Intracellular Extraocular Muscle Light- and Heavy-Chain Deposition Disease Contributing to Compressive Optic Neuropathy in a Patient with Preexisting Graves’ Orbitopathy

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Key Words
Monoclonal immunoglobulin deposition disease · Light- and heavy-chain deposition disease · Compressive optic neuropathy · Graves’ orbitopathy · Multiple myeloma

Abstract
Purpose: Light- and heavy-chain deposition disease (LHCDD) is a rare form of nonamyloidal monoclonal immunoglobulin deposition disease (MIDD) in which light- and heavy-chain immunoglobulin fragments accumulate systemically, typically leading to end organ dysfunction. Herein we describe the case of a 64-year-old female with a history of Graves’ orbitopathy and multiple myeloma who presented with bilateral asymmetric compressive optic neuropathies. Procedure: A biopsy of the right medial rectus muscle was taken during orbital decompression surgery. Results: Light and electron microscopy of the biopsy specimen led to a diagnosis of intracellular skeletal muscle LHCDD. Conclusion: This is the first published report to describe the findings of: (1) intracellular deposition of nonamyloidal MIDD; (2) orbital involvement of nonamyloidal MIDD, and (3) compressive optic neuropathy resulting from any form of MIDD.

In 2006, a 64-year-old woman presented with gradually decreasing vision OD > OS. Her medical history included multiple myeloma, Graves’ hyperthyroidism, paroxysmal atrial flutter, chronic obstructive pulmonary disease, osteoporosis, pernicious anemia and thrombocytopenia. In 1993, she developed bilateral Graves’ orbitopathy (GO), which did not require medical or surgical intervention.

On examination, visual acuities were counting fingers OD and 20/60 OS. Color vision was decreased OD > OS with a right relative afferent papillary defect. There were bilaterally decreased eye movements and increased exophthalmos (Hertel exophthalmometry: 27 mm OD, 28 mm OS) compared with her most recent examination in 2004 (Hertel exophthalmometry: 21 mm OD, 20 mm OS). A CT scan of the orbits (fig. 1) revealed bilateral thickening and enhancement of the medial, superior and inferior rectus muscles and tendons, as well as the right lateral rectus muscle and tendon. Radiolucent areas were present within the bellies of these rectus muscles bilaterally, consistent with the presence of fat. There was bilateral (R > L) apical crowding, in keeping with an R > L compressive optic neuropathy. A CT scan of the orbits (fig. 1) revealed bilateral thickening and enhancement of the medial, superior and inferior rectus muscles and tendons, as well as the right lateral rectus muscle and tendon. Radiolucent areas were present within the bellies of these rectus muscles bilaterally, consistent with the presence of fat. There was bilateral (R > L) apical crowding, in keeping with an R > L compressive optic neuropathy. The CT scan also demonstrated optic nerve sheath thickening and enhancement and enhancing infiltrates within the orbital fat, bilaterally. Comparative CT orbital imaging from 2001 (most recent imaging available) demonstrated a similar pattern of bilateral extracocular muscle thickening, but to a significantly lesser degree, without apical compression, muscle tendon thickening or optic nerve sheath enhancement. Serum protein analysis revealed monoclonal IgG heavy chains and monoclonal IgG λ light chains. Renal, liver and thyroid testing (thyroid-stimulating hormone 2.81 mU/l, free thyroxine...
15.5 pmol/l, free triiodothyronine 2.81 pmol/l) were all normal. An echocardiogram demonstrated mild diastolic dysfunction.

Pulse intravenous methylprednisolone (1 g daily for 3 days) provided initial, although incomplete, improvement to 20/300 OD and 20/50 OS, suggesting that the inflammatory component made a small contribution, but the main factor was a change in mass. This was supported by vision subsequently deteriorating over 1 week to hand motions OD and 20/60 OS, and by the failure of the subsequently administered orbital radiotherapy (2,000 cGy over 10 fractions) to improve vision. The lack of a more significant and longer-lasting improvement from the pulse corticosteroids and radiotherapy, as well as the CT features, was felt to be atypical of a case of GO.

Urgent bilateral orbital decompression surgery (medial and inferior orbital wall infracturing) was performed in an attempt to alleviate the compressive optic neuropathies. Although a recurrence of GO was considered a possible diagnosis based on clinical signs and symptoms, the history of multiple myeloma, lack of expected visual improvement with corticosteroids and radiotherapy, and atypical imaging features not present on older orbital imaging (extraocular muscle tendon thickening, optic nerve sheath enhancement, enhancing infiltrates within the orbital fat) led to the consideration of other causes, including infiltrative multiple myeloma, monoclonal immunoglobulin deposition disease (MIDD) and other inflammatory conditions. In order to elucidate the underlying cause of the optic neuropathy, a right medial rectus muscle biopsy was taken at the time of decompression.

Following the surgical decompression, visual acuities improved to 20/50 OU, which remained stable at 1 month of follow-up. No further follow-up was obtained as the patient was unable to attend subsequent clinic appointments. She died 6 months following the orbital surgery due to a cardiac arrest secondary to a presumed pulmonary embolism, although no autopsy was performed.

Materials and Methods

A right medial rectus muscle biopsy was obtained during orbital decompression surgery. The specimen was examined by light and electron microscopy using standard methods.

Results

Light-microscopic examination of the biopsy specimen (fig. 2a–d) revealed numerous amorphous, eosinophilic globules within the sarcolemma of extraocular skeletal muscle fibers. There were no lymphocytes or edema between muscle fibers, features that would be expected in active GO. Affected muscle fibers appeared swollen in size compared with adjacent unaffected fibers. The amorphous globules stained with periodic acid-Schiff and did not stain for actin and desmin, suggesting that they were not composed of muscle proteins. Masson trichrome staining demonstrated mature-looking fibroblasts and dense collagenous fibrosis between muscle fibers. Alcian blue staining for glycosaminoglycans was negative. Overall, the biopsy findings of a lack of lymphocytes, edema and glycosaminoglycans, along with the presence of extensive fibrosis and inactive fibroblasts, are more consistent with old GO without significant reactivation. There was no staining with Congo red, ruling out an amyloid component. By immunoperoxidase staining, the globules stained for IgG heavy chains and light chains, and were negative for IgM and IgA heavy chains, and k light chains. Electron microscopy (fig. 2e, f) confirmed the presence of amorphous, dense globules, consistent with proteinaceous material, within the cytoplasm of the skeletal muscle fibers. Based on these histological findings, a diagnosis of light- and heavy-chain deposition disease (LHCDD) was made, with the bilateral compressive optic neuropathies the result of extraocular muscle volume expansion at the orbital apices from deposited LHCDD material superimposed upon preexisting fibrotic muscle thickening from GO.
Discussion

MIDD represents a group of disorders in which systemic deposition and accumulation of abnormal immunoglobulins result in compromised end organ function. MIDD can be broken down into amyloidal and nonamyloidal subtypes. The amyloidal group consists of primary amyloidosis and heavy-chain amyloidosis, while the non-amyloidal group consists of light-chain deposition disease, LHCDD and heavy-chain deposition disease. In amyloidal MIDD, abnormal light or heavy chains with a β-pleated sheet structure form fibrillar, Congo-red-binding deposits in various tissues [1]. In the nonamyloidal forms, systemic deposition of abnormal light chains, heavy chains or both occurs, but the deposits appear granular or amorphous, and do not bind Congo red or form β-pleated sheets [1, 2]. The deposits found in the medial rectus biopsy of our patient exhibited the appropriate features of nonamyloidal MIDD and contained both IgG heavy chains and λ light chains, leading to the diagnosis of LHCDD.
Light-chain deposition disease is the most common form of nonamyloidal MIDD, with the LHCDDD subtype comprising less than 10% of reported cases [3]. For both amyloidic and nonamyloidic MIDD, the most commonly affected tissue sites are the kidney, heart and liver, frequently leading to organ compromise [1, 3]. Multiple myeloma is present in 50–60% of nonamyloidic MIDD patients [3]. Serum and urine protein analysis often detect the presence of a monoclonal immunoglobulin in patients with MIDD [1]. In our patient, the immunoglobulin types found in her biopsy specimen, IgG heavy chains and λ light chains, were the same as those measured in her serum.

There are several reports of nonamyloidic MIDD involving skeletal muscle; however, ours is the first to describe skeletal muscle involvement (extraocular muscle) in LHCDDD. Rott et al. [4] describe the findings of IgG heavy-chain deposits in a skeletal muscle biopsy from a patient with heavy-chain deposition disease. The deposits were located in the endomysium along sarcolemmas, in vessel walls and in the perimysium. These locations are typical of MIDD as deposition most often occurs along basement membranes of targeted tissues, suggesting that the proteins likely have an affinity for some membrane component [1]. Ours is the first published report to document a case of nonamyloidic MIDD with intracellular skeletal muscle deposition.

This is also the first published report describing non-amyloidic MIDD involving orbital tissues, as well as the first to report any type of MIDD leading to compressive optic neuropathy. There are 2 published cases of orbital primary amyloidosis requiring orbital decompression surgery, but neither exhibited preoperative compressive optic neuropathy [5, 6].

In conclusion, although rare, MIDD (both amyloidic and nonamyloidic forms) should be considered in the differential diagnosis of orbital infiltrative diseases, especially if there is a history of multiple myeloma or atypical findings of the optic nerve sheath, rectus muscle and/or orbital fat enhancement on orbital imaging.

References