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The presence of neuroendocrine features generates a broad differential diagnosis in the fine-needle aspiration of bone and soft tissue neoplasms

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Introduction Biopsy of bone and soft tissue (BST) lesions occasionally yields neoplasms with neuroendocrine (NE) features. We identify a differential diagnosis for neoplasms containing NE features when encountered on fine-needle aspiration (FNA) of BST masses.

Materials and methods The cytopathology archives of the Johns Hopkins Hospital were searched for any BST FNA specimen diagnosed as a neoplasm with NE features or in which NE immunohistochemical (IHC) markers were ordered. Specimen diagnoses were reviewed and specimens were excluded if neuroendocrine features were not considered at the time of original diagnosis.

Results A total of 179 specimens met the inclusion criteria. Of these, 64 (36%) and 115 (64%) neoplasms were primary and metastatic, respectively. A total of 29 distinct entities were identified. Sixteen were entities with established NE differentiation and 13 were entities not typically regarded as having an NE origin. The most commonly encountered neoplasms included small cell carcinoma of all primary locations (38), Ewing sarcoma (37), medullary thyroid carcinoma (24), Merkel cell carcinoma (23), and paraganglioma (10). NE IHC markers were ordered in 45% of cases; 86% were positive by at least one NE marker. Entities with established NE differentiation were more likely to be positive for NE IHC than those not typically regarded as having NE differentiation (100% and 59%, respectively).

Conclusions A variety of BST lesions—including neoplasms not typically thought to have neuroendocrine differentiation—can possess NE cytomorphologic features and/or NE IHC marker positivity. The patient's clinical presentation and history can help narrow the differential diagnosis.

Introduction

Neuroendocrine (NE) cells produce neurotransmitters such as acetylcholine, biogenic neuroamines, and/or neuropeptides. These cells are embryologically diverse and are

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present in a variety of organ systems and anatomic locations such as the skin, soft tissue, thyroid, gastrointestinal and bronchopulmonary tracts, and the central and peripheral nervous systems.[1,2] NE neoplasms vary considerably in their degree of differentiation and clinical behavior.[2-8] Further, non−neuroendocrine-derived malignancies can undergo neuroendocrine differentiation and assume one or more features typically seen in NE cells.[9] As such, neoplasms with neuroendocrine features can be diagnostically challenging.

Primary bone and soft tissue (BST) NE neoplasms are rare, as are metastatic NE neoplasms to BST.[10] Thus, encountering NE neoplasms in BST poses a particular diagnostic challenge. Based on location, fine-needle aspiration (FNA) with or without a core biopsy is often the least invasive and most favored first-line diagnostic test utilized for a BST mass. Owing to the limited evaluable material that is often obtained from these procedures, adequately triaging the diagnostic workup and providing an appropriate differential when a specific diagnosis cannot be made is paramount. We performed a retrospective study over a 26-year period describing neoplasms with NE features found in BST by FNA.

Materials and methods

Approval was received by our institutional review board to conduct this study with a consent waiver. The electronic cytopathology archives of the Johns Hopkins Hospital were searched for BST FNA specimens yielding the diagnosis of a neoplasm with NE differentiation over a 26-year period (January 1, 1989, to December 31, 2015). The demographic information, history, biopsy site, and diagnosis were recorded by the authors for each case with NE cytomorphologic features or at least one positive NE immunohistochemical (IHC) marker (synaptophysin, chromogranin, CD56, and/or neuron-specific enolase [NSE]). Although CD56 and NSE are nonspecific, surrogate markers for NE differentiation, these markers were included in order to identify NE neoplasm with a high sensitivity. Cases in which a NE neoplasm was not considered in the original differential diagnosis were excluded based on the final specimen diagnosis, the differential diagnosis provided in the specimen diagnosis, and/or the utilization of the NE-specific IHC markers listed above. Diagnoses were then divided into two groups: established NE neoplasms and "NE-like" neoplasms that are not considered to have NE differentiation.

Results

Demographics and diagnoses

A total of 179 specimens met the study's inclusion criteria. The mean patient age was 45.3 years, ranging from <1 to 91 years. Of these, 101 (56.4%) patients were male and 135 (75.4%) were white (Table 1). Biopsy sites included the head and neck (50), bone (37), lower extremity (15), upper extremity (13), abdominal wall (10), paraspinal (10), retroperitoneum (9), axilla (8), chest (7), omentum (6), mediastinum (5), inguinal (4), buttocks/gluteal (3), pelvis (1), and supraclavicular (1). A total of 29 distinct neoplasms were identified; 16 were NE neoplasms (entities established in literature to have a NE origin) and 13 were "NE-like" neoplasms (entities not thought to have an NE origin). The most commonly encountered neoplasms were small cell carcinoma of all primary locations (38), Ewing sarcoma (37), medullary thyroid carcinoma (24), Merkel cell carcinoma (23), and paraganglioma (10).

Case characteristics

Sixty-four (35.8%) and 115 (64.2%) neoplasms were primary and metastatic, respectively, and 96 (53.6%) patients had a history of neoplasm prior to biopsy (Fig. 1). Patients diagnosed with a primary neoplasm were less likely to have a history of neoplasm (14; 21.9%) versus patients diagnosed with a metastatic neoplasm (82; 71.3%). Ancillary testing for at least one NE marker was performed in 80 (44.7%) cases; 69 (86.3%) cases were positive for at least one NE marker. IHC was performed on 24 (48.0%) and 21 (63.6%) cases with no history of neoplasm for primary versus metastatic neoplasms, respectively. When performed in patients with no history of malignancy, IHC was positive in 18 (75.0%) and 20 (95.2%) primary and metastatic neoplasms, respectively. The overall positivity rate for at least one NE IHC marker for NE neoplasms and NE-like neoplasms was 100.0% (53 of 53) and 59.3% (16 of 27), respectively. The most common primary neoplasms included Ewing sarcoma (31), paraganglioma (10), and ganglioneuroma (6), and the most common metastatic neoplasms included small cell carcinoma of all primary locations (38), medullary thyroid carcinoma (24), and Merkel cell carcinoma (22). The most common origins of metastasis were lung (25), thyroid (24), skin (22), and nasal/sinonasal tract (5). The most common sites of metastasis included soft tissue of the head and neck (39), bone (17), abdominal wall (10), soft tissue of the axilla (8), and soft tissue of the upper extremity (8).

Small cell carcinoma

Thirty-eight patients were diagnosed with metastatic small cell carcinoma (Tables 1 and 2). The average age at diagnosis was 64.2 (range: 23-82) years and 68.4% were male. Primary locations included the lung (25), *human papillomavirus*−related base of tongue (3), larynx (2), prostate (2), cervix (2), bladder (1), endometrium (1), sinonasal tract (1), and *human papillomavirus*−related oropharynx (1). Sites of metastasis included bone (8), soft tissue of the head and neck (6), abdominal wall (5), soft tissue of axilla (4),