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НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE

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АНАЛИЗ ПАТОГЕНЕТИЧЕСКОЙ ВЗАИМОСВЯЗИ ЛОКАЛЬНЫХ И СИСТЕМНЫХ ИММУНОЛОГИЧЕСКИХ ИЗМЕНЕНИЙ В МЕХАНИЗМАХ ПРОГРЕССИРОВАНИЯ ЭПИДУРАЛЬНОГО ФИБРОЗА

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✓ ***Резюме***

Схема патогенетической модели имеет два самостоятельных направления, которые доказывают, что удаленная желтая связка сама по себе не являлась прямым источником рубца, а общей в патогенезе оказалась индивидуальная направленность иммунного и матриксного ответа в двух анатомически различных ситуациях, что позволяет нам сформировать основу для разработку критериев их прогнозирования и персонализированной иммунопрофилактики.

Ключевые слова: поясничный отдел позвоночника, желтая связка, эпидуральный фиброз, позвоночный канал.

EPIDURAL FIBROZ PROGRESSSIYASI MEXANIZMLARINDAGI MAHALLIY VA TIZIMLI IMMUNOLOGIK O'ZGARISHLAR O'RTASIDAGI PATOGENETIK MUNOSABATNING TAHLILI

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✓ ***Rezyume***

Patogenetik model ikkita mustaqil komponentga ega bo'lib, olib tashlangan ligamentum flavumning o'zi chandiqning bevosita manbai emasligini, balki umumiy patogenez ikkita anatomik jihatdan farqli vaziyatda immun va matritsa javoblarining individual yo'nalishi ekanligini ko'rsatadi. Bu bizga ularni bashorat qilish va shaxsiylashtirilgan immunoprofilaktika mezonlarini ishlab chiqish uchun asos yaratish imkonini beradi.

Kalit so'zlar: bel umurtqasi, ligamentum flavum, epidural fibroz, orqa miya kanali.

ANALYSIS OF THE PATHOGENETIC INTERRELATIONSHIP BETWEEN LOCAL AND SYSTEMIC IMMUNOLOGICAL CHANGES IN THE MECHANISMS OF EPIDURAL FIBROSIS PROGRESSION

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✓ ***Resume***

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; rather, the common pathogenetic factor was the specific nature of the immune and matrix responses in two anatomically distinct scenarios, a finding that provides a basis for developing criteria to predict these outcomes and implement personalized immunoprophylaxis.

Keywords: lumbar spine, ligamentum flavum, epidural fibrosis, spinal canal.

Relevance

Globally, degenerative lumbar spinal stenosis is a leading cause of neurogenic intermittent claudication, radicular pain, and functional impairment, and it ranks among the most common indications for spinal surgery. The number of patients worldwide with this condition exceeds 103 million; among 239 patients with stenosis, hypertrophy of the ligamentum flavum is observed in 42.7% of cases, with the prevalence rising from 18.5% in the 21–30 age group to 93.9% in the 61–70 age group, and the L4–L5 level being the most common site. In cases of single-level stenosis, the thickness of the ligamentum flavum was identified as an independent factor associated with severe neurogenic claudication, with an odds ratio of 1.73. The prevalence of the disease, the age-related increase in its incidence, and the clinical significance of the ligamentous component underscore the importance of improving the prediction of surgical outcomes (1, 3, 5).

In recent years, global research has focused on elucidating the immuno-inflammatory and fibrotic mechanisms underlying ligamentum flavum hypertrophy, 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, while also highlighting the heterogeneity of the available evidence (7, 8, 9, 10). Current treatment modalities for lumbar stenosis have been summarized, demonstrating that surgical decompression yields more rapid pain relief and functional recovery in appropriately selected patients. Postoperative epidural fibrosis is regarded as an enduring limitation of spinal surgery, given that most proposed preventive measures have not been adopted into standard clinical practice (2, 4, 6). The potential to assess an individual's immune-related risk—and adjust postoperative management accordingly—prior to the formation of significant scar tissue remains insufficiently explored.

To investigate the relationship between local and systemic immunological changes and the mechanisms underlying the progression of epidural fibrosis.

Materials and methods

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

The reference group consisted of 40 patients (18.7%) who underwent surgery for a lumbar intervertebral disc herniation but showed no MRI evidence of ligamentum flavum hypertrophy or clinically significant degenerative spinal stenosis. This group served as a biological benchmark for morphological, immunohistochemical, and baseline systemic immunological analyses.

Results and discussions

Correlation analysis focused on 32 patients with progressive epidural fibrosis; this approach enabled us to determine which components of the baseline tissue phenotype maintained a systemic reflection following decompression and how the strength of associations shifted as the scarring and adhesion process developed. As early as one month post-operatively, 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 correlated with IL-6 ($r=-0.689$, $p<0.001$), whereas the area of the collagen matrix showed a direct correlation with IL-6 ($r=0.664$, $p<0.001$); furthermore, tissue SPP1 expression correlated with both circulating SPP1 and IL-6. These associations linked the structural severity of remodeling with persistent post-operative inflammatory and pro-fibrotic activity. In contrast, the correlation between CD68 and the absolute monocyte count was moderate ($r=0.509$) and did not imply a direct correspondence between tissue and circulating pools; notably, during the first month, nuclear p-Smad3 did not correlate with systemic TGF-β1, and the type I/III collagen ratio was unrelated to the MMP-9/TIMP-1 ratio. Thus, despite the shared directionality of the phenotype, specific local and systemic levels remained asynchronous, although these associations became more organized by the three-month mark.

The collagen matrix area correlated with CRP ($r=0.717$), and tissue SPP1 with circulating SPP1 ($r=0.709$) and the absolute monocyte count ($r=0.703$); conversely, the residual elastic fiber area was

inversely associated with TGF-β1 (r=-0.707). This pattern of relationships reflected a transition from the early postoperative response to a stable systemic trajectory consistent with the initial tissue substrate. Meanwhile, the type I/III collagen ratio remained uncorrelated with MMP-9/TIMP-1, as the composition of the established tissue matrix and the current balance of its circulating regulators reflected different levels of the process—a distinction that, at the 6-month mark, was manifested in a strong association between tissue SPP1 and systemic TGF-β1 (r=0.789). The area of fibrosis correlated with circulating SPP1 and TGF-β1 (r=0.755 and r=0.745, respectively), whereas tissue SPP1 maintained an association with its own systemic concentration and with TIMP-1; simultaneously, the residual area of elastic fibers was inversely associated with TIMP-1 (r=-0.720), forming a coherent pattern wherein the severity of initial matrix damage coincided with a sustained profibrotic and antiproteolytic systemic response. While the association between CD68 and monocyte count weakened to a borderline level at 6 months (r=0.344, p=0.054), α-SMA correlated with monocytes and the area of fibrosis with NLS, indicating a late-stage systemic profile that reflected not merely the quantity of tissue macrophages but the persistence of the cell-matrix program they had established. This was illustrated by a diagram showing significant individual variation in the most indicative local-systemic correlations in cases of unfavorable surgical outcomes, yet the overall trend remained consistent: tissue SPP1 increased alongside systemic SPP1, the area of fibrosis increased with TGF-β1, and the preservation of elastic fibers declined as TIMP-1 levels rose.

In the subgroup of patients with a favorable postoperative outcome, similar associations were observed but proved weaker; the correlation between tissue and systemic SPP1 levels at 6 months was r=0.114, between fibrosis area and TGF-β1 was r=0.271, and between residual elastic fiber area and TIMP-1 was r=-0.248. This attenuation of local-systemic coordination coincided with the normalization of most circulating markers and the absence of progressive scar tissue formation. In contrast, the normalized area of epidural scar tissue at 3 months was 13.71±0.32% in the favorable outcome group versus 23.05±0.40% in the unfavorable group (t=-18.19, p<0.001); at 6 months, the corresponding values were 11.94±0.30% and 30.58±0.70% (t=-24.46, p<0.001); and at 12 months, they were 10.67±0.28% and 36.98±0.67% (t=-36.26, p<0.001). Notably, in the favorable outcome subgroup, the scar formation area progressively decreased from the 3-month to the 12-month mark—reflecting the maturation and densification of the localized reparative tissue—whereas in patients with an unfavorable course, the area increased at each subsequent stage. The mean grade (according to the Ross scale) 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, whereas in the subgroup of patients with a favorable outcome, the corresponding value decreased from 1.11±0.06 units to 0.96±0.06 units and then to 0.78±0.07 units; based on this, we found 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 of this subgroup, the progression of fibrosis was detected via MRI. Specifically, MRI at 3 months in patients with a favorable outcome revealed a thin, localized area of posterior epidural scar tissue adjacent to the dorsal surface of the dural sac—without altering its configuration or extending into the lateral aspects of the spinal canal—and at 6 months, neither the area nor the extent of the scar tissue had increased significantly; the contours of the dural sac remained smooth and symmetrical, with no signs of compression or reduction in the free epidural space, and even at 12 months, the scar component remained confined to the initial surgical site, having become more compact.

In contrast to the stable outcome, the progressive variant showed a distinct evolution: at 3 months, scar tissue occupied the posterior and partially posterolateral sections of the epidural space, adhering closely to the dural sac and causing early alterations to its dorsal contour; by 6 months, there was an increase in the area and extent of the epidural scar tissue, which spread along the posterolateral surfaces of the dural sac while simultaneously reducing the free epidural space and causing more pronounced deformation of the dural sac at the level of the decompression. By 12 months, the scarring and adhesion process had become extensive, characterized by dense epidural tissue occupying the posterior and posterolateral regions of the spinal canal and partially enveloping the dural sac, resulting in its flattening and asymmetric deformation; this progression was marked by an increase in both the area of fibrous tissue and the extent of its contact with the dural sac, reflecting the continuous progression of postoperative epidural fibrosis.

In other words, a favorable MRI outcome was characterized by the stabilization of a localized epidural scar without alteration to the dural sac's shape, whereas an unfavorable outcome involved a progressive increase in the area and extent of scar tissue accompanied by worsening epidural space deformation; the final scar area correlated with the initial area of ligamentum flavum fibrosis (r=0.662) and inversely with the preservation of elastic fibers (r=-0.530), yet among immunohistochemical markers, only SPP1 maintained a robust association (r=0.597)—while CD68 and p-Smad3 failed to reach statistical significance in direct comparison with the 12-month scar area—and among systemic markers, the strongest correlation

was observed with TGF-β1 at 6 months (r=0.688), followed by SPP1, MLS, and TIMP-1. This sequence did not imply that the resected ligamentum flavum was the direct source of the epidural scar, as the tissue merely reflected a long-established pattern of immuno-fibrotic response; rather, following decompression, the new reparative stimulus played out within a different anatomical substrate: in cases with a moderate initial phenotype, systemic activity subsided, matrix turnover approached equilibrium, and the scar stabilized, whereas pronounced macrophage-, SPP1-, and TGF-β1-associated remodeling sustained a prolonged pro-fibrotic trajectory, amplified the influence of TIMP-1, and drove continued matrix accumulation. In this case, the association of IL-6 with the area of fibrosis, the collagen component, and the reduction of elastic fibers was consistent with the oxidative-inflammatory program of ligamentum flavum remodeling. Since we did not directly investigate oxidative markers, it was decided to cite this potential mechanism solely as a literature-based explanation for the persistence of the IL-6-associated response, rather than as an additional finding.

Conclusion

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; rather, the common pathogenetic factor was the specific nature of the immune and matrix responses in two anatomically distinct scenarios. This insight provides a foundation for developing criteria to predict these outcomes and for implementing personalized immunoprophylaxis.
2. Following decompression, the new reparative stimulus played out within a different anatomical context: in cases with a moderate initial phenotype, systemic activity subsided, matrix turnover approached equilibrium, and the scar stabilized; conversely, in cases characterized by pronounced remodeling—associated with macrophages, SPP1, and TGF-β1—a sustained profibrotic trajectory persisted, the influence of TIMP-1 intensified, and matrix accumulation continued.

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