Peripheral Nerve Sheath Tumors of the Thyroid Gland: A Series of Four Cases and a Review of the Literature

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Abstract

Primary peripheral nerve sheath tumors (PNSTs) of the thyroid gland are exceptionally rare. Two schwannomas and two malignant PNSTs (MPNSTs), arising primarily within the thyroid gland, were identified in the files of the Endocrine Tumor Registry at the Armed Forces Institute of Pathology. The patients included two females, age 69 and 80 yr, and two males, age 18 and 33 yr. The patients presented with a mass in the thyroid gland confined to a single lobe of the thyroid without involvement of the cervical neck region. None of the patients had a history of neurofibromatosis. The benign tumors were encapsulated, one of them cystic, with the characteristic cellular and nuclear features of schwannomas. The MPNSTs were invasive tumors, effacing the thyroid parenchyma, with a fascicular pattern of growth composed of neural appearing cells with increased cellularity, increased mitotic activity and with focal necrosis. Immunoreactivity for S-100 protein and vimentin was seen in all tumors. The patients with schwannomas, treated only by surgical resection, were alive without evidence of disease, over a period of 5–33 yr. Both patients with MPNSTs died of the disease 8 mo and 42 mo, respectively, with widely disseminated disease. Primary thyroid PNSTs are exceptionally rare tumors. MPNSTs, in this limited experience, have a fatal outcome irrespective of aggressive adjuvant therapy.

Key Words: Thyroid; schwannoma; neurilemoma; malignant peripheral nerve sheath tumor; immunohistochemistry.

This work was presented at the 85th Annual Meeting of the US and Canadian Academy of Pathology, Washington, DC, March 1996.

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Endocrine Pathology, vol. 7, no. 4, 309–318, November 1996

1046–3976/96/7:309–318/$7.50

Introduction

Primary thyroid peripheral nerve sheath tumors (PNSTs) (schwannomas and malignant PNSTs [MPNSTs]) are rare. Single reports of primary thyroid schwannomas have been documented in the literature [1–5]. To the best of our knowledge, primary thyroid MPNSTs have not been previously reported. We discuss the tumors' clinical information and pathologic features, including the immunohistochemical and ultrastructural findings, in light of a review of the literature. Our findings document the existence of true PNSTs originating in the thyroid gland, confirming that MPNSTs are not a sarcomatous component of an anaplastic carcinoma.

Materials and Methods

Two schwannomas and two MPNSTs of the thyroid gland were identified in the files of the Endocrine Tumor Registry at the Armed Forces Institute of Pathology. H&E stained slides, available in all cases, were reviewed. The cases met the criteria of a spindle cell tumor with features of Schwann cell (neural) differentiation [6].

Paraffin blocks and/or unstained slides were available in three cases. Four-micron sections were used for immunophenotypic analysis according to the avidin–biotin method of Hsu et al. [7]. A panel of commercially available antibodies included S-100 protein (rabbit polyclonal, 1:800 dilution, Dakopatts, Glostrup, Denmark),

Table 1. Clinical Features[a]

Histologic diagnosis	Age, sex	Size, cm	Clinical presentation	Outcome
Schwannoma				
Case 1	18, M	5	Enlarging mass	NED, 33 yr, LTF
Case 2	80, F	5	Growing, cystic mass	NED, 5 yr, alive
MPNST				
Case 3	33, M	3.5	Rapidly increasing mass	Died, DD, 42 mo
Case 4	69, F	7	Recently enlarging mass	Died, DD, 8 mo

[a]Abbreviations: DD, disseminated disease; LTF, lost to follow-up; NED, no evidence of disease.

vimentin (mouse monoclonal, 1:100 dilution, BioGenex Labs, San Ramon, CA), smooth muscle actin (mouse monoclonal, 1:8000 dilution, Sigma, St. Louis, MO), muscle-specific actin (mouse monoclonal, 1:50 dilution, Enzo Diagnostics, New York, NY), desmin (mouse monoclonal, 1:200 dilution, Dako, Carpinteria, CA), thyroglobulin (rabbit polyclonal, 1:100 dilution, Dako), a cytokeratin cocktail (AE1/AE3 and CK1) (AE1/AE3, mouse monoclonal, 1:50 dilution, Boehringer Mannheim, Indianapolis, IN and CK-1, mouse monoclonal, 1:200 dilution, Dako), and chromogranin (mouse monoclonal, 1:1600 dilution, Boehringer Mannheim). Cytokeratin required predigestion for 3 min with 0.05% Protease VIII (Sigma) in a 0.1*M* phosphate buffer at a pH of 7.8 at 37°C. Appropriate positive and negative controls were used throughout.

Electron microscopy was performed in three cases on formalin-fixed, paraffin-embedded tissue that was reprocessed. The blocks were deparaffinized in xylene, hydrated with graded alcohols, postfixed in osmium tetroxide, dehydrated in graded alcohols, cleared in propylene oxide, and embedded in ethylpoxy (Ernest Fullam Laboratory). Thin sections were stained with uranyl acetate and lead citrate, and were examined with a transmission electron microscope (Zeiss 109).

Results

The four patients with PNSTs had the following clinical findings (*see* Table 1).

1. Case 1: An 18-yr-old Caucasian male presented with a nodule in the right lobe of the thyroid gland. The patient had noticed an increase in size over the past 5 mo. There was no other clinical abnormality, nor was there any history of neurofibromatosis. The lesion was resected. After being followed for 33 yr without evidence of recurrence, he was recently lost to follow-up.
2. Case 2: An 80-yr-old Caucasian female presented with a slowly growing, cystic mass in the left lobe of the thyroid gland. There was no other clinical abnormality, nor was there any history of neurofibromatosis. The lesion was surgically excised, and she is alive without evidence of disease 5 yr after initial presentation.
3. Case 3: A 33-yr-old Caucasian male presented with a mass in the thyroid gland, which had suddenly increased in size over the previous 2–3 wk. He did not have any associated clinical disorders, such as neurofibromatosis. A thyroid scan demonstrated a single, cold nodule. The lobe of the thyroid gland was resected. Complications during the surgery required a tracheostomy. Within a few months of his initial thyroid surgery, a screening chest X-ray demonstrated multiple metastatic lung lesions. He was treated with radiation and chemotherapy. However, 2 yr later the metastatic lung disease had increased in size; he had developed cervical adenopathy as well as recurrence of the primary tumor at the tracheostomy stoma. He died 42 mo after initial presentation, with extensive disseminated disease, including lung, liver, and bone.

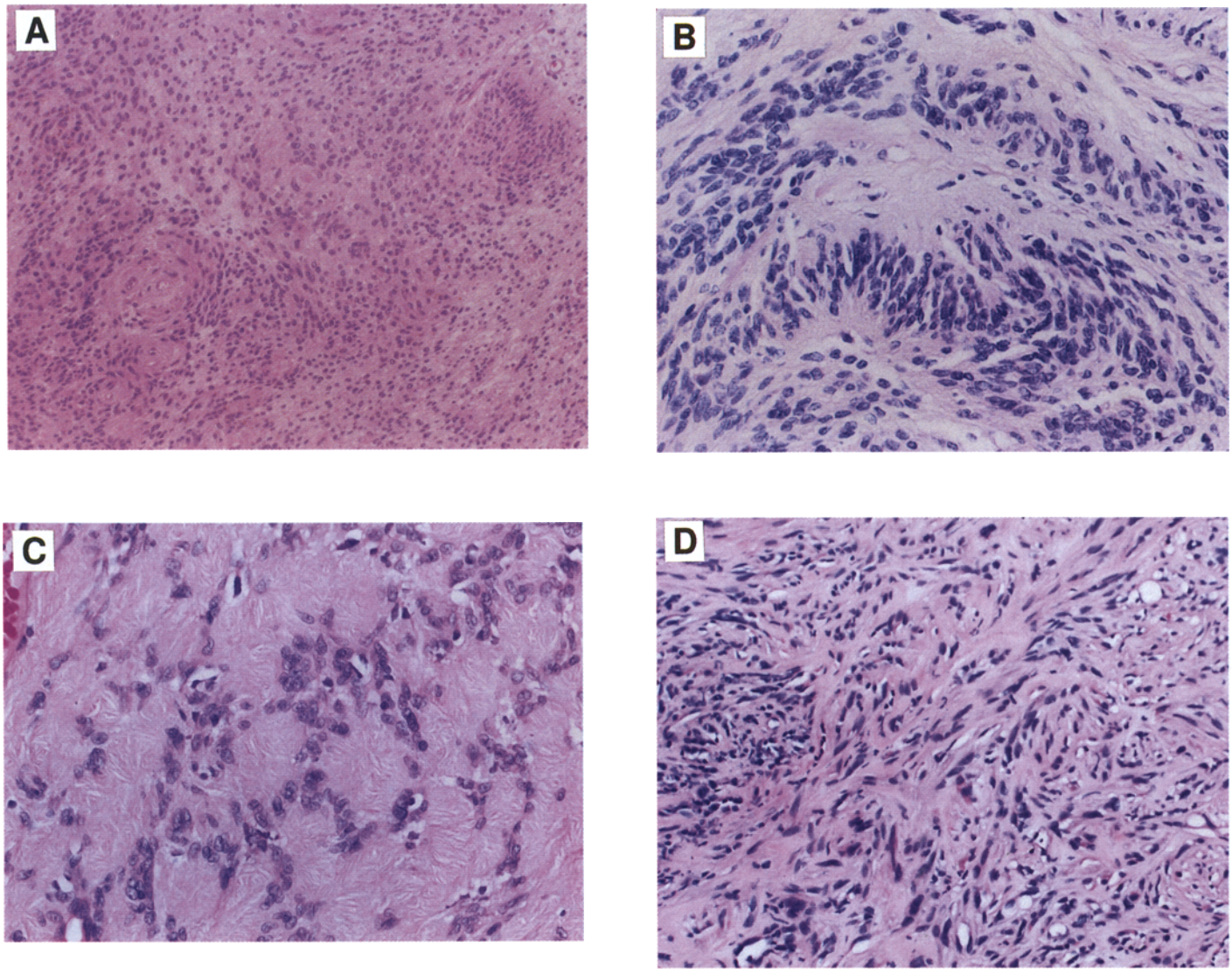

Fig. 1. (A) Low power of primary thyroid schwannoma with variable cellularity and vague palisaded arrangement. **(B)** Verocay body formations composed of spindled cells with "wavy" nuclei around acellular myxoid stroma in a thyroid schwannoma. **(C)** High power demonstrating acellular fibrous connective tissue alternating with palisaded nuclei. **(D)** Wavy to spindled appearance to the cytoplasmic extensions with elongated nuclei in a thyroid schwannoma.

4. Case 4: A 69-yr-old Caucasian female presented with Horner's syndrome and an associated lateral thyroid mass. She had no other clinical symptoms, although there had been some recent weight loss. The thyroid tumor mass was multinodular when resected, extending beyond the capsule of the thyroid gland. After the initial surgical resection, she refused any additional therapeutic intervention. She died in <1 yr with disseminated disease present in the lungs and liver.

Pathologic Features

The schwannomas (neurilemomas) were encapsulated tumors of the thyroid gland, measuring 5.0 cm in greatest dimensions. One of the schwannomas was cystic, duplicated on the histology, with a clear to yellow fluid extruded on sectioning the tumor. The tumors were variably cellular, with densely cellular areas (Antoni A) alternating with hypocellular areas (Antoni B), situated within a variably hyalinized matrix (Fig. 1A–C).

Occasional Verocay body formation was seen (Fig. 1B). The cells were fusiform with elongated cytoplasmic extensions, presenting a "wavy" to spindled appearance, containing elongated nuclei (Fig. 1B,D). The nuclei showed little pleomorphism, coarse nuclear chromatin distribution, and inconspicuous nucleoli (Fig. 1A–D). Rare mitotic figures were present but there were no atypical forms. There were several small to medium sized blood vessels with hyalinized walls (Fig. 1A). Axons were not identified within the tumor. There was no vascular or capsular invasion, necrosis or hemorrhage.

The MPNSTs measured 3.5 and 7 cm in greatest dimension, respectively. The tumors were a single dominant mass, infiltrating into the surrounding thyroid with effacement of the thyroid parenchyma (Fig. 2A, p. 314). Normal entrapped thyroid follicles could be seen at the periphery of the tumor. The tumor cells were fusiform, arranged in tightly packed fascicles woven into a vague "herringbone" type pattern (Fig. 2B,C, p. 314). In other areas the wavy cells with fibrillar cytoplasmic extensions were arranged in a loose background. The tumors were highly cellular, composed of pleomorphic cells. There were numerous mitotic figures, ranging from 6–12 mitoses per 10 high-power fields, including atypical forms (Fig. 2C). There were areas of necrosis and hemorrhage in both cases, with a slight increase in cellularity immediately surrounding the vessels. Vascular invasion was identified. Despite the invasive growth into the thyroid tissue, there was limited evidence of extrathyroidal invasion and extension of the tumor into the soft tissues of the neck. The remaining thyroid parenchyma was unremarkable.

Immunohistochemistry

The tumors showed immunoreactivity with S-100 protein (Fig. 3, p. 314) and vimentin. The S-100 protein reactivity was uncharacteristically intense in the MPNSTs. Thyroglobulin, cytokeratin, chromogranin, smooth muscle actin, muscle-specific actin, desmin, and collagen type IV were negative in the neoplastic cells (*see* Table 2).

Ultrastructural Features

By electron microscopy, features of Schwann cell derivation were present in the three cases studied. The cells demonstrated narrow to broad, entangled cell processes covered by a discrete basement membrane substance. Collagen fibers were banded together and inserted into the basal lamina. Intermediate filaments were contained within the cytoplasm. Primitive junctions were identified between tumor cells. The so called "fibrous long-spacing collagen," with its distinct periodicity, was demonstrated. We were unable to definitively identify axons on electron microscopy.

Table 2. Immunohistochemical Results[a]

Histologic diagnosis	S-100 protein	Vimentin	Muscle-specific actin	Smooth muscle actin	Type IV collagen	Keratin	Thyroglobulin
Schwannoma							
Case 1	+	n/a	n/a	–	n/a	–	–
Case 2	+	+	–	–	–	–	–
MPNST							
Case 3	+	+	–	–	–	–	–
Case 4	n/a	n/a	n/a	n/a	n/a	n/a	n/a

[a]Abbreviation: n/a, no blocks available.

Table 3. Review of the Literature[a]

Histologic diagnosis	Age, sex	Size, cm	Clinical presentation	Outcome
Schwannoma				
Andrion et al. [1,2]	33, F	5	Firm nodule in thyroid gland	Alive, NED, 1 yr (LTF)
Delaney and Fry [3]	50, F	4	Painless swelling in neck	n/s
Frantz [4]	n/s	n/s	n/s	n/s
Goldstein et al. [5]	45, M	8	Enlarging thyroid mass	n/s

[a]Abbreviations: LTF, lost to follow-up; NED, no evidence of disease; n/s, not stated.

Discussion

Primary mesenchymal tumors of the thyroid gland are rare [1–5,8–26], and primary thyroid PNSTs are an extraordinary occurrence [1–5]. Primary MPNSTs of the thyroid gland, to our knowledge, have not been previously reported, although a case of a malignant triton tumor of the thyroid gland has been reported [10]. The clinical data for the thyroid primary schwannomas that have been reported are summarized in Table 3. Similar to our schwannoma cases (case 1 and 2), the cases in the literature occurred in both genders without a specific age predilection, presented as an isolated mass or swelling, were encapsulated and confined to the thyroid, demonstrated the characteristic pathologic features, and were cured with limited but complete surgical excision [1–5]. There was no indication that any of these patients had any other thyroid disorder, neurofibromatosis, or other systemic diseases.

In contrast to their benign counterparts, the two primary thyroid MPNSTs we are reporting demonstrated malignant histologic features characterized by increased cellularity, fascicular "herringbone" arrangement, nuclear and cellular pleomorphism, coarse nuclear chromatin, prominent mitotic activity, necrosis, hemorrhage, and invasive growth. The immunohistochemical and ultrastructural evaluation we performed, confirmed the tumors' nerve sheath origin as defined in the literature [6,27–40]. No nerves or axons were identified, nor was there an associated neurofibroma. The lack of an associated nerve or neurofibroma is not uncommon, especially in relationship to MPNSTs and in patients who do not have associated neurofibromatosis [27,32,37,38,41,42].

The possibility of metastatic tumor to the thyroid must be considered. All of the thyroid PNSTs occurred in patients who did not have a primary PNST elsewhere. Numerous comprehensive studies have shown that of all the tumors to metastasize to the thyroid gland [25,43–52], very few are sarcomas [25,46,53–56]. There was no clinical association with neurofibromatosis, as defined in the recent literature [42].

Whether primary sarcomas of the thyroid gland of any cell type exist or represent anaplastic carcinomas with sarcomatoid transformation, as is believed by many authors [9,21,24,57–70], is perhaps the most argumentative issue relative to these sarcomas. In support of an epithelial derivation are reports that show anaplastic carcinomas demonstrate dual expression of cytokeratin and vimentin [24,58,59,61,62,66,69–71] but not S-100 protein, desmin, muscle-specific actin, smooth muscle actin, chromogranin, or calcitonin [24,58,59,62,66,70]. The most convincing finding of thyroid epithelial cell origin for anaplastic carcinomas with sarcomatoid transformation has been the electron microscopic findings demonstrating features consistent with an epithelial tumor

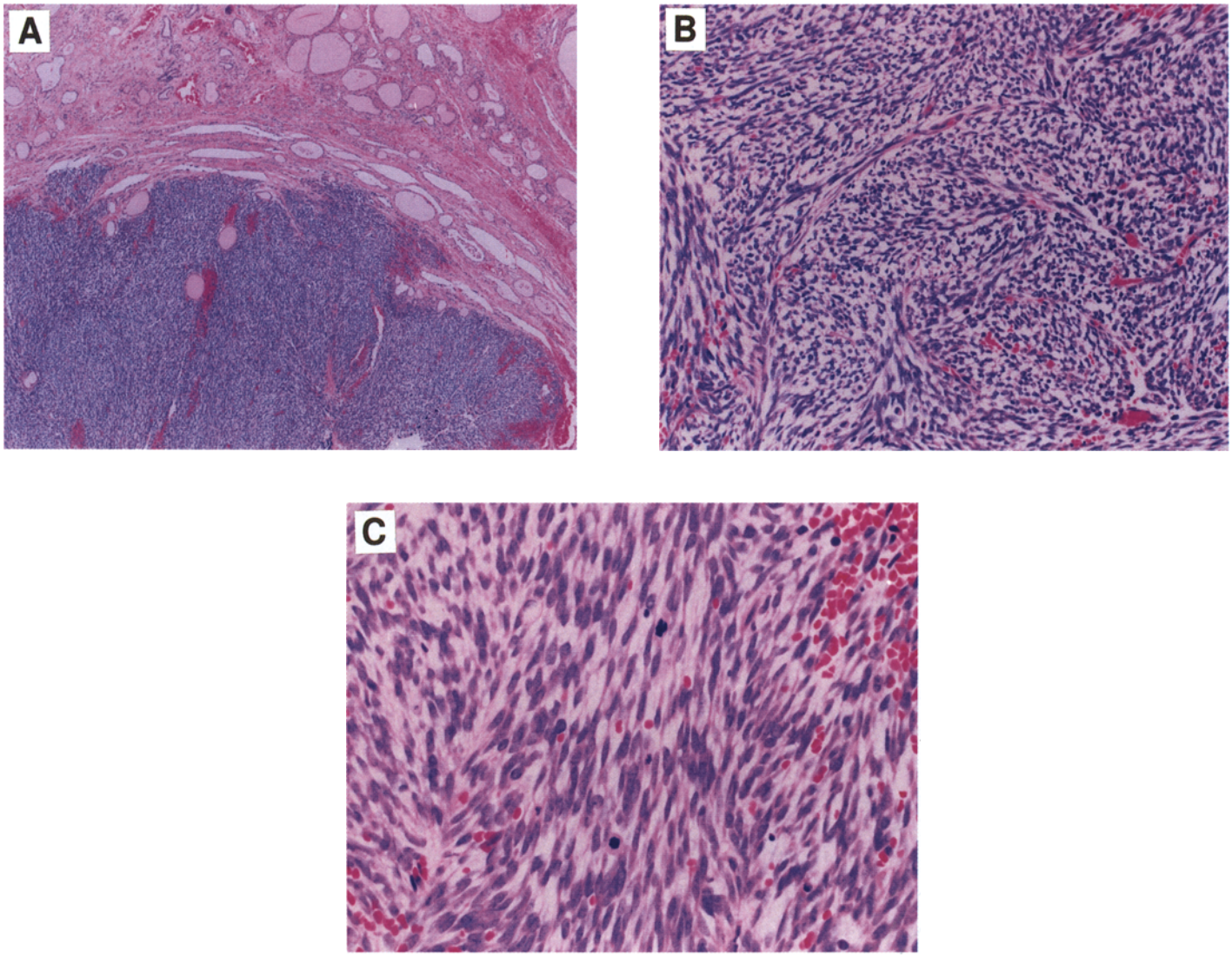

Fig. 2. (A) MPNST with invasion through the thin capsule into the surrounding thyroid parenchyma. **(B)** Tightly packed fascicles in a vague "herringbone" type pattern in a MPNST. **(C)** Pleomorphic cells with numerous mitotic figures in a MPNST.

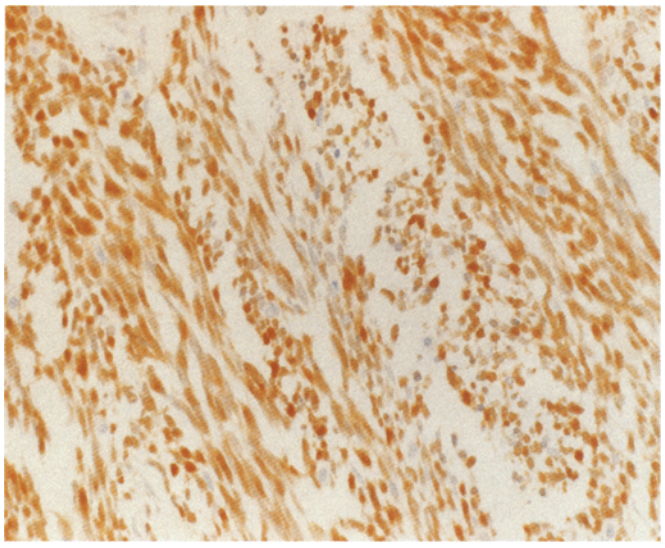

Fig. 3. S-100 protein reactivity in the tumor cells of a MPNST.

including junctional complexes, desmosomes, and terminal bars [16,24,60,72]. The fact that many anaplastic carcinomas are often seen in association with a previous thyroid lesion (long-standing goiter or carcinoma) [9,21,57,60–70,73] or show a transition between a differentiated follicular cell-derived tumor (e.g., papillary or follicular carcinoma) and the sarcomatoid foci [15,16,57,59,61,62,64–70,72,74], further supports an epithelial histogenesis.

The WHO classification of thyroid tumors requires that a primary thyroid sarcoma should only be diagnosed when there is a complete absence of all epithelial differentiation and there is definite evidence of specific sarcomatous differentiation [75]. We believe that the magnitude of evidence in our cases supports a diagnosis of primary PNST of the thyroid gland. The existence of thyroid schwannomas is indisputable. Therefore, if a thyroid schwannoma exists, then it is reasonable to presume that its malignant counterpart may also arise in this organ. The existence of thyroid MPNSTs is bolstered by their clinical presentation and pathologic features. The MPNSTs occurred as isolated masses that developed over a short interval, were unassociated with a pre-existing thyroid lesion (goiter or neoplasm), and occurred in glands that had not been previously irradiated (external or radioiodine). Further, none of our cases occurred in patients with any history of a primary (PNST) tumor elsewhere. These clinical features sharply contrast with those associated with either anaplastic carcinoma or metastatic sarcomas to the thyroid gland. There was also a lack of clinical evidence for neurofibromatosis. Pathologically, the MPNSTs were confined to a single lobe with an infiltrative growth into the thyroid parenchyma. These tumors showed morphologic and ultrastructural characteristics of a MPNST and had an immunophenotype consistent with Schwann cell origin including S-100 protein and vimentin. More importantly, these tumors were uniformly negative with thyroglobulin, keratin, chromogranin, and calcitonin, which, in concert with the aforementioned reactions, virtually negates the possibility of epithelial or neuroendocrine derivation from follicular epithelial cells or C-cells, respectively. There was no other immunohistochemical reactivity to support the notion of another type of sarcoma (i.e., fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma, or angiosarcoma).

We believe the histogenesis of thyroid gland PNSTs includes the sympathetic and parasympathetic innervation (cervical plexus) or possibly the sensory nerves [5,30,37,38,41,76] (i.e., theoretically any of the nerves in or around the thyroid gland). Although we were unable to identify a specific nerve within the tumor, one of our cases (case 4) presented clinically with Horner's syndrome. This may support an origin from the cervical sympathetic plexus nerves, although we cannot definitively exclude invasion by the tumor into the nerve plexus.

We believe that the constellation of clinical and pathologic findings in our cases confirms the existence of primary thyroid PNSTs. Certainly, the possibility that the tumors have been inadequately sampled, potentially overlooking a small portion of epithelial differentiation or transitional zone between a differentiated thyroid tumor and the sarcomatoid foci, needs to be considered [15,23,65]. However, our cases have been extensively sampled.

Unfortunately, primary thyroid MPNSTs share a similar biology with thyroid anaplastic carcinomas. These are high-grade and aggressive tumors that are lethal within a short time following diagnosis and appear unresponsive to all modes of therapy. This

is similar to MPNSTs in other anatomic locations, which have a 5-yr survival rate of 16–53% [35,37,38,41,77,78].

Acknowledgments

The authors thank Robin-Anne V. Ferris for her expert photography, Efran Perez-Rosario for his electron microscopy work, and Pamela A. Thompson for her conscientious research assistance. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy, Department of the Army, or the Department of Defense.

References

1. Andrion A, Bellis D, Delsedime L, Bussolati G, Mazzucco G. Leiomyoma and neurilemoma: report of two unusual non-epithelial tumours of the thyroid gland. Virchows Arch A Pathol Anat 413:367–372, 1988.
2. Andrion A, Mazzucco G, Torchio B. FNA cytology of thyroid neurilemoma (Schwannoma). Diag Cytopathol 8:311, 312, 1992.
3. Delaney WE, Fry KE. Neurilemoma of the thyroid gland. Ann Surg 160:1014–1016, 1964.
4. Frantz VK. Pathology of the thyroid. In: Werner SC, ed. The thyroid: a fundamental and clinical text. 2nd ed. New York, NY: Hoeber Medical Books, Harper and Row, 1962; 321.
5. Goldstein J, Tovi F, Sidi J. Primary Schwannoma of the thyroid gland. Int Surg 67: 433,434, 1982.
6. Enzinger FM, Weiss SW. Benign and malignant tumors of peripheral nerves. In: Enzinger FM, Weiss SW, eds. Soft tissue tumors. 3rd ed. St. Louis, MO: CV Mosby, 1995; 821–928.
7. Hsu SM, Raine L, Fanger H. Use of avidin-biotin peroxidase complex (ABC) in immunoperoxidase techniques. A comparison between ABC and unlabeled antibody (PAP) procedures. J Histochem Cytochem 29:557–580, 1981.
8. Adachi M, Wellmann KF, Garcia R. Metastatic leiomyosarcoma in brain and heart. J Pathol 98:294–296,1969.
9. Aldinger KA, Samaan NA, Ibanez M, Hill CS Jr. Anaplastic carcinoma of the thyroid. A review of 84 cases of spindle and giant cell carcinoma of the thyroid. Cancer 41:2267–2275, 1978.
10. Boos S, Meyer E, Wimmer B, Windfuhr M. Malignant triton tumor of the thyroid gland. Rad Med 9:159–161, 1991.
11. Bosse MD. Hemangioendothelial sarcoma of thyroid. Arch Pathol 36:316, 1943.
12. Chan YF, Ma L, Boey JH, Yeung HY. Angiosarcoma of the thyroid. An immunohistochemical and ultrastructural study of a case in a Chinese patient. Cancer 57:2381–2388, 1986.
13. Chesky VE, Dreese WC, Hellwig CA. Hemangioendothelioma of the thyroid. Review of the literature and report of a case. J Clin Endocrinol 13:801–808, 1953.
14. Chesky VE, Hellwig CA, Welch JW. Fibrosarcoma of the thyroid gland. Surg Gynecol Obstet 111:767–770, 1960.
15. Chetty R, Clark SP, Dowling JP. Case report: leiomyosarcoma of the thyroid: immunohistochemical and ultrastructural study. Pathology 25:203–205, 1993.
16. Fisher ER, Gregorio R, Shoemaker R, Horvat B, Hubay C. The derivation of so-called giant-cell and spindle cell undifferentiated thyroidal neoplasms. Am J Clin Pathol 61:680–689, 1974.
17. Glass HG, Waldron GW, Brown WG. Coexistent sarcoma, adenocarcinoma and Hashimoto's disease in a thyroid gland. Cancer 9:310–316, 1956.
18. Hendrick JW. Leiomyoma of thyroid gland. Surg 42:597–599, 1957.
19. Hedinger C. Sarcomas of the thyroid gland. In: Hedinger E, ed. Thyroid cancer. New York, NY: Springer-Verlag, 1969; 47–52.
20. Iida Y, Katoh R, Yoshioka M, Oyama T, Kawaoi A. Case report: primary leiomyosarcoma of the thyroid gland. Acta Pathol Jpn 43:71–75, 1993.
21. Kaur A, Jayaram G. Thyroid tumors: cytomorphology of medullary, clinically anaplastic, and miscellaneous thyroid neoplasms. Diag Cytopathol 6:383–389, 1990.
22. Kawahara E, Nakanishi I, Terahata S, Ikegaki S. Leiomyosarcoma of the thyroid gland: a case report with a comparative study of five cases of anaplastic carcinoma. Cancer 62:2558–2563, 1988.

23. Meissner WA, Warren S. Other benign tumors and Other sarcomas. In: Atlas of tumor pathology, 2nd ser., Fascicle 4, Washington, DC: Armed Forces Institute of Pathology, 1969; 53, 123–126.
24. Miettinen M, Franssila K, Lehto V-P, Paasivuo R, Virtanen I. Expression of intermediate filament proteins in thyroid gland and thyroid tumors. Lab Invest 50:262–270, 1984.
25. Shimaoka K, Sokal JE, Pickren JW. Metastatic neoplasms in the thyroid gland. Pathological and clinical findings. Cancer 15:557–565, 1962.
26. Shin W-Y, Aftalion B, Hotchkiss E, Schenkman R, Berkman J. Ultrastructure of a primary fibrosarcoma of the human thyroid gland. Cancer 44:584–591, 1979.
27. Daimaru Y, Hashimoto H, Enjoji M. Malignant peripheral nerve-sheath tumors (malignant Schwannomas). An immunohistochemical study of 29 cases. Am J Surg Pathol 9:434–444, 1985.
28. Dickersin GR. The electron microscopic spectrum of nerve sheath tumors. Ultrastruct Pathol 11:103–146, 1987.
29. Erlandson RA. Peripheral nerve sheath tumors. Ultrastruct Pathol 9:113–122, 1985.
30. Fletcher CDM. Malignant peripheral nerve sheath tumours. In: Harms D, Schmidt D, eds. Current topics in pathology, vol. 89. Berlin-Heidelberg: Springer-Verlag, 1995; 333–354.
31. Gray MH, Rosenberg AE, Dickersin GR, Bhan AK. Glial fibrillary acidic protein and keratin expression by benign and malignant nerve sheath tumors. Hum Pathol 20:1089–1096, 1989.
32. Harkin JC, Reed RJ. Tumors of the peripheral nervous system. Atlas of tumor pathology, 2nd ser., Washington, DC: Armed Forces Institute of Pathology, 1969; 67–107.
33. Herrera GA, de Moraes HP. Neurogenic sarcomas in patients with neurofibromatosis (von Recklinghausen's disease). Light, electron microscopy and immunohistochemical study. Virchows Arch [Path Anat] 403:361–376, 1984.
34. Hirose T, Hasegawa T, Kudo E, Seki K, Sano T, Hizawa K. Malignant peripheral nerve sheath tumors: an immunohistochemical study in relation to ultrastructural features. Hum Pathol 23:865–870, 1992.
35. Matsunou H, Shimoda T, Kakimoto S, Yamashita H, Ishikawa E, Mukai M. Histopathologic and immunohistochemical study of malignant tumors of peripheral nerve sheath (malignant Schwannoma). Cancer 56:2269–2279, 1985.
36. Nakajima T, Kameya T, Watanabe S, Hirota T, Sato Y, Shimosato Y. An immunoperoxidase study of S-100 protein distribution in normal and neoplastic tissues. Am J Surg Pathol 6:715–727, 1982.
37. Vege DS, Chinoy RF, Ganesh B, Parikh DM. Malignant peripheral nerve sheath tumors of the head and neck: a clinicopathological study. J Surg Oncol 55:100–103, 1994.
38. Wanebo JE, Malik JM, VandenBerg SR, Wanebo HJ, Driesen N, Persing JA. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 28 cases. Cancer 71:1247–1253, 1993.
39. Weiss SW, Langloss JM, Enzinger FM. Value of S-100 protein in the diagnosis of soft tissue tumors with particular reference to benign and malignant Schwann cell tumors. Lab Invest 49:299–308, 1983.
40. Wick MR, Swanson PE, Scheithauer BW, Manivel JC. Malignant peripheral nerve sheath tumor. An immunhistochemical study of 62 cases. Am J Clin Pathol 87:425–433, 1987.
41. Ducatman BS, Scheithauer BW, Piepgras DG, Reiman HM, Ilstrup DM. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. Cancer 57:2006–2021, 1986.
42. Riccardi VM. Neurofibromatosis update. Neurofibromatosis 2:284–291, 1989.
43. Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma. Analysis of 1000 autopsied cases. Cancer 3:74–85, 1950.
44. Czech JM, Lichtor TR, Carney JA, van Heerden JA. Neoplasms metastatic to the thyroid gland. Surg Gynecol Obstet 155:503–505, 1982.
45. Elliott RHE Jr, Frantz VK. Metastatic carcinoma masquerading as primary thyroid cancer: a report of authors' 14 cases. Ann Surg 151:551–561, 1960.
46. Ivy HK. Cancer metastatic to the thyroid: a diagnostic problem. Mayo Clin Proc 59:856–859, 1984.
47. McCabe DP, Farrar WB, Petkov TM, Finkelmeier W, O'Dwyer P, James A. Clinical and pathologic correlations in disease metastatic to the thyroid gland. Am J Surg 150:519–523, 1985.
48. Mortensen JD, Woolner LB, Bennett WA. Secondary malignant tumors of the thyroid gland. Cancer 9:306–309, 1956.

49. Rice CO. Microscopic metastases in the thyroid gland. Am J Pathol 10:407–412, 1934.
50. Silverberg SG, Vidone RA. Metastatic tumors in the thyroid. Pacif Med Surg 74:175–180, 1966.
51. Watanabe I, Tsuchiya A. Secondary carcinoma of the thyroid gland. Jap J Surg 10:130–136, 1980.
52. Wychulis AR, Beahrs OH, Woolner LB. Metastasis of carcinoma to the thyroid gland. Ann Surg 160:169–177, 1964.
53. Bode-Lesniewska B, Schröder S, Gemsenjäger E, Stäubli M, Pfaltz M. Leiomyosarcoma in the thyroid gland—primary or metastatic tumor? Pathologe 15:303–307, 1994.
54. Cruickshank JC. Case report: leiomyosarcoma metastatic to the thyroid gland. Ear Nose Throat J 67:899–910, 1988.
55. Gattuso P, Castelli MJ, Reyes CV. Fine needle aspiration cytology of metastatic sarcoma involving the thyroid. South Med J 82:1158–1160, 1989.
56. Shimota H, Satoh T, Ishi K, Iwase A. An autopsy case of primary lung leiomyosarcoma. Jpn J Clin Pathol 39:666–670, 1991.
57. Carcangiu ML, Steeper T, Zampi G, Rosai J. Anaplastic thyroid carcinoma: a study of 70 cases. Am J Clin Pathol 83:135–158, 1985.
58. Dockhorn-Dworniczak B, Franke WW, Schröder S, Czernobilsky B, Gould VE, Böcker W. Patterns of expression of cytoskeletal proteins in human thyroid gland and thyroid carcinomas. Differentiation 35:53–71, 1987.
59. Eckert F, Schmid U, Gloor F, Hedinger C. Evidence of vascular differentiation in anaplastic tumours of the thyroid: an immunohistological study. Virchows Arch A 410: 203–215, 1986.
60. Johannessen JV, Gould VE, Jao W. The fine structure of human thyroid cancer. Hum Pathol 9:385–400, 1978.
61. LiVolsi VA. Surgical pathology of the thyroid. In: Major problems in pathology, vol. 2. Philadelphia: Saunders, 1991; 253–270.
62. LiVolsi VA, Brooks JJ, Arendash-Durand B. Anaplastic thyroid tumors: immunohistology. Am J Clin Pathol 87:434–442, 1987.
63. Mills SE, Stallings RG, Austin MB. Angiomatoid carcinoma of the thyroid gland. Anaplastic carcinoma with follicular and medullary features mimicking angiosarcoma. Am J Clin Pathol 86:674–678, 1986.
64. Nel CJC, van Heerden JA, Goellner JR, Gharib H, McConahey WM, Taylor WF, Grant CS. Anaplastic carcinoma of the thyroid: a clinicopathologic study of 82 cases. Mayo Clin Proc 60:51–58, 1985.
65. Nishiyama RH, Dunn EL, Thompson NW. Anaplastic spindle-cell and giant-cell tumors of the thyroid gland. Cancer 30:113–127, 1972.
66. Ordóñez NG, El-Naggar AK, Hickey RC, Samaan NA. Anaplastic thyroid carcinoma. Immunohistochemical study of 32 cases. Am J Clin Pathol 96:15–24, 1991.
67. Rosai J, Carcangiu ML. Pitfalls in the diagnosis of thyroid neoplasms. Pathol Res Pract 182:169–179, 1987.
68. Schneider V, Frable WJ. Spindle and giant cell carcinoma of the thyroid. Cytologic diagnosis by fine needle aspiration. Acta Cytol 24:184–189, 1980.
69. Schröder S, Dockhorn-Dworniczak B, Kastendieck H, Böcker W, Franke WW. Intermediate-filament expression in thyroid gland carcinomas. Virchows Arch [Pathol Anat] 409:751–766, 1986.
70. Venkatesh YSS, Ordóñez NG, Schultz PN, Hickey RC, Goepfert H, Samaan NA. Anaplastic carcinoma of the thyroid: a clinicopathologic study of 121 cases. Cancer 66:321–330, 1990.
71. Beltrami CA, Criante P, Di Loreto C. Immunocytochemistry of anaplastic carcinoma of thyroid gland. Appl Pathol 7:122–133, 1989.
72. Graham H, Daniel C. Ultrastructure of an anaplastic carcinoma of the thyroid. Am J Clin Pathol 61:690–696, 1974.
73. Hedinger C. Geographic pathology of thyroid diseases. Pathol Res Pract 171:285–292, 1981.
74. Ibanez ML, Russell WO, Albores-Saavedra J, Lampertico P, White EC, Clark RL. Thyroid carcinoma: biologic behavior and mortality. Postmortem findings in 42 cases, including 27 cases in which the disease was fatal. Cancer 19:1039–1052, 1966.
75. Hedinger C, Williams ED, Sobin LH. Histologic typing of thyroid tumors. 2nd ed. In: International histologic classification of tumours. Berlin, Germany: WHO Springer Verlag, 1988; 13–15.
76. Katz AD, McAlpin C. Face and neck neurogenic neoplasms. Am J Surg 166:421–423, 1993.
77. Das Gupta TK, Brasfield RD. Solitary malignant Schwannoma. Ann Surg 171:419–428, 1970.
78. Doorn PF, Molenaar WM, Buter J, Hoekstra HJ. Malignant peripheral nerve sheath tumors in patients with and without neurofibromatosis. Eur J Surg Oncol 21:78–82, 1995.