

Radio-pathological Factors that Predict the Surgical Outcome of Ossification of *Ligamentum flavum* of Spine – Series of 31 Cases

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Abstract

Introduction: Ossification of the *Ligamentum flavum* (OLF) is a pathological condition that affects the ligament and causes slowly progressive myeloradiculopathy in adults.

Aim: To study the radiological and pathological factors that are predictive of the surgical outcome of patients with OLF.

Materials and Methods: A prospective study of 31 consecutive patients, including 24 men and 7 women with a mean age of 50.45 years, was conducted from 2013 to 2016. Radio-pathological factors included are: Number of segments affected by OLF, Sato's computed tomography-based classification, and the presence of intramedullary hyper-intensity on T₂w magnetic resonance imaging and calcium pyrophosphate dihydrate (CPPD) crystal deposition (pseudogout). All cases underwent decompressive laminectomies. Specimen sent for polarized-light microscopic studies and analyzed for characteristic rod-shaped, birefringent CPPD crystals. Follow up done with a mean duration of 5 months. Recovery rate was calculated with pre-operative and post-operative "Modified Japanese Orthopedic Association" scoring system.

Results: Recovery was excellent in 10 cases, good in 6 cases, fair in 12 cases, poor in 3 cases. The author conducted a review of literature in English, Japanese and Korean literature and compared their studies.

Conclusion: Early and correct diagnosis is required to avoid poorer results. Long-term follow up needed to determine the factors that predict the surgical outcome. This study also shows how this disease is highly under-reported in India.

Key words: Calcium pyrophosphate dihydrate crystals, Modified Japanese Orthopedic Association score, Ossification of *Ligamentum flavum*, Prognostic factors, Pseudo gout, Sato's classification

INTRODUCTION

Ossification of the *Ligamentum flavum* (OLF) is a pathological condition that causes myelopathy, radiculopathy or both in a patient. It is relatively common in the Japanese population compared to that in American or European populations.^[1] However, nowadays it has been reported from other areas also, especially from Asian countries. It has been highly

underreported in India. The etiology of hypertrophy and OLF is still not fully understood, but an association with ossification of the posterior longitudinal ligament (OPLL) or diffuse idiopathic skeletal hyperostosis (DISH) has been found.^[2] Microscopic findings in OLF specimens showed an overgrowth of Type II collagen preceding the development of ossification. There was also a reduction in the amount of elastin [Picture 1]. OLF was confirmed to be mainly enchondral ossification. Additional intramembranous ossification was, however, seen at the tip of the nodule-shaped ossification.^[3] Ossification extended along the superficial layer of the hypertrophied ligament, as in OPLL. It was suggested that the mechanism of OLF development depends intimately not only on dynamic and static mechanical stresses but also on the role of some growth

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factors as well. OLF can be diagnosed by lateral radiographs, manifesting as ossification of the spinal foramen [Picture 2]. When comparing the narrowing of the spinal canal as seen by computed tomography (CT) or magnetic resonance imaging (MRI), the CT scan may provide information superior to that of MRI because it shows precisely the areas where there is protruding ossification from the posterior to the anterior aspect of the spinal canal.^[4]

Historically, OLF was first observed on lateral radiographs [Picture 2] and reported by Polgarin 1920. In 1938, Anza described the first case with neurological symptoms and identified OLF in a specimen removed during the operation. Oppenheimer also observed OLF on plain radiographs in DISH and ankylosing spondylitis. He speculated that such Ossification might be responsible for a radicular neuropathy. In 1960 Yamaguchi *et al.* reported an operative case with severe myelopathy; Koizumi, Yanagi, *et al.* and Nagashima subsequently reported similar cases.^[5-8]

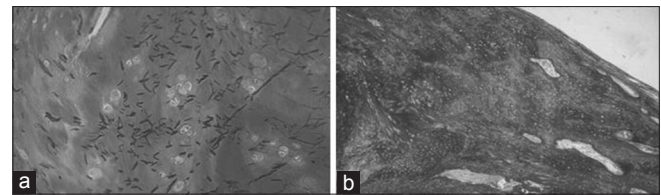
Most cases of OLF occur in the thoracic spine, especially the lower third of thoracic or the thoracolumbar spine; OLF rarely occurs in the cervical spine. Because thoracic spinal canal stenosis resulting in thoracic myelopathy or radiculopathy has been noted recently, OLF is now recognized as a clinical entity causing thoracic myelopathy manifesting as OPLL and spondylosis. When OLF was considered a contributing factor in patients with herniated thoracic discs, the surgical results were poorer than those in patients without OLF. However, outside Japan, unlike OPLL in the cervical spine, thoracic myelopathy secondary to OLF is sometimes overlooked or misdiagnosed as degenerative overgrowth by the posterior spinal element consisting of the superior articular processes.^[9] This error results from a lack of knowledge about this pathological condition. OLF has been recognized as a composite lesion because of the combination of ossification of the spinal ligaments with hyperostotic changes. Small degrees of OLF may be considered a degenerative change, as its incidence in radiographic studies of the spinal columns of aged persons has ranged from 4.5% to 25.0%. It has been suggested that the mechanism of hypertrophy, overgrowth, and progression of ossification of the ligaments plays an important role in the pathological process of myelopathy.

Aim

To study the Radiological and pathological factors that are predictive of the surgical outcome of patients with OLF.

MATERIALS AND METHODS

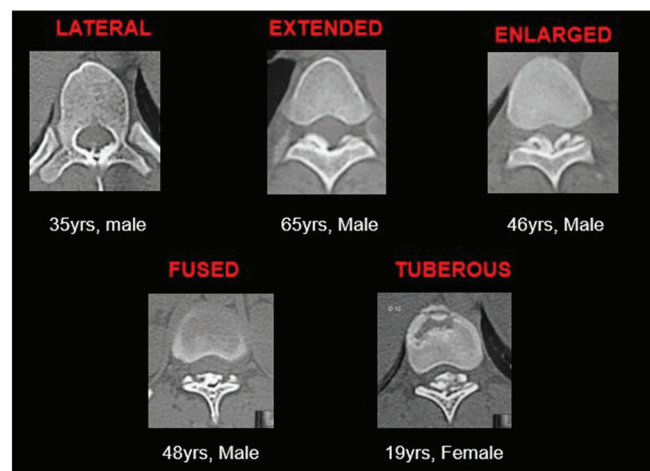
This was a prospective study, which was done on patients suffering from OLF of Spine. This study was conducted



Picture 1: Photomicrograph of ossification of *Ligamentum flavum* (OLF). (a) Enchondral type of ossification in OLF, (b) Cartilage cells among increased and swollen collagen fibres; the elastic were scanty and ruptured



Picture 2: Ossification of the *Ligamentum flavum* (OLF) in a 74-year-old women. (a) Lateral radiograph shows oval nodular masses in the posterior spinal canal at the C3-C4 and C5-C6 levels (arrows), (b) sagittal T1-weighted magnetic resonance imaging shows a round area of very low signal intensity at the corresponding location that indents the posterior aspect of the spinal cord at the C5-C6 level (arrow). Intervertebral disc herniation is also seen at the C4-C5 level



Picture 3: Computed tomography classification

over the period from February 2013 to February 2016.

Due clearance were obtained from the ethical committee of Government Rajaji Hospital and Madurai Medical College, Maduraiprior to this study.

Thirty one patients consecutively diagnosed of OLF of Spine with myelopathy. They were diagnosed on the basis of clinical examination, radiological imaging and histopathological confirmation. All the surgeries were done at the same operation theatre in Government Rajaji Hospital, Madurai.

Decompressive laminectomy, with removal of the OLF, was performed for all patients. Polarized-light microscopic examinations done on the excised *L. flavum* for characteristic rod-shaped, birefringent crystals. No. of segments of the spine involved, Sato's CT classification^[15] of OLF [Picture 3], presence of intramedullary signals on MRI, presence of calcium pyrophosphate dihydrate (CPPD) crystals in Light microscopy, modified Japanese Orthopedic Association (JOA) cervical spine myelopathy functional assessment scale data were collected.

RESULTS

Mean age of these patients were 50.1 years with range of 19–70 years. From radiological studies, patients were grouped into 5 groups according to the number of levels of spine involved. One level involved in 8 cases (26%), two levels involved in 9 cases (29%), three levels involved in 7 cases (22%), four levels involved in 4 cases (13%) and more than 4 levels involved in 3 cases (10%) [Figure 1].

Based on Sato's^[15] CT based classification, the types of OLF was classified as: Lateral (52%), extended (16%), enlarged (10%), fused (3%) and tuberos (19%) [Figure 2].

Intramedullary signal changes in T2w MRI images were positive in 45% and absent in 55% of cases [Figure 3].

Surgically excised *L. flavum* of each level were sent for histopathological examination and analysis under polarized light microscopy for the presence of “CPPD” crystals which will be seen as rhombic shaped birefringent crystals [Picture 4]. 8 cases were positive for CPPD crystals [Figure 4].

Recovery rate from symptoms was calculated using the following formula;

$$\text{Recovery rate (\%)} = \frac{(\text{Post operative mJOA score} - \text{Pre operative mJOA score})}{(11 - \text{Pre operative mJOA score})} \times 100$$

Based on the results the patients were grouped into 4 Types of recovery.

They are excellent (>75%), good (50–75%), fair (25–50%) and poor (<25%) as Figure 5.

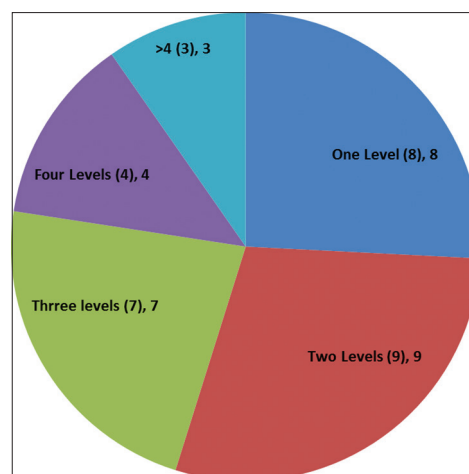


Figure 1: Distribution of number of segments

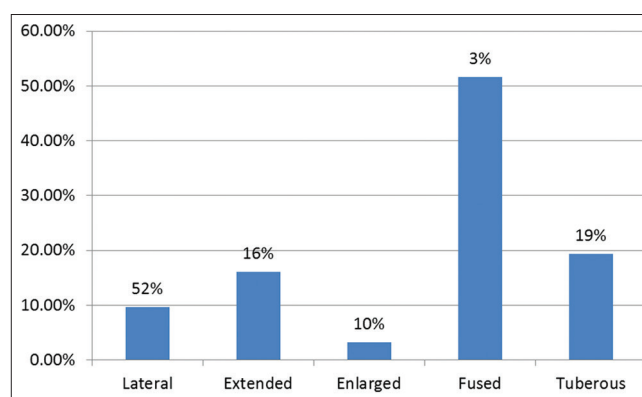


Figure 2: Distribution of computed tomography classification

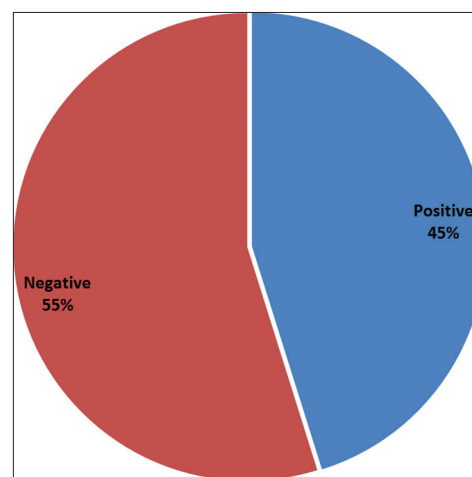


Figure 3: Distribution of magnetic resonance imaging intramedullary signals

All the patients were followed up post operatively at OPD. Out of 31 patients, 14 cases (14%) for <3 months, 15 cases (48%) for 4–6 months, 1 case (3%) for 7–12 months and 1 case (3%) for more than a year done. Only short term follow up were possible for most cases. We need to continue the follow up for longer term for

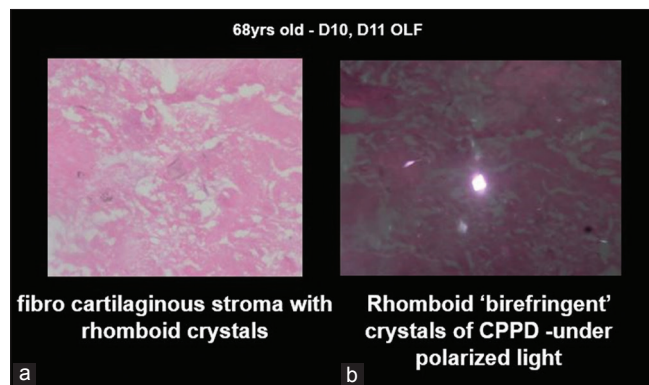
more accurate prediction of surgical outcome for OLF of Spine.

Relationship between Recovery and Radio-pathological Factors

All the four radio-pathological factors analyzed were statistically evaluated and determined whether it has significant influence in predicting the surgical outcome of OLF of Spine. The results were tabulated as follows;

Recovery and no of segments of the spine involved:
 $P = 0.2607$; not significant

1. Recovery and Sato's CT classification of OLF:
 $P = 0.0933$; not significant



Picture 4: Calcium pyrophosphate dihydrate crystals. (a) Fibro cartilaginous stroma with rhomboid crystals, (b) rhomboid "birefringent" crystals of calcium pyrophosphate dihydrate – under polarized light

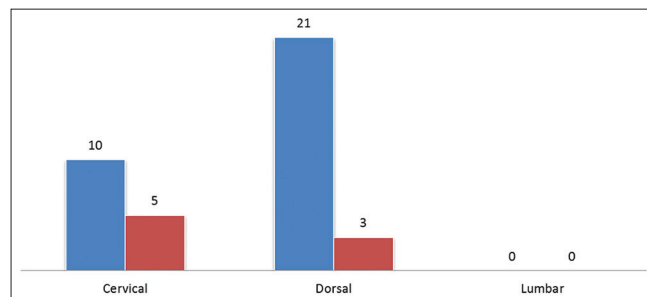


Figure 4: Distribution of calcium pyrophosphate dihydrate positivity

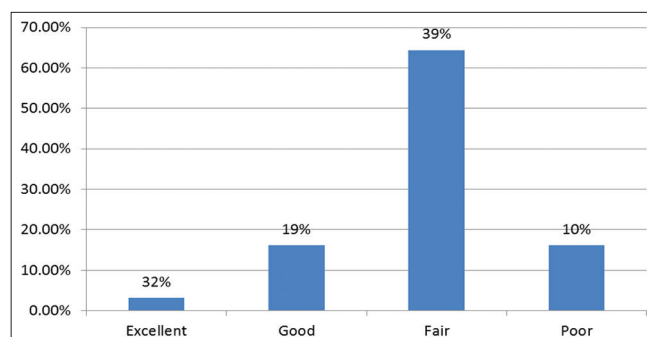


Figure 5: Recovery from symptoms – types

2. Recovery and presence of intramedullary signals on MRI: $P = -0.6001$; significant [Figure 6]

Recovery and presence of CPPD crystals in Light microscopy: $P = -0.3032$; significant [Figure 7].

Above statistical analysis results shows that the radio-pathological factors that likely to predict the outcome for surgery for OLF spine are:

1. MRI signal changes
2. CPPD positivity.

DISCUSSION

Development of OLF

In most OLF cases, the initial changes in the *L. flavum* occur at the site of attachment of the caudal portions [Picture 5], and ossification extends from the lateral aspect to the center along the superficial layer of the hypertrophied *L. flavum* and then above to the anterior parts of cephalic portions. Ossification of the cephalic portions progresses to the caudal portions, and hyperostosis of the pedicle occurs, resulting in nodular formations. However, the cephalic and caudal parts of OLF never unite completely in the intervening space, even in specimens with thickened nodular OLF in the fibro cartilaginous matrix.

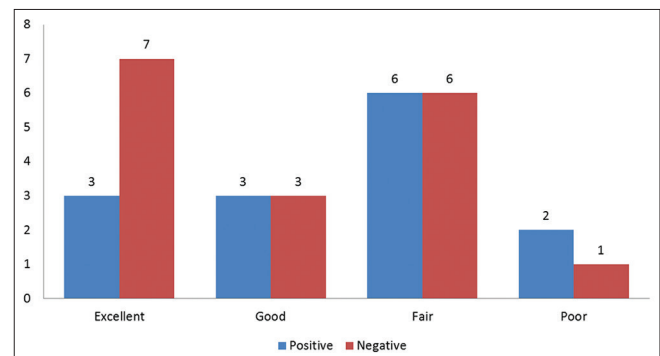


Figure 6: Recovery and magnetic resonance imaging signal changes

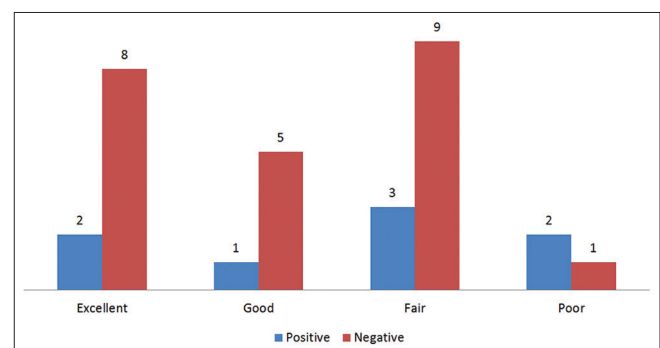
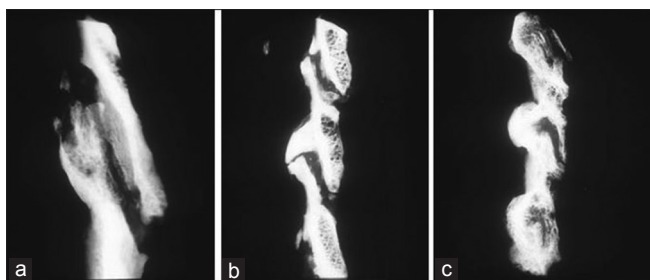


Figure 7: Recovery and calcium pyrophosphate dihydrate positivity



Picture 5: Development of ossification of *Ligamentum flavum* (OLF). (a) Initial ossification at the attachment of the caudal portion, (b) nodular type OLF, (c) final stage of OLF. Both the cephalic and caudal portions of OLF were fused but never united in the intervening space

Histopathology of the *L. flavum*

Anatomically 20, the *L. flavum* exists in the interlaminar space and supporting tissue, forming part of the posterior wall of the spinal canal. The *L. flavum* has two portions at each intervertebral disc level: The central (inter-laminar) and lateral (capsular) portions. The average composition of the fibers is 80% elastin and 20% collagen, as described by Yong-Hing *et al.*^[10] This composition changes with age, however, and it has been reported that collagen increases in relation to decreasing elastin [Figure 2]. The bony attachment of the *L. flavum* is a four-layered structure, the enthesis, as described by Niepel and Sitaj.^[11] The four layers are the ossification layer, calcified cartilage, non-mineralized cartilage, and ligament. The enthesis also occupies a key position in the pathological process of the diseases or so-called enthesopathy. It is well known that the enthesis has a rich vascular supply, highly active metabolism, an ample and specialized nerve supply, and a few scattered fibrocartilage cells with reserved activity, among other structures. With aging, small osteophytes develop in the *L. flavum* at the ligamento-osseous junction (enthesis), which shows marked intraligamentous calcification, swelling, and hyalinization of the collagen fibers, the appearance of fibrocartilagenous cells, and a reduction in the elastic fibers [Picture 1]. It is thought that this small OLF is a degenerative enthesophytes that developed from the enthesis.

Differentiation between Degenerative Osteophytes and OLF

To understand the cause of the overgrowth of cartilaginous tissue that precedes the development of OLF, we investigated the changes in the enthesis of the *L. flavum* immunohistochemically using type-specific human monoclonal anti-collagen antibodies I–VI. Collagen Types I, III, and VI were found in the unossified ligaments. Type II collagen was demonstrated only in the ossified cartilage and non-mineralized cartilage layers of the enthesis [Picture 1]. There was no significant difference in the width of the ossified cartilage layer, but the difference in the width of the non-mineralized layer between the OLF group and the controls was substantial.

Active production of Type II collagen by the chondrocytes was revealed in the hyperplastic extracellular matrix. Therefore, it was thought that proliferation of Type II collagen at the enthesis resulted in the formation of a hypertrophied ligament before it developed into OLF.^[12]

Pathology of OLF

The OLF extended along the superficial layer of the hypertrophied ligament, as in OPLL. However, numerous fibro-cartilaginous cells with abundant matrices including Type II collagen were seen more abundantly in OLF than in OPLL. At the transitional areas adjacent to the ossified areas, there were various morphological phenomena: Irregular arrangement of the fibrous structures; abundant collagen fibers; irregular, ruptured, and fewer elastic fibers; numerous cartilage cells; calcified tissues; premature ostens; and proliferating vessels. These characteristic histological findings suggest that numerous Fibro cartilaginous cells existed in the abundant collagen fibers and produced a large amount of Type II collagen. Thus, the developmental mode of OLF was confirmed to be mainly endochondral ossification. The accompanying hypertrophic cartilaginous proliferation, however, showed additional intramembranous ossification at the margin of the thickened OLF.^[13]

Factors Related to the Development of Ossification

Role of mechanical stress

When considering the mechanism of ossification development, the theory states that both dynamic and static mechanical stresses act as local factors in the development of OLF under a general ossifying diathesis. Yamazaki *et al.* described disc degeneration and vertebral wedging acting as local factors that increase the tension of the *L. flavum*. They, therefore, indicated that localized mechanical stress that affected the *L. flavum* was a contributing factor to ossification development.^[14] Anatomically, the *L. flavum* in the thoracic region is subjected to static stress continuously, and it is greater in flexion than in extension. Therefore, it is thought that the development of OLF depends on mechanical stress. However, the formation of the ossified tissue at the enthesis (enthesopathy) is self-limited, and massive ossification is uncommon. OLF is therefore due to something more than enthesopathy.

Role of growth factors

Growth factors are believed to be important in the pathogenesis of the OPLL and the *L. flavum*. Bone morphogenetic proteins (BMPs) and transforming growth factor- β (TGF- β) may have important roles in the pathogenesis of OPLL and OLF. BMPs initiate cartilage and bone differentiation and induce new cartilage and bone formation *in vivo*, whereas TGF- β stimulates cartilage and bone formation via determined chondroprogenitor and osteoprogenitor cells *in vivo*. A recent study also

showed differentiation of spinal ligament fibroblasts into chondrocytes as a result of induction by BMP-2. On the other hand, Ono *et al.* examined the appearance and localization of TGF β 1, fibronectin, and bone alkaline phosphatase in OLF lesions from four patients. Based on these results, it is believed that TGF β 1 and fibronectin may contribute to the hypertrophy and ossification of the *L. flavum*. Recently, a key molecule called cartilage-derived morphogenetic protein (CDMP-1) and has been identified as a member of the TGF β super family. Nakase *et al.* reported that CDMP-1 was immunolocalized in spindle-shaped cells distant from the ossification front.^[15]

CONCLUSION

Radio-pathological factors that are likely to negatively affect the short term outcome includes MRI intramedullary signal changes and CPPD crystals positivity. Thus detailed radiological and histopathological studies are also required to predict the outcome. Long term follow up needed to determine the factors that predict the surgical outcome.

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