Hybrid Neurofibroma/Schwannoma is Overrepresented Among Schwannomatosis and Neurofibromatosis Patients

Anja Harder, MD, Martin Wesemann,* Christian Hagel, MD,† Jens Schittenhelm, MD,‡ Susan Fischer,* Marcos Tatagiba, MD,§ Christoph Nagel, MD,§ Astrid Jeibmann, MD,* Axel Bohring, MD,‖ Victor-Felix Mautner, MD,¶ and Werner Paulus, MD**

Abstract: We analyzed the histologic features of peripheral nerve sheath tumors occurring in 14 patients with schwannomatosis. Among a total of 31 tumors, 19 tumors (61%) showed schwannoma-like nodules within a neurofibroma-like tumor, corresponding to hybrid neurofibroma/schwannoma. At least 1 hybrid tumor occurred in 10 of 14 (71%) schwannomatosis patients. We then retrieved cases of hybrid tumors without documented relation to schwannomatosis from our database and identified 41 tumors arising in 23 patients. More than half of these patients (14/23) were reported to suffer from multiple peripheral nerve sheath tumors, favoring a tumor syndrome. Indeed, analysis of clinical records revealed the diagnosis of neurofibromatosis type 2 (NF2) in 26% (6/23), neurofibromatosis type 1 (NF1) in 9% (2/23), definite schwannomatosis in 4% (1/23), and possible schwannomatosis in 13% (3/23) of patients with multiple nerve sheath tumors. Our findings suggest that hybrid neurofibroma/schwannoma represents a common tumor type in schwannomatosis and shows a striking association with neurofibromatoses.

Key Words: hybrid neurofibroma/schwannoma, hybrid tumor, schwannomatosis, neurofibromatosis, NF1, NF2, SMARCB1, nerve sheath tumor

(*Am J Surg Pathol* 2012;00:000–000)

Schwannomas and neurofibromas are common entities of benign peripheral nerve sheath tumors that arise both sporadically and in the setting of neurofibromatoses such as neurofibromatosis type 1 (NF1, MIM 162200), neurofibromatosis type 2 (NF2, MIM 101000), and schwannomatosis (MIM 162091), also called NF3. They differ not only by histologic features but also by distinct molecular genetic events.[5] In general, neurofibromas originate from biallelic *NF1* gene (17q11.2) mutations with loss of neurofibromin function, whereas schwannomas typically harbor biallelic loss of the *NF2* gene (22q12.2) function leading to loss of merlin protein activity. In contrast to schwannomas, neurofibromas are complex, composed of fibroblasts, perineurial cells, and Schwann cells. Mast cells typically occur within the tumors.[22] Although both are benign, neurofibromas and schwannomas have to be distinguished, because therapy, malignant potential, and assignment to tumor syndromes are different. Occasionally, hybrid neurofibromas/schwannomas have been described, defined as nerve sheath tumors with schwannoma-like nodules within a neurofibroma-like tumor.[10]

More recently, schwannomatosis has been identified as a separate tumor syndrome characterized by multiple schwannomas arising from peripheral and cranial nerves but sparing the vestibular nerve and lacking other signs of NF2.[3,18] More than 95% of cases are sporadic (nonfamilial), whereas incomplete penetrance can cause diagnostic difficulties.[1,19,20] Disease onset is usually in the second and third decades, and pain is regarded as a major symptom.[11,20] Interestingly, in some familial schwannomatosis cases, multiple meningiomas have been described akin to NF2.[2,7] In NF2 patients, schwannomas occur because of a second hit of the *NF2* gene, such as *NF2* mutations, loss of heterozygosity, or methylation. In contrast, schwannomatosis has been linked to mutations of the *SMARCB1* gene on chromosome 22q11.23 in some families, although other genetic causes possibly entailing increased susceptibility to mitotic recombination have been suggested.[2,4,12,13,16,29] A recent French study of schwannomatosis patients revealed deleterious *SMARCB1* germline mutations in 5 sporadic cases out of 56 patients investigated by genomic sequencing, thus demonstrating only 9% of *SMARCB1* mutations in this cohort.[27] Other studies showed involvement of *SMARCB1* in about half of the familial schwannomatosis cases.[4,12] Interestingly, germline *SMARCB1* mutations in the setting of familial and sporadic malignant rhabdoid tumors tend not to occur together with schwannomatosis in affected families, except for very rare cases.[9,32] In schwannomas and men-

From the *Institute of Neuropathology; ‖Institute of Human Genetics, University Hospital Münster, Münster, Germany; †Institute of Neuropathology; ¶Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ‡Department of Neuropathology, Institute of Pathology and Neuropathology; and §Department of Neurosurgery, University of Tübingen, Tübingen, Germany.

Conflicts of Interest and Source of Funding: Supported by "Innovative Medical Research," University of Münster Medical School (HA121006). No funding was received for this work from the National Institutes of Health; Wellcome Trust and Howard Hughes Medical Institute.

Correspondence: Anja Harder, MD, Institute of Neuropathology, University Hospital Münster, Albert-Schweitzer-Campus 1, Building A7, 48149 Münster, Germany (e-mail: anja.harder@ukmuenster.de).

ingiomas of schwannomatosis patients, a 4-hit mechanism of gene inactivation of *SMARCB1* and *NF2* has been suggested.[2,4,7,12,29] Although occurrence of multiple schwannomas was eponymous for the disease, neurofibromas have also been rarely described in schwannomatosis.[26] Further subtypes of nerve sheath tumors have not been reported so far.

MATERIALS AND METHODS

Patients

Thirty-one peripheral nerve sheath tumors of 14 schwannomatosis patients were reviewed histologically. Schwannomatosis was diagnosed according to published criteria.[18] Hence, definite schwannomatosis was diagnosed if patients were more than 30 years of age and 2 or more nonintradermal schwannomas (at least 1 with histologic confirmation and no evidence of vestibular tumor and no *NF2* constitutional mutation) or 1 pathologically confirmed nonvestibular schwannoma plus a first-degree relative who meets the above criteria was identified. Accordingly, possible schwannomatosis was diagnosed as defined.[18]

Furthermore, neuropathologic reports of the following institutions were screened for hybrid neurofibroma/schwannoma: Institute of Neuropathology, University Hospital Münster; Institute of Neuropathology, University Medical Center Hamburg-Eppendorf; and Institute of Pathology and Neuropathology, University of Tübingen. Data on sex, age (age at histologic diagnosis), localization, and number of tumors were analyzed from clinical records.

Histologic Criteria

As diagnostic consensus criteria for hybrid neurofibromas/schwannomas do not exist, we diagnosed a hybrid neurofibroma/schwannoma when the following features were fulfilled: intermingled areas with features of both typical neurofibroma [World Health Organization (WHO) grade I] and typical schwannoma (WHO grade I) must be observed within the same lesion (simple collision is not accepted). Neurofibroma differentiation should be clearly different from schwannoma Antoni B regions.

Immunohistochemistry

Sections were deparaffinized, rehydrated, and washed. For antigen retrieval, slides were pretreated, cooled in ice water for 15 minutes, and washed. Slides were blocked with peroxidase blocking solution for 5 minutes and then incubated with the following primary antibodies: mouse monoclonal antineurofilament (clone 2F11, 1:3000, Dako Cytomation Denmark A/S), rabbit polyclonal anti-S100β (1:4000, Dako Cytomation Denmark A/S), mouse monoclonal anti-BAF47 (Smarcb1/Ini1, 1:200, BD Biosciences), rabbit polyclonal anti-Glut-1 (1:100, Immuno-Biological Laboratories Co., Japan), rabbit polyclonal anti-GFAP (1:4000, Dako Cytomation Denmark A/S), mouse monoclonal anti-EMA (clone 29, 1:100, Dako Cytomation Denmark A/S), mouse monoclonal anti-CD34 (1:80 Dako Cytomation Denmark A/S), and mouse monoclonal anti-Ki-67 (clone MIB1, 1:100, Dako Cytomation Denmark A/S). Slides for EMA, Glut1, and CD34 staining were pretreated at pH 6.1 and boiled. After washes, the slides were incubated with a biotinylated secondary antibody, streptavidin peroxidase, and diaminobenzidine (DAB) using the Dako REAL Detection system (Dako REAL Detection system, peroxidase/DAB+, Rabbit/Mouse, code K5001, Dako Denmark A/S) for automated immunostaining. Finally, sections were counterstained with hematoxylin. The Ki-67 index was obtained by counting 1000 tumor cells within the area exhibiting the highest labeling index. Histologic and immunohistologic stainings were evaluated by 3 neuropathologists (A.H., A.J., and W.P.).

RESULTS

Clinical Characterization and Tumor Spectrum

To characterize schwannomatosis-associated tumors, a total of 31 peripheral nerve sheath tumors of 14 schwannomatosis patients were analyzed histopathologically. Among these tumors, 61% hybrid neurofibromas/schwannomas (19/31), 26% schwannomas (8/31), and 13% neurofibromas (4/31) were identified (Table 1, Fig. 1A). In all, 71% (10/14) of schwannomatosis patients showed at least 1 hybrid neurofibroma/schwannoma, and 3 schwannomatosis patients (21%) contributed multiple hybrid neurofibromas/schwannomas (Fig. 1B).

We then retrieved cases of hybrid neurofibromas/schwannomas with an unknown relationship to schwannomatosis or other tumor syndromes from neuropathologic records. We identified 41 hybrid neurofibromas/schwannomas arising in 23 patients (Table 2). Clinical records were retrospectively reviewed to identify multiplicity of tumors and signs and symptoms for NF1, NF2, or schwannomatosis. For 39% of patients (9/23) with a diagnosis of hybrid neurofibroma/schwannoma, additional clinical data could not be retrieved at all. Remarkably, clinical records of more than half (61%) of the 23 patients (14/23) reported multiple peripheral nerve sheath tumors in terms of a tumor syndrome. Indeed, 26% (6/23) were diagnosed as NF2, 9% (2/23) as NF1, 4% (1/23) as definite schwannomatosis, and 13% (3/23) as possible schwannomatosis according to established diagnostic criteria (Figs. 1C, D). Overall, 30% of patients with hybrid tumors (7/23) presented not only with multiple benign nerve sheath tumors but also with multiple hybrid neurofibromas/schwannomas (Table 2). For example, patients 17 and 26 suffered from peripheral nerve sheath tumors and from vestibular schwannomas and meningiomas, thus fulfilling diagnostic criteria for NF2. One patient (patient 25) presented with peripheral tumors at different locations, whereas other signs of NF1 and NF2 and mutations by a comprehensive analysis of *NF1* and *NF2* were excluded. For this patient (patient 25) and for patients 21 and 37, possible schwannomatosis was our working diagnosis because of the absence of additional NF1-associated or NF2-associated features. However, clinical records were not absolutely sufficient to ensure this, as all tumors represented only hybrid neurofibromas/schwannomas histologically, and conventional schwannomas were not seen histologically.

TABLE 1. Thirty-One Peripheral Nerve Sheath Tumors of 14 Patients With Definite Diagnosis of Schwannomatosis According to Diagnostic Criteria[16]

Patient No.	Age	Sex	Macroscopy	Histological Diagnoses (n) [Size]	Special Pattern	Localization of Tumors
1	31	F	Nodular, elastic, with capsule	Hybrid neurofibroma/schwannoma (1) [d = 4 cm]	—	Pelvic, groin, spinal, neck, foot
2	48	F	Yellow, elastic	Hybrid neurofibroma/schwannoma (1) [—]	Plexiform (1)	Thigh, groin
3	49	M	White, nodular	Hybrid neurofibroma/schwannoma (1) [d = 0.8 cm]	—	Spinal, thoracal, dermal, back, thigh
4	42	F	—	Hybrid neurofibroma/schwannoma (1) [—] Neurofibroma (WHO grade I) (3) [—]	—	Ulnar nerve, upper and lower arm, antebrachial nerve
5	41	F	White, solid	Schwannoma (WHO grade I) (4) [d = 2.3 cm]	—	Spinal, occipital
6	42	M	Gray, elastic	Schwannoma (WHO grade 1) (1) [d = 0.9 cm]	—	Spinal, neck, plexus brachialis
7	48	M	Yellow-tan, solid, capsule	Hybrid neurofibroma/schwannoma (1) [3.5, 2, 1.8 cm]	—	Plexus brachialis, back
8	51	—	Yellow-tan, capsule, cystic	Neurofibroma (WHO grade I) (1) [2.3, 2, 1.3 cm]	—	Unknown
9	60	M	White, solid, in part capsule	Schwannoma (WHO grade 1) (1) [1.2, 0.4, 0.3 cm]	Myxoid (1)	Median, femoral, and peroneal nerve
10	53	F	Yellow-gray, elastic	Hybrid neurofibroma/schwannoma (1) [1 mL]	—	Ear
11	56	F	White, elastic, in part capsule	Hybrid neurofibroma/schwannoma (1) [3 mL]	—	Cervical
12	33	F	White-yellow-gray, smooth, even surface, section cystic	Hybrid neurofibroma/schwannoma (4) [21 mL] Schwannoma (WHO grade I) (2) [2.3 mL]	—	Extremity, thoracal, thigh, upper leg
13	30	M	White or yellow-gray, elastic or smooth, surface smooth	Hybrid neurofibroma/schwannoma (6) [2.1 mL]	Plexiform (1)	Spinal, brachial plexus, arm, foot, lower leg
14	41	M	White-yellow, elastic, surface smooth	Hybrid neurofibroma/schwannoma (2) [53 mL]	Plexiform (1)	Thoracal

(n) indicates number of individual nerve sheath tumors; [size], tumor size given in volume or diameter (d) (in case of multiple tumors mean value of the size is given).

Overall, 60 hybrid neurofibromas/schwannomas were diagnosed in our series. The age of the patients (n = 33) with hybrid tumors ranged between 15 and 70 years (median 42), and the male:female ratio was 1:0.9.

Hybrid neurofibromas/schwannomas were localized at the peripheral nerves, except for 1 case involving the hypoglossal nerve. Major and minor superficial peripheral nerves were involved. Smaller peripheral nerves were far more often affected compared with spinal root nerves. Besides the periphery, a preferred localization at certain nerves or body regions was not seen. We did not see clear differences from conventional neurofibroma or schwannoma with regard to gross pathology. In 7 patients with hybrid neurofibroma/schwannoma, follow-up data were available and ranged between 1 and 23 years after operation. Four patients survived for >10 years without malignancy, and the longest survival without development of malignancy was 23 years.

Histologic Characterization

According to our criteria, hybrid neurofibromas/schwannomas consisted of 2 parts: one part being typical of neurofibroma and another part being typical of schwannoma. These 2 different regions were present at a variable degree (Fig. 2). Schwannoma-like nodules typically appeared as Antoni A regions. Occasionally, in larger schwannoma-like nodules, Antoni B regions were additionally seen. In the neurofibroma-like part there was often abundant collagen and myxoid change, and tumor cells showed a characteristic elongated and wavy appearance. In the schwannoma-like part, elongated cells with typical palisading were present (Fig. 2). Increased mitotic activity was seen in only 1 case. Twenty-five percent of hybrid tumors (15/60) showed a plexiform growth pattern. Those plexiform tumors contained the schwannoma-like areas in the center of fascicles. In all cases the neurofibroma tissue surrounded the schwannoma-like nodules (eg, Fig. 2B), although sometimes the schwannoma-like nodules became larger and only a small rim of neurofibromatous tissue was encountered (eg, Fig. 2D). In general, the schwannoma-like nodules were often sharply encapsulated by collagen bundles from the surrounding neurofibroma-like tissue (eg, Fig. 2F). In some cases pronounced lymphocytic infiltrates were present, especially at the margin of the lesion. Among the 60 hybrid neurofibromas/schwannomas we did not see histopathologic patterns indicating malignant change such as cell crowding, general nuclear enlargement, hyperchromasia, or increased mitotic activity, except for 1 tumor. This specimen showed a focal increase of mitotic activity; thus, focal transformation to low-grade malignant peripheral nerve sheath tumor could not be excluded.

Immunohistochemistry was performed for neurofilament, S100β, Smarcb1/Ini1, EMA, Glut-1, GFAP, CD34, and Ki67 (Figs. 2, 3). Half of the cases (50%) had detectable axonal structures by neurofilament staining in the neurofibroma part. Residual nerve fibers of peripheral nerves were occasionally seen at the tumor border. The Ki-67 index ranged between 0.8% and 18.5%. Smarcb1/Ini1 expression was retained in all tumors. S100β staining confirmed the dense package of Schwann cells in the schwannomatous component. Perineurial-like cells with finely elongated cell bodies were abundant in the neurofibroma-like

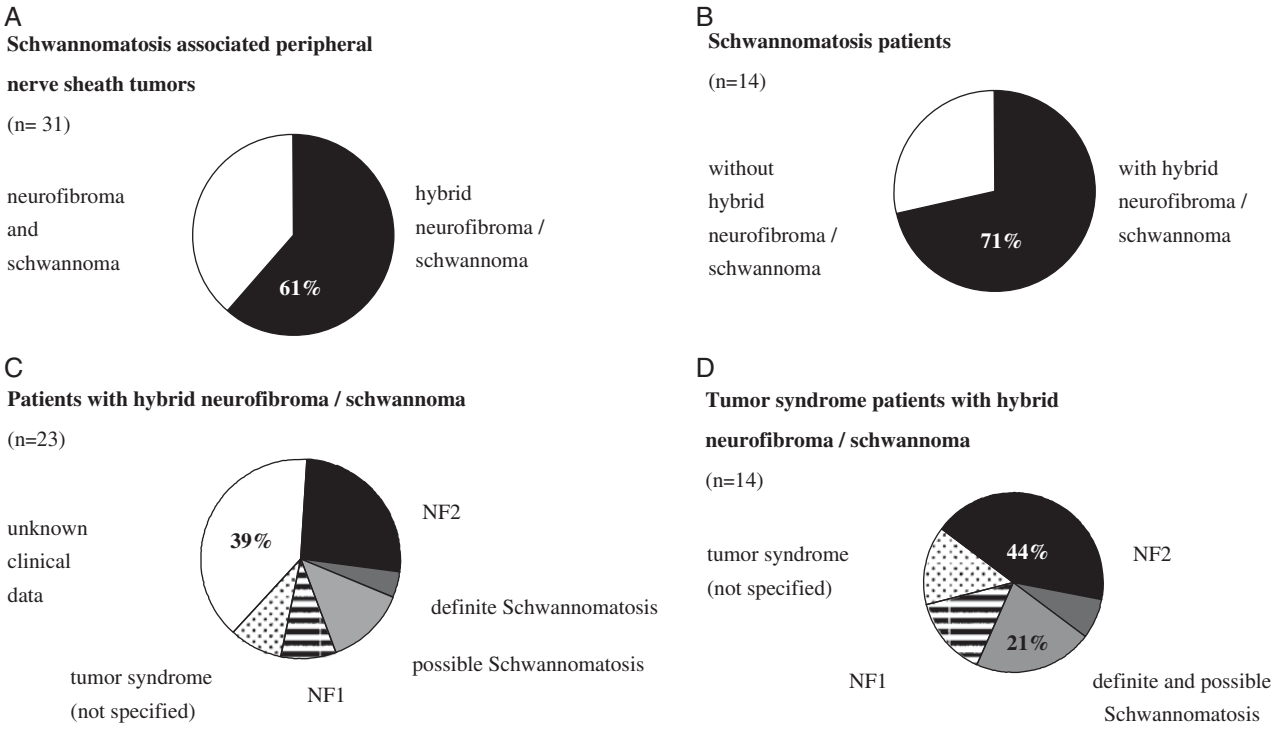

FIGURE 1. Peripheral nerve sheath tumors (n = 31) of 14 schwannomatosis patients were evaluated histologically and revealed a high percentage (61%) of hybrid neurofibromas/schwannomas (A, B). In addition, nerve sheath tumors with hybrid features (n = 41) of 23 patients were retrospectively retrieved from our databases, and in 61% of these patients a tumor syndrome could be diagnosed (C). Of those patients with a tumor syndrome, NF2 and schwannomatosis were most common (D).

part and in the tumor capsule (residual perineurium) as shown with anti-Glut-1 antibody. Within the compact schwannoma-like part, Glut-1 immunohistochemistry was mainly negative, whereas in a few cases a mosaic pattern of intermingled immunopositive and immunonegative cells was seen. Staining for EMA largely corresponded to that for Glut-1, although it was decreased in the neurofibroma-like part. Anti-CD34 staining was strikingly abundant in reticular components such as in neurofibroma-like parts and in Antoni B regions of schwannoma-like areas but was clearly absent from areas of densely packed (Antoni A) schwannoma-like nodules. GFAP immunohistochemistry was negative in most tumors, whereas some tumors revealed clusters of GFAP-positive Schwann cells, both in the neurofibroma-like and in the schwannoma-like part.

DISCUSSION

We analyzed the histologic features of peripheral nerve sheath tumors occurring in 14 patients with definite schwannomatosis. Patients with schwannomatosis, as diagnosed by established criteria, develop schwannomas at peripheral and intracranial nerves excluding the vestibular nerve, the latter being distinctive for NF2.[18] Interestingly, among 14 schwannomatosis patients we not only diagnosed schwannomas, which are considered to constitute the hallmark neoplasm in this disease, but also neurofibromas and a high percentage (61%) of hybrid neurofibromas/schwannomas. The high percentage of the latter is remarkable as even neurofibromas are not usually regarded to be among schwannomatosis-associated tumors. Nevertheless, only 2 cases with superficial neurofibromas in the setting of schwannomatosis have been reported in the literature.[26] The occurrence of hybrid neurofibromas/schwannomas therefore widens the spectrum of tumor entities involved in schwannomatosis. As some of the previously diagnosed schwannomas of our schwannomatosis patients were reclassified as hybrid neurofibroma/schwannoma in this study, some questions arise: Is there another schwannomatosis-like syndrome with multiple hybrid neurofibromas/schwannomas for which defined diagnostic criteria do not exist? Do all schwannomas of diagnosed schwannomatosis patients need to be reevaluated histologically to cope with diagnostic criteria as hybrid neurofibromas/schwannomas are not part of any criteria? At least 2 cases of our series with multiple hybrid neurofibromas/schwannomas as the only manifesting tumor support the first hypothesis.

Hybrid neurofibromas/schwannomas have already been described in the literature (for review see Table 3), even in other species.[25] To characterize the clinicopathologic features of hybrid neurofibroma/schwannoma we screened our neuropathologic records for hybrid tumors and identified another 23 cases (contributing 41 tumors) including patients with tumor syndromes (61%) such as NF1, NF2, and definite and possible schwannomatosis. The remaining patients (39%) were not further characterized;

TABLE 2. Forty-One Hybrid Neurofibromas/Schwannomas in 23 Patients by Retrospective Analysis

Patient No.	Age	Sex	Tumor Syndrome*	n†	Pattern (n)	Localization	Tumor Size (cm)	Additional Information
15	53	F	Yes	1	Plexiform (1)	—	$d = 2$	Multiple schwannomas of head and neck
16	40	F	Unknown	1	—	n. ulnaris	3.5, 2.8, 1.7	—
17	66	M	NF2	2	Plexiform (1)	Spinal (Th11)	2, 1.5, 1.4 and 2.5, 2.2, 0.6	Multiple peripheral and vestibular schwannomas and meningiomas
18	17	M	NF2	1	Plexiform (1)	Axillary	4, 2.2, 2.3	Schwannomas: lumbal (L2/3), at Vth and VIIIth nerves bilaterally; multiple meningiomas: spinal (th), cranial
19	44	M	Unknown	1	—	n. ulnaris	1.7, 1, 1	—
20	49	F	Unknown	1	—	n. ulnaris	2.2, 1.2, 1.1	—
21	28	F	Schw?	4	—	Legs, forehead, interdigital	2.0, 2.0, 0.6	Multiple benign peripheral and spinal nerve sheath tumors
22	29	F	Unknown	1	—	Thigh	6.6, 3.8, 3.5	—
23	50	M	Unknown	1	—	Spinal (L5)	6.1, 2.7, 1.9	—
24	51	M	Unknown	1	—	n. medianus	globular, 11.8 g	—
25	35	M	Schw?	7	Plexiform (6)	n. medianus, n. tibialis, n. ischiadicus, forearm, digits	2.8, 1.6, 1.4	Multiple peripheral nerve sheath tumors, neither *NF1* nor *NF2* mutation
26	15	M	NF2	3	Plexiform (3)	Chest, occipital, forehead	4.0, 1.8, 1.5	Vestibular schwannoma, meningiomas
27	70	M	Unknown	1	—	n. tibialis	$d = 1.5$	—
28	44	M	Unknown	1	—	n. hypoglossus	—	Intracranial, extracranial tumor
29	62	F	Unknown	1	—	n. medianus	0.8, 0.5, 0.4	—
30	35	F	NF2	1	—	Forearm	1, 1, 0.5	Distal anterial forearm
31	38	M	NF2	1	Diffuse	Hand	$d = 0.7$	Wrist joint, radial
32	41	M	Schw	1	—	Thoracal	2, 1, 1	Lateral thorax
33	31	M	NF1	1	—	Neck	21, 3.5, 1.5	Supraclavicular
34	42	F	Mosaic NF1	2	—	Retroauricular, neck	$d = 0.5$ to 0.8	Multiple retroauricular, retropharyngeal and nuchal neurofibromas
35	56	M	NF2	2	—	—	—	Multiple schwannomas, neurofibroma, lymphadenitis
36	21	F	Yes	1	—	Left groin	$d = 5$	Plexiform neurofibromas at femoral and ulnar nerve
37	42	F	Schw?	5	—	Thigh, groin, spinal	3, 2.5, 1.5	Multiple schwannomas

*Schw, NF1, and NF2 were diagnosed by clinical criteria or by mutation analysis.
†Number of hybrid tumors; tumor size is given as diameter (*d*) in cm or as weight in g (in cases of multiple tumors the largest tumor size is presented).
Schw indicates schwannomatosis; Schw?, possible schwannomatosis.

thus, they could suffer from a tumor syndrome or could just present sporadic cases. Occurrence of hybrid neurofibromas/schwannomas has already been reported in 1 NF1 and in 1 NF2 patient (Table 3). We hypothesize that occurrence of these tumors may be underestimated in part because current WHO classification requires these tumors to be classified as schwannomas or as neurofibromas.

Although several authors (Table 3) have described the histopathologic features of single hybrid neurofibromas/schwannomas, Feany and colleagues have reviewed the histopathologic features of 9 hybrid neurofibromas/schwannomas in more detail and already pointed out that plexiform features are common.[8,10,17,23,30,34,35] As in the series of Feany and colleagues, all tumors of our series showed distinct regions with typical features of both neurofibroma and schwannoma. The neurofibroma component with myxoid, loose and wavy areas, elongated cells, comma-shaped nuclei, and abundant collagen usually enclosed Antoni A nodules, showing densely packed spindled Schwann cells with nuclear palisading. In larger lesions, interspersed Antoni B components were rarely seen within the schwannoma-like component, and in many cases the demarcation of the 2 components was sharp (Fig. 2). Immunohistochemical characterization was according to current knowledge of neurofibromas and schwannomas, such as occurrence of perineurial-like cells in neurofibromas and CD34 positivity in neurofibromas and in Antoni B regions of schwannomas.[6,24,33] The histologic pattern appears to be characteristic in our series, and some cases reported as hybrid neurofibromas/schwannomas in the literature may not fulfill these features and rather may correspond to collision tumors of neurofibromas and schwannomas.[30,31] Schwannoma-like nodules in neurofibromas appearing as small schwannomas have already been reported in textbooks as especially arising in plexiform tumors.[28] We would like to emphasize that those tumors be referred to as hybrid neurofibromas/schwannomas to distinguish them from neurofibromas. Unequivocal pathologic diagnosis of neurofibroma versus schwannoma is needed for a final diagnosis according to diagnostic criteria of NF1, NF2, or schwannomatosis, especially in cases that lack other clinical data. In those cases, identifying a hybrid neurofibroma/

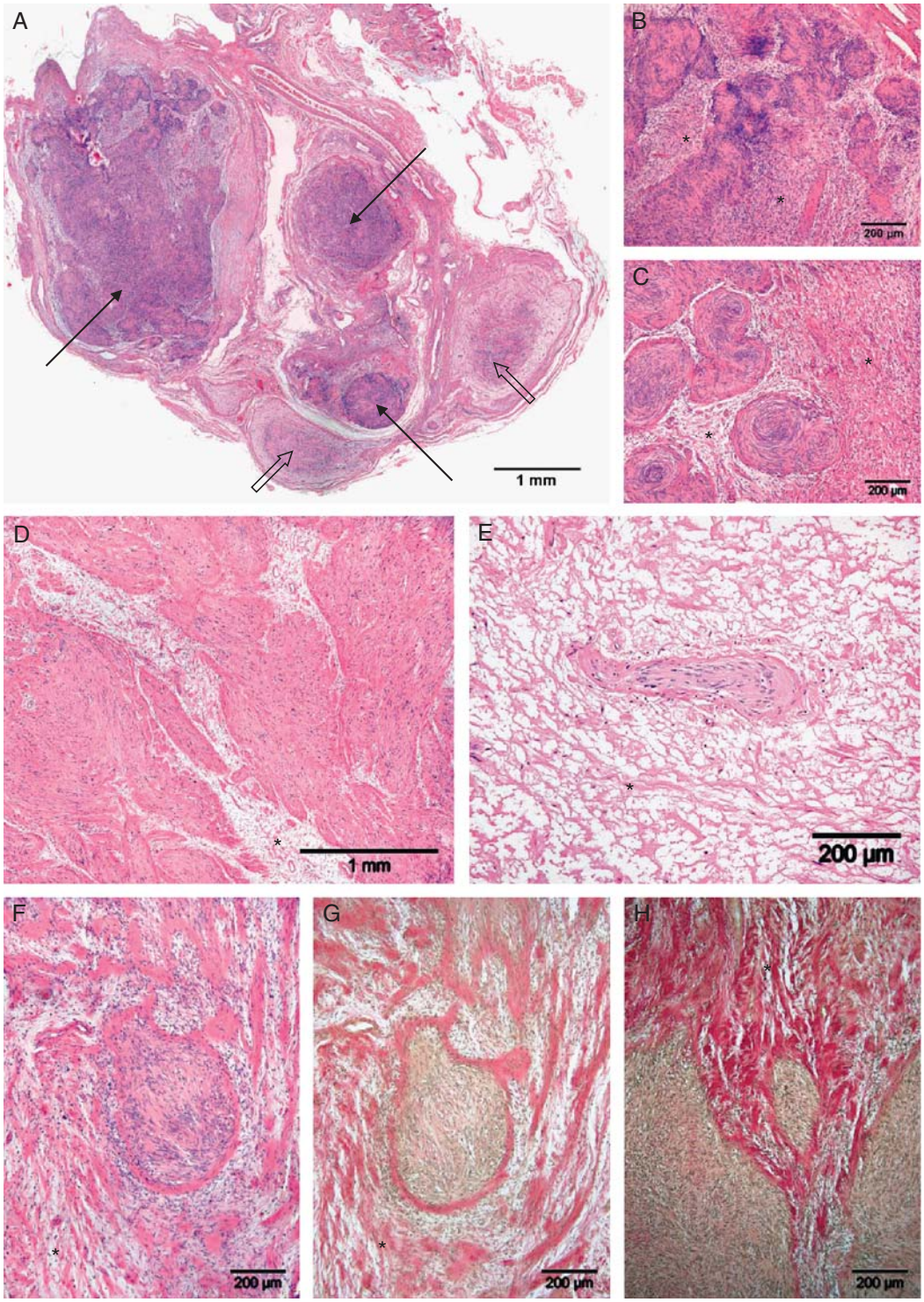

FIGURE 2. Typical histopathologic features of hybrid neurofibromas/schwannomas. A plexiform hybrid neurofibroma/schwannoma with schwannoma-like nodules (arrows) and neurofibroma-like areas (open arrows) within the tumor (A). Typical intermingled neurofibroma-like (marked by asterisks in B–H) and schwannoma-like nodules (B, C) may be present at variable degrees: large (D) and small schwannoma-like nodules (E–G) within neurofibroma-like tissue (asterisks). Elastica van Gieson staining shows schwannoma-like nodules encapsulated by collagen, and abundant collagen bundles in the surrounding neurofibroma-like areas (F, H).

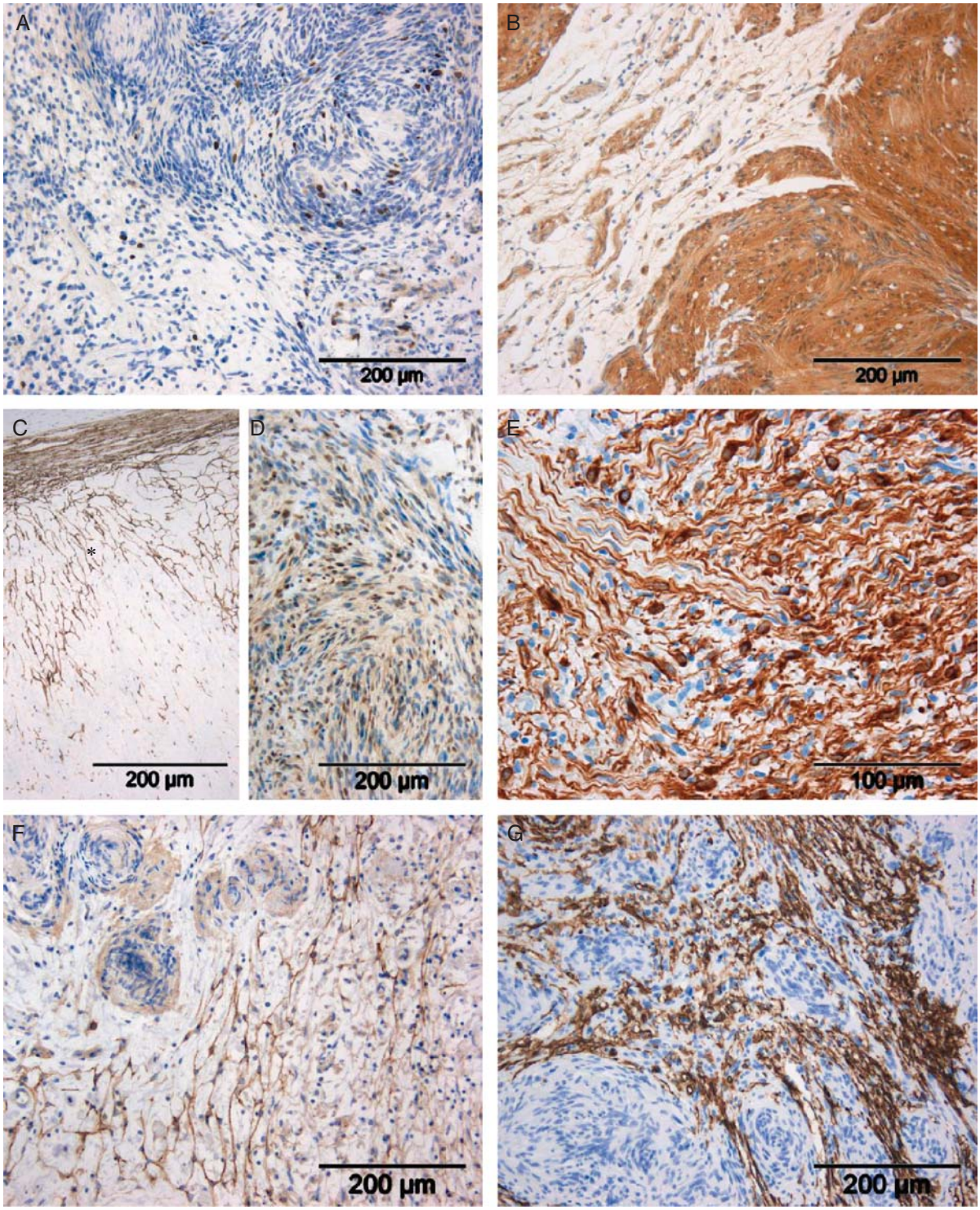

FIGURE 3. Immunohistochemical characterization of hybrid neurofibromas/schwannomas revealed moderate Ki-67 indices in both parts (A). S100β staining showed dense package of Schwann cells in the schwannoma-like component (B). Elongated perineurial cells in the neurofibroma-like region (asterisk) and residual perineurium at the tumor border were marked with anti-Glut-1 antibody (C). Mosaic Glut-1 immunopositivity in the schwannoma-like part (D) was seen in several cases. Some tumors revealed clusters of GFAP-positive Schwann cells, both in the neurofibroma-like and schwannoma-like parts (E). EMA-positive cells were marked at the margin, consistent with residual perineurium, and sparsely within the neurofibroma-like part (F). Abundant CD34 immunopositive cells were present in reticular components such as in neurofibroma-like parts but were absent from densely packed schwannoma-like nodules. CD34-positive small vessels were also present (G).

TABLE 3. Reported Cases of Human Hybrid Neurofibromas/Schwannomas

References	n*	Associated Tumor Syndrome	Localization
Masson[21]	1	Unknown	Unknown
Harkin and Reed[15]	1	Unknown	Unknown
Yamamoto et al[34]	1	None	Lumbar region
Dubuisson et al[8]	1	None	n. ischiadicus
Halliday et al[14]	1	NF2	Lumbal
Sintzoff et al[30]	1	Unknown	n. ischiadicus
Kayem et al[17]	1	Unknown	n. facialis
Feany et al[10]	9	1/9 with NF1	Peripheral nerves/sites, plexiform (5/9)
Muraresecu et al[23]	1	None	Thoracal
Spinner et al[31]	1	None	Brachial plexus
Youens et al[35]	1	None	Orbital

*Number of reported cases.

schwannoma would make a difference in assignment to tumor syndromes and thus would have diagnostic implications.

To conclude, we have described a large series of 60 hybrid neurofibromas/schwannomas with a striking accumulation in tumor syndromes such as NF2 and NF1, especially in schwannomatosis. We emphasize that these tumors be recognized as a separate entity of peripheral nerve sheath tumors apart from schwannomas and neurofibromas, as it has implications for the diagnosis of NF1, NF2, and schwannomatosis. As molecular genetic events are still unknown, and the potential for malignant transformation such as in plexiform neurofibromas is unidentified in hybrid tumors, further studies on this special tumor entity are required.

ACKNOWLEDGMENT

The authors thank Ralf Mersmann for the dedicated and helpful handling of designing color illustrations.

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