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Original Research Article.

The Role of Calretinin and S100 Protein Tumor Markers in Differentiating Between Schwanomma and Neurofibroma

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ABSTRACT

Aim: To determine the diagnostic value of calretinin in differentiating between neurofibroma and schwannomas.

Materials and Methods: Sixty eight paraffin blocks consist of schwannomas (28 cases) and neurofibromas (40 cases), were selected, deparaffinized, rehydrated, and put out with hydrogen peroxide. Antigen retrieval was done. The slides were put down in an autostainer (DAKO) and stained with antibodies to S- 100 protein and calretinin. Immunoreactivity was detected using DAKO EnVision methods.

Results: Twenty-six cases (93%) of schwannoma cases displayed a moderate to strong intensity of staining with calretinin. While only 2 (5%) of 40 cases of neurofibroma were immunohistochemically positive for calretinin. All 28 cases of schwannoma (100%) were positive for S-100 protein. All 40 cases of neurofibroma also were positive for S-100 protein, with moderate to strong intensity in more than 75% of cells in 60% of cases.

Conclusion: Calretinin can be used in addition to S100 protein to differentiate between schwannoma and neurofibroma.

Keywords: Schwanomma, Neurofibroma, S100 Protein, Calretinin.

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INTRODUCTION

Schwannomas and neurofibromas are the two most common types of benign neoplasms that are derived from the peripheral nerves.[1] Schwannoma, is associated with somatic and germline mutations in NF2, mainly composed of Schwann cells.[2] Schwannomas has biphasic architecture composed of organized cellular areas that often display nuclear palisading (Antoni A area) and paucicellular areas (Antoni B area).[1,3]

Neurofibromas are of three main types, the most common one is the localized type, the other two types are the diffuse, and plexiform type. The majority of neurofibromas occur sporadically (90%) and have an extremely low risk of malignant transformation, however, the plexiform type is pathognomonic for neurofibromatosis type 1 (NF 1) and it carries a high risk of malignant transformation.[4] Neurofibromas represent a mixed population of cells, with a predominance of Schwann cells combined with perineurial-like cells and fibroblasts.[3]

In general, schwannomas and neurofibromas are not difficult to differentiate by standard light microscopy, however, there may be considerable morphologic overlap between them in few cases. Nuclear palisading is not present in all schwannomas, making some lesions potentially difficult to separate from cellular neurofibromas. Furthermore, schwannomas consisting exclusively of Antoni B areas are sparsely cellular and myxomatous and might mimic the histologic appearance of neurofibromas.

Making the distinction between schwannomas and neurofibromas is very important for a surgeon to be able to determine the choice of operative procedure during intervention.

In addition, neurofibromas show a small, but non-negligible potential for malignant transformation and they are associated substantially more often with von Recklinghausen disease or neurofibromatosis type 1 (NF-1) than schwannomas.[5,6] Immunohistochemical staining for S-100 protein has been used as an adjuvant marker in the differential diagnosis of schwannoma and neurofibroma.[7] Calretinin, is a calcium-binding protein linked to the same protein family of S-100.[8] is mainly expressed in cells of the central and peripheral nervous systems.[9,10]

In the present study, we evaluated and compared the expression of calretinin with that of S-100 to determine the diagnostic value of calretinin in differentiating between neurofibroma and schwannomas.

MATERIALS AND METHODS

In this retrospective study, formalin-fixed, paraffin-embedded tissue blocks of schwannomas (28 cases) and neurofibromas (40 cases), were selected from the surgical pathology archives of Specialized surgical hospital in medical city. All the selected sections were deparaffinized, rehydrated, and put out with hydrogen peroxide. Antigen retrieval was carried out through the following steps: for calretinin and S-100 stains, slides were incubated with DAKO Epitope Buffer (DAKO, Carpinteria, CA) in a steam bath at 95°C for 45 minutes. After equalization in phosphate-buffered saline for 15 minutes, the slides were put down in an autostainer (DAKO) and stained with antibodies to S-100 protein (polyclonal, 1:4,000 dilution; DAKO), calretinin (polyclonal, 1:50 dilution; Zymed, San Francisco, CA). Immunoreactivity was detected using DAKO EnVision methods (DAKO) according to manufacturer-recommended procedures. For negative control experiments, slides were treated with the same procedure, including antigen retrieval, except for replacement of primary antibodies with a negative diluent (Zymed). Evaluating the immunoreaction intensity was done by labeling (–, 1+, 2+, and 3+) and percentage of cells stained (<25%; 25%-75%, and >75%).

Table 1: Neoplastic Cells Stained in present study

Percentage of Neoplastic Cells Stained	Calretinin	S-100
Schwannoma	**26/28 (93%)**	**28/28 (100%)**
<25	4/26 (15.4%)	0/28 (0%)
25-75	18/26 (69.2%)	0/28 (0%)
>75	4/26 (15.4%)	28/28 (100%)
Neurofibroma	**2/40 (5%)**	**40/40 (100%)**
<25	2/2 (100%)	0/40 (0%)
25-75	0/2 (0%)	16/40 (40%)
>75	0/2 (0%)	24/40 (60%)

RESULTS

We studied 28 cases of Schwanomma and 40 cases of neurofibroma, as shown in table 1, 26 cases (93%) of 28 cases of schwannoma displayed a moderate to strong intensity of staining (2+,3+) with calretinin ,of the 26 cases, 4 cases (15.4%) had less than 25% of the tumor cells stained, 18 (69.2%) had 25% to 75% of tumor cells stained, and 4 (15.4%) had more than 75% of tumor cells stained. Both cytoplasmic and nuclear stains for calretinin were noted.

In contrast with schwannomas, only 2 (5%) of 40 cases of neurofibroma were immunohistochemically positive for calretinin, the 2 labeled cases each displayed 1+ to 2+ staining in fewer than 25% of neoplastic cells.

All 28 cases of schwannoma (100%) were positive for S-100 protein. In all cases, staining was detected in more than 75% of cells, and 27 of 28 cases showed strong intensity (3+). All 40 cases of neurofibroma also were positive for S-100 protein, with moderate to strong intensity (2+ to 3+) in more than 75% of cells in 24 cases (60%) and in 25% to 75% of cells in 16 cases (40%).

DISCUSSION

Neurofibromas and Schwannomas both are originated from the peripheral nerves.[1,11,12] Schwannomas composed mainly of Schwann cells, while neurofibromas consist of different cells , including Schwann cells, perineurial-like cells and endoneurial fibroblasts.[1,3] Schwannomas usually appear as well-encapsulated, firm masses, tan in color with a varying degree of yellow coloration, and their growth within the nerve is eccentric, In contrast to schwannomas, neurofibromas manifest a mixed population of cells, with the prevalence of Schwann cells admixed with perineurial-like cells, fibroblasts, interspersed non-neoplastic nerve fibers, collagen fibers and a myxoid background. Grossly, they are glistening and grayish, they vary in consistency from gelatinous to firm and the secondary degenerative changes common to schwannomas are absent.[3,12-14] Calretinin is a calcium-binding protein connected to the family of EF-hand proteins that comprise S-100 protein. The EF-hand proteins are identified by a helixloop-helix structure, which act as the calcium-binding site.[8] Calretinin is mainly expressed in certain types of neurons in the central and peripheral nervous systems.[9,10]

In 1996, Doglioni et al[15] displayed that calretinin was a marker of mesothelial cells in humans and of mesothelioma. Thereafter, others have demonstrated the usefulness of calretinin for differentiating mesothelioma from adenocarcinoma[16,17] for diagnosing specific types of ovarian epithelial and stromal cells[18-20], and as a marker for few types of ovarian sex–cord stromal tumors[18-20], testicular Leydig cell tumors[21,22], tumors of adrenal cortex[23], and adenomatoid tumors.[22,24] Although calretinin is well known to be expressed in peripheral neural tissues[9,10], its existence in peripheral nerves tumors has not been well established .

S-100 protein is a suitable marker for identifying cells/tumor/tissue with a nerve origin. In the present study, we demonstrated that calretinin staining was positive in 26 (93%) of 28 schwannomas. Although the percentage of cells stained varied from focal (<25%) to diffuse (>75%), the staining intensity was moderate to strong in all positively stained cases. In contrast, only 2 (5%) of 42 neurofibromas were stained with calretinin, with weak or moderate intensity in less than 25% of the tumor cells.

These results strongly suggest that calretinin is a useful marker for differentiating schwannomas from neurofibromas.

Our results also demonstrate that calretinin is superior to S-100 protein, the latter of which was positive in all schwannomas and neurofibromas. These results are in agreement with Fine et al.[1] Their study included 25 schwannomas, and 24 of those tumors (96%) showed moderate to strong staining for calretinin, which occurred in either a focal or diffuse fashion. In contrast, only 3 of 42 neurofibromas (7%) demonstrated staining with calretinin. Those that did stain demonstrated weak to moderate staining in less than 25% of the tumor cells and have suggested that calretinin alone or in combination with S-100 protein is useful for differentiating schwannomas from neurofibromas. However, few cases with cytomorphologic and immunohistochemical overlap do exist and so the exact distinction between the two tumors is still not very clear.

CONCLUSION

We, recommend that calretinin replace or at least be used in combination with S-100 protein for differentiating schwannomas from neurofibromas.

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