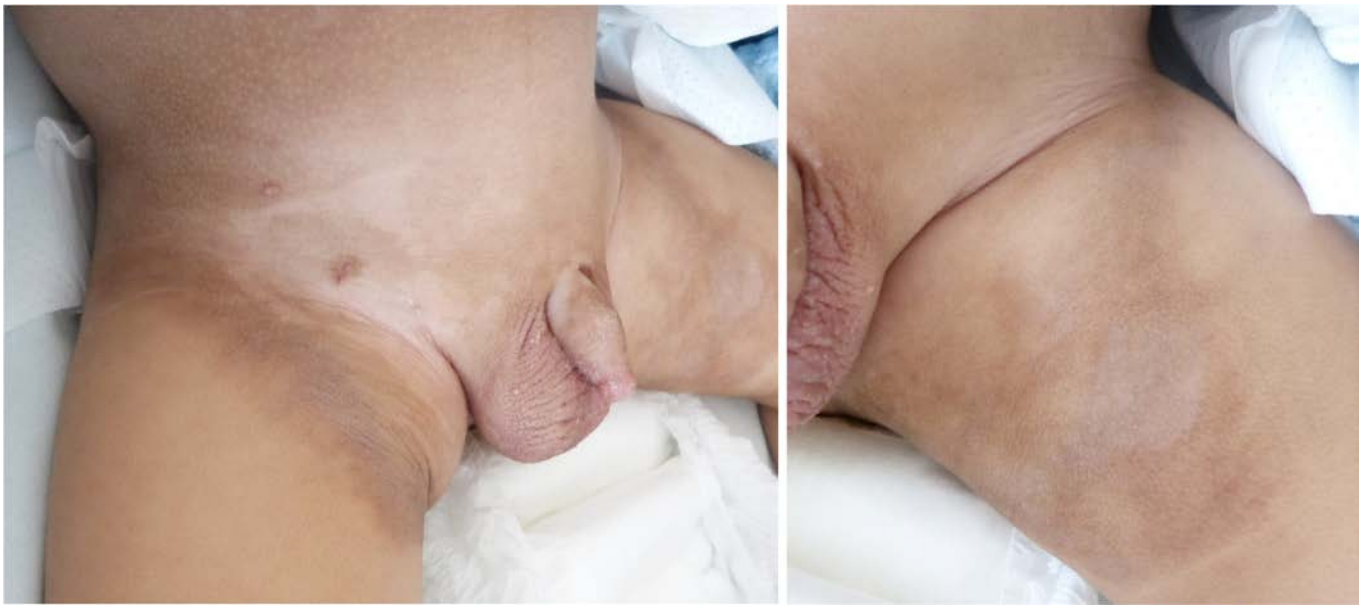


Figure 1. Cutaneous presentation. A) Peripheral brown hyperpigmentation in both armpits, with a lax and hypochromic center. B) Notorious laxity and skin atrophy in axillary folds. C) Hyperpigmented peripheral and hypopigmented center pattern in inguinal folds.

Discussion

Cutaneous findings may precede or accompany other clinical manifestations that characterize these mitochondrial syndromes [7]. Dermatologic manifestations are classified as benign tumors, pigmentation disorders, or changes in skin appendages [3]. Lipomas, poikiloderma, petechiae, brittle hair, hirsutism, cutis marmorata, anhidrosis, vitiligo, and non-specific hyperpigmentation have also been described [8,11], though these findings are heterogeneous and poorly recognized [12].

The patient in this case was preceded by a sister who died from complications of Alpers syndrome, a condition within the spectrum of mitochondrial myopathies without skin manifestations. Thus, his cutaneous involvement demonstrates the clinical heterogeneity of these syndromes even among siblings. His hyperpigmentation may have been related to a pro-oxidant state that induces the synthesis and transfer of melanin [13], as melanocytes may respond to oxidative stress by increasing melanogenesis [14].

Skin atrophy and laxity among patients with mitochondrial dysfunction has been associated with high levels of organic acids in skin fibroblasts [15]. However, these cells are morphologically normal and not accompanied by structural changes in elastin fibers [16]. Unfortunately, no fibroblast culture was performed in our case. The theory of the energy threshold suggests that clinical manifestations in mitochondriopathies are inversely proportional to the energy deficit in the tissues [6]. However, further research is required to confirm this hypothesis, specifically for cutaneous manifestations.

In conclusion, this case illustrates the importance of recognizing the existence of dermatologic manifestations in the clinical spectrum of mitochondriopathies and suggests that the pattern of atrophy and pigmentation in skin folds could be distinctive.

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