Original Article

The Cytopathology of Malignant Peripheral Nerve Sheath Tumor

A Report of 55 Fine-Needle Aspiration Cases

Paul E. Wakely, Jr, MD[1]; Syed Z. Ali, MD[2]; and Justin A. Bishop, MD[2]

BACKGROUND: Among sarcomas, a diagnosis of malignant peripheral nerve sheath tumor (MPNST) is often one of exclusion due to the absence of unequivocally characteristic histopathology, a conclusive immunohistochemical profile, or even a unique chromosomal anomaly. Because of this, the fine-needle aspiration (FNA) cytopathology of MPNST is extremely challenging. In the current study, the authors review their FNA experience with this neoplasm. **METHODS:** The authors searched their combined departmental cytology files for all lesions signed out as MPNST or suspicious for MPNST, as well as their own surgical pathology files for any cases of MPNST that had corresponding cytology. FNA was performed using standard techniques. **RESULTS:** A total of 55 cases of MPNST, all with tissue confirmation, and 1 misdiagnosed example of melanoma were retrieved from 52 patients (M:F ratio of 1.5:1; average age, 46 years), 26 of whom had a history of neurofibromatosis type 1 (NF-1). Aspirates were from primary (27 cases), locally recurrent (14 cases), or metastatic (10 cases) MPNST; 4 primary tumor aspirates were of ex vivo specimens. Sites included the extremities (22 cases), trunk/pelvis (22 cases), head and neck (6 cases), and deep-seated masses (6 cases). FNA diagnoses were MPNST (24 patients); consistent with MPNST (5 patients); sarcoma, not otherwise specified (10 patients); atypical (3 patients); spindle cell neoplasm (6 patients); malignant neoplasm (1 patient); and nondiagnostic (3 patients). A definitive diagnosis of either MPNST or consistent with MPNST was issued in 30%, 93%, and 70%, respectively, of primary, locally recurrent, and metastatic lesions. **CONCLUSIONS:** FNA cytopathology is limited as a diagnostic instrument for the initial diagnosis of MPNST, but is exceedingly accurate and valuable in the recognition of metastatic and locally recurrent MPNST. ***Cancer (Cancer Cytopathol)* 2012;000:000–000.** © *2012 American Cancer Society.*

KEY WORDS: fine-needle aspiration biopsy, malignant peripheral nerve sheath tumor, sarcoma, epithelioid.

INTRODUCTION

As defined in the latest World Health Organization classification, malignant peripheral nerve sheath tumor (MPNST) is one of the few sarcomas in which the clinicoradiologic knowledge is nearly as important as any histopathologic feature. This classification states that MPNST is defined as a sarcoma that either arises from a peripheral nerve; a preexisting benign nerve sheath neoplasm; demonstrates nerve sheath differentiation in a patient with neurofibromatosis type 1 (NF-1; von Recklinghausen disease); or exhibits the histopathology, immunohistology, or ultrastructural features of Schwann cell or perineural differentiation in a non-NF-1 patient.[1,2] These sarcomas are among the least common mesenchymal malignancies, and

Corresponding author: Paul E. Wakely, Jr, MD, Department of Pathology, Wexner Medical Center, Ohio State University, 414 Doan Hall/410 West 10th Ave, Columbus, OH 43210; Fax: (614) 293-7626; paul.wakely@osumc.edu

[1]Department of Pathology, Wexner Medical Center, Ohio State University, Columbus, Ohio; [2]Department of Pathology, Johns Hopkins Hospital, Baltimore, Maryland.

Received: February 22, 2012; **Accepted:** February 27, 2012

Published online in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/cncy.21195, wileyonlinelibrary.com

slightly greater than one-half of all cases arise in individuals with NF-1. NF-1 associated neoplasms develop approximately 10 years earlier than sporadic examples of MPNST.

Among patients with sarcoma, a diagnosis of MPNST is elusive, and absent the clinical criteria alluded to previously is often one of exclusion due to the lack of a universally distinctive histopathology, a conclusive immunohistochemical profile, or even a unique chromosomal anomaly. Because of its rarity, diagnostically demanding nature, and limited exposure in the cytology literature, we sought to review our fine-needle aspiration (FNA) biopsy experience (and attendant pitfalls) with this neoplasm in what to our knowledge is the largest series collected to date.

MATERIALS AND METHODS

Case Selection

We reviewed our cytology files from the past 16 years in search of all cases signed out as MPNST or malignant schwannoma. Surgical pathology files also were searched for any examples of MPNST with a prior FNA to capture any false-negative cases.

Technique

Percutaneous FNA biopsy was performed using a standard technique with 21-gauge or 22-gauge needles. Three to 4 passes were made into a lesion, and each pass was rinsed in a balanced salt solution after expelling cell material onto glass slides for the creation of conventionally made direct smears. Slides were stained using both Papanicolaou and Romanowsky stains. Formalin-fixed, paraffin-embedded cell block sections were stained with hematoxylin and eosin.

Immunohistology performed from cell block material used antibodies to epithelial membrane antigen (EMA), vimentin, neuron-specific enolase, synaptophysin, muscle-specific actin, desmin, S-100 protein, myogenin, CD117, CD45, and cytokeratin AE1/3 in an inconsistent fashion. Antibody use was predicated on the amount of material in the cell block, if any, and diagnostic considerations at the time.

RESULTS

We recovered 55 cases of MPNST and 1 case of amelanotic malignant melanoma that was erroneously diagnosed as epithelioid MPNST from 52 patients. Patients ranged in age from 9 years to 92 years (average age, 46 years) with a male:female ratio of 1.5:1. One-half of the patients (26 of 52 patients) had NF-1. There were no examples of postradiation MPNST. FNA samples were obtained from primary soft tissue neoplasms (32 cases), locally recurrent neoplasms (14 cases), or metastatic deposits (10 cases). Four of the primary FNA specimens were obtained from ex vivo specimens (Table 1). The extremities were the most common site for FNA biopsy (22 cases), followed by the trunk/pelvis (22 cases), head and neck (6 cases), and other deep-seated masses (6 cases). Twenty-nine FNA samples were diagnosed categorically as MPNST (24 cases) or consistent with MPNST (5 cases). One example (case 14) erroneously diagnosed as epithelioid MPNST was found to be amelanotic malignant melanoma. The remaining cytologic diagnoses were sarcoma, not otherwise specified (10 cases); atypical cells (3 cases); spindle cell neoplasm (6 cases); malignant neoplasm (1 case); and nondiagnostic (3 cases). A categorical diagnosis of either MPNST or consistent with MPNST (excluding 4 ex vivo aspirates and 1 incorrect diagnosis) was issued in 28 of 51 cases (55%). When the cases were subdivided further, only 8 of 27 (30%) but 13 of 14 (93%) and 7 of 10 (70%) aspirates of primary, locally recurrent, and metastatic lesions, respectively, were diagnosed specifically. Of 14 patients with NF-1 who had an FNA biopsy performed on their primary neoplasm, 50% (7 patients) had a diagnosis of MPNST or consistent with MPNST made; 4 of these individuals did not demonstrate evidence on smears that was sufficient for even a diagnosis of sarcoma.

Cytologic features were similar in all but 4 FNA specimens. The majority of smears were highly cellular, but this was somewhat variable because in a minority of FNAs either fibrosis within the sarcoma precluded aspirating large numbers of cells in some or abundant blood aspirated with neoplastic cells in others had a dilutional effect. Cell arrangement was comprised of numerous single dissociated cells, and syncytial cell clusters of uneven size and cellularity in nearly every case. Many clusters were sufficiently hypercellular to produce a 3-dimensional effect leading to the inability to observe cells in the center of these aggregates. In some cases, parallel cell polarity created a vague fascicular arrangement within aggregates (Figs. 1A and 1B). Individual cell necrosis was inconspicuous in general, and large

Table 1. Clinical Features of 56 FNA Samples Diagnosed as MPNST

Case No.[a]	Age, Years/Sex	Tumor Site	FNA Diagnosis	Cell Block	P/Re/M	IHC From FNA	History of NF-1
1	30/Male	Shoulder	MPNST	No	Re	No	No
2	22/Female	Arm	Sarcoma c/w MPNST	No	P	No	Yes
3	49/Male	Thigh	Ex vivo FNA	NA	P	NA	No
4	42/Male	Chest wall	MPNST	No	Re	No	No
5	84/Female	Wrist	Suspicious for MPNST	No	P	No	No
6	52/Male	Chest	MPNST	No	Re	No	No
7	79/Female	Right thigh	Sarcoma with epithelioid features	Yes	P	No	No
8	29/Male	Left thigh	MPNST	Yes	Re	No	Yes
9	65/Male	Buttock	Ex vivo FNA	NA	P	NA	No
10	28/Female	Left neck	Suspicious for MPNST	Yes	P	No	Yes
11	56/Male	Right forearm	MPNST	Yes	P	No	Yes
12	62/Male	Right lung apex	Spindle cell sarcoma	Yes	Re	No	No
13	31/Male	Left leg	MPNST	Yes	Re	No	Yes
14	89/Female	Anterior calf	MPNST, epithelioid	Yes	P	Positive for vimentin and S-100 protein; negative for EMA, MSA, HMB-45, CD31, and CK	No (true diagnosis MM)
15	25/Male	Left buttock	MPNST	No	Re	No	Yes
16	40/Female	Right hip	Ex vivo FNA	NA	P	NA	Yes
17	53/Female	Left flank	Sarcoma c/w MPNST	Yes	M	No	No
18	72/Male	Left calf	Spindle cell sarcoma	Yes	P	No	No
19	49/Male	Right arm	MPNST	Yes	P	No	Yes
20	38/Female	Left arm	MPNST	Yes	Re	No	Yes
21	40/Male	Head of pancreas	MPNST	Yes	M	Positive for vimentin, CD10, and S-100 protein; negative for CK	No
22	39/Male	Left neck	MPNST	Yes	P	No	Yes
23	39/Male	Left neck	Spindle cell sarcoma	Yes	P	No	Yes
24	31/Male	Thigh	Ex vivo FNA	NA	P	NA	Yes
25	36/Female	Right chest wall	MPNST	No	M	No	Yes
26	48/Female	Posterior thigh	c/w MPNST	Yes	Re	No	No
27	52/Male	Right cheek	MPNST	Yes	Re	No	Yes
28	26/Female	Pelvis	Atypical cells	Yes	P	Noncontributory	Yes
29	64/Male	Rib	Nondiagnostic	Yes	P	No	No
30	38/Female	Right thigh	High-grade sarcoma	Yes	P	No	Yes
31	75/Female	Right kidney	MPNST	Yes	M	Positive for S-100 protein; negative for CK	No
32	41/Female	Arm	Nondiagnostic	Yes	P	Noncontributory	No
33	62/Female	Pelvis	Spindle cell lesion	Yes	P	Positive for vimentin and Ki-67; negative for S-100 protein, desmin, CK, and CD45	Yes
34	32/Male	Pleura	MPNST	Yes	M	Positive for S-100 protein; negative for calretinin	Yes
35	32/Male	Lung	MPNST	Yes	M	Positive for S-100 protein and vimentin.; negative for CK, desmin, and HMB-45	Yes
36	32/Male	Right clavicle	MPNST	Yes	M	No	No
37	17/Male	T12 soft tissue	Sarcoma	Yes	M	Positive for S-100 protein and vimentin; negative for CK, EMA, and CD34	No

(Continued)

Table 1. Clinical Features of 56 FNA Samples Diagnosed as MPNST (Continued)

Case No.[a]	Age, Years/Sex	Tumor Site	FNA Diagnosis	Cell Block	P/Re/M	IHC From FNA	History of NF-1
38	45/Male	Right buttock	MPNST	Yes	Re	Positive for S-100 protein and NSE; 20% positive for Ki-67	Yes
39	39/Female	Right neck	MPNST	Yes	Re	No	No
40	52/Male	Left calf	MPNST	Yes	Re	Focal positivity for S-100 protein; negative for CK, desmin, and myogenin	Yes
41	30/Male	Left buttock	Spindle cell neoplasm	Yes	P	No	Yes
42	38/Female	Left supraclavicular	MPNST	No	Re	No	Yes
43	31/Male	Right posterior thigh	MPNST	Yes	P	Negative for myogenin	Yes
44	60/Male	Retroperitoneum	Spindle cell neoplasm	Yes	P	Positive for S-100 protein; negative for CK, c-kit, desmin, and mdm-2	No
45	33/Male	Right brachial plexus	High-grade sarcoma	Yes	P	No	No
46	47/Female	Left forearm	Spindle cell sarcoma	No	P	No	No
47	71/Female	Left knee	Atypical cells	No	P	No	Yes
48	53/Female	Right brachial plexus	MPNST	Yes	P	Focal positivity for S-100 protein; high Ki-67 index	Yes
49	26/Male	T10-11 soft tissue	High-grade malignant neoplasm	Yes	P	Negative for S-100 protein	Yes
50	70/Female	Left femur	Nondiagnostic	No	M	No	No
51	59/Female	Right pelvis	Malignant spindle cell neoplasm	No	P	No	No
52	9/Male	Right pelvis	Spindle cell neoplasm	No	P	No	No
53	56/Male	Right brachial plexus	Spindle cell sarcoma	Yes	P	No	No
54	35/Male	Sacrum	High-grade sarcoma	Yes	P	No	Yes
55	35/Male	Right chest wall	Spindle cell neoplasm	Yes	M	No	Yes
56	92/Male	Sternum	Rare atypical spindle cells	No	P	No	No

Abbreviations: CK, cytokeratin; c/w, consistent with; EMA, epithelial membrane antigen; FNA, fine-needle aspiration; IHC, immunohistochemistry; MM, malignant melanoma; M, metastatic; MPNST, malignant peripheral nerve sheath tumor; MSA, muscle-specific actin; NA, not applicable; NF-1, neurofibromatosis type 1; NSE, neuron-specific enolase; P, primary; Re, locally recurrent.
Cases 8 and 13, 22 and 23, 34 and 35, and 54 and 55 are the same patients.

foci of necrosis were apparent in only 2 cases. Smear background was mostly clean, but some aspirates contained strips of collagen or fibrillar metachromatic-staining stroma (Figs. 1C and 1D). The most common appearance of singly dispersed cells was *uniformity* of size and shape. Primarily nuclei were oval, but were also elongated with smooth contours and inconsistently tapered or blunt-ended. In some cases, nuclei had a slight "hook" at 1 pole, producing a so-called comma shape. Slender serpiginous waviness of nuclear outlines, although present, was not universal, nor was even the dominant shape except in a few FNA samples; true nuclear palisades were absent. The cells had finely granular, evenly dispersed nuclear chromatin with small chromocenters; coarsely granular chromatin and macronucleoli were rare findings (Figs. 2A-2C). Only a very small number of FNA specimens contained conspicuous anisonucleosis or multinucleation. Marked cellular pleomorphism was encountered in 2 cases in which the histopathology demonstrated poorly differentiated MPNST (Figs. 2D and 2E). Cytoplasm was typically sparse and had no special features. In some aggregates, the cell cytoplasm had long interconnecting processes creating a reticular network (Fig. 2B). Bare nuclei were common.

None of our cases were examples of MPNST with glandular differentiation or contained foci of angiosarcoma; however, 1 case demonstrated heterologous chondroid differentiation in the resection specimen and another case exhibited rhabdomyoblastic differentiation (ie, malignant triton tumor) (not sampled by FNA in both cases). Four cases had smears populated almost exclusively by cells with rounded nuclei. Two of these had minimal cytoplasm imitating to some degree the

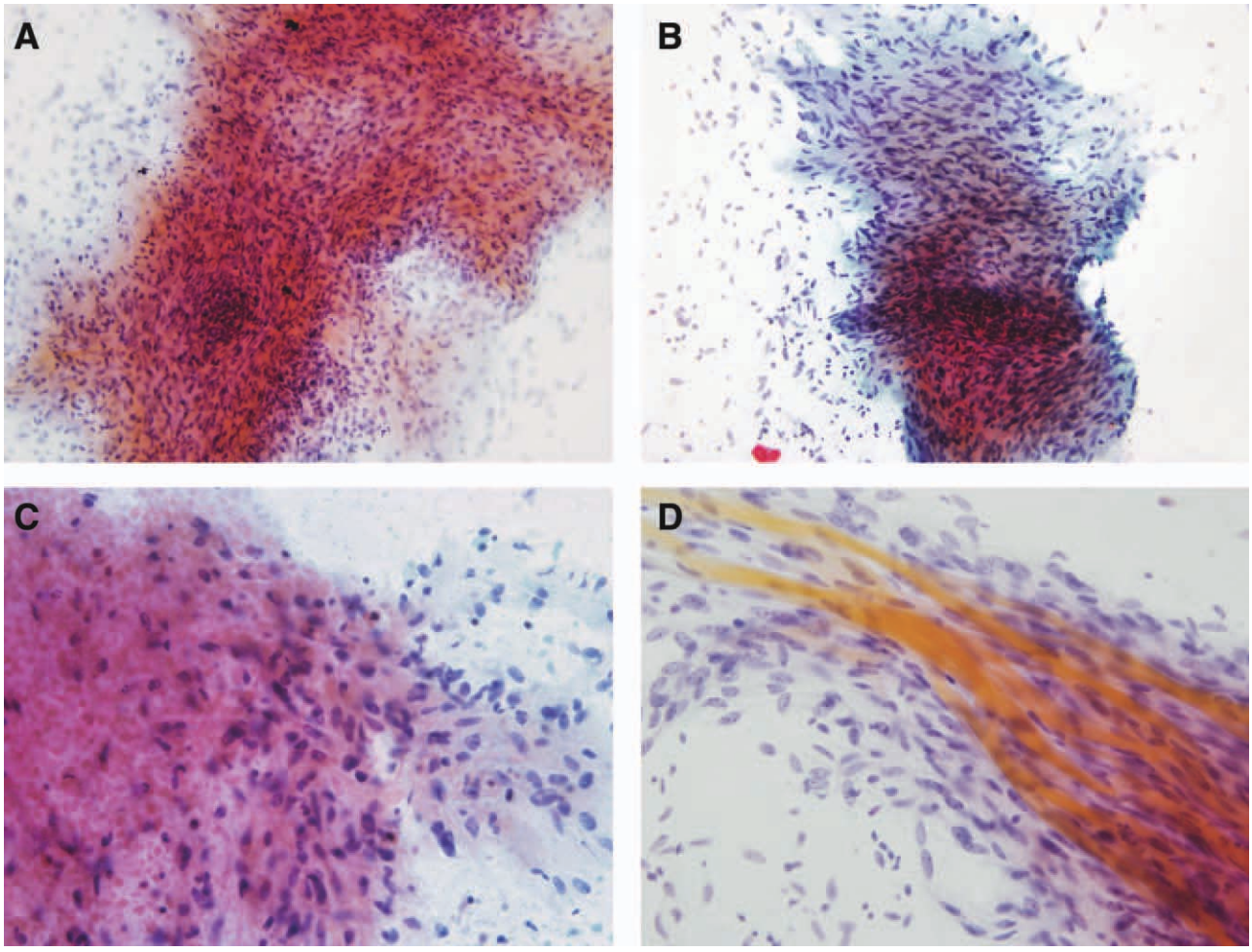

FIGURE 1. (A) A dense 3-dimensional aggregate with many dissociated single forms at the periphery is shown. (B) Fascicle formation with horizontally arranged cells in parallel is shown. Some nuclei have a squiggly contour. (C) Necrosis affects the left one-half of this cell cluster. Anisonucleosis is present. (D) Monotonous cells separate individual collagen fibers. Note the finely granular chromatin (all panels: Papanicolaou stain).

appearance of a malignant small round cell tumor (Fig. 3). Histologically, only 1 of these was a true epithelioid variant of MPNST (case 7), whereas the others were conventional MPNST with foci of rounded cells, and 1 was a malignant melanoma mistaken for an epithelioid MPNST.

DISCUSSION

No standardized histologic criteria exist to distinguish MPNST from a high-grade spindle cell sarcoma, not otherwise specified. This is particularly so because > 90% of MPNSTs exhibit a fascicular spindled morphology. Coupled with the absence of any consistent, peculiar immunoprofile (with the exception of the rare epithelioid variant) or karyotypic abnormality, the histologic or cytologic diagnosis of primary MPNST becomes exceedingly difficult.[1,2] As noted in our large series, we were able to recognize MPNST specifically in only approximately one-third (30%) of new patients. Helpful histopathologic features demonstrating tumor growth within nerve fascicles; loose, somewhat myxoid, zones sharply alternating with areas of dense cellularity; and whorled perivascular accentuation of cells commonly seen in whole tissue sections[3] become imperceptible in FNA smears.

The cytopathology literature regarding MPNST is comprised largely of case reports or small series of 3 to 4 patients.[4-6] In addition, many of these are reports of metastatic tumor. To our knowledge, the largest cytologic collection of MPNST cases prior to the current study is a

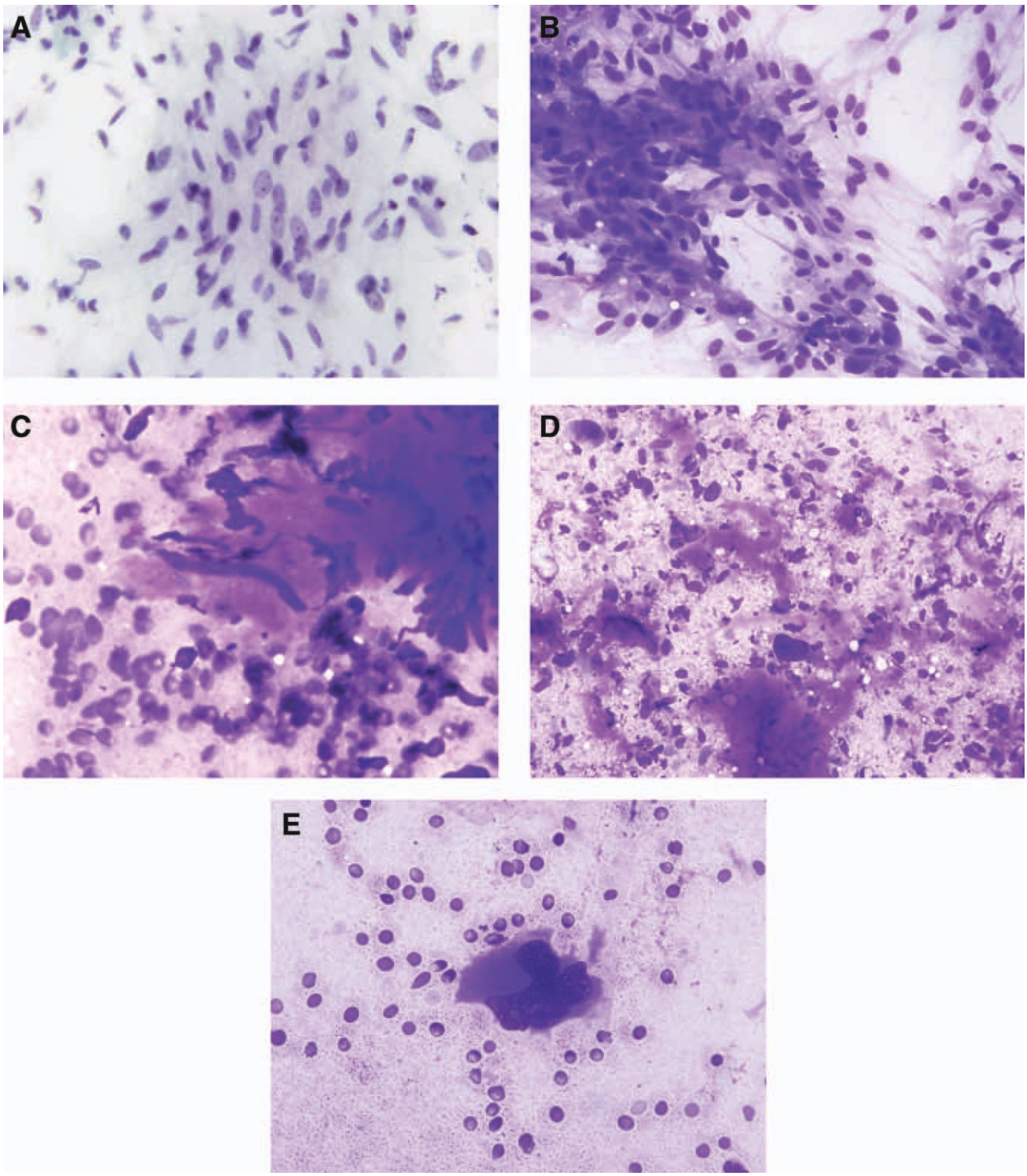

FIGURE 2. (A) Viewed en face, the nuclei are oval/elongated and smoothly contoured; on edge they appear slender with a slight curve noted in some (Papanicolaou stain). (B) Long cytoplasmic processes are present in some loose aggregates (Romanowsky stain). (C) Long, slender, serpiginous nuclei are uncommon (Romanowsky stain). (D) A case demonstrating anisonucleosis, moderate pleomorphism, and fibrous tissue is shown (Romanowsky stain). (E) A markedly pleomorphic multilobed nucleus is a rare finding (Romanowsky stain).

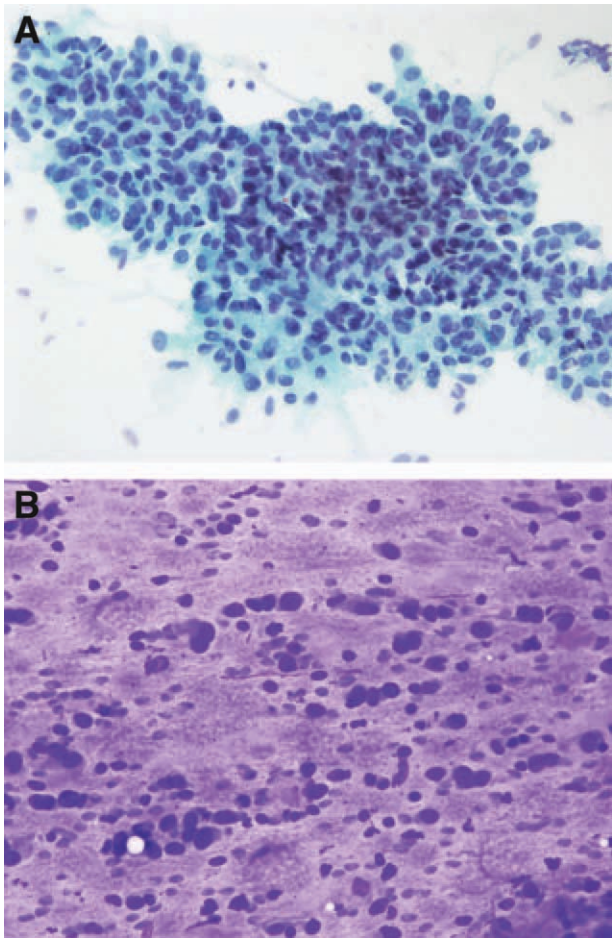

FIGURE 3. (A) A cell cluster dominated by epithelioid cells is shown (Papanicolaou stain). (B) Dispersed cells with high nuclear:cytoplasmic ratios mimicking a malignant small round cell tumor are shown (Romanowsky stain).

report of 24 cases from 17 patients.[7] Analysis of those data indicated an ability to correctly recognize MPNST in merely 17% of cases, and in only 1 of 13 primary tumors (8%). A literature review by these same authors found MPNST was accurately diagnosed in 32 of 79 specified cases (40.5%), whereas 51.9% were diagnosed as another type of sarcoma, 3.8% were classified as suspicious, and 3.8% represented false-negative diagnoses, but it is not known what percentages were from new patients compared with those with known MPNST.[7] As in the current series, the authors found no evidence of nuclear palisading, but described wavy nuclei in > 50% of their aspirates. This is in contrast to our cytologic cases, in which nuclear "buckling" (a feature long associated with nerve sheath differentiation) was inconsistent and in many cases a minor feature. Our experience parallels that of Gupta et al, in which so-called wavy nuclei appeared in only 1 of 8 examples.[8] Cellular anaplasia, another feature often commented on by others as being common,[4,7] was noted in only a few of the cases in the current study. This discrepancy is no doubt a reflection of the spectrum of differentiation that one encounters in MPNST.

Because the majority of our cases were examples of well-differentiated MPNST, we found that cell monotony and the presence of large numbers of singly dissociated cells combined with cell aggregates were the overwhelmingly common morphologic features. This appearance raised the differential diagnoses of other banal-appearing spindle cell neoplasms, including monophasic synovial sarcoma, malignant solitary fibrous tumor, well-differentiated leiomyosarcoma, dermatofibrosarcoma protuberans (if superficial), cellular schwannoma, and low-grade dedifferentiated liposarcoma (if retroperitoneal). Each of these entities can be distinguished from well-differentiated MPNST if one obtains sufficient material for immunohistochemistry and, if needed, fluorescence in situ hybridization analysis.

The epithelioid variant of MPNST (EMPNST) is exceedingly rare. In the current study, there were 4 cases in which smears had the appearance of an epithelioid malignancy: 2 examples of conventional spindle MPNST with round cell foci, 1 a true EMPNST, and 1 a misdiagnosed amelanotic malignant melanoma. EMPNST is foremost confused with amelanotic malignant melanoma, which is a well-known pitfall that we encountered.[9,10] Other less frequent diagnostic considerations include clear cell sarcoma of soft parts, epithelioid sarcoma, and anaplastic carcinoma. Our melanoma example was erroneously diagnosed as EMPNST (case 14) based on a combination of its deep location, uniformly epithelioid morphology, and intense positive S-100 staining coupled with negative staining of the tumor (from the cell block) with HMB-45, EMA, CD31, pankeratin, and muscle-specific actin. Nonetheless, immunohistology of the resected specimen demonstrated positive staining with S-100, but also with melanoma markers HMB-45 and Melan-A in whole-tissue sections. The reason for this discrepancy is unclear. Retrospective review of this false-positive case demonstrated a subtle feature of melanoma that included a high percentage of cells with mirror-image binucleation. Our single example of EPMNST had no specific cytomorphologic features to allow for its

recognition. Dodd et al reached a similar conclusion, stating that this neoplasm is difficult to classify using FNA.[9]

As demonstrated in this and prior studies of MPNST cytopathology, when one encounters a new patient without a history of NF-1 or without knowledge that the neoplasm is in proximity to, or appears to arise from, a major nerve, a specific diagnosis is exceptionally difficult. This is because the cytomorphologic overlap with other sarcomas is too pronounced. The results of the current study demonstrate that features espoused by others (including elongated slender, wavy, or hook-shaped nuclei; focally pronounced nuclear atypia; bizarre giant cells; and fibrillary metachromic stroma) are "soft signs" and are not categorically specific of an MPNST. Because no cytologic feature or set of features appears to be specific, a primary FNA-based diagnosis of MPNST remains quite difficult. However, if one has preexisting knowledge of the clinical situations in which MPNST typically occurs, then a correct diagnosis is more likely. Conversely, FNA cytology is highly accurate in recognizing metastatic and locally recurrent MPNST.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Scheithauer BW, Louis DN, Hunter S, et al. Malignant peripheral nerve sheath tumour. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds. WHO Classification of Tumours of the Central Nervous System. Lyon, France: International Agency for Research on Cancer; 2007:160-162.
2. Scheithauer BW, Woodruff JM, Erlandson RA. Tumors of the Peripheral Nervous System. Atlas of Tumor Pathology. 3rd series. Fascicle 24. Washington, DC: Armed Forces Institute of Pathology; 1999.
3. Fletcher CDM. Peripheral neuroectodermal tumors. In: Fletcher CDM, ed. Diagnostic Histopathology of Tumors. 3rd ed. London, UK: Churchill Livingstone Elsevier; 2006:1747-1750.
4. McGee RS Jr, Ward WG, Kilpatrick SE. Malignant peripheral nerve sheath tumor: a fine-needle aspiration biopsy study. *Diagn Cytopathol*. 1997;17:298-305.
5. Vendraminelli R, Cavazzana AO, Poletti A, Galligioni A, Pennelli N. Fine-needle aspiration cytology of malignant nerve sheath tumors. *Diagn Cytopathol*. 1992;8:559-562.
6. Jimenez-Heffernan JA, Lopez-Ferrer P, Vicandi B, Hardisson D, Gamallo C, Viguer JM. Cytologic features of malignant peripheral nerve sheath tumor. *Acta Cytol*. 1999;43:175-183.
7. Klijanienko J, Caillaud JM, Lagace R, Vielh P. Cytohistologic correlations of 24 malignant peripheral nerve sheath tumor (MPNST) in 17 patients: the Institut Curie experience. *Diagn Cytopathol*. 2002;27:103-108.
8. Gupta K, Dey P, Vashisht R. Fine-needle aspiration cytology of malignant peripheral nerve sheath tumors. *Diagn Cytopathol*. 2004;31:1-4.
9. Dodd LG, Scully S, Layfield LJ. Fine-needle aspiration of epithelioid malignant peripheral nerve sheath tumor (epithelioid malignant schwannoma). *Diagn Cytopathol*. 1997;17:200-204.
10. Weiss SW, Goldblum JR. Malignant tumors of peripheral nerves. In: Weiss SW, Goldblum JR, eds. Enzinger and Weiss's Soft Tissue Tumors. 5th ed. St. Louis, MO: Mosby; 2008:921-925.