MON-129 An Unusual LMNA Mutation Causing a Complex Phenotype: When the Genetic Diagnosis Uncovers Novel Features

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Abstract

**Background:** Lipodystrophy syndromes are characterized by loss of body fat. Although classical Familial Partial Lipodystrophy (FPLD) and Congenital Generalized Lipodystrophy (CGL) have different clinical presentations, we have encountered a unique case where the distinction was quite challenging. **Clinical Case:** Our patient first presented to an endocrinologist at age 19 with secondary amenorrhea and hypothyroidism. After normalization of TSH, further investigation revealed central hypogonadism, hypertriglyceridemia (>3,000 mg/dL, normal<150mg/dL), xanthomas and fatty liver disease. By that time, she had adiposity changes such as lack of subcutaneous fat in the limbs and abdomen and prominent muscles. She believed she had those traits since early childhood. After puberty, she developed generalized muscle pain and was noted to have elevated CK. At 59 years old, she developed diabetes as well as liver fibrosis. These led to the diagnosis of lipodystrophy (initially classified as FPLD due to inheritance pattern). However, physical examination revealed acromegaloid features, BMI of 23.2 kg/m2, minimal fat palpable around the neck and minimal fullness of the supraclavicular fossa. The rest of the body was virtually devoid of subcutaneous fat tissue, consistent more with the CGL phenotype and inspection of older photos demonstrated progressive fat loss. She displayed prominent and hypertrophic muscles, phlebomegaly on limbs and trunk, umbilical hernia and acanthosis nigricans around the neck.
and armpits. Enlarged spleen and liver were also noted. There was labial hypertrophy with no cliteromegaly. Dual-Energy X-ray Absorptiometry (DEXA) showed total fat percentage of 22% and a "fat shadow" was obtained highlighting the generalized pattern of fat loss. Genetic analysis revealed a pathogenic variant (p. Arg541Pro) at exon 8 of the LMNA gene. Upon identification of the variant, her previously obtained muscle biopsy was reevaluated as muscular dystrophy. Cardiovascular investigations demonstrated first-degree atrioventricular block and non-sustained ventricular tachycardia on the ECG and fibrosis on cardiac MRI. Given her family history of sudden death, a dual-chamber implantable cardioverter-defibrillator was placed. When her HbA1c rose to 7.2% on Metformin monotherapy and her triglycerides exceeded 250 mg/dL on fibrates, we presented her case to her insurance company. She was approved for Metreleptin therapy even though she does not meet the consensus definition of generalized lipodystrophy. **Conclusion:** We present a unique case with lipodystrophy who had progressive fat loss from partial to generalized. Making the correct classification is important in the US where treatment with Metreleptin is approved only for generalized lipodystrophy. We also highlight a complex genotype-phenotype association of laminopathy that challenges the distinction between FPLD and CGL.

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