Mandibuloacral Dysplasia Type B in an Infant: A Rare Progeroid Genodermatosis

Mandibuloacral dysplasia (MAD) type B is a rare genodermatosis with early-onset dermatologic, skeletal, and craniofacial abnormalities and long-term renal morbidity.

Report of a Case | A 5-month-old boy of non-consanguineous parents presented with congenital brown pigmentation on his ankles that progressed to the knees, shins, and wrists. Born at 35 weeks’ gestation via cesarean delivery, he had facial asymmetry and leg contractures initially attributed to breech positioning in utero. He had poor weight gain but normal vision and hearing. At age 3 months, he underwent a skeletal survey that revealed mandibular hypoplasia and osseous abnormalities of the clavicles, humeri, and tibia. Results of a chromosomal screen were negative. No known relations, including 2 paternal half-siblings, had similar findings.

Physical examination showed a cheerful boy with micrognathia, a small nose, prominent eyes, large, open fontanelles, and thin, contracted lower extremities (Figure, A). Non-indurated light brown patches were present on the wrists, bilateral tibias, and ankles. The clinical and radiologic findings suggested a progeroid laminopathy. An atypical progeroid syndrome was considered, but the patient’s young age favored MAD type B.

Analysis of the ZMPSTE24 gene confirmed MAD type B, revealing a compound heterozygous mutation that combined a missense mutation (Asn265Ser) inherited from the patient’s mother with a nonsense mutation (Leu362Phefs*19) inherited from his father.

At age 10 months, his skin was notably thinner, appearing more tautly stretched over increasingly lipoatrophic lower legs (Figure, B). Acro-osteolysis was becoming apparent with noticeably shortened distal phalanges and broad, hypoplastic fingernails. His diagnosis prompted nephrologic and endocrinologic consultations and management for long-term morbidity.

Discussion | MAD is an especially uncommon autosomal recessive disorder with phenotypic and genetic heterogeneity characterized by micrognathia, joint contractures, hypoplastic clavicles, acro-osteolysis, open fontanelles, mottled pigmen-
tation, and failure to thrive. Phenotypic severity correlates with the level of prelamin accumulation or lack of mature lamin A that result from mutations in LMNA (encodes lamin A/C) or ZMPSTE24 (a zinc metalloproteinase that processes prelamin A to mature lamin A). Lamin is crucial for proper nuclear lamina formation. Subtypes A and B differ in the extent of lipodystrophy, age at presentation, and long-term sequelae.

Patients with MAD type A do not show characteristic syndromic features or partial lipodystrophy until age 4 or 5 years.1

MAD type B is rarer. To our knowledge, only 10 cases have been reported prior to the present one.1-3 Compound heterozygous nonsense and missense mutations in ZMPSTE24 pre-dominate, with 1 report of a homozygous missense mutation in ZMPSTE24 and 1 case of a homozygous null ZMPSTE24 mutation combined with a “rescue” LMNA mutation.2 Dysmorphic progeroid features, mottled pigmentation, and joint contractures present early in infancy. Skeletal dysplasias develop by age 1 to 2 years. Generalized lipodystrophy presents variably from the toddler to teen years. Metabolic disease is poorly defined but has been reported in young adulthood.

Two unique long-term sequelae for MAD type B are progressive glomerulopathy and subcutaneous calcified nodules. Clinically relevant kidney disease presents in patients who have reached their 20s,1,3,6 but microhematuria with proteinuria is reported in early childhood.5 Calcified nodules start as early as age 2 years.1 Significantly, 2 patients in their late 20s or 30s have died from a combination of vascular calcifications and renal failure,1,3,6

Interestingly, though our patient has the same compound heterozygous mutation as was found in 2 other cases,2,3 their clinical presentations are not identical. Indeed, neither LMNA or ZMPSTE24 mutations were found in 3 other patients with MAD type B,1 suggesting that undiscovered mutations may modulate the clinical phenotype.

Dermatologists may be consulted to evaluate dyspigmentation but can be instrumental in the diagnosis of MAD type B by recognizing its earlier multisystem constellation of symptoms. Earlier diagnosis would alert physicians of the particular need, among others, for early renal monitoring. However, disease heterogeneity suggests that management should be tailored to phenotypic severity.

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Edema and Telangiectasia of the Chest Caused by Neuroendocrine Carcinoma

Superior vena cava (SVC) syndrome includes a constellation of signs and symptoms resulting from SVC obstruction that produces elevated pressure in the afferent veins and increased blood flow through collateral vessels.

Report of a Case | A man in his 60s was referred for a subcutaneous nodule that had appeared in the right supraclavicular region about 1 year earlier. The patient, who had a 5-year history of chronic obstructive pulmonary disease, complained of hoarseness, cough, and tachycardia. At physical examination, the nodule, measuring about 4 cm in diameter, was round and fixed with irregular ill-defined margins. Edema and erythema of the neck area and a well-defined net of superficial dilated vessels in the thoracic and epigastric areas were also detected (Figure 1A).

Blood tests showed elevated levels of lactate dehydrogenase (1180 U/L; normal range, 250-500 U/L) and slightly raised levels of carcinoembryonic antigen (CA 19-9, carcinoembryonic antigen, and α-fetoprotein were within the normal range. Otolaryngology consultation revealed paralysis of the right vocal cord. Chest radiography showed an opaque thoracic mass approximately 12 cm in diameter located on the right apical side that caused left tracheal deviation. Thoracic computed tomography confirmed the presence of an expansive solid mass in the mediastinum infiltrating the right side of the trachea, the SVC, and the left brachiocephalic vein (Figure 1B). The mass also compressed the interazygos esophageal system, with vascular shunts detectable in the right paramediastinal side.

A punch biopsy of the nodule revealed a large-cell neuroendocrine carcinoma showing a proliferation of atypical medium and large undifferentiated cells and areas of necrosis and hemorrhage (Figure 2A). Immunohistochemical staining was positive for the neuroendocrine marker synaptophysin (Figure 2B). The diagnosis of mediastinal neuroendocrine carcinoma of unknown origin associated with SVC syndrome prompted referral for complete surgical excision. The patient died a few weeks later after multiple postsurgical complications.

Discussion | Historical causes of SVC syndrome are usually reported as infective, such as tuberculosis or syphilis. Cur-