Degenerative Spine Disease

Pathologic Findings in 985 Surgical Specimens

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Key Words: Calcium pyrophosphate dehydrate; Chondrocyte cluster; Neovascularization; Synovial metaplasia; Intervertebral disk

DOI: 10.1309/89FVRT04EGBVEUD9

Abstract

A number of pathologic changes have been reported in spinal surgery specimens. The frequency of many of these is not well defined.

We retrospectively reviewed the histologic features of 985 extradural spinal surgery specimens. Of the cases, 1.6% were identified clinically as synovial cysts. In addition, synovial tissue was seen in another 5.3% of cases, often embedded within disk material. Neovascularization of disk tissue was present in 8.1% of cases, chondrocyte clusters in 18.3%, and calcium pyrophosphate crystals in 2.8%, predominantly within disk material. With the exception of crystal deposits, all of these changes were significantly more common in the lumbar spine.

A better understanding of cell-based degenerative changes will become essential with increasing research into cell-based therapies for spinal disk disease. We report data on the frequency of different pathologic changes and describe synovial metaplasia as a reactive change not previously reported.

Procedures done for a clinical diagnosis of degenerative spine disease account for a large proportion of spinal surgeries. Most often, these surgeries are performed to alleviate pain or neurologic deficits caused by nerve root or spinal cord compression.

The main components of the vertebral column are the intervertebral disks, synovial facet joints, ligaments, and the bony elements, including vertebral bodies, pedicles, and spinous and transverse processes.[1] All of these elements can exhibit normal aging changes and different degenerative or regenerative alterations.[1] The intervertebral disk has a central role in this context, and disk disease can be an important factor in the development of other abnormalities such as osteoarthritis of the facet joints or degeneration of the yellow ligament.[2]

The intervertebral disks connect adjacent vertebral bodies to give the otherwise rigid vertebral column controlled, restricted movement. The disks include 3 main components that are developmentally, histologically, and metabolically distinct[2-6] **Image 1A**: (1) The anulus fibrosus is derived from mesenchymal precursors and consists of distinct lamellae of fibrocartilage arranged in several layers of alternating orientation. It is rich in type I and type II collagens that are oriented in parallel bundles and contains a relatively small amount of proteoglycans and water. (2) The nucleus pulposus originates as notochord remnant. In humans, the notochordal physaliferous cells become replaced by mesenchymally derived chondrocyte-like cells during the first decade of life. This is in sharp contrast with many other mammals and rodents in which the physaliferous cells persist throughout adulthood. The only abundant collagen is type II. The collagen fibrils are arranged haphazardly, and the matrix has a high content of proteoglycans and water. (3) The cartilage

endplates form the interface between the disk and the adjacent vertebral body. They are important in regulating the perfusion of nutrients and waste to and from the normally avascular intervertebral disk. Normal disks are one of the most paucicellular tissues; the cells depend on diffusion across distances of up to 8 mm.[2]

Normal aging changes of the disk include the disappearance of notochordal cells, a decrease in the water content of the nucleus pulposus, splitting and thickening of the lamellae of the anulus, and loss of the distinct junction between anulus and nucleus pulposus.

Many studies of degenerative changes in spinal disease were conducted on whole motion segments obtained from autopsies or selectively obtained surgical specimens.[7-11] The degenerative disk changes described in these studies include cellular changes and alterations in the extracellular matrix. Cellular changes include chondrocyte clusters **Image 1D** (also known as chondron clusters and chondrocyte cloning),[7,8,10,11] cell death and apoptosis,[7,12] and neovascularization of the normally avascular disk.[7-10] Abnormalities in the matrix[1,7-10] include fraying, granular change, mucous degeneration, radial tears, and concentric tears. Other reported degenerative changes are not limited to the intervertebral disk or occur in other tissues of the spine. This latter group includes the formation of juxtafacet cysts **Image 1E** and **Image 1F**[13-21] and the deposition of crystals **Image 1B** and **Image 1C**.[22-26]

In contrast with the specimens used in these studies, the tissue specimens received by pathologists in everyday practice typically are fragmented and artifactually distorted. These changes preclude the exact analysis of anatomic relationships and make it more difficult to evaluate changes in the matrix. An obvious advantage of studying routine surgical specimens lies in the large number of cases available. In addition, the study of routine specimens provides information that is integrated easily into daily diagnostic practice.

This study has 2 main components: (1) evaluation of previously described degenerative or regenerative changes to determine the frequency with which these are found in a large series of unselected extradural spinal surgery specimens and to show differences between the frequency with which different levels of the spine are affected and (2) more specific analysis of the synovial changes to test the hypothesis that synovial metaplasia can occur as a regenerative change in the spine.

Materials and Methods

The study protocol was approved by the institutional review board of the University of Chicago Hospitals, Chicago, IL. The pathology database at the University of Chicago Hospitals was reviewed retrospectively to identify the specimens of 985 cases of spinal surgeries that were done for degenerative spine disease between August 20, 1999, and December 31, 2002: Cases were excluded from the study if they were intradural surgeries or surgeries performed for malformations such as spina bifida or tethered cord or if the surgery confirmed a preoperative clinical diagnosis of a neoplasm or infection. To assess the latter, the pathology report was reviewed to determine whether the pathologist had information at the time of surgery that alerted him or her to such a diagnosis. These criteria assume that all surgeries not done for a different established diagnosis were performed because of a clinical diagnosis of degenerative spine disease. The criteria also were chosen to include all cases in which significant pathologic findings such as a tumor or infection were incidental and not part of the preoperative differential diagnosis.

All specimens were fixed in 10% neutrally buffered formalin and paraffin embedded. Specimens with bony components were decalcified in EDTA and hydrochloric acid after fixation.

All slides were reviewed to document the following features: (1) types of normal anatomic tissues identified, (2) the presence of chondroid clusters in intervertebral disk material, (3) cellular proliferations that could be classified as neovascularization of intervertebral disk tissue or as synovial tissue (in the case of synovial tissue, the anatomic relationship to intervertebral disk, yellow ligament, or other connective tissue elements was determined), and (4) deposits of refractile and polarizing crystals.

Immunohistochemical stains for CD34 and CD44[27,28] were performed on 30 selected cases to evaluate the usefulness of these stains in distinguishing vascular elements from synovial tissue. Immunohistochemical stains were done according to standard protocols using commercially available antibodies (CD34, clone QB End/10, dilution 1:50, Novocastra, Newcastle upon Tyne, England; CD44, clone DF1485, dilution 1:50, DAKO, Glostrup, Denmark). The latter antibody has been shown to recognize the standard isoform, CD44s, that does not contain any of the alternatively spliced in exons.[29,30] For both antibodies antigen retrieval was performed by microwave treatment in citrate buffer.

The ages of the patients and the location of the surgery, ie, cervical, thoracic, or lumbar spine, were available from the pathology reports. In addition, the pathology reports were reviewed to determine whether the pathologist had data to suggest an inflammatory or neoplastic process at the time the specimen was received. In cases that showed synovial tissue, the reports were reviewed to identify cases in which a synovial cyst was part of the preoperative or intraoperative differential diagnosis.

We used χ^2 testing for statistical comparisons between subgroups of cases.

DOI: 10.1309/89FVRT04EGBVEUD9

Results

General Findings

Results are summarized in **Table 1**. Of the 985 cases 353 (35.8%) were from cervical, 26 (2.6%) from thoracic, and 606 (61.5%) from lumbar surgeries. Intervertebral disk tissue was found in 867 cases, bone in 526, dense connective tissue in 441, yellow ligament in 201, skeletal muscle in 128, and adipose tissue in 68. In 665 cases (67.5%) none of the pathologic changes that were analyzed in this study appeared.

Synovium and Neovascularization

A number of cases exhibited cellular proliferations in the form of neovascularization of the intervertebral disk or synovial tissue embedded within the intervertebral disk, yellow ligament, or connective tissue. In some cases, it was difficult to make a morphologic distinction between synovial tissue with vascular stroma and granulation tissue–like neovascularization.

Neovascularization of intervertebral disk tissue was present in 80 cases (8.1%). It was significantly more common in the lumbar spine than in the thoracic or cervical spine (75 cases vs 0 and 5 cases, respectively; $P \leq .001$).

In 16 (1.6%) of 985 specimens, there was synovial tissue that was identified by the surgeon as a synovial cyst. All of these were resected from the lumbar spine. Three of the cysts were located at least in part in the yellow ligament. None of the cysts involved the intervertebral disks. The histologic features of these lesions varied from cases that consisted primarily of hyperplastic synovium with little cyst content to others with a thin synovial membrane in which the bulk of the lesion was composed of sometimes rather dense amorphous-appearing cyst content (Image 1).

In addition to these 16 cases, 52 cases (5.3%) showed microscopic evidence of synovial tissue including vascular stroma, as well as evidence of a synovial lining. In 23 of these cases, the synovial tissue was embedded within intervertebral disk tissue **Image 2**, in 4 cases it was within the yellow ligament, and in 25 cases, the synovial tissue was within dense connective tissue.

Of the 68 cases with synovial cysts or other synovial proliferations, 62 (91%) occurred in the lumbar spine. Overall, these changes were significantly more common in the lumbar spine than in the thoracic or cervical spine (62 cases vs 2 and 4 cases, respectively; $P \leq .001$).

Although CD34 and CD44 are expressed in a number of tissues, they are helpful for differentiating synovial tissue from neovascularization **Image 3**. Cells with a synovial phenotype in synovial cysts and other synovial proliferations are CD44+ and CD34–, whereas vascular structures and neovascularization are CD34+ and CD44–.

Chondroid Clusters

Of the 985 cases, 180 (18.3%) showed chondroid clusters in the intervertebral disk material that consisted of aggregates of several chondrocyte-like cells in a single lacune (Image 1D).[7] These chondroid clusters occurred significantly more frequently in the lumbar spine than in the thoracic or cervical spine (145 cases vs 1 and 34 cases, respectively; $P \leq .001$).

Crystal Deposition

Deposits of birefringent, weakly polarizing crystalline deposits were seen in 29 cases (2.9%). In 28 of these cases,

Table 1
Summary of Results*

	Cases				
	All (N = 985)	In Cervical Spine (n = 353)	In Thoracic Spine (n = 26)	In Lumbar Spine (n = 606)	P†
Intervertebral disk tissue	867 (88.0)	313 (88.7)	20 (77)	534 (88.1)	
Dense connective tissue	441 (44.8)	133 (37.7)	13 (50)	295 (48.7)	
Yellow ligament	201 (20.4)	31 (8.8)	8 (31)	162 (26.7)	
Synovial changes					
Synovial cysts (clinically diagnosed)	16 (1.6)	0 (0.0)	0 (0)	16 (2.6)	.01
Other synovial proliferations	52 (5.3)	4 (1.1)	2 (8)	46 (7.6)	.001
Synovial tissue within intervertebral disk tissue	23 (2.3)	1 (0.3)	0 (0)	22 (3.6)	.01
Synovial tissue within yellow ligament	4 (0.4)	0 (0.0)	1 (4)	3 (0.5)	.025
Total cases with synovial proliferations	68 (6.9)	4 (1.1)	2 (8)	62 (10.2)	.001
Neovascularization of disk material	80 (8.1)	5 (1.4)	0 (0)	75 (12.4)	.001
CPPD deposition					
CPPD in disk material	28 (2.8)	6 (1.7)	1 (4)	21 (3.5)	>.05
CPPD in other tissues	4 (0.4)	0 (0.0)	0 (0)	4 (0.7)	
Total cases	29 (2.9)	6 (1.7)	1 (4)	22 (3.6)	>.05
Chondroid clusters	180 (18.3)	34 (9.6)	1 (4)	145 (23.9)	.001

CPPD, calcium pyrophosphate dehydrate.
* Data are given as number (percentage). Some cases showed CPPD deposits in disk material as well as other tissues.
† For the statistical significance of the difference between lumbar, cervical, and thoracic cases.

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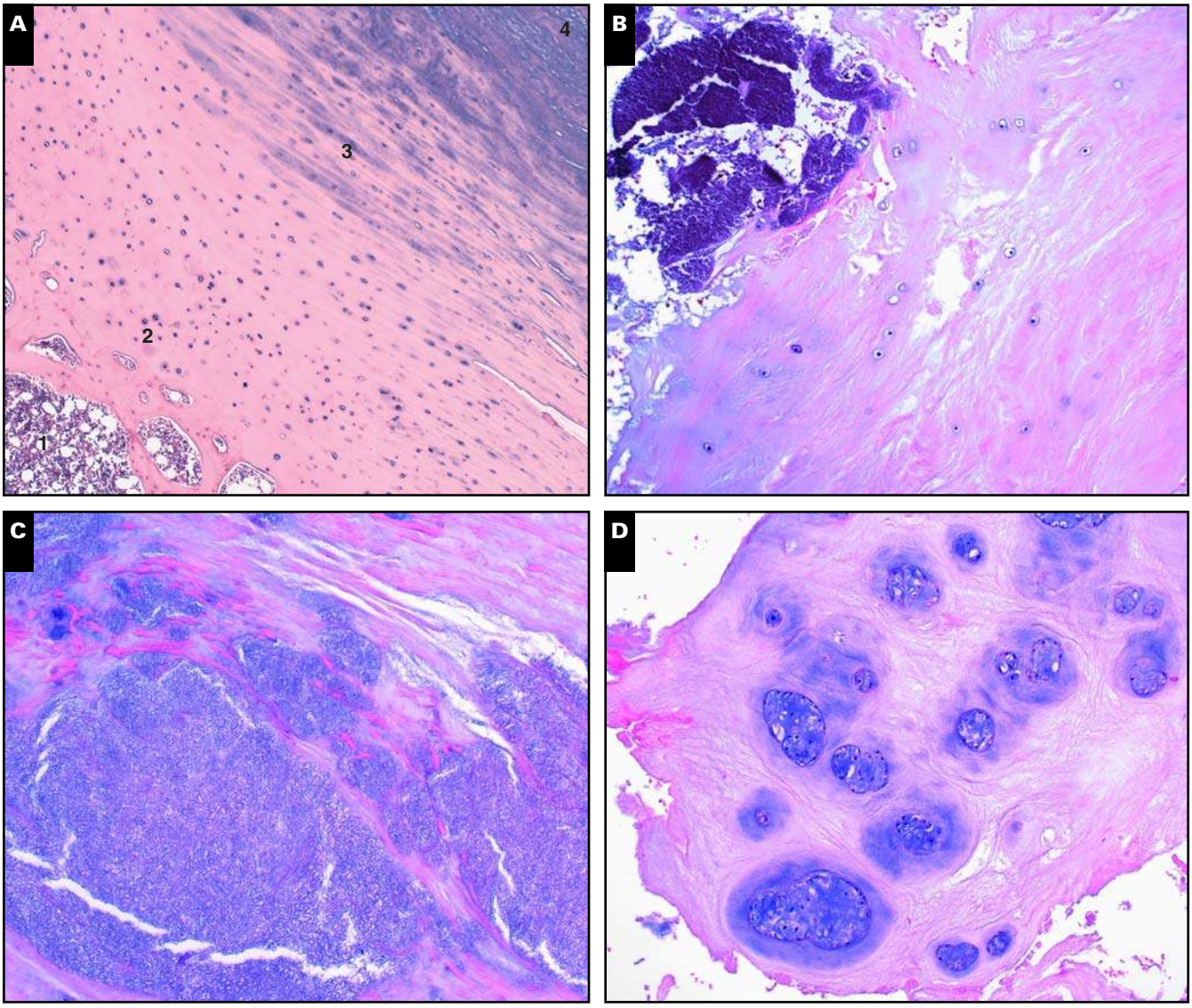

Image 1 Normal histologic features, calcium pyrophosphate dehydrate (CPPD) deposits, chondrocyte clusters, and synovial cysts. **A**, Anterior aspect of a thoracic intervertebral disk showing, in successive order from the lower left to the upper right corner (1) vertebral body bone, (2) the cartilage endplate with a hyaline cartilage–like appearance, (3) the anulus fibrosus with fibrocartilage arranged into longitudinally arranged bundles, and (4) nucleus pulposus (H&E, ×4). **B** and **C**, Low- and high-power views of CPPD deposits within the intervertebral disk and degenerative yellow ligament, respectively (**B**, H&E, ×10; **C**, H&E, ×20). **D**, Chondroid clusters within intervertebral disk tissue (H&E, ×10).

deposits were present in intervertebral disk tissue (Image 1B); in 1 case, they additionally involved the yellow ligament (Image 1C), and in 3 cases, deposits were found in collagenous connective tissue. The crystals were morphologically similar in all cases and were consistent with calcium pyrophosphate dehydrate (CPPD) deposition. They were seen more commonly in the lumbar spine, but the regional distribution was not statistically significant. Eighteen percent of cases with CPPD also showed synovial tissue in the same specimen in contrast to the cases without CPPD that only showed synovial tissue in 5% ($P \leq .01$).

Age Distribution of Degenerative Changes and Metastatic Disease

The mean ± SD age of patients in all reviewed cases was 52.4 ± 14 years. We found no significantly different age distributions for the described lesions.

Discussion

Chondrocyte Clusters

Some studies report these as a finding specific for herniated intervertebral disks.[10,11] Cells in the chondrocyte clusters

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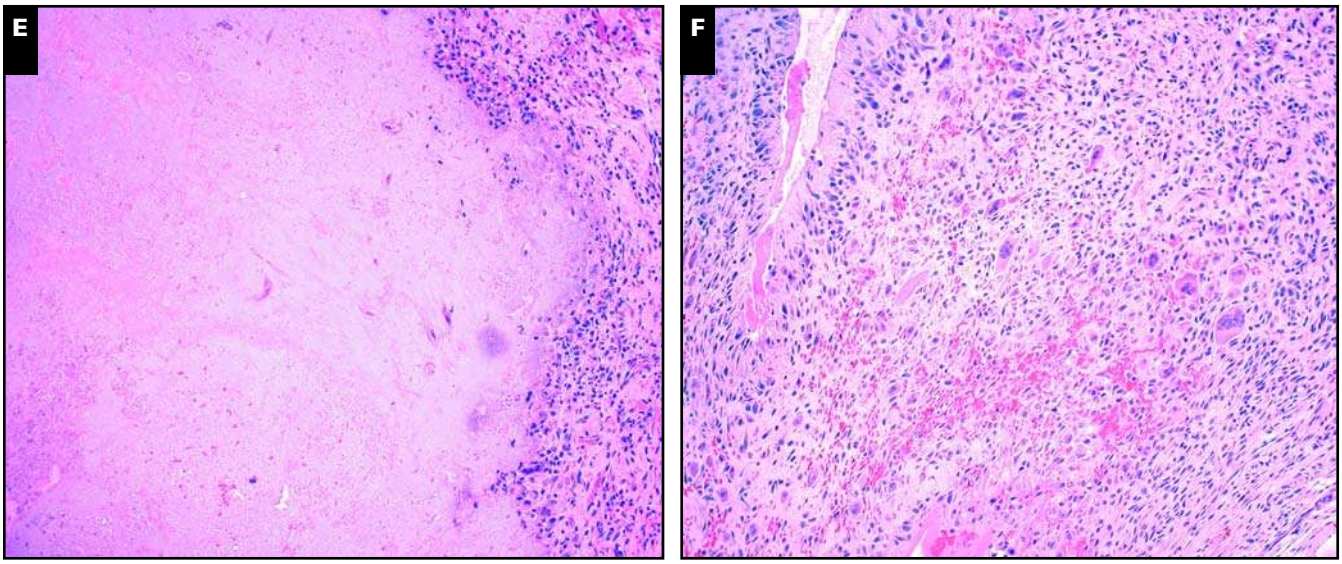

E and **F**, Clinically identified synovial cysts illustrating the spectrum of these lesions from lesions almost completely composed of cyst content with only some residual lining (**E**) to those in which the bulk of the lesion appears to be an exuberant synovial proliferation with osteoclast-like giant cells (**F**) (**E**, H&E, ×10; **F**, H&E, ×10).

show increased labeling with the proliferative marker Ki-67,[11] and it has been speculated that these clusters represent reactive clonal expansions of chondrocytes.[10] This response may further accelerate the degeneration of the disk by increasing the cellularity and the metabolic demand of the tissue. In this series, chondrocyte clusters were significantly more common in the lumbar spine and occurred overall in 18.3% of specimens.

Neovascularization

Several authors describe neovascularization of intervertebral disk tissue as a reactive change.[7,9,10] Studies that looked more specifically at herniated disks reported neovascularization in roughly half the cases.[9,10] In addition to being a secondary change, neovascularization also might contribute to the development of pathologic changes by altering the milieu of this otherwise avascular tissue.[3] In our series, neovascularization was found in only 8.1% of cases. Several factors might explain this relatively low number: (1) Cases with vascular synovial tissue were regarded as a separate subgroup. (2) Our study included material from different types of spine surgeries and was not limited to cases of herniated disk disease. (3) As shown in the present study, neovascularization is more common in the lumbar spine. The proportion of lumbar cases in a study, therefore, could influence the frequency with which this change is found.

Crystal Deposition

It is well described that CPPD deposition (pseudogout) can be found in the ligamentum flavum,[24,25] intervertebral disks,[22,25] and the facet joints.[23] CPPD deposits can cause acute disease[26] or tophaceous accumulations that elicit mass effect.[24,25] The clinical importance of these deposits, however, is not always clear: Ligamentous cervical deposits may be present in up to 70% of patients with systemic CPPD deposition disease and are associated with neck pain and spinal stenosis.[24,26] In contrast, deposits in intervertebral disk tissue may be related to trauma or previous surgery and might not be part of systemic CPPD deposition disease.[22] In the present study, CPPD deposits were found in 2.9% of extradural spine surgery specimens. Most of these were found in intervertebral disk tissue. The special acidic milieu of avascular disk tissue might facilitate the localized formation of crystals.

Synovial Changes

A number of cystic and synovial lesions have been described in the spine. In many cases, these are indistinguishable clinically or radiologically and are referred to as *juxtafacet cysts.* But based on the histopathologic features, ganglion cyst, synovial cyst, and synovial excrescence have been distinguished.[14,21] Synovial cysts in the spine usually are thought of as arising from the synovium of the facet joints. These cysts are found most commonly in the lumbar spine, in particular, the L4-5 level.[13-16,20,31] They are viewed as a regenerative change that is associated with hypermobility and instability of a motion segment as seen with spondylolisthesis and facet joint instability.[15,21,31] Besides reports of true synovial cysts, there are studies of degenerative cysts without synovial lining that can occur in the ligamentum flavum, the intervertebral disk, or other parts of the vertebral column.[16,17,19,21] At least some of these indeed might be part of the spectrum of

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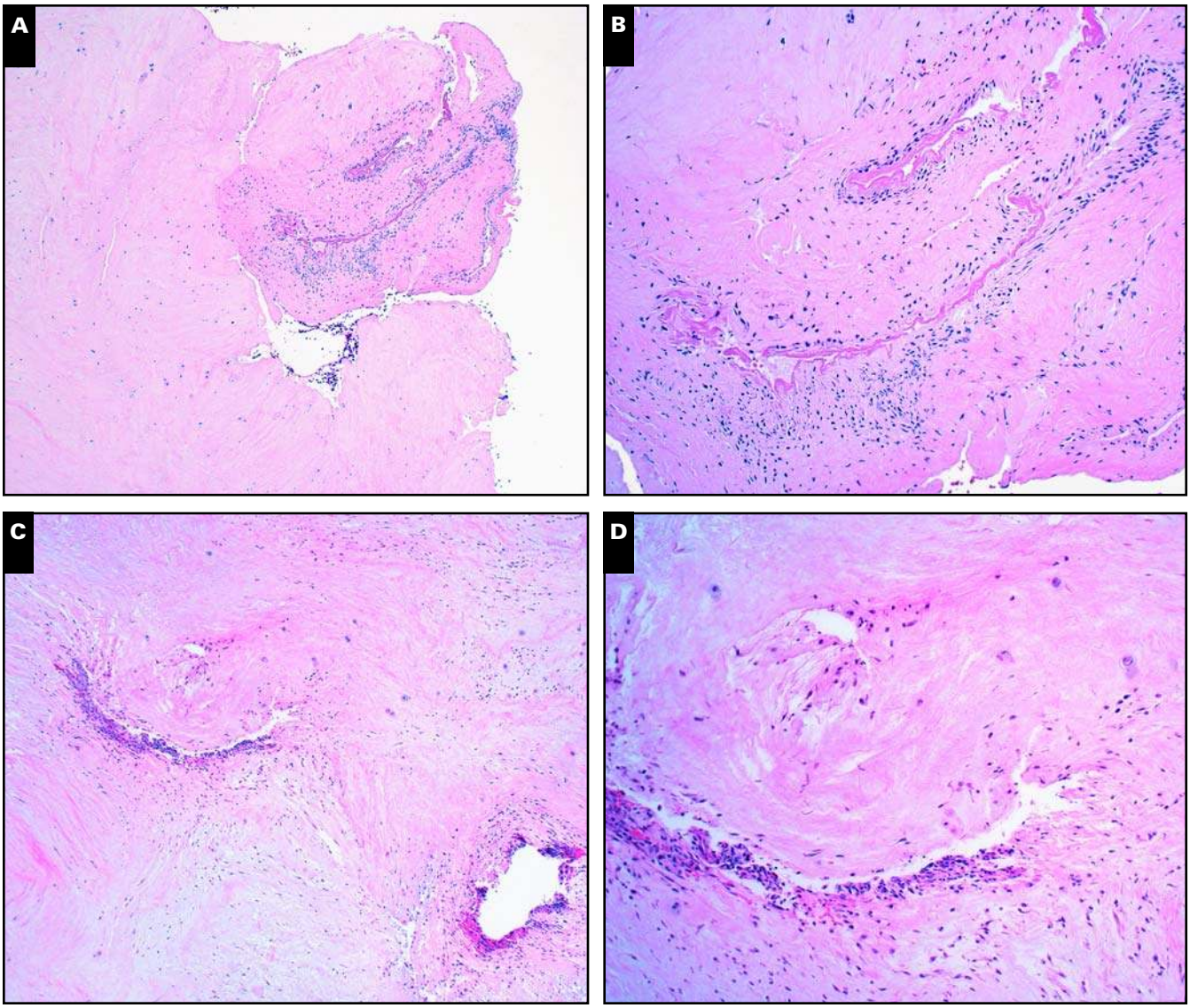

Image 2 Synovial metaplasia. **A**-**H**, Four sets of low- and high-power views of different cases with synovial metaplasia within intervertebral disk tissue (H&E, **A**, **C**, **E**, and **G**, ×4; **B**, **D**, **F**, and **H**, ×10).

synovial cysts and represent cases with degenerative denudation of the lining.[14,21]

In the present study, 52 cases showed synovial tissue, even though no cyst was diagnosed clinically. In 29 cases, the synovial tissue was present within dense connective tissue or yellow ligament. In these cases, it is difficult to exclude an extension of the synovial lining of the facet joints. In 23 cases, these synovial proliferations were embedded within intervertebral disk tissue (Image 2)—a feature not present in any of the clinically confirmed true synovial cysts.

CD44 has been shown to be expressed in synovial membrane–like interface tissue of aseptic hip prostheses failure.[28] In addition, CD44 is known to have a key role in the embryonic development of the cavities of synovial joints.[27] Although CD44 is not a specific synovial marker, it is useful in this context and in conjunction with CD34 staining to distinguish synovium from (neo)vascularization (Image 3).

Previous studies have described neovascularization[7-10] and CD68+ phagocytic cells in degenerative disk tissue.[32] Although vessels and phagocytic cells are part of a synovial membrane, synovial tissue as such has not been reported previously in intervertebral disk tissue. We suggest that the synovial proliferation found in intervertebral disk tissue represents reactive synovial metaplasia. The same could be true for at least some of the synovium found in the yellow ligament and in other spinal connective tissues. In other settings, synovial metaplasia is a well-described phenomenon: It is found with aseptic failure of joint prostheses[28,33]; around various implants, eg, testicular or breast implants[34]; in the skin at the site of old surgical incisions[35]; and in animal models after subcutaneous air injections.[36]

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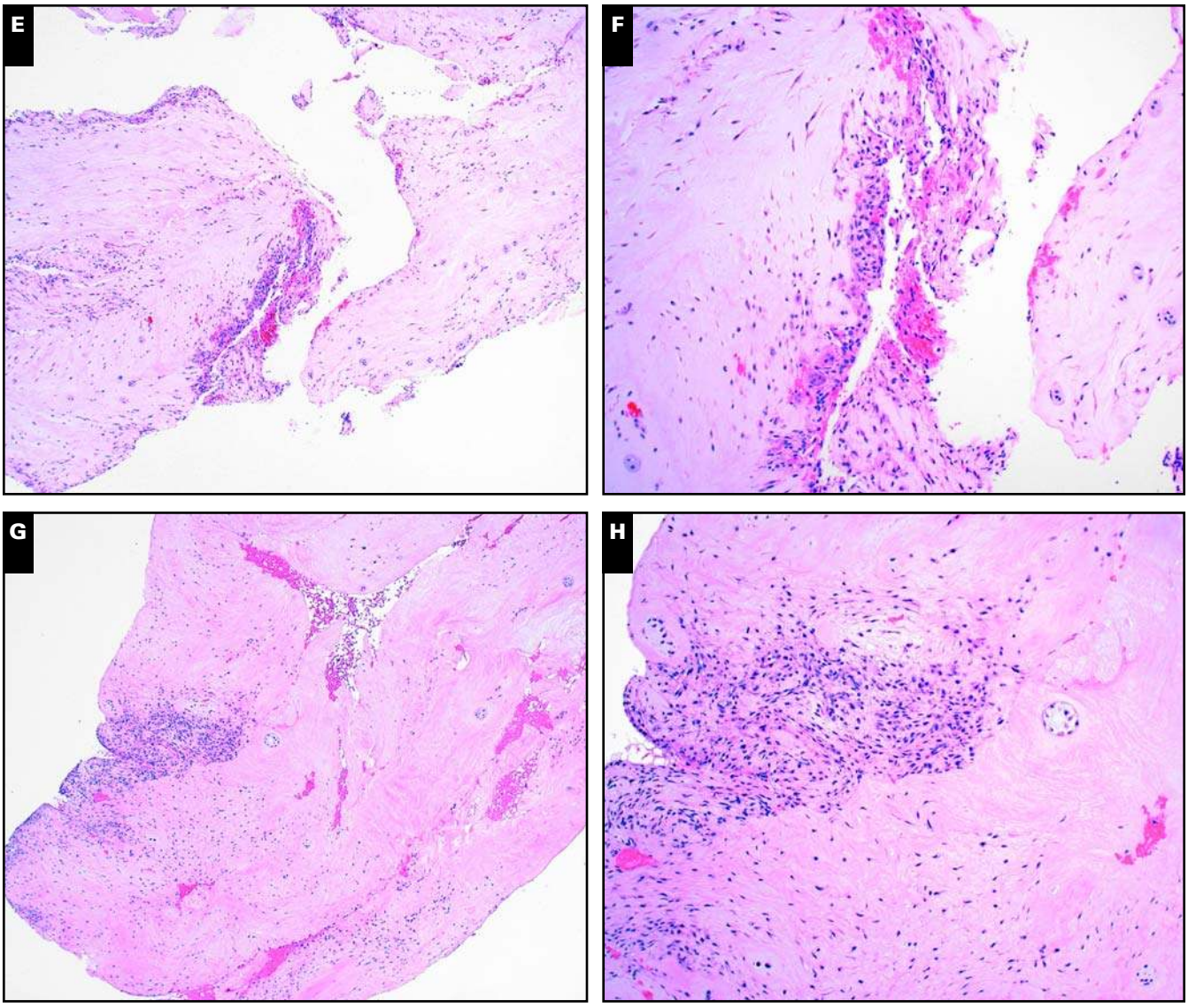

One could speculate that this type of synovial metaplasia develops secondary to abnormal friction or movement between crystal deposits or tissue fragments of a degenerative disk. In the present study, synovial metaplasia was significantly more common in cases with CPPD deposition than in cases without (18% in cases with CPPD vs 5% in cases without CPPD; $P \leq .01$). Chang et al[18] reported a rare case of a synovial cyst in the transverse ligament of the atlas. Treatment solely by immobilization through atlantoaxial fusion resulted in spontaneous regression of the cyst.[18]

This type of newly formed reactive synovium must be distinguished from other pathologic processes. Although this synovial metaplasia usually represents only a microscopic change, it theoretically could give rise to symptomatic synovial lesions such as synovial cysts or other lesions such as synovial-type giant cell tumor of the spine and pigmented villonodular synovitis of the spine.[37,38]

Other Findings

A number of cases showed more than one of the described changes, whereas 665 cases (67.5%) showed none of the histologic changes that were studied. This relatively large number reflects the fact that this study was limited to cell-based changes and did not include abnormalities of the extracellular matrix. In agreement with the findings of previous studies that focused on the cost-benefit analysis of performing histologic analysis on routine diskectomy specimens,[39,40] the present study found no unexpected tumors or infections.

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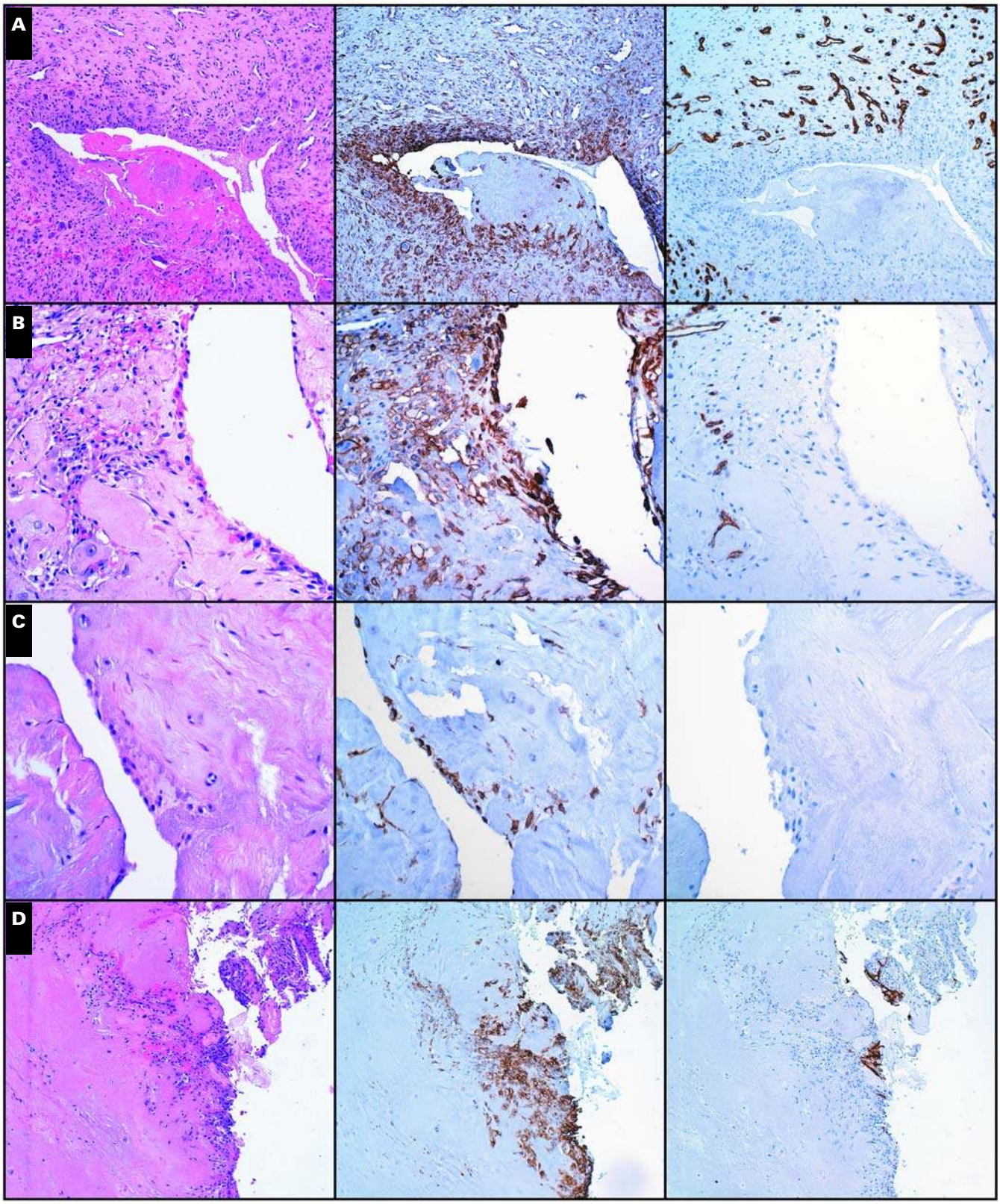

Image 3 Immunohistochemical staining. **A**, H&E, CD44, and CD34 stains on the same area of a case of a synovial cyst (×10). **B**, **C**, and **D**, H&E, CD44, and CD34 stains on the same area of 3 cases of synovial metaplasia in intervertebral disk tissue (**B**, ×20; **C**, ×20; and **D**, ×10).

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Summary

A number of pathologic changes are the morphologic correlate of what is clinically diagnosed as degenerative spine disease. Most of these pathologic findings, such as neovascularization, synovial metaplasia, and chondrocyte clusters, are of little importance to the submitting surgeon whose primary interest is to exclude any unexpected malignancy or inflammatory process. Only CPPD disease outside the disk is of some clinical significance because it often is associated with systemic disease.[24,26]

Mechanical stress, imbalance of nutritional supply and demand of the disk tissue, as well as genetic factors, cause changes in the cellular composition of the disk and its extracellular matrix.[2,6] Cellular changes such as chondrocyte clusters, neovascularization, and synovial metaplasia seem to be a misguided response to injury. By further altering the milieu and the metabolic equilibrium of the normally avascular disk, these cellular changes might lead to disease progression rather than reconstitution. A better understanding of these changes is important for the development of future treatment alternatives to surgical diskectomies. Injections of growth factors and transplantation of mature cells or stem cells are under investigation as possible new therapies.[2,6] Any of these changes in therapy also might redefine the role of the pathologic examination of these specimens.

The present study showed the frequency with which degenerative changes such as chondrocyte clusters and CPPD deposits are found in a large series of routine specimens obtained during extradural spinal surgeries. Based on our findings, we suggest that synovial metaplasia can be seen as a reactive change in degenerative spine disease independent of synovial cysts that are associated with osteoarthritic changes of the facet joints.

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DOI: 10.1309/89FVRT04EGBVEUD9