VOLUME-4, ISSUE-9

UDC 616.711.61-007.271:612.017.1

IMMUNOLOGICAL ALTERATIONS IN THE MECHANISMS OF EPIDURAL FIBROSIS PROGRESSION

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Background. In recent years, global research has focused on elucidating the immuno-inflammatory and fibrotic mechanisms underlying ligamentum flavum hypertrophy, as well as on refining decompression techniques and preventing epidural scarring. A systematic review of 26 studies identified type I and III collagens, TGF-β1, and IL-6 as the factors most frequently associated with ligamentum flavum hypertrophy, though it also highlighted the heterogeneity of the existing evidence base (1, 2, 3). Postoperative epidural fibrosis remains a persistent limitation in spinal surgery, as most proposed preventive measures have not been adopted into standard clinical practice (4, 5). The possibility of assessing an individual's immune-mediated risk—and subsequently tailoring postoperative management accordingly—before the development of significant scarring remains insufficiently explored.

Objective. To investigate the relationship between local and systemic immunological alterations in the mechanisms driving the progression of epidural fibrosis.

Material and methods. The study is based on the findings from the examination and surgical treatment of 86 (40.2%) patients with degenerative lumbar spinal stenosis and hypertrophy of the ligamentum flavum. In a retrospective comparative analysis, we divided all patients into subgroups based on their clinical course—favorable (54/86 patients; 62.7%) or unfavorable (32/86 patients; 37.3%)—depending on the progression of epidural scar tissue.

Results and discussion. The correlation analysis focused on the 32 patients with progressive epidural fibrosis. This approach allowed us to determine which components of the initial tissue phenotype remained reflected systemically following decompression, and how the strength of these associations shifted as the scarring and adhesive process developed. As early as one month postoperatively, the strongest correlation was observed between the initial area of fibrosis and systemic SPP1 levels ($r=0.764$; $p < 0.001$).

The residual area of elastic fibers was inversely associated with IL-6 ($r = -0.689$; $p < 0.001$), whereas the area of the collagen matrix showed a direct association with IL-6 ($r = 0.664$; $p < 0.001$). Furthermore, tissue expression of SPP1 correlated with both circulating SPP1 and IL-6; these associations linked the structural severity of remodeling with persistent post-surgical inflammatory and profibrotic activity. The correlation between CD68 and the absolute monocyte count was moderate ($r = 0.509$), indicating a lack of direct correspondence between the tissue and circulating pools. During the first month, nuclear p-Smad3 did not correlate with systemic TGF-β1, and the ratio of type I to type III collagen was not associated with the MMP-9/TIMP-1 ratio; thus, specific local and

systemic levels remained asynchronous, despite a shared phenotypic direction—though by the third month of the study, these associations became more organized. The area of the collagen matrix correlated with CRP (r=0.717), while tissue SPP1 correlated with circulating SPP1 (r=0.709) and the absolute monocyte count (r=0.703); conversely, the residual area of elastic fibers showed an inverse relationship with TGF-β1 (r=-0.707). This set of associations reflected a transition from an early postoperative response to a stable systemic trajectory—one consistent with the underlying tissue substrate—while the ratio of collagen types I/III remained uncorrelated with the MMP-9/TIMP ratio.

The late-stage systemic profile reflected not merely the quantity of tissue macrophages, but the stability of the cell-matrix program they established. While the data—as shown in the corresponding diagram—revealed significant individual variation in key local-systemic associations among cases with unfavorable surgical outcomes, the overall trend remained consistent: tissue-level SPP1 levels rose in tandem with systemic SPP1, the extent of fibrosis correlated with TGF-β1, and the preservation of elastic fibers declined as TIMP-1 levels increased.

In the subgroup of patients with favorable postoperative outcomes, similar associations were observed, though they were less pronounced. Specifically, the correlation between tissue and systemic SPP1 at 6 months was r=0.114; between the area of fibrosis and TGF-β1, it was r=0.271; and between the remaining area of elastic fibers and TIMP-1, it was r=-0.248. This reduced local-systemic coherence coincided with the normalization of most circulating biomarkers and an absence of progressive scar tissue formation. At 3 months, the normalized area of epidural scar tissue was 13.71±0.32% in the favorable outcome group, compared to 23.05±0.40% in the unfavorable group ($t=-18.19$, $p < 0.001$). By 6 months, these values were 11.94±0.30% and 30.58±0.70%, respectively ($t=-24.46$, $p < 0.001$), and by 12 months, they reached 10.67±0.28% and 36.98±0.67% ($t=-36.26$, $p < 0.001$). (<0.001). In the subgroup of patients with a favorable outcome, the area of scar formation decreased progressively from 3 to 12 months—reflecting the maturation and densification of the localized reparative tissue—whereas in patients with an unfavorable clinical course, this area increased at each subsequent stage. The mean grade (according to the Ross system) shifted from 2.25±0.08 units at 3 months to 3.22±0.12 units at 6 months and 3.91±0.05 units at 12 months. In contrast, for the subgroup with a favorable outcome, this metric decreased from 1.11±0.06 units to 0.96±0.06 units, and further to 0.78±0.07 units. Based on these findings, we determined that a clinically significant cicatricial-adhesive process developed in 17/32 (53.1%) patients with progressive fibrosis, while in the remaining 15/32 (46.9%) patients within this subgroup, the progression of fibrosis was primarily detected via MRI.

A favorable outcome, as observed on MRI, was characterized by the stabilization of a localized epidural scar with no change in the shape of the dural sac. In contrast, an unfavorable outcome involved a progressive increase in both the area and the topographical extent of the scar tissue, accompanied by worsening deformation of the epidural space. The long-term scar area correlated positively with the initial extent of fibrosis in the ligamentum flavum (r=0.662) and negatively with the preservation of

elastic fibers (r=-0.530). Among the immunohistochemical markers, SPP1 showed a consistent association (r=0.597), whereas CD68 and p-Smad3 did not reach statistical significance when compared directly with the scar area at twelve months. Among systemic markers, the strongest association was observed with TGF-β1 at 6 months (r=0.688), followed by SPP1, MLS (macrophage-like cells), and TIMP-1. This sequence does not imply that the resected ligamentum flavum itself served as the direct source of the epidural scar; rather, the tissue reflected a long-established pattern of an immuno-fibrotic response. Following decompression, a new reparative stimulus manifested within a different anatomical substrate: in cases with a moderate initial phenotype, systemic activity subsided, matrix turnover approached equilibrium, and the scar stabilized; conversely, in cases marked by significant macrophage-, SPP1-, and TGF-β1-associated remodeling, a persistent pro-fibrotic trajectory was maintained, the influence of TIMP-1 intensified, and matrix accumulation continued.

Conclusions:

1. The proposed pathogenetic model comprises two distinct pathways, demonstrating that the excised ligamentum flavum was not, in itself, the direct source of the scar tissue. Instead, the common factor in the pathogenesis lies in the specific, individual nature of the immune and matrix responses—manifesting across two anatomically different scenarios—which provides a foundation for developing predictive criteria and personalized immunoprophylactic strategies.
2. Following decompression, the new reparative stimulus unfolded within a different anatomical substrate. In cases with a moderate initial phenotype, systemic activity subsided, matrix turnover approached equilibrium, and the scar tissue stabilized. Conversely, in cases characterized by significant remodeling—driven by macrophages and associated with SPP1 and TGF-β1—a persistent profibrotic trajectory was maintained, the influence of TIMP-1 intensified, and the accumulation of matrix components continued.

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