CASE REPORT

Thoracic myelopathy due to calcification of the *ligamentum flavum* with hyperproteinorachia and responsive to steroid therapy: case report

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ABSTRACT

Calcification and ossification of the ligamentum flavum or of the posterior longitudinal ligament are causes of compressive myelopathy, more frequent in the lower thoracic levels, and extremely rare in Western populations. Surgical decompression is the only therapy, but the disease is usually progressive, and its recurrence after surgery is common. Inflammatory mediators might play a role in the progression of compressive myelopathy, but, to our knowledge, the therapeutic approach involving anti-inflammatory agents has never been tried before. We report a case of compressive myelopathy due to calcification of the ligamentum flavum, in which hyperproteinorachia and response to steroid therapy have been observed. Those data have not been published before and might provide new ideas for the disease understanding.

Keywords: *ligamentum flavum*, ossification of the posterior longitudinal ligament, spinal cord compression, cerebrospinal fluid.

INTRODUCTION

Calcification and ossification of the *ligamentum flavum* (CLF and OLF, respectively) or of the posterior longitudinal ligament (PLL) of the spine are often reported in Far Eastern countries, where they are common causes of compressive myelopathy, usually at the thoracic level. However, that disorder is extremely rare in Western populations, in which only cervical and lumbar degenerative myelopathies or radiculopathies are commonly found.[1] Most of the pathophysiological mechanisms of that condition and reasons for its peculiar prevalence in Eastern countries are unknown. Hypertrophy of the spinal ligaments might begin in response to mechanical stress, but in patients with genetic or systemic predisposing factors, that process progresses with ligament hyperplasia, vascular neoformation, cartilaginous metaplasia, calcification, and, eventually, replacement by compact bone.[2] The local expression of growth factors, such as bone morphogenetic proteins (BMP)[3] and transforming factor-β (TGF-β),[4] can be a predisposing element. Thus, cytokines might play a role in the progression of calcification and ossification of the spinal canal ligaments, but no therapeutic intervention has been proposed to act on those elements.

We report the case of a female patient with compressive thoracic myelopathy caused by CLF, a rare disease in the Brazilian population. Informed written consent was provided by the patient for the publication of her data and images. Although a previous case has already been reported in the Brazilian literature,[1] ours is particularly relevant, because the initial diagnosis of systemic lupus erythematosus (SLE) led to the observation of hyperproteinorachia and response to steroid therapy. Such findings have never been reported in the medical literature and might contribute to the better understanding of that entity.

CASE REPORT

The patient is a 47-year-old woman who sought the emergency service with spastic paralysis of her lower limbs, which had begun five days before with no history of trauma. On physical examination, she had grade 0 strength in her lower limbs with hyperreflexia and clonus, anesthesia below T10 level, and facial erythematous exanthem, predominating in her malar regions and nasal bridge, but also present in the frontal and perioral regions, with telangiectasia and some small pustules (Figure 1). The patient also had type 2 diabetes mellitus and systemic arterial hypertension, for which she had been using metformin and captopril for five years. Her Body Mass Index was 35. Her complementary exams were performed at the emergency, and neither her vertebral column nor her skull showed abnormalities on computed tomography. Lumbar puncture was performed, and the analysis of the cerebrospinal fluid showed important hyperproteinorachia (784 mg/dL), with mild hypercellularity (10 cells/mm^3, lymphocytes and monocytes). The patient was positive for the antinuclear antibody (ANA) with titers of 1/80 and fine speckled pattern. The diagnosis of SLE with inflammatory transverse myelitis was proposed, and pulse therapy with methylprednisolone, 1 g/day for three days, was initiated immediately. Anticoagulation with enoxaparin was also initiated, considering the possibility of ischemic myelopathy as an alternative diagnosis.

A significant improvement was observed, with disappearance of the clonus on the next day and strength recovery. Ten days later, the patient had grade 3 strength in both lower limbs, when a new analysis of the cerebrospinal fluid revealed protein levels almost normal (60 mg/dL). The search for the following elements was negative: oligoclonal bands, HTLV–I, HTLV–II, *Schistossoma mansoni*, bacteria, mycobacteria, and fungi.

However, except for the facial exanthem and low ANA titers, the patient lacked any other criteria for SLE. The following exams were normal: anti-DNA, anti-Sm, complete blood count, creatinine, urinary sediment, serum complement erythrocyte sedimentation rate, and C-reactive protein. There was no evidence of peripheral neuropathy. The anticardiolipin and lupus anticoagulant antibodies were not found, and the echocardiogram was normal. The skin biopsy identified rosacea, and the diagnosis of SLE was definitely ruled out.

Magnetic resonance imaging (MRI) of her skull was normal, making the diagnosis of multiple sclerosis less likely. However, the MRI of the vertebral column revealed hypertrophy of the *ligamentum flavum* between the T2–T10 levels, with spinal cord compression (Figure 2). Anticoagulation
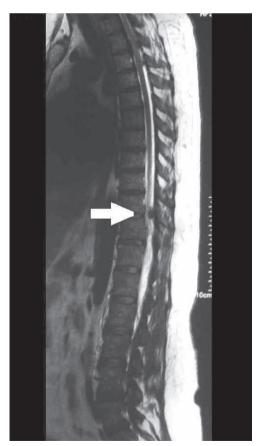

Figure 2
Magnetic resonance of the vertebral column at the T2 level, evidencing hypertrophy of the *ligamentum flavum* with spinal compression at the T10 level (arrow).

Figure 1
Facial erythematous exanthem, mainly in her malar regions, but also present in the frontal region, with telangiectasia and some pustules.

was suspended and decompressive laminectomy performed, with further improvement in the strength of her lower limbs. The biopsy of the *ligamentum flavum* revealed hypertrophic tissue with several foci of hyalinization and calcification. This pattern established the diagnosis of CLF as the cause of the patient's compressive myelopathy. Her serum levels of calcium, phosphorus, and parathyroid hormone were normal. The radiographs of her hands, wrists, and knees showed no chondrocalcinosis, and there was no history of arthritis. One year after surgery, the patient remained asymptomatic from the neurological viewpoint, but her facial rosacea persisted.

DISCUSSION

Calcification of the *ligamentum flavum* probably represents an initial stage of OLF, both conditions being closely related to those affecting the PLL, calcification and ossification of the PLL (CPLL and OPLL, respectively). Ossification of the PLL has been more extensively investigated.

Both CPLL and OPLL might be multifactorial diseases, in which complex genetic and environmental factors interact. Polymorphisms in the collagen 11A2 and 6A1 genes have been associated with OPLL. The role of collagen VI and collagen XI in that condition is still uncertain, but they are supposed to serve as a framework for chondrocytes to elaborate the ossification process, propitiated by those mutations.

There are two models of OPLL in animals. The tiptoe walking mouse is a natural mutant with extensive heterotopic calcification. He has a single mutation in the nucleotide pyrophosphatase gene, which regulates the physiological calcification of tissues by producing pyrophosphates.[3] The Zucker rat, an animal model of obesity, dyslipidemia, and hyperinsulinemia, also develops ossification of the spinal ligaments.

The local expression of cytokines and growth factors has also been reported in the OPLL. The BMP-2 and TGF-β have been more intensively investigated, being present in the tissue matrix adjacent to the ossified ligaments.[4] Thus, the major hypothesis for the pathophysiology of OPLL is that mechanical stress is converted into a biological response that induces inadequate production of specific cytokines that act as growth factors, leading to calcification and ossification of pathologically predisposed collagen fibers of the spinal ligaments.[5]

In most cases reported, totally developed ossification of the ligament has been found at the time of diagnosis. However, there are transitory stages between the normal ligament and its complete ossification. Hypertrophy of the PLL (HPLL) is considered to be the precursor of the OPLL. Mizuno et al.[2] have suggested that HPLL is replaced by

lamellar bone in an individual with HPLL due to a mechanical degenerative process, in the presence of genetic factors that propitiate the appearance of secondary calcification and progressive ossification. In HPLL histological studies, ligament hyperplasia and metaplasia have been described, as well as focal areas of calcification, where depositions of calcium pyrophosphate dihydrate and calcium hydroxyapatite are commonly found.[6] Those findings support the hypothesis that OPLL is a progressive disease with different stages, described as "OPLL in evolution" by Epstein.[7] This disease probably progresses with ligament hypertrophy, vascular neoformation, cartilaginous metaplasia of the ligaments, calcification with crystal deposits, and, eventually, ossification of the ligaments inside the spinal canal. Briefly, Okada et al.[8] have reported that, initially, the ligament undergoes hypertrophy and calcifies, and, then ossifies.

For didactic purposes, those four conditions (OPLL, CPLL, OLF and CLF) could be gathered under the same group denomination as "disease of the spinal canal ligaments" (DSCL). Those conditions are a frequent cause of compressive myelopathy in Far Eastern countries. Its prevalence reaches 3.6% in South Korea[9] and 2.8% in Taiwan.[10] They affect mainly the lower thoracic levels of the spinal cord, causing progressive spastic paraplegia. Surgical decompression is the only therapy, and the shorter the time until surgery, the better the neurological prognosis.[11] In the largest epidemiological study about thoracic myelopathy carried out in Japan,[12] OLF accounted for 56% of the cases, followed by OPLL (11%) or the association of both conditions (9%). Disc herniations (11%) or osteophytes (8%) were less common causes of spinal compression at that level.[12] Patients with several metabolic disorders, such as hypoparathyroidism, hypophosphatemic rickets, and type 2 diabetes mellitus, have a higher prevalence of DSCL than the general population. Recent studies have been concentrated on the fact that obesity and type 2 diabetes mellitus are independent risk factors for the appearance of DSCL, probably due to hyperinsulinemia.[5]

Regarding correlated disorders, diffuse idiopathic skeletal hyperostosis (DISH), unlike DSCL, is more common in Caucasians and rare in the Eastern populations. It consists in ossification of the anterior longitudinal ligament of the vertebral column, outside the spinal canal. Despite those differences, DISH shares with DSCL two risk factors: obesity and diabetes mellitus. On the other hand, it is worth emphasizing that the diseases that affect the PLL and the *ligamentum flavum* occur preferentially in the same population (Asians), share their risk factors and have similar histological and histochemical findings, being considered parts of the same spectrum.[5]

Because our patient had no ossification on biopsy, one could question whether the calcium deposits found could be attributed to another deposition disease. In fact, some authors have reported cases of myelopathy caused by CLF, especially in Western countries, as being caused by calcium pyrophosphate deposition disease (CPDD).[13] However, calcium pyrophosphate deposition in spinal ligaments, in most cases, could also be attributed to the metaplasia and calcification observed in DSCL. Under such conditions, chondrocytes produce inorganic pyrophosphate that binds to ionized calcium and deposits on collagen fibers.[5] Focal depositions of calcium pyrophosphate along the hypertrophied ligament are commonly found in DSCL.[6] It is worth noting that nucleotide pyrophosphatase dysfunction might play a role in the DSCL pathogenesis.[3] In a review of 25 cases of compressive myelopathy attributed to CPDD reported in the literature, only nine (35%) evidenced peripheral arthritis attributed to CPDD.[14] However, most of the remaining cases could be true examples of calcium pyrophosphate deposition in spinal ligaments due to DSCL, instead of true CPDD.

Our patient showed neither clinical nor radiological evidence of CPDD. She had obesity and type 2 diabetes mellitus, both risk factors for DSCL, and the biopsy revealed important hypertrophy of the *ligamentum flavum*, with focal deposition of calcium on the areas of cartilaginous metaplasia. Those findings are strong evidence that DSCL is the major cause of calcium deposition on hypertrophied ligaments with metaplasia, and not that the calcium deposition is the initial cause of the ligament disease. However, DSCL seems to be very rare in Western countries, where thoracic compressive myelopathy is much less common than the degenerative stenoses of the cervical or lumbar spinal canal.[15] In our patient, DSCL was not even suspected in the initial approach, and the presumptive diagnosis of SLE led us to perform cerebrospinal fluid analysis and steroid therapy, which significantly improved her symptoms. This led us to intriguing observations.

To our best knowledge, this is the first report about abnormality of the cerebrospinal fluid in a patient with DSCL, although dura mater involvement has been reported in such cases.[16] Significant hyperproteinorachia suggests the inflammatory process relevance in the DSCL pathogenesis. Some inflammatory mediators might act as growth factors for the spinal ligaments, leading to ossification.[17] In addition, this is apparently the first description of a therapeutic approach for myelopathy due to DSCL, including high dosage steroid therapy prior to surgical decompression.

In our patient, laminectomy was performed two weeks after symptom onset, representing a significant delay. Nevertheless, an excellent result was obtained. In addition, our patient had an acute onset of compressive symptoms, which is considered a sign of poor prognosis. In the series by Fong et al.,[6] from Singapore, patients with acute myelopathy had persistent symptoms, with ambulatory disability despite surgical decompression and rehabilitation programs. Thus, we believe that steroid therapy might have acted as a "bridge" therapy, allowing relief from the spinal compression until the definite surgical decompression. Our report supports the use of corticosteroids in cases of compressive myelopathy due to DSCL, when neurosurgery is not available.

In addition, although DSCL improves after surgery, it usually has a long-term progression. In a review of eight studies, Inamasu et al.[5] have reported radiological progression in 36%–86%, with clinical recurrence of compressive myelopathy in 2%–53% of the cases.[5] In face of that, one might ask whether long-term anti-inflammatory therapy in the post-operative period could prevent disease recurrence and which patients could benefit from that.

Finally, we could ask whether our patient's pustular dermatosis was somehow related to the triggering of DSCL. One case of the association of the SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) syndrome and DSCL has already been reported.[18] Ours is the first report of the association of DSCL and rosacea. The small experience of a single case does not allow any definitive conclusion, but one might hypothesize that patients with pustular dermatosis and DSCL could represent a special group, in which inflammatory mediators would be the major cause of ligament hypertrophy and its progressive ossification.

We suggest that some cases of DSCL leading to thoracic myelopathy depend on inflammatory phenomena, being, thus, responsive to steroid therapy. That therapy might be useful when surgical decompression cannot be performed immediately, since the final prognosis depends on the total duration of the symptoms associated with spinal compression. One relationship between DSCL and pustular dermatosis can be hypothesized, but, due to the scarcity of such cases in Brazil, further studies are required in countries where such condition is more frequently found.

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