Case Report:
Novel Presentation of Central Core Disease with Nemaline Bodies (Rods) in the Setting of Diploid/Triploid Mosaicism

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Abstract. Diploid/triploid mosaicism is an uncommon malformation syndrome thought to result from incorporation of the second polar body into a blastomere nucleus of the developing embryo. Clinical manifestations include mental and growth retardation, truncal obesity, body asymmetry, hypotonia, syndactyly, clino-/camptodactyly, malformed low-set ears, and small phallus. Although muscular atrophy has been documented in 35% of cases of diploid/triploid mosaicism, to our knowledge histologic evidence of myopathy has not been reported. We present a novel case of diploid/triploid mosaicism with evidence of central core disease and nemaline bodies (rods). The histologic and ultrastructural features are described. A review of the literature is provided, including discussion of the various theories regarding the co-expression of central cores and nemaline rods.

Keywords: diploid/triploid mosaicism, central core disease, nemaline bodies; congenital myopathy

Introduction

Diploid/triploid mosaicism is a rare malformation syndrome with 25 reports described in the literature to date. Affected individuals present with mental and growth retardation, truncal obesity, body asymmetry, hypotonia, syndactyly, clino-/camptodactyly, malformed low-set ears, and small phallus. In addition to the normal diploid cell line, a second triploid cell line is present in these patients with varying tissue distribution [1]. In most instances, cytogenetic analysis of lymphocytes has revealed a normal diploid chromosome complement, while the triploid cell line has been detected in fibroblasts on skin biopsy. Study of short tandem repeat polymorphisms in patient and parent DNA has demonstrated maternal origin of the supernumary chromosomes. These data support the theory that diploid/triploid mosaicism results from incorporation of the second polar body into a blastomere nucleus of the developing embryo [2].

Hypotonia is a common clinical feature of diploid/triploid mosaicism, and muscular atrophy of extremities has been reported in 35% of cases [1]. To our knowledge histologic evidence of myopathy has not been described. We present a case of central core disease with nemaline bodies (rods) occurring in a patient with diploid/triploid mosaicism.

Case Report

This 25-yr-old woman was first diagnosed with diploid/triploid mosaicism at the age of 9 yr. She exhibited delayed milestones and developmental testing showed mild mental retardation. Physical examination was significant for truncal obesity, facial asymmetry, syndactyly of fingers and toes, transverse palmar creases, and patchy areas of hyperpigmentation. Skin biopsy revealed a mosaic chromosomal pattern with 65% 46,XX and 35% 69,XXX [3].

The patient recently consulted her neurologist because of back and lower extremity pain, rapid onset of kyphosis, and skin lesions in the lumbar area. On physical examination, she was alert, oriented, and communicated without difficulty despite mild dysarthria. Her strength was decreased in the distal hand musculature. Reflexes were symmetrically elicited. Significant thoracolumbar kyphosis was evident on standing.

Needle electromyogram (EMG) was performed to test for a myopathic process. Muscles of the upper extremity demonstrated a normal pattern, with no evidence of
denervation or myopathy. In the thoracic and lumbar paraspinal muscles, however, small amplitude polyphasic potentials of 100-400 µV with a duration ranging from 5-10 msec were seen, unaccompanied by fibrillations or positive waves. These findings were consistent with an axial myopathy involving the paraspinal muscles; therefore a biopsy of the affected muscle group was performed.

Pathological Findings

Muscle biopsy was obtained from the paraspinal musculature, as this represented the affected muscle group. Fresh frozen cryostat sections were stained with H&E and modified Gomori trichrome. Nicotinamide adenine dinucleotide (NAD), cytochrome oxidase (COX), succinic acid dehydrogenase (SADH), and adenosine triphosphatase (ATPase) (preincubated at pH 4.3, 4.6, and 9.4) reactions were also performed. A small portion of the biopsy sample was fixed in phosphate-buffered glutaraldehyde (2.5%, pH 7.2), and the tissue was post-fixed in osmium tetroxide and embedded in epoxy resin. Sections, 1 µm thick, were stained with toluidine blue. Thin sections were stained with uranyl acetate and lead citrate and were evaluated by detailed ultrastructural analysis.

Microscopically, myofiber size variability with scattered hypertrophic myofibers and occasional small round and angular myofibers were seen on H&E-stained sections (Fig. 1A). A mild increase in endomysial connective tissue was noted, and occasional central nuclei were present. Scattered degenerating and regenerating myofibers were seen along with rare fibers undergoing myophagocytosis (Fig. 1B). Smudged, dark staining was seen in the central aspects of many myofibers (Fig. 1C), and these same areas corresponded with core-like structures devoid of enzyme activity seen with the oxidative preparations (Fig. 1D). On Gomori trichrome-stained sections, linear rod-like material was occasionally noted in both subsarcolemmal and central myofiber locations, suggestive of nemaline rods (Fig. 1E). The core-like structures mainly involved type 1 myofibers, and occasional cores were surrounded by a thin rim of increased oxidative activity. Fiber typing showed mild type 1 myofiber predominance with rare type grouping (Fig. 1F). The infrequent small round and angular fibers were mainly type 1 myofibers.

Ultrastructurally, many fibers contained central areas with marked disorganization of myofibrils, Z-disc staggering and streaming, and fewer mitochondria consistent with central cores. In addition, electron-dense bodies characteristic of nemaline rods were present in numerous fibers, occasionally within the central cores (Fig. 2). Sarcotubular elements and mitochondria were unremarkable, and lipid and glycogen were normal in amount and distribution.

Discussion

Diploid/triploid mosaicism is an uncommon clinical syndrome with a subtle but distinctive phenotype [4]. The syndrome is thought to result from the incorporation of the second polar body into a blastomere nucleus of the developing embryo. The resultant triploid cell line is variably expressed in tissues. Lymphocytes usually have a normal diploid complement, while the triploid cell line is often detectable in fibroblasts on skin biopsy [2].

Clinical manifestations of diploid/triploid mosaicism include mental and growth retardation, truncal obesity, asymmetry, hypotonia, syndactyly, clino-/camptodactyly, malformed low-set ears, and small phallus. Although muscular atrophy has been described in 35% of cases of diploid/triploid mosaicism [1], histologic evidence of myopathy has not previously been documented. We describe the first case of central core disease with nemaline bodies (rods) occurring in a 25-yr-old woman with diploid/triploid mosaicism.

Central core disease is classically described as an autosomal dominant congenital myopathy and was first described by Shy and Magee in 1956 [5]. The disease is non-progressive and presents with diffuse muscular weakness and hypotonia during infancy, delayed motor development, and reduced muscle bulk [6]. The disease can also first become symptomatic during adult life or remain asymptomatic. These patients often have skeletal abnormalities such as congenital dislocation of the hips, pes cavus, and scoliosis. Histological examination of muscles shows the presence of cores, large round areas within myofibers devoid of oxidative enzyme activity. Cores are commonly located in the center of the myofiber and may be surrounded
by a small rim of enhanced oxidative enzyme activity. Type 1 myofiber predominance, variation in myofiber diameter, and endomysial fibrosis may be seen. Ultrastructurally, the core is characterized by a well demarcated area of sarcomeric disorganization, excessive Z-band streaming, and absent mitochondria [7]. Genetic studies have shown that central core disease can be caused by missense mutations of the ryanodine receptor gene (RYR1), a gene encoding a calcium release channel located...
in the sarcoplasmic membrane [6]. Malignant hyperthermia can also be seen with mutations of RYR1 and is strongly associated with central core disease [7]. The presence of triploidy in somatic cells of our patient and the relatively long clinical course suggests a mild form of the myopathy, possibly representing a heterozygous mutation; further genetic studies of this patient would be enlightening.

Rare cases of simultaneous detection of central cores and nemaline rods have been reported in the literature [6,8,9-15]. The percentage of myofibers displaying both central cores and nemaline rods ranged from <1% to 25% [8]. Several theories have emerged. Perhaps these cases represent an independent nosological entity as an outcome of a special genetic defect that has various means of expression [9]. Nemaline bodies have also been found as non-specific phenomena in HIV myopathy, chloroquine therapy, and polymyositis. The co-occurrence of central cores and nemaline bodies could merely signify cases of central core disease with the
simultaneous presence of nemaline bodies as a nonspecific phenomenon [8]. Recently, missense mutations in the RYR 1 gene have been identified in this complex myopathy, suggesting that these patients genetically have central core disease, and for still unexplained reasons, associated rods [7].

Our patient was the second-born female twin of healthy parents, with 2 phenotypically normal older male siblings. She exhibited delayed developmental milestones, mild mental retardation, and dysmorphism. Skin biopsy performed at the age of 9 yr revealed a mosaic chromosomal pattern with 65% 46,XX and 35% 69,XXY. Her monozygotic twin sister also had evidence of borderline mental retardation and mild dysmorphism; however skin biopsies failed to reveal mosaicism [3].

Sixteen years later our patient presented to her neurologist with back pain and rapid onset of thoracolumbar kyphosis, and her electromyogram was found to have isolated myopathic changes in the paraspinal musculature. Muscle biopsy revealed evidence of myopathy and central cores with nemaline rods.

Association between diploid/triploid mosaicism and central core disease with nemaline rods has not been previously studied. The unique occurrence of both entities in our patient may represent a random event; however further analysis of such patients may elucidate a better explanation. Of clinical importance is the strong association of central core disease with malignant hyperthermia [7]. Our patient underwent general anesthesia for performance of the muscle biopsy and once in the past for tonsillectomy without adverse consequences. We suggest however that in cases of diploid/triploid mosaicism with evidence of muscle weakness and hypotonia, biopsy for histologic and ultrastructural evidence of central core disease be performed and general anesthesia be approached with caution.

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References