Galectin-3 Expression is Ubiquitous in Tumors of the Sellar Region, Nervous System, and Mimics

An Immunohistochemical and RT-PCR Study

Fausto J. Rodriguez, MD, Bernd W. Scheithauer, MD,* Federico Roncaroli, MD,† Ana I. Silva, MD,‡ Kalman Kovacs, MD, PhD,§ Daniel J. Brat, MD, PhD,‖ and Long Jin, MD**

Abstract: Galectin-3 expression has been reported in spindle cell oncocytoma, certain pituitary adenoma subtypes, astrocytomas, oligodendrogliomas, and meningiomas. We evaluated galectin-3 protein expression by immunohistochemistry in 201 cases of a variety of nervous system and sellar tumors, as well as mRNA expression by reverse transcription-polymerase chain reaction in formalin-fixed paraffin-embedded tissue in a subset (20 cases). Immunohistochemical results were evaluated in a semiquantitative fashion on a 4-tiered scale (0 to 3). Strong (3+) immunoreactivity was seen in most of the cases (61%), followed by 2+(22%), and 1+(13%) staining. Only 4% of the lesions studied were immunonegative. Galectin-3 mRNA was present in 15 of the 18 cases (83%) in which reverse transcription-polymerase chain reaction was successful. Significant differences in protein expression were noted in the following 2 settings: specific meningioma subtypes ($P = 0.004$, Fisher exact test) wherein clear cell meningioma demonstrated weak protein expression when compared with other meningioma variants. No significant difference was noted with respect to World Health Organization grade. Galectin-3 was also strongly expressed in benign nerve sheath tumors but only moderately expressed in malignant peripheral nerve sheath tumors ($P = 0.0009$, Fisher exact test). Although galectin-3 positivity is a key feature of the immunophenotype of spindle cell oncocytoma, its consistent expression in other morphologically similar tumors (meningioma, pituicytoma, nerve sheath tumors, granular cell tumor, metastases) makes it of little use in the differential diagnosis of sellar region tumors, a setting in which it should be discouraged. Diagnostic uses of this marker may be limited to specific settings, including some meningioma subtypes and nerve sheath tumors.

Key Words: galectin-3, tumor, nervous system, sella, differential diagnosis, immunohistochemistry, RT-PCR

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From the *Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; †Hammersmith Hospital, Imperial College, London, England; ‡Hospital Sao Marcos, Braga, Portugal; §St Michael's Hospital, Toronto, Ontario, Canada; and ‖Department of Pathology, Emory University, Atlanta, GA.

Reprints: Fausto J. Rodriguez, MD, Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905 (e-mail: rodriguez.fausto@mayo.edu).

Galectin-3 is a β-galactoside binding protein recently found to be expressed in a variety of endocrine tumors, including papillary thyroid carcinoma[33] and adenohypophyseal cell tumors,[24,32] in particular prolactin and adrenocorticotropic hormone (ACTH) producing adenomas and carcinomas. This has engendered interest in the role of this molecule in the development and progression of endocrine tumors. The immunoexpression of galectin-3 as an aid in diagnosis and tumor grading has also been studied in meningiomas[7,12,13] and in localized and infiltrative gliomas.[4,8,20,30]

Among sellar lesions, spindle cell oncocytoma (SCO) is a recently described tumor thought to originate from folliculostellate cells[25] on the basis of uniform galectin-3, epithelial membrane antigen (EMA), and S-100 protein immunoreactivity and on the negativity for other markers, including pituitary hormones, glial fibrillary acidic protein, and synaptophysin. The differential diagnosis of SCO is varied. Indeed, a variety of primary and metastatic tumors may mimic it. As a result, galectin-3 expression in this considerable spectrum and its mimics deserves attention.

The goal of this study was 2-fold: first, to evaluate galectin-3 expression and its role in the differential diagnosis of primary and secondary, nonendocrine tumors affecting the central and peripheral nervous system, including some rare entities; second, to explore the diagnostic utility of this marker in the sellar region, specifically in morphologic mimics of SCO. Galectin-3 expression in endocrine tumors of the sellar region has been addressed elsewhere.[14,24–27]

MATERIALS AND METHODS

The files of Mayo Clinic Tissue Registry (Rochester, MN) and Charing Cross Hospital (Imperial College, London, England) were searched for representative primary and metastatic tumors of the nervous system and sellar region, as well as neoplasms included in the differential diagnosis of SCO. Histologic types and locations of the lesions are summarized in Table 1.

Immunohistochemistry

Immunostains were performed in all 201 cases using a monoclonal antibody directed against galectin-3

TABLE 1. Galectin-3 Immunoreactivity by Tumor Type

	Immunohistochemical Score N (%)			
Histology	**0**	**1**	**2**	**3**
Meningiomas				
Fibrous	—	—	—	6
Meningothelial	—	—	3	7
Transitional	—	—	2	1
Clear cell	—	4	1	1
Secretory	—	1	—	1
Angiomatous	—	—	—	1
Microcystic	—	—	1	1
Papillary/rhabdoid	—	1	1	—
Chordoid	—	—	—	1
Subtotal		6 (18%)	8 (24%)	19 (58%)
Reactivity by WHO Grade I	—	1	4	9
Grade II	—	4	3	6
Grade III	—	1	1	4
Nerve sheath tumor				
Schwannoma conventional	—	—	2	5
Cellular	—	—	—	8
MPNST	—	1	5	2
Conventional neurofibroma	—	—	—	7
Atypical neurofibroma	—	—	—	1
Cellular neurofibroma	—	—	—	1
Subtotal		1 (3%)	7 (22%)	24 (75%)
Sarcomas				
Synovial sarcoma (sellar)				1 (epithelial element; score of 2+ in spindle element)
Synovial sarcoma (soft tissue)		1	1	
Metastatic leiomyosarcoma to brain		1		
Leiomyosarcoma (soft tissue)	1	3		
Fibrosarcoma (brain)			1	
Fibrosarcoma (soft tissue)			2	1
Pleomorphic spindle cell sarcoma (brain)				2
Pleomorphic spindle cell sarcoma (soft tissue)		1		2
Metastatic myxoid chondrosarcoma to brain				1
Subtotal	1 (6%)	6 (33%)	5 (28%)	7 (39%)
Hemangiopericytoma of dura				
Grade II		1		1
Grade III	2		2	1
Solitary fibrous tumor				
High-grade malignant				1
Benign/low-grade malignant		3		
Subtotal	2 (18%)	4 (36%)	2 (18%)	3 (28%)
Metastatic nonsmall cell carcinoma				
Lung			1	5
Prostate	1			
Breast				4
Gynecologic			2	
Renal cell				1
NOS			1	4
Subtotal	1 (5%)		4 (21%)	14 (74%)
Choroid Plexus Tumors				
Papilloma		1	2	1
Atypical papilloma		1		
Carcinoma	1	2		
Subtotal	1 (13%)	4 (50%)	2 (25%)	1 (13%)
Melanoma involving the CNS		1 (11%)	1 (11%)	7 (78%)
Ependymoma				
WHO Grade II	—	2	1	1
WHO Grade III	1	—	—	2
Subtotal	1 (14%)	2 (29%)	1 (14%)	3 (43%)
Granular cell tumor of pituitary				4 (100%)
Pituicytoma			1 (25%)	3 (75%)
Other				
Pilocytic astrocytoma			3	5
Pilomyxoid astrocytoma				3
PXA			1	4
SEGA				4

TABLE 1. (*continued*)

	Immunohistochemical Score N (%)			
Histology	**0**	**1**	**2**	**3**
Chordoid glioma		2	2	2
Ganglioglioma				5
DIG			2	
Gliosarcoma			3	2
Glioblastoma	1		2	6
Langerhans cell histiocytosis	1	1	—	2
Chordoma				5
Total	8 (4%)	27 (13%)	43 (22%)	123 (61%)

CNS indicates central nervous system; DIG, desmoplastic infantile ganglioglioma; MPNST, malignant peripheral nerve sheath tumor; NOS, not otherwise specified; PXA, pleomorphic xanthoastrocytoma; SEGA, subependymal giant cell astrocytoma; WHO, World Health Organization.

(Novocastra, Burlingame, CA; clone 9C4, dilution 1:50). Five-micron sections from representative blocks were deparaffinized in xylene and dehydrated in serial alcohols. Pretreatment was performed in 1-mM ethylenediamine tetra-acetate solution, pH 8.0, at 98°C for 30 minutes. This was followed by peroxidase block and incubation with the primary antibody for 30 minutes, and 20 minutes in the Envision + Dual Link detection system on a Dako autostainer. Diaminobenzidine served as the chromogen. Semiquantitative scoring of the reaction was performed by 2 observers (F.J.R. and B.W.S.) on a 4-tiered scale (0 = absent, 1 = weak staining intensity to moderate staining in < 10% of cells, 2 = moderate staining in less than 50% of cells, 3 = moderate-to-strong intensity staining in greater than 50% of cells).

Reverse Transcription-Polymerase Chain Reaction

We also performed reverse transcription-polymerase chain reaction (RT-PCR) to confirm expression of galectin-3 mRNA and see if it correlated with detection of the protein by immunohistochemistry. Total RNA was extracted from formalin-fixed paraffin-embedded tissue sections and used for RT-PCR in a subset of cases (n = 20) for which adequate material was available from the same block used for immunohistochemical analyses. Only blocks composed almost entirely (> 95%) of tumor cells were included. The RNA concentration was measured with a NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies Inc, Wilmington, DE). Total RNA (400 ng) was used for reverse transcription in a 20 uL of total volume, using reagents from the Strata-Script First-Strand Synthesis System kit (Stratagene, La Jolla, CA) following the manufacturer's instructions. PCR primers used for galectin-3 transcription included: 5′-CAA CTG CCA CCG GAG CCT A (forward) and 5′-CTG TTT GCA TTG GGC TTC ACC (reverse), the PCR product size being 148 base pairs (GenBank access no.: NM_000291). Phosphoglycerate kinase served as a loading gel control (189-bp product size). Amplification was performed in a 25-uL final reaction volume containing 2 uL of RT product as template DNA, 1x PCR buffer, 2.5-mM $MgCl_2$ 0.2 mM of each deoxynucleotide, 0.3 uM of forward and reverse primers, and 1.0 U of Taq DNA polymerase (Invitrogen, Carlsbad, CA). Programmable temperature cycling (GeneAmp PCR System 9700 thermal cycler, PE Applied Biosystems, Foster City, CA) was performed using the following schedule: initial denaturation at 95°C, for 2 minutes, followed by 40 cycles of denaturation at 94°C for 30 seconds, annealing at 55°C for 30 seconds, extension at 72°C for 1 minute, and final extension at 72°C for 10 minutes. Formalin-fixed paraffin-embedded tissue sections from a papillary thyroid carcinoma served as a positive control, and omission of reverse transcriptase in the RT reaction as a negative control.

Statistics

Statistical analyses were performed using contingency tables and the Fisher exact test for comparing proportions. *P* value less than 0.05 was considered statistically significant.

RESULTS

Immunohistochemistry

Results of immunohistochemical scoring are summarized by tumor type in Table 1, representative illustrations being shown in Figures 1 to 3. Reactivity was generally cytoplasmic and sometimes nuclear, especially in the tumors showing strong galectin-3 expression. In summary, strong (3 +) immunoreactivity was noted in most of the specimens (61%), followed by 2 + (22%), and 1 + (13%). Only 4% of the cases were immunonegative, including 2 hemangiopericytomas of the dura, and 1 each metastatic carcinoma of the prostate, choroid plexus carcinoma, grade III ependymoma, glioblastoma, leiomyosarcoma, and Langerhans cell histiocytosis. Mimics of SCO, including granular cell tumor and pituicytoma were strongly immunoreactive (100% and 75% of cases, respectively). Other tumors demonstrating 3 + immunoreactivity included melanoma (78%), nerve sheath tumors (75%), metastatic nonsmall cell carcinoma (74%), and meningiomas (58%) (Table 1). Sarcomas showed variable

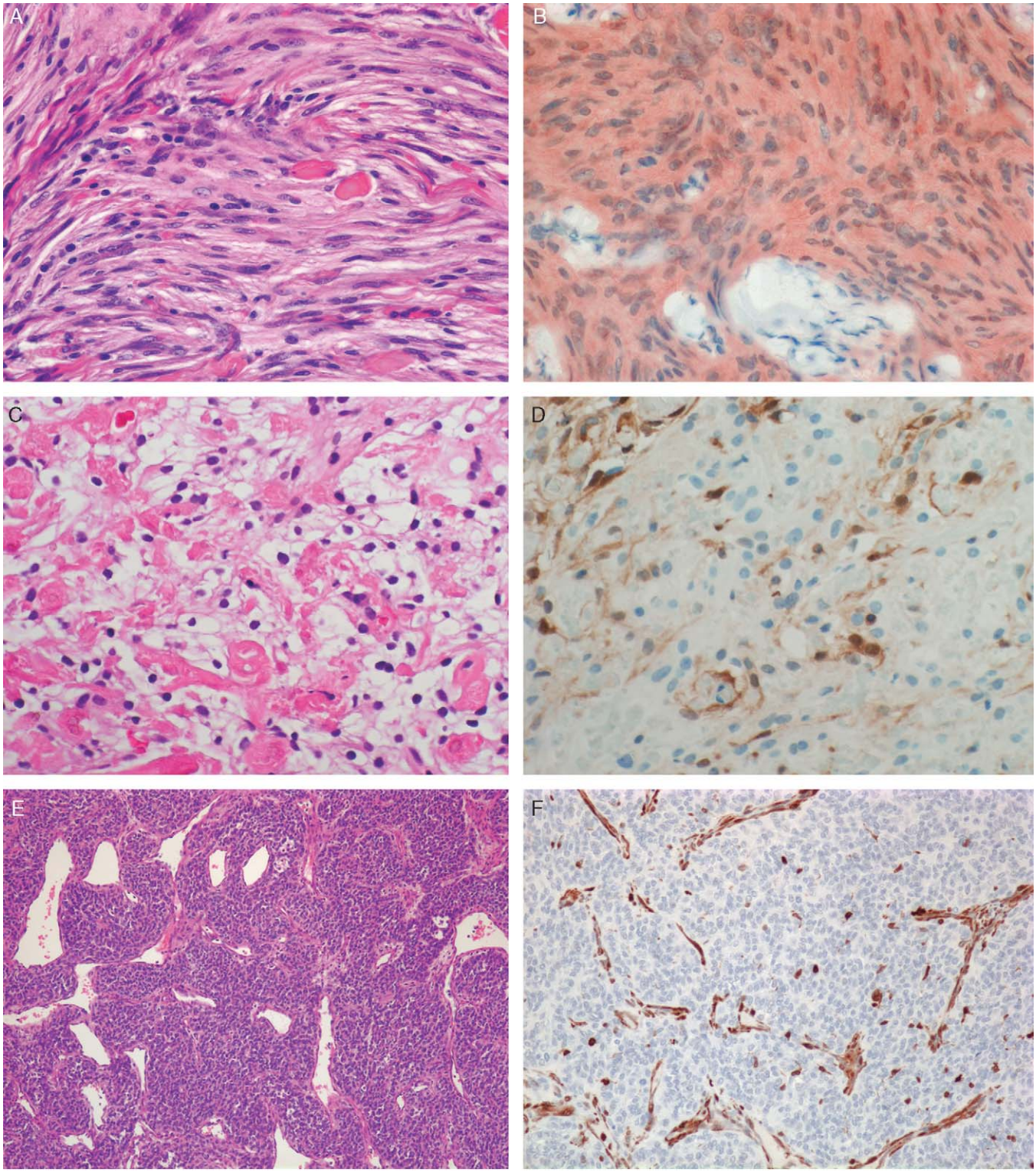

FIGURE 1. Galectin-3 immunoreactivity in dura-based neoplasms. All cases of fibrous meningioma (A) demonstrated strong diffuse immunoreactivity (B). Conversely, clear cell meningiomas (C) showed limited staining of a minority of tumor cells and vessels (D). One example of hemangiopericytoma, characterized by dense cellularity and branching vessels, (E) showing no immunostaining for galectin-3. The conspicuous vascularity was a useful internal positive control (F).

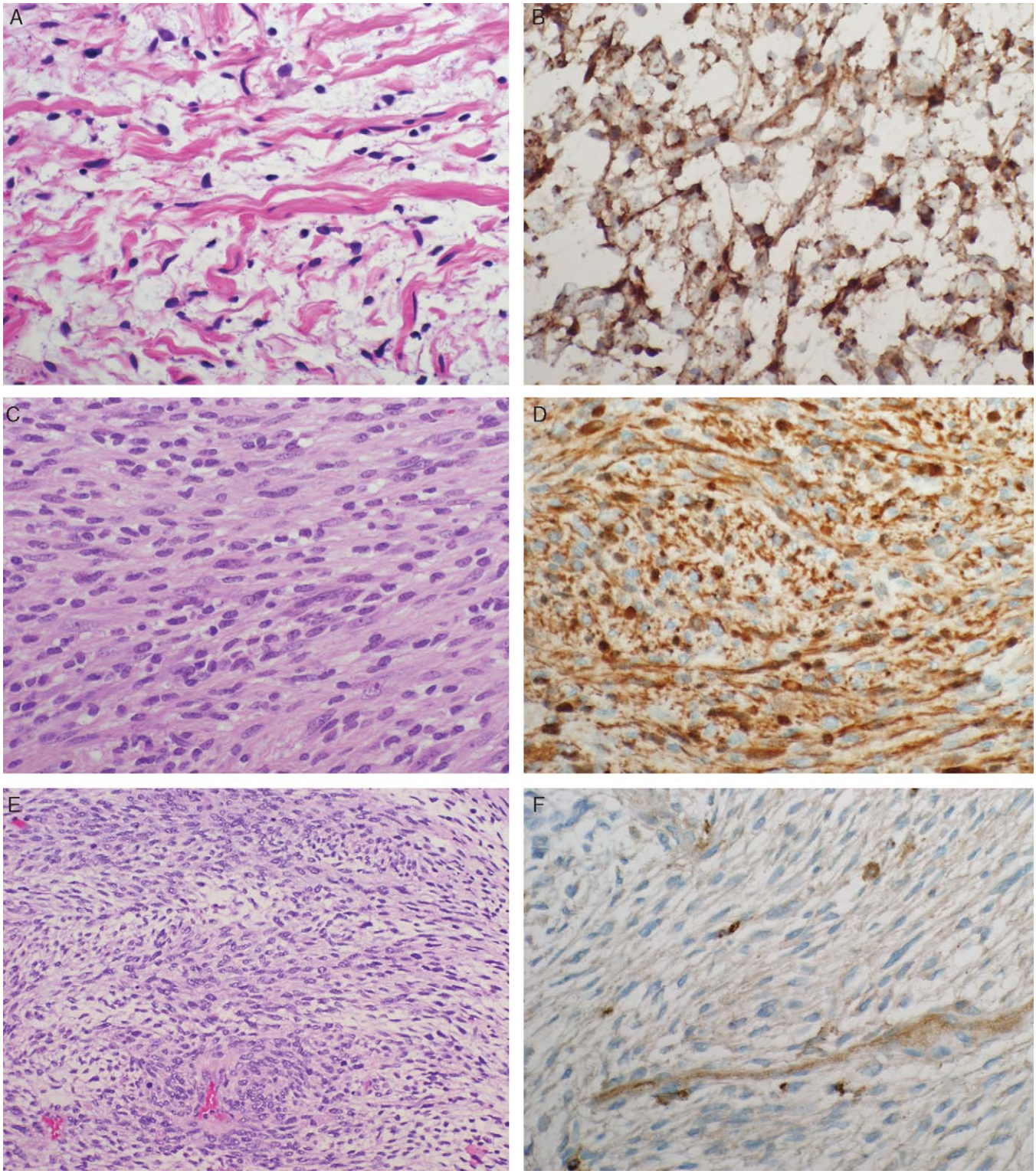

FIGURE 2. Galectin-3 immunoreactivity in nerve sheath tumors. Neurofibroma with its benign, wavy nuclei and delicate collagenous matrix (A) showing diffuse immunoreactivity (B). All cellular schwannomas (C) were similarly positive (D). Malignant peripheral nerve sheath tumors (E) in general demonstrated weaker staining than the benign tumors (F).

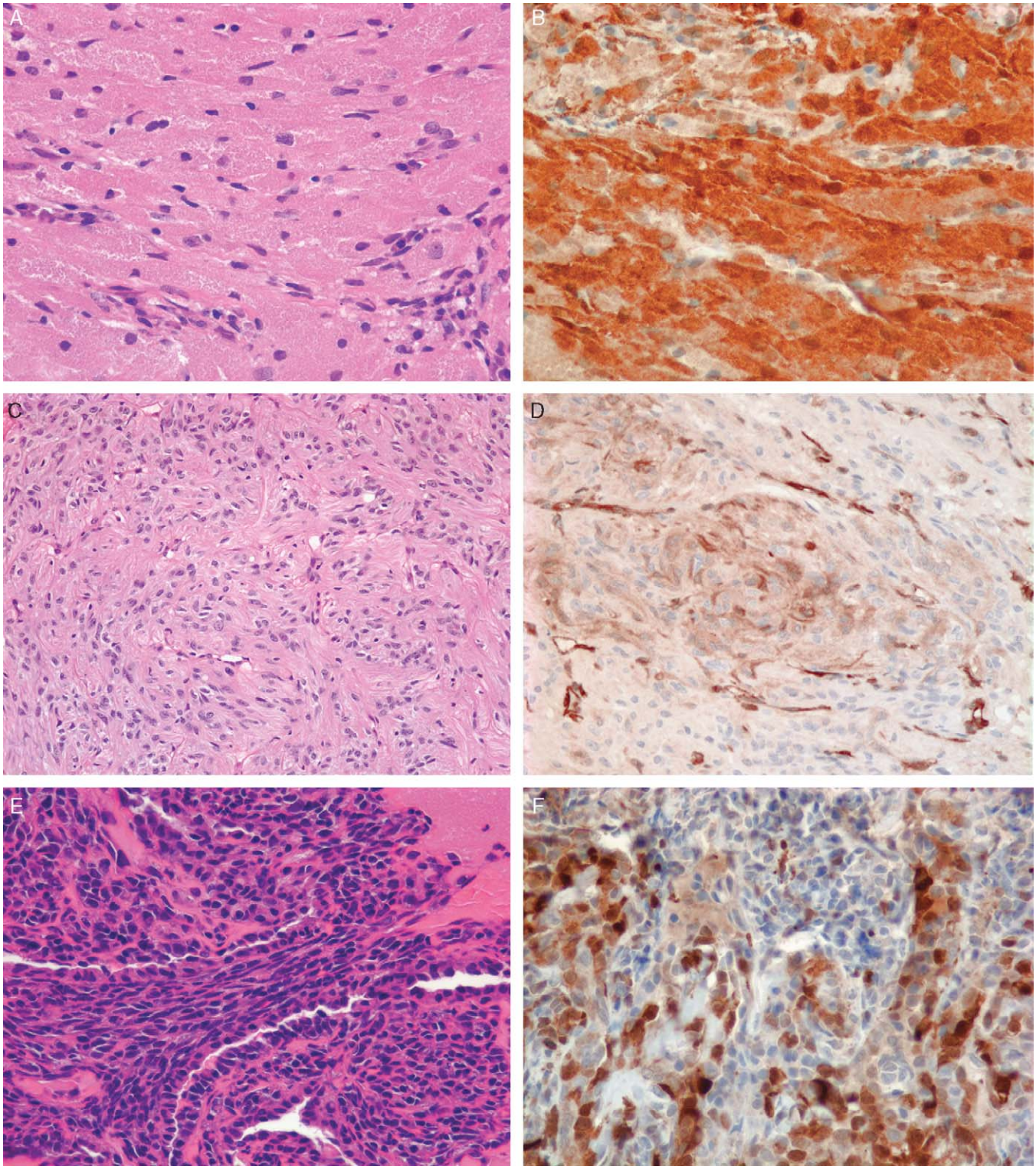

FIGURE 3. Galectin-3 immunoreactivity in the differential diagnosis of spindle cell oncocytoma. All granular cell tumors (A) were diffusely and strongly immunoreactive (B). The majority of pituicytomas were also strongly immunoreactive (C), although 1 tumor showed only moderate staining (D). One rare example of primary synovial sarcoma of the sellar region showing characteristic, biphasic morphology (E) and staining of both components, immunoreactivity being stronger in the glandular than in spindle cells (F).

immunoreactivity, but with an overall lower frequency of 3+ staining (39%). Although all leiomyosarcomas tested showed 0 to 1+ immunoreactivity, this divergence did not reach statistical significance when compared with other sarcomas ($P = 0.07$).

Meningiomas demonstrated differences in immunoreactivity among its subtypes ($P = 0.004$, Fisher exact test). Weak immunoreactivity (1+) was limited to clear cell (4 of 6 cases), secretory (1 of 2), and papillary/rhabdoid types (1 of 2). In the category of nerve sheath tumors, 6 of 8 malignant examples demonstrated 1–2+ immunoreactivity versus 2 of 24 benign nerve sheath tumors ($P = 0.0009$); the remaining tumors demonstrated 3+ reactivity. When comparing chordomas versus chordoid gliomas, all chordomas (5 of 5) demonstrated 3+ staining compared with similar reactivity in 2 of 6 chordoid gliomas ($P = 0.046$). In the choroid plexus, tumor group 3 of 3 carcinomas and a single atypical papilloma showed absent to 1+ immunoreactivity as compared with 2-3+ staining in 3 of 4 papillomas; this difference showed only a trend toward statistical significance ($P = 0.07$).

RT-PCR

The results of RT-PCR studies are illustrated in Figure 4. Only 2 failures were encountered based on an absent or weak band for phosphoglycerate kinase (results not shown). Positive and negative controls reacted appropriately. Galectin-3 mRNA was identified in 15 (83%) of the 18 cases tested; the majority demonstrated variable immunoreactivity, including 3+ (n = 8), 2+ (n = 2), and 1+ (n = 4). One each of metastatic melanoma, ependymoma, and hemangiopericytoma were negative. The hemangiopericytoma and melanoma samples negative by RT-PCR were, nonetheless, immunopositive for galectin-3, reactivity in the melanoma being patchy and not present in all fields. In a third case, another hemangiopericytoma, galectin-3 mRNA was identified by RT-PCR, but not by immunohistochemistry despite an adequate internal vessel-positive control. The single grade III ependymoma negative for galectin-3 mRNA by RT-PCR was also immunonegative for the protein.

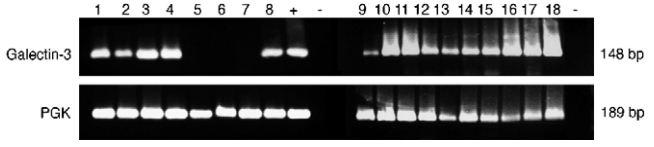

FIGURE 4. Galectin-3 mRNA is ubiquitously expressed in nervous system tumors and in mimics of SCO as demonstrated by reverse transcription-polymerase chain reaction. A 2% agarose gel stained with ethidium bromide and viewed under ultraviolet light demonstrates a galectin-3, 148-bp product in most tumors tested (top lane). Phosphoglycerate kinase served as a loading control (bottom lane). Case numbers correspond to the following tumor types: 1–meningothelial meningioma, 2–hemangiopericytoma, 3–schwannoma, 4–fibrous meningioma, 5–anaplastic ependymoma, 6–hemangiopericytoma, 7–metastatic melanoma, 8–schwannoma, 9–leiomyosarcoma, 10–neurofibroma, 11–subependymal giant cell astrocytoma, 12–solitary fibrous tumor, 13–gliosarcoma, 14–leiomyosarcoma, 15–gliosarcoma, 16–malignant peripheral nerve sheath tumor, 17–metastatic carcinoma, 18–chordoma. A papillary thyroid carcinoma was used as positive control (+), and omission of reverse transcriptase was used as negative control (−). Two cases represented reverse transcription-polymerase chain reaction failures owing to an absent/weak phosphoglycerate kinase band (not shown).

DISCUSSION

Galectins are a sizable family of lectin proteins that bind β-galactoside sugars.[1,22] Galectin-3 has been identified in a variety of mammals, including humans, dogs, rats, and mice. Weighing 31 kd,[19] it features a carbohydrate binding domain, a short N-terminal domain, and a proline, glycine, and tyrosine-rich domain. Galectin-3 is involved in a variety of basic cell processes, including growth, adhesion, differentiation, and regulation of apoptosis. Furthermore, it seems to play a role in tumor progression.[24,35]

In the past decade, there has been increasing interest in the role of galectin-3 in human neoplasia. High levels of expression of this molecule have been observed in a variety of tumors, including colon,[5] lung,[18] salivary gland,[31,34] thyroid,[9,33] and uterus.[28] In the pituitary, galectin-3 has been found to be expressed in normal prolactin, ACTH, and folliculostellate cells.[24] In pituitary neoplasms, galectin-3 is expressed in endocrinologically functioning prolactin and ACTH adenomas, but not in others.[14,24] Higher levels of expression have been also identified in prolactin and ACTH carcinomas.[24,27] What follows is a discussion of findings in various other tumor groups.

Gliomas

Galectin-3 is expressed in a variety of cell types within the nervous system, including neurons of dorsal root ganglion neurons, microglial cells, and macrophages in reactive processes.[10] There have been several reports of galectin-3 expression in tumors of the central nervous system, both primary and metastatic.[4] These include diffusely infiltrative gliomas,[4,6,8,10,20,30] in which some authors have reported an association between its expression and increasing World Health Organization (WHO) grade in astrocytic tumors.[4] Yet other authors have found that galactin-3 expression varies among different clones of a given tumor[10] and may also be expressed by non-neoplastic components within the tumor, including macrophages, microglia, and endothelial cells.[30] Galectin-3 expression has also been reported in glioma cell lines.[17] Other investigators have explored galectin-3 expression in glioma invasion, where the biology of this molecule may be more complex and not completely understood. For example, galectin-3 may be cleaved by several metalloproteinases[19,21] and the secreted form and/or cleaved products may partially account for invasive behavior in cell lines.[19]

SCO

The SCO is a recently described, unique tumor of the sellar region characterized by immunopositivity for S-100 protein, EMA, vimentin, and galectin-3.[25] Its behavior resembles that of WHO grade I meningiomas and is generally favorable. Recurrence has been documented in 1 bona fide example, that being case 1 in the series of Kloub et al.[16] The differential diagnosis of SCO includes a variety of tumors featuring spindle and epithelioid cells, ones either primary in the sellar region or involving it by direct extension or metastasis. These include meningioma, especially of the fibrous type, hemangiopericytoma, pituicytoma, schwannoma, solitary fibrous tumor, astrocytomas, melanoma, carcinoma, and sarcoma. Although relative absence of marked cytologic malignancy should aid in the distinction of SCO from most metastatic tumors, SCO may show considerable, often focal cellular and nuclear pleomorphism,[25,29] a feature of unknown significance.

It is of note that galectin-3 immunoreactivity has been described in tumors mimicking SCO. For example, Das and colleagues[7] found immunoreactivity in the majority of meningiomas; all their examples of the transitional subtype showing moderate to strong staining. Interestingly, our current study revealed strong, diffuse galectin-3 immunoreactivity in a wide variety of tumors in the differential diagnosis of SCO, including all granular cell tumors, most pituicytomas and all fibrous meningiomas. Even Langerhans cell histiocytosis was strongly immunoreactive in 2 of 4 cases tested.

Pituicytoma in particular is an important tumor in the differential diagnosis with SCO, given its spindle cell morphology and S-100 immunoreactivity. Although this tumor is presumably glial in origin, glial fibrillary acidic protein immunoreactivity may be weak or entirely absent.[3] However, EMA is generally negative, and ultrastructurally, the tumor lacks conspicuous mitochondrial accumulation unlike SCO. Galectin-3, as confirmed by our current study, may be expressed by this tumor and should not be used to distinguish it from SCO. As it is true of most challenging differential diagnoses in surgical pathology, a judicious panel of immunostains is of optimal benefit.

Meningiomas

It is of interest that previous authors explored a possible association between low-level galectin-3 expression and histologic atypia in meningiomas. Hancq et al[13] described strong expression of galectin-3 binding ligands in 64% of benign (WHO grade I) meningiomas, but found it only in 29% of atypical (grade II) examples. However, they found no difference in galectin-3 staining in reactive tumors within the 2 groups. The same was true of reactivity in another study of recurrent versus nonrecurrent WHO grade I meningiomas.[12] Das and colleagues[7] also found moderate-to-strong galectin-3 immunoreactivity in 90% of WHO grade I meningiomas, full 100% of the transitional subtype being positive. Our study reinforces these findings, as there was no statistically significant difference in galectin-3 immunoreactivity by WHO grade. Nonetheless, clear cell meningiomas showed weaker expression than other histologic variants or the group as a whole.

Nerve Sheath Tumors

Also of interest is our finding of consistent galectin-3 immunoreactivity in all nerve sheath tumors and galectin-3 mRNA expression in 4 of the 4 examples tested. Similar findings were reported in the study of Bigotti et al,[2] who found strong immunoreactivity in all nerve sheath tumors tested, benign and malignant. Galectin-3 staining was also found in non-neoplastic Schwann cells in a peripheral nerve injury model.[23] Of note, in our study was the finding of decreased immunoexpression in malignant peripheral nerve sheath tumors as compared with the benign nerve sheath tumors, the difference being statistically significant and perhaps useful in differential diagnosis.

Sarcomas

In the present study, we found variable galectin-3 staining in sarcomas, there being only a trend toward weaker staining in leiomyosarcomas. Bigotti and colleagues,[2] in a study of galectin-3 expression in soft tissue tumors and pseudotumors similarly showed that most lesions express the marker, although smooth and skeletal muscle tumors do so to a lesser extent. Conversely, Schwartz et al[28] in a study of smooth muscle tumors of the uterus demonstrated an increase in galectin-3 expression and binding sites in the malignant subgroup. Lastly, our study of chordomas demonstrated strong diffuse expression in all cases. Similar findings were previously reported.[11,15] Interestingly, galectin-3 expression in the developing notochord, remnants of which are presumed to give rise to chordomas, increases with advanced gestational age.[11]

SUMMARY

Our study demonstrated that galectin-3 was identifiable by immunohistochemistry in a wide variety of tumors of the sellar region and nervous system, including ones that enter in the differential diagnosis of SCO. In addition, galectin-3 mRNA was identified in most of the cases tested, although discordant immunohistochemistry and mRNA expression results were observed in 3 cases out of the 18 tested. Prior studies have also generally shown good correlation between galectin-3 protein and mRNA expression, although the concordance is not necessarily perfect.[9] The reason for minor discrepancies may be multifactorial. For example, 1 melanoma case was negative by RT-PCR and although it showed immunopositivity for galectin-3, the latter was patchy, many microscopic fields lacking its expression. Therefore, the discrepant results may be explained in part by tumor heterogeneity. In addition, our study used a monoclonal antibody directed against galectin-3, thus differences in the sequences recognized by the RT-PCR primers and the

protein epitope demonstrated by the antigalectin-3 antibody may be an alternative explanation.

In conclusion, moderate-to-strong expression of galectin-3 is seen in a variety of tumor types, both in the central and peripheral nervous system, and also in the sellar region. Although this marker is of potential use in the differential diagnosis of tumor groups and is a requisite to the diagnosis of SCO, we discourage its use in differential diagnosis of morphologically similar tumors, and recommend instead an immunohistochemical panel in combination with a careful morphologic assessment.

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