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CLINICAL CASE REPORT

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Microcystic/Reticular Schwannoma of the Mandible First Case Report and Review of the Literature

Yu Yin, PhD, Tao Wang, MS, Yong-Ping Cai, PhD, Xiao-Juan Huang, MS, Yu-Jie Li, MS, Shun-Hua Chen, MS, Rong Qin, PhD, Chao-Fu Wang, PhD, and Qiang Wu, PhD

Abstract: Schwannoma comprises a group of nerve sheath tumors. Morphologic variants of schwannoma have no distinct relationship to clinical behavior, but unawareness of rare variants may lead to diagnostic pitfall and risk of mistreatment. Microcystic/reticular schwannoma is a recently described rare variant of schwannoma. We report a case of a 61-year-old female with a 5.0 cm × 3.5 cm × 3.0 cm mass in the right mandible, which has never been reported to date. Light microscopic evaluation showed that the mass was circumscribed with focal infiltration. Arranged in a prominent microcystic and reticular growth pattern, tumor cells were spindle-shaped with eosinophilic cytoplasm. No evidence of cytologic atypia, mitosis, or necrosis was observed. The stroma of the tumor mainly contained myxoid material with local infiltration of hyalinized collagen. Tumor cells showed diffuse and strong nuclear and cytoplasmic immunoreactivity for S100 protein. Tumor cells were also positive for CD34, CD99, and NSE, but negative for CK, EMA, CK5/6, P63, Calponin, CD10, SMA, Desmin, GFAP, NF, Syn, and CgA. The proliferation marker MIB-1 showed <1% nuclear reaction. Furthermore, we reviewed the clinical and pathological features of 24 previously reported cases of microcystic/reticular schwannoma.

Unlike classic schwannoma, the reticular variant showed striking microcystic and reticular architecture microscopically. Recognition of these distinct entities is essential in avoiding misdiagnosis. Unlike classic schwannoma with a complete capsule, some masses were reported to lack encapsulation or contain focal infiltration. Further follow-up of tentative or identified cases is necessary to better understand this schwannoma.

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Abbreviations: EMC = extraskeletal myxoid chondrosarcoma, GIST = gastrointestinal stromal tumors, NF1 = neurofibromatosis type 1, NF2 = neurofibromatosis type 2.

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From the Department of Pathology, Anhui Medical University, Hefei, Anhui Province (YY, Y-PC, X-JH, Y-JL, S-HC, RQ, QW) and Department of Pathology, Shanghai Cancer Center, Fudan University, Shanghai, China (TW, C-FW).
Correspondence: Chao-Fu Wang, Department of Pathology, Shanghai Cancer Center, Fudan University, Shanghai 200032, China (e-mail: wangchaofu@126.com). Qiang Wu, Department of Pathology, Anhui Medical University, Hefei 230032, Anhui Province, China (e-mail: aydjohn@yahoo.com).
YY and TW contributed equally to this work.
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INTRODUCTION

Schwannoma comprises a group of nerve sheath tumors that are divided into 2 types based on clinical, morphological, and genetic features: conventional schwannoma, which is common and benign; and melanotic schwannoma, which is rare with low malignancy potential.[1] Schwannoma affects all ages and usually arises in patients 40 to 60 years old with no race or sex predilection. Schwannoma is observed in a wide variety of tissues, with the majority occurring in the skin and subcutaneous tissue of the head and neck or the distal extremities. Schwannoma is rare in the gastrointestinal tract, mediastinum, retroperitoneum, spinal cord, cerebellopontine angle, or bone. Mainly solitary and globoid, schwannoma has a smooth surface and measures <10 cm. A large majority of tumors are characterized by a biphasic pattern composed of alternating Antoni A tissue (spindle-shaped cells showing occasional palisading) and Antoni B tissue (loosely arranged foci). Morphologic variants of schwannoma include ancient (degenerated) schwannoma,[2] cellular schwannoma,[3] plexiform schwannoma,[4] epithelioid schwannoma,[5] melanotic schwannoma,[6,7] hybrid schwannoma/neurofibroma,[8] hybrid schwannoma/perineurioma,[9] gastrointestinal schwannoma,[10] lipoblastic schwannoma,[11] neuroblastoma-like schwannoma,[12] and microcystic/reticular schwannoma.[13] The tumor cells show diffuse and strong cytoplasmic and nuclear staining for S100 protein.[14] Generally, these variants have no distinct relationship to clinical behavior, but unawareness of rare variants may lead to diagnostic pitfall and risk of mistreatment.

Herein, we report a case of microcystic/reticular schwannoma occurring in the mandible, which has not been described before. The clinical and pathological features of all 25 cases of microcystic/reticular schwannoma are summarized, including cases reported previously.

CASE REPORT

Clinical Features

A 61-year-old woman presented right facial asymmetry for 1 year. Computed tomography scan revealed a round, soft mass shadow with low density in the right mandible, measuring 3.9 cm × 3.4 cm in size (Fig. 1A). The mass was circumscribed with expansion growth to the outside (Fig. 1B). No obvious abnormal density shadow was observed in the bilateral parotid gland and salivary gland, and the patient had no features of Type 1 or Type 2 neurofibromatosis (NF1, NF2). Ethical approval was given by the biomedical ethics committee of Anhui Medical University with the number of 2015008.

Pathological Features

The resected mass, which measured 5.0 cm × 3.5 cm × 3.0 cm, was well circumscribed with a locally lobular appearance (Figure 2A). Cut sections were white to whitish

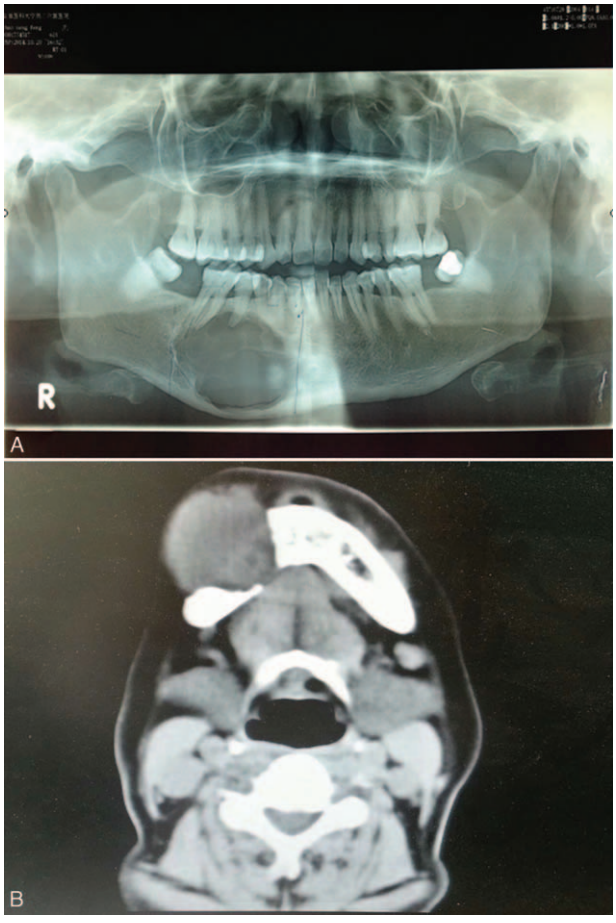

FIGURE 1. Computed tomography scan. (A) A soft, round mass shadow with low density was found in the right mandible. (B) The mass was circumscribed by expansive growth to the outside.

yellow, rubbery, and homogeneously solid with a myxoid appearance (Figure 2B).

Light microscopic evaluation showed that although the tumor was largely surrounded by a thin fibrous capsule (Figure 3A), focal infiltration into adipose tissue had occurred (Figure 3B). The fibrous capsule extended into the mass locally, which showed lobular features (Figure 3C). Tumor cells were spindle-shaped with eosinophilic cytoplasm. No cytologic atypia, mitosis, or necrosis was observed. Cells were arranged in a prominent microcystic pattern with evidence of reticular growth (Figure 3D). The stroma of the tumor mainly contained myxoid material with local infiltration of hyalinized collagen (Figure 3E). Focal regions resembling nerve fibers could also be seen close to the capsule (Figure 3F).

Immunohistochemistry was performed using the standard EnVision method on paraffin-embedded sections. Tumor cells showed diffuse and strong nuclear as well as cytoplasmic immunoreactivity for S100 protein. Tumor cells were also positive for CD34, CD99, and NSE. The proliferation marker MIB-1 showed $<1\%$ nuclear reaction. All tumor cells were negative for CK, EMA, CK5/6, P63, Calponin, CD10, SMA, Desmin, GFAP, NF, Syn, and CgA (Figure 4).

DISCUSSION

Schwannoma is a type of benign and nonrecurring mesenchymal neoplasm. As a rare variant of schwannoma, microcystic/reticular schwannoma remains under-recognized and poorly understood. A total of 24 cases have been reported to date in the literature.[13,15–26] Given its overlapping features with other neoplasms, this type of schwannoma may be misdiagnosed and mistreated to some extent. To avoid diagnostic confusion, especially with malignant neoplasms, a better understanding of the clinical and pathological features of this type of schwannoma is necessary.

In order to provide a framework to better understand the case described herein, we reviewed a total of 25 cases of microcystic/reticular schwannoma reported in the literature (Table 1). We found that 14 cases occurred primarily in the digestive tract, including 4 in the colon, 3 in the small intestine, 2 in the cecum, 2 in the stomach, and 1 each in the esophagus, rectum, and meso-appendix. Five cases arose in the subcutaneous and soft tissue, including 2 in the right arm, 2 in the

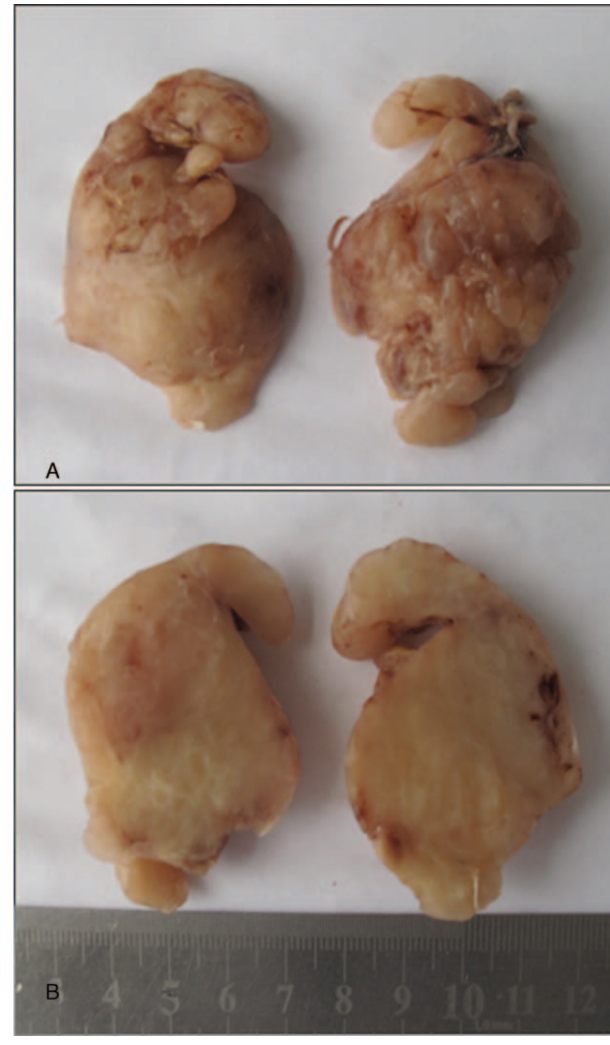

FIGURE 2. Gross findings. (A) The resected mass was well circumscribed with a locally lobular appearance. (B) Cut sections were white to whitish yellow in color, rubbery, and homogeneously solid with a myxoid appearance.

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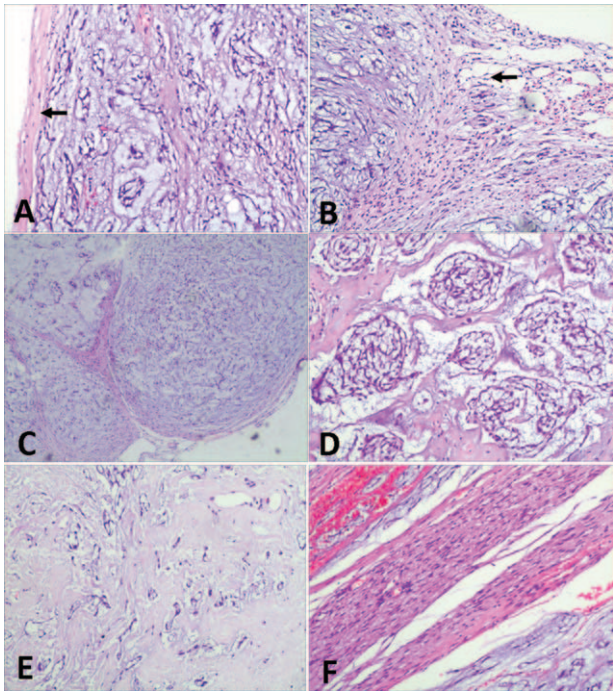

FIGURE 3. Microscopic findings (hematoxylin–eosin staining). (A) The tumor was largely surrounded by a thin fibrous capsule; (B) Tumor cells infiltrated into adipose tissue focally; (C) Fibrous capsule extended into the mass locally, showing lobular features; (D) Tumor cells arranged in a prominent microcystic and reticular growth pattern; (E) Stroma of the tumor showing hyalinized collagen locally; and (F) Focal region resembling nerve fibers can be seen close to the capsule.

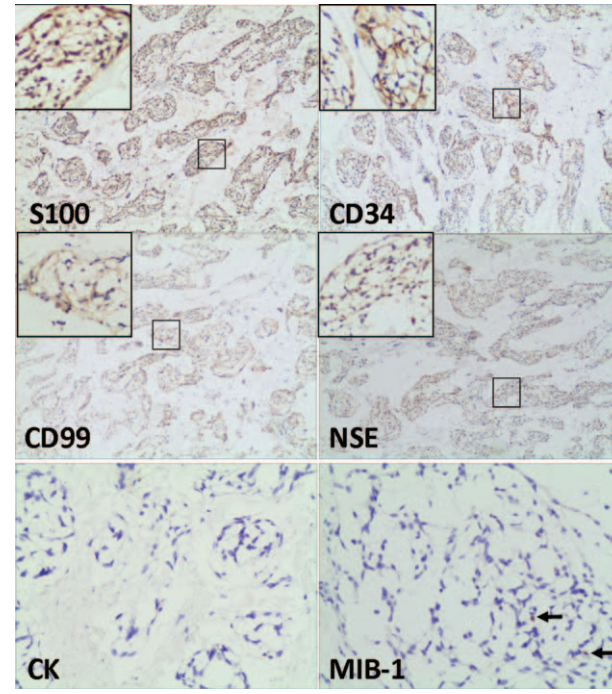

FIGURE 4. Immunohistochemical staining for S100, CD34, CD99, NSE, CK, and MIB-1 proteins (EnVision method).

back, and 1 in the masticator space. In addition, 1 case each was found in the pancreas, bronchus, left adrenal mass, parotid gland, and cervical spine. Our report describes the first case of microcystic/reticular schwannoma arising in the mandible.

All cases occurred in patients' ages 11 to 93 years and the overall median and average ages of all cases were 60 and 54 years, respectively. The tumors occurred approximately equally in male and female, with a male/female ratio of 1:1.3. However, predilection exists for females among patients who developed the tumor in the digestive tract, with a male/female ratio of 1:2.5.

The majority of patients presented with an asymptomatic mass. The tumors were discovered incidentally by patients themselves, via imaging examinations during routine check-up, or during operation for other reasons. Few patients experienced indigestion, epigastric pain, obstructive sensation during swallowing,[15] or recurrent upper lobe pneumonia.[13] To date, none of the patients have shown clinical evidence of NF1 or NF2. Follow-up data were available in 14 cases and ranged from 2 to 60 months after surgical resection. No recurrences were reported.

The tumor size ranged from 0.4 to 23.0 cm with a median size of 4.3 cm and an average size of 4.5 cm. A total of 13 masses were circumscribed but nonencapsulated, and only 4 masses were circumscribed and encapsulated. Five masses, including that in the case described here, were circumscribed with focal infiltration. Unlike classic schwannoma with a complete capsule, microcystic/reticular schwannoma may exhibit special biological behavior. Therefore, close follow-up after surgery may be necessary.

Lacking the distinctive features of Antoni A and Antoni B areas normally found in classic schwannoma to some extent, all 25 cases showed striking microcystic and reticular architecture microscopically. Myxoid, fibrillary, or collagenous/hyalinized stroma appeared between spindle tumor cells. Incognizance of this microscopic image can result in misdiagnosis, and erroneous diagnoses of malignant carcinoma may lead to inappropriate treatment of patients. Immunohistochemistry is helpful in differential diagnosis. All tumors showed diffuse and strong nuclear and cytoplasmic immunoreactivity for S100 protein. Of the 20 cases in which GFAP staining was performed, 17 were positive and 3 were negative. NF protein was focally positive in 1 case (case 6) and negative in 10 cases. Immunohistochemical staining for NSE and CD99 was performed in 2 cases (#24 and #25) and 1 case (#25), respectively, and was positive in all of those cases. Staining for epithelial markers such as CKpan, AE1/AE3, or Cam 5.2 was performed in 17 cases and was negative in all cases. In 6 out of 18 cases, EMA was expressed or focally expressed. CD34 was expressed or focally expressed in 5 out of 14 cases. CD117 was highly focally expressed in 2 out of 16 cases. In 2 out of 3 cases, CD56 was focally expressed. SMA, Desmin, DOG1, P63, Syn, and CgA staining were performed in some cases and were negative in all of those cases. Staining for the proliferation marker MIB-1 was performed in 5 cases and showed low nuclear reaction of $<1\%$ in 3 cases and $<2\%$ in 1 case, and focal expression in 1 case (Table 2).

Since microcystic/reticular schwannoma is relatively poorly known, it can easily be misdiagnosed. The case

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TABLE 1. Clinical and Pathological Features of 25 Cases

Case	Location	Sex	Age, yr	Size, cm	Gross Appearance	Outcome, mo	References
Digestive tract							
1	Esophagus	F	39	3.5	Nonencapsulated	ANED at 60	Gu et al[15]
2	Stomach	F	72	2.0	Nonencapsulated	ANED at 24	Liegl et al[13]
3	Stomach	F	63	1.9	Nonencapsulated	ANED at 60	Chetty et al[16]
4	Mid-jejunum	F	67	2.2	UA	ANED at 2	Agaimy et al[17]
5	Jejunum	F	93	1.6	Nonencapsulated	ANED at 7	Liegl et al[13]
6	Small intestine	M	78	0.8	Focal infiltration	Recent case	Liegl et al[13]
7	Meso-appendix	F	43	4.0	Encapsulated	ANED at 10	Tang et al[18]
8	Cecum	M	68	0.4	Focal infiltration	ANED at 24	Liegl et al[13]
9	Cecum	F	67	1.0	Focal infiltration	ANED at 12	Agaimy et al[17]
10	Ascending colon	F	32	1.4	Focal infiltration	UA	Lee et al[19]
11	Sigmoid colon	M	70	1.0	Nonencapsulated	UA	Kienemund et al[20]
12	Sigmoid colon	F	70	1.0	UA	UA	Kienemund et al[20]
13	Sigmoid colon	M	61	0.7	Nonencapsulated	ANED at 24	Trivedi et al[21]
14	Rectum	F	73	0.85	Nonencapsulated	ANED at 36 (died of metastatic colon carcinoma)	Liegl et al[13]
Subcutaneous and soft tissue							
15	Right arm	F	50	2.0	Encapsulated	ANED at 6	Liegl et al[13]
16	Right forearm	M	55	6.0	Encapsulated	ANED at 2	Chaurasia et al[22]
17	Back	F	56	1.0	Encapsulated	UA	Liegl et al[13]
18	Upper back	M	11	8.8	Nonencapsulated	ANED at 3	Liegl et al[13]
19	Masticator space	M	26	7.0	Nonencapsulated	UA	Lau et al[23]
Others							
20	Pancreas	M	62	5.0	Nonencapsulated	UA	Liegl et al[24]
21	Bronchus	F	76	3.0	Nonencapsulated	Died of postoperative complications	Liegl et al[13]
22	Left adrenal mass	M	53	23.0	Focal infiltration	ANED at 3	Liegl et al[13]
23	Parotid gland	M	59	3.0	Nonencapsulated	UA	Pang et al[25]
24	Cervical spine	M	35	3.5	Nonencapsulated	UA	Li et al[26]
25	Right mandible	F	61	5.0	Focal infiltration	Recent case	Our case

ANED = alive with no evidence of disease, UA = unavailable.

described here received an initial tentative diagnosis of extraskeletal myxoid chondrosarcoma (EMC). EMCs usually show myxoid stroma and multinodular growth patterns. The cordlike and lacelike architecture in EMC may show some morphologic overlap in microcystic/reticular schwannoma. However, tumor cells in EMC are larger and have more obvious eosinophilic cytoplasm. Moreover, only a part of EMC shows S100 positivity, usually with a scattered pattern, whereas S100 positivity was detected in all of the 25 microcystic/reticular schwannoma cases with strong and diffuse patterns.

Given that the tumor is located in the mandible in the present case, differential diagnoses for ameloblastoma and odontogenic myxoma should be considered. Ameloblastoma is an odontogenic epithelial tumor that stains positive for epithelial markers, whereas odontogenic myxoma shows spindle cells scattered in mucus fiber matrix without microcystic and reticular structure. Furthermore, reticular perineurioma histologically mimics microcystic/reticular schwannoma. However, a positive result for EMA immunoreactivity and negative result for S100 and GFAP immunoreactivity are helpful in distinguishing between these entities.

Given that approximately half of the 25 cases occurred in the digestive tract, gastrointestinal stromal tumors (GIST) may also be considered for differential diagnosis. Distinction is warranted between microcystic/reticular schwannoma and GIST because the treatment courses for these conditions are very different. GISTs are composed of spindle cells, epithelioid cells, or mixed cell types with myxoid stroma occasionally and without any feature of microcystic architecture. The diagnosis is generally confirmed by immunostaining for CD117 and DOG1. Mutational analysis for KIT and PDGFRA genes can also be used for identification.

In some cases of microcystic/reticular schwannoma, the epithelioid morphology or microcystic architecture, together with a myxoid background, may cause confusion with poorly differentiated adenocarcinoma or signet ring cell carcinoma.[13,21] Erroneous diagnosis will lead to inappropriate treatment. The absence of nuclear atypia and negativity for epithelial markers could allow the differentiation of microcystic/reticular schwannoma from carcinoma.

In summary, we describe herein a case of microcystic/reticular schwannoma occurring in the mandible, which has not been reported before. We also reviewed the clinical and pathological features of all 25 microcystic/reticular schwannoma cases described to date. Unlike classic schwannoma, the reticular variant showed striking microcystic and reticular architecture microscopically. Recognition of these distinct entities is essential in avoiding misdiagnosis. Unlike classic schwannoma with a complete capsule, some masses were reported to lack encapsulation or contain focal infiltration. Further follow-up of tentative

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TABLE 2. Immunohistochemical Features of 25 Cases

Case	S-100	GFAP	NF	NSE	CD99	CKpan/AE1/AE3/Cam 5.2	EMA	SMA	Desmin	CD34	CD117	DOG1	P63	Syn	CgA	CD56	MIB-1
1	(+) Diffusely	(−)	/	/	/	(−)	/	(−)	/	(−)	(−)	/	/	(−)	(−)	/	/
2	(+) Diffusely and strongly	(+) Partly	/	/	/	/	(−)	(−)	(−)	(−)	(−)	/	/	/	/	/	/
3	(+) Strikingly	(+) Focally	(−)	/	/	(−)	(−)	(−)	(−)	(+) Focally	(−)	(−)	/	/	/	/	/
4	(+)	(+) Focally	/	/	/	/	/	/	/	(−)	(−)	(−)		/	/	(+) Focally	/
5	(+) Diffusely and strongly	(+) Partly	(−)	/	/	(−)	(+) Focally	/	(−)	(−)	(−)	/	/	/	/	/	/
6	(+) Diffusely and strongly	(+) Partly	(+) Focally	/	/	(−)	(+) Focally	/	/	/	(−)	/	/	/	/	/	/
7	(+) Diffusely and strongly	(+)	/	/	/	(−)	(−)	(−)	(−)	(−)	(+) Focally	(−)	/	(−)	/	/	<1%
8	(+) Diffusely and strongly	(+) Partly	(−)	/	/	/	(−)	(−)	/	/	(−)	/	/	/	/	/	/
9	(+)	(+) Focally	/	/	/	/	/	/	/	(−)	(−)	(−)	/	/	/	(+) Focally	/
10	(+) Strongly	/	/	/	/	(−)	/	(−)	(−)	/	/	/	/	(−)	(−)	/	/
11	(+) Strongly	/	/	/	/	/	/	(−)	(−)	(−)	(−)	/	/	/	/	/	/
12	(+) Strongly	/	/	/	/	/	/	(−)	(−)	(−)	(−)	/	/	/	/	/	/
13	(+) Diffusely	/	/	/	/	(−)	/	(−)	/	(+) Focally	(−)	/	/	(−)	(−)	(−)	<2%
14	(+) Diffusely and strongly	(+) Partly	(−)	/	/	(−)	(+) Focally	/	(−)	/	/	/	/	/	/	/	/
15	(+) Diffusely and strongly	(+) Partly	(−)	/	/	/	(+)	(−)	(−)	/	/	/	/	/	/	/	/
16	(+) Diffusely and strongly	/	/	/	/	(−)	(−)	(−)	(−)	(−)	(−)	/	/	(−)	/	/	/
17	(+) Diffusely and strongly	(+) Partly	/	/	/	/	(+)	/	/	/	/	/	/	/	/	/	/
18	(+) Diffusely and strongly	(+) Partly	/	/	/	(−)	(−)	(−)	(−)	/	/	/	(−)	/	/	/	/
19	(+) Diffusely and strongly	(−)	/	/	/	(−)	(−)	(−)	(−)	/	/	/	(−)	/	/	/	/
20	(+) Diffusely and strongly	(+) Partly	(−)	/	/	(−)	(+) Focally	(−)	(−)	/	(−)	/	(−)	/	/	/	<1%
21	(+) Diffusely and strongly	(+) Partly	(−)	/	/	(−)	(−)	/	(−)	/	(+) Focally	/	/	/	/	/	/
22	(+) Diffusely and strongly	(+) Partly	(−)	/	/	(−)	(−)	(−)	(−)	(+) Weakly	(−)	/	(−)	/	/	/	/
23	(+) Diffusely and strongly	(+)	/	/	/	(−)	(−)	(−)	(−)	(+)	/	/	(−)	/	/	/	/
24	(+) Strongly	(+) Strongly	(−)	(+) Strongly	/	(−)	(−)	(−)	/	/	/	/	/	/	/	/	(+) Focally
25	(+) Diffusely and strongly	(−)	(−)	(+)	(+)	(−)	(−)	(−)	(−)	(+)	/	/	/	(−)	(−)	/	<1%

(−) = Negative, (+) = positive, / = unavailable.

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or identified cases is necessary to better understand this schwannoma.

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