A Review of Cytologic Findings in Neuroendocrine Carcinomas Including Carcinoid Tumors with Histologic Correlation

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BACKGROUND. The nosology of neuroendocrine neoplasia has evolved substantially in recent years. The aim of this study was to review the authors’ institutional experience and diagnostic accuracy for cytologic specimens of neuroendocrine carcinoma (NEC) and to identify features most suggestive of neuroendocrine differentiation.

METHODS. The cytologic and histologic findings of 29 archival NEC in which cytology preceded biopsy or resection were compared. The study was comprised of 6 carcinoid tumors, 3 atypical carcinoid tumors, 17 high grade NEC (5 small cell, 9 large cell, and 3 mixed small/large cell), and 3 combined NEC/nonneuroendocrine carcinomas. Cytologic material was derived from 21 fine-needle aspirates (FNA), 6 bronchial brushing/washings, and 2 gastrointestinal tract brushings.

RESULTS. Of the 29 cases, the correct cytologic diagnosis was rendered in 11. Two cases were identified as NEC but were graded incorrectly. The remaining 16 cases were interpreted as nonsmall cell carcinoma (8 cases); diagnostic or suspicious of carcinoma, not otherwise specified (7 cases); and atypical, indeterminate for malignancy (1 case). On review, neuroendocrine features were identified in 14 of the latter 16 cases.

CONCLUSIONS. The cytologic diagnosis of NEC, both high and low grade, can be difficult. Because of acinus-like formations and columnar cell shapes, low grade NEC may be mistaken for adenocarcinoma. Small cell carcinomas, especially in bronchial brush and wash preparations, may be difficult to classify beyond malignancy. Large cell NEC may be confused with nonneuroendocrine carcinomas because of abundant cytoplasm and nucleoli. Attention to the presence of loose cell aggregates in a background of singly dispersed cells; feathery patterns created by tumor cells clinging to capillaries; rosette formations; delicate, granular cytoplasm; inconspicuous nucleoli; and, most important, speckled or dusty chromatin patterns are useful in identifying neuroendocrine differentiation in cytologic specimens. Cancer (Cancer Cytopathol) 2000;90:148–61. © 2000 American Cancer Society.

T he elucidation and categorization of neuroendocrine (NE) neoplasia has evolved substantially over the past 20 years but remains a topic of controversy and debate. A degree of uncertainty persists regarding diagnostic criteria and classification, which are central to the prediction of future behavior and decisions regarding therapy, particularly in reference to pulmonary tumors. Although carcinoid tumors (CT) and small cell carcinomas (SCC) are well established polar opposites, ongoing debate addresses the nosology of the
broader spectrum of NE tumors.4–7 Contentious issues have included diagnostic criteria for both atypical carcinoids (AC)8–11 and large cell neuroendocrine carcinomas (LCNEC),12–14 as well as the subclassification of SCC.15–18 Diverse terminology has made it difficult for surgical pathologists to know how to classify the more malignant neuroendocrine tumors correctly.

Against this backdrop there has been a marked expansion in the role of cytopathology in the diagnostic workup of mass lesions. This has resulted in an increased number of NE tumors first sampled as cytology specimens. Compared with the surgical pathology literature, less has been written concerning the distinguishing features of this family of neoplasms in cytologic specimens. Given the confusion that exists in surgical pathology, one might anticipate that this would be reflected in difficulties in recognition and classification of NE neoplasia in fine-needle aspirates (FNAs) and exfoliative cytology. Consequently, the aim of this study was to review our institutional experience and diagnostic accuracy with NE neoplasias initially encountered in cytologic specimens, in which histologic follow-up in the form of biopsy or resection was available for comparison. When possible, we identified the obstacles to recognition and documented those features indicative of NE differentiation, concentrating on those entities not well established in the cytologic literature including atypical carcinoid (AC), LCNEC, and combined NE and non-NE carcinomas (NEC and non-NEC).

**MATERIALS AND METHODS**

The computer records at the Lauren V. Ackerman Laboratory of Surgical Pathology, Washington University Medical Center were searched for diagnostic codes including “carcinoid,” “atypical carcinoid,” “small cell carcinoma,” “oat cell carcinoma,” “large cell neuroendocrine carcinoma,” “mixed,” “combined,” and “un-

| Case no. | Cytologic specimen | Diagnosis | Histologic specimen | Diagnosis |
|---------|--------------------|-----------|---------------------|-----------|
| 1       | Liver FNA          | Carcinoid tumor | Liver Bx            | Carcinoid tumor |
| 2       | Liver FNA          | c/w adenocarcinoma | Liver Bx            | Carcinoid tumor |
| 3       | BB&W               | Probable oat cell ca | Liver Bx            | Carcinoid tumor |
| 4       | Liver FNA          | Carcinoid tumor | Liver Bx            | Carcinoid tumor |
| 5       | Lung FNA           | Spindle cell carcinoma | Liver Bx            | Spindled carcinoma |
| 6       | Lung FNA           | Atypical carcinoid | Liver Bx            | Spindled carcinoma |
| 7       | Liver FNA          | Small malignant cells | Liver Bx            | Atypical carcinoid |
| 8       | Liver FNA          | Favor adenoc | Liver Bx            | Atypical carcinoid |
| 9       | Lymph node FNA     | Favor adenoc | Liver Bx            | Atypical carcinoid |
| 10      | Lung FNA           | Possible oat cell ca | Liver Bx            | SCC |
| 11      | Pleural fluid      | Carcinoma, NOS | Liver Bx            | SCC |
| 12      | Lung FNA           | SCC         | Wedge Bx            | SCC |
| 13      | Liver FNA          | Ca, diff dx includes NEC | Liver Bx            | SCC |
| 14      | BB&W               | Rare atypical cells | Bronchial Bx       | SCC |
| 15      | Liver FNA          | Adenoc | Liver Bx            | SCC |
| 16      | Liver FNA          | Carcinoma of NE origin | Liver Bx            | LCNEC |
| 17      | Liver FNA          | NSCC, favor SqCC | Liver Bx            | LCNEC |
| 18      | Lung FNA           | High grade NEC, mixed | Lobectomy       | LCNEC |
| 19      | BB&W               | Suspicious for ca | Lung node Bx        | LCNEC |
| 20      | BB&W               | PD NSCC    | Lung node Bx        | LCNEC |
| 21      | Esophageal brush   | Small cells suspicious for ca | Esophagectomy | LCNEC |
| 22      | Lung FNA           | LCNEC      | Lobectomy           | LCNEC |
| 23      | Liver FNA          | Met epithelial neoplasm | Ant. mediastinal Bx | LCNEC |
| 24      | BB&W               | SCC        | Lobectomy           | MixedSq&LCca |
| 25      | BB&W               | PD NSCC, can’t t/o NEC | Bronchial Bx       | MixedSq&LCca |
| 26      | Lymph node FNA     | Suspicious for ca | Excisional Bx       | MixedSq&LCca |
| 27      | Lung FNA           | Adenoc, NE features | Lobectomy          | Combd SCC & adenoca |
| 28      | CBD brush          | Indeterminate for malignancy | Duodenal Bx       | Combd NEC & non-NEC |
| 29      | Lung FNA           | SqCC       | Lobectomy           | Combd SCC & SqCC |

FNA: fine-needle aspiration; Bx: biopsy; c/w: consistent with; BB&W: bronchial brushing and washing; Ca: carcinoma; adenoc: adenocarcinoma; SCC: small cell carcinoma; NOS: not otherwise specified; diff dx: differential diagnosis; NEC: neuroendocrine carcinoma; LCNEC: large cell neuroendocrine carcinoma; NSCC: nonsmall cell carcinoma; SqCC: squamous cell carcinoma; PD: poorly differentiated; Met: metastatic; Ant: anterior; SC&LC: small cell and large cell; r/o: rule out; combd: combined; CBD: common bile duct.
differentiated” NEC. The cytology files were reviewed to determine in which cases was a cytologic specimen procured prior to or simultaneously with biopsy or resection. Cases with a previously established diagnosis of an NE neoplasm were rejected, and only those cases in which a novel diagnosis was made by cytologic examination were retained.

The resulting group of 29 cases were comprised of 20 FNAs (9 of the liver, 9 of the lung, and 2 of the cervical lymph nodes), 6 bronchial brushing and washing specimens (BB&W), 1 pleural fluid, and 2 gastrointestinal tract (GIT) brushings. The majority of cases represented pulmonary tumors (15 cases) with 8 FNAs, 6 BB&Ws, and 1 pleural fluid, followed by metastatic NEC to the liver (10 cases) and lymph nodes (2 cases) and 2 primary GIT tumors. Papanicolaou and Diff-Quik stained preparations were reviewed in each case. Immunocytochemical studies had been performed in two cases of CT and one LCNEC.

All histology was reviewed. Because many biopsies originally were recorded as metastatic NEC with descriptive morphologic comments, and given that the study group dated from 1989 (thus encompassing varied terminology), current morphologic definitions with respect to classification were followed. Diagnostic criteria were described elsewhere. This yielded six CT, three AC, five SCC, nine LCNEC, three mixed small and large cell NEC, and three combined NEC/non-NEC. Of 29 cases, 18 also had been studied by immunohistochemistry, and NE differentiation was confirmed by demonstrating reactivity with a panel of markers that included neuron specific enolase, synaptophysin, chromogranin, and Leu7, in addition to cytokeratin in two of four CT, two of three AC, two of five SCC, six of eight LCNEC, three of three mixed small and large cell NEC, and two of three combined NEC/non-NEC. Two LCNEC not stained with NE markers are best regarded as large cell carcinomas with NE morphology and the NE component of the single unstained combined case was SCC.

The corresponding cytologic specimens were reviewed with respect to the following questions. Were NE features identified and correctly classified? If not, why was there a discrepancy between the cytologic and histologic diagnoses? What features appreciated on review might have suggested NE differentiation? The following cytologic features were examined: uniformity of tumor cell population, presence of syncytial aggregates and single cell dispersion, rosette formation, nuclear morphology, chromatin quality, presence of nucleoli, delicacy of cytoplasm, necrosis, mitotic activity, molding, and the presence of streak artifact.

RESULTS
The 29 cases are tabulated in Table 1. A comparison of cytologic and revised histologic diagnoses is plotted in Table 2.

Carcinoid Tumor
This group of six cases was comprised of three liver FNAs, two lung FNAs, and a single BB+W. Three were reported correctly as CT (Fig. 1A and B). A spindled CT was misinterpreted as AC, apparently because of modest variation in cell size, perceived irregularities of the nuclear membrane, and the presence of apoptotic debris, although the absence of mitotic figures and necrosis was commented on. Cellular degeneration and sparse cellularity were contributing factors in the misdiagnosis of another case as probable oat cell carcinoma. Incorrect interpretation of rosette formation
as evidence of glandular differentiation resulted in the final erroneous diagnosis of adenocarcinoma.

**Atypical Carcinoid**
None of three cases best regarded by morphology as AC was recognized as such in FNAs of two livers and one lymph node. Adenocarcinoma was the favored diagnosis in two cases that showed rosette formation, stippled nuclear chromatin, inconspicuous nucleoli, and fine cytoplasm with some stripping (Fig. 2A and B). Foci of necrosis were identified in the third case, which otherwise resembled typical CT but that was reported as “small malignant tumor cells present.”

**Small Cell Carcinoma**
Of five cases, including two lung FNAs, one liver FNA, one BB&W, and one pleural fluid, the correct diagnosis of SCC was made in three instances (Fig. 3A and B). Problematic cases included a pleural fluid with rare, slightly degenerated cell clusters reported as carcinoma,

![Figure 1](image-url)
not otherwise specified (NOS) and a hypocellular BB&W that appropriately commented on “rare atypical cells.”

**Large Cell Neuroendocrine Carcinoma**

Nine LCNEC were sampled by four liver FNAs, two lung FNAs, two BB&Ws, and one esophageal brushing. A cytologic diagnosis of LCNEC was rendered in three FNAs, in which characteristic NE speckling of nuclear chromatin in addition to vesicular nuclei with prominent nucleoli was appreciated (Fig. 4A and B). A case reported as metastatic epithelial neoplasm illustrated the more cohesive cell groups, the misleadingly large cell size, and ample cytoplasm of LCNEC (Fig. 4C). The smear background showed an abundance of dysplastic, singly dispersed cells (Fig. 4D). In these areas of single cell scatter, there was a tendency toward cytoplasmic stripping and focally there was a suggestion of nuclear molding (Fig. 4E). A LCNEC case reported as
adenocarcinoma demonstrated ball-like cell clusters, vesicular nuclei, single prominent nucleoli, and significant pleomorphism. There were only focal areas in which cells assumed rosette formations (Fig. 5), and the cytomorphology did not suggest NE differentiation. The LCNEC favored as squamous cell carcinoma (SqCC) had a deceptively flattened pseudocobblestone architecture compared with cell clusters in FNA smears (Fig. 6A). On second look, the nuclei did have stippled, hyperchromatic chromatin and inconspicuous nucleoli (Fig. 6B). In the LCNEC classified as poorly differentiated NSCC by BB&W, interpretation was limited by poor cell preservation, but stippling of nuclear chromatin was appreciated on review. Two further hypocellular specimens were suspicious but not diagnostic for malignancy.

**Mixed Small and Large Cell NEC**

This group of three cases was sampled by cervical lymph node FNA and two BB&Ws. The small cell
component was identified correctly in one BB&W. It was commented that NE differentiation could not be excluded in another sample that showed clusters of small cells with stippled chromatin and some molding and on review was considered diagnostic of SCC. The final case was reported as suspicious for carcinoma. On review, marked streak artifact together with clusters of small hyperchromatic cells in FNA smears of a lymph node prompted consideration of NEC (Fig. 7).

**Combined NEC and Non-NEC**

Three cases were derived from two lung FNAs and a common bile duct (CBD) brushing. Combined adenocarcinoma and SCC was recognized, in which two cell populations with distinct small cell and glandular fea-
tures were appreciated (Fig. 8A and B). The squamous cell component alone was recognized in a combined SqCC and SCC whereas clusters of SCC were overlooked. The CBD brushing was reported appropriately as atypical but indeterminate for malignancy.

**DISCUSSION**

The most common NE neoplasms seen in daily cytopathologic practice, CT and SCC, are underrepresented in the current study because of our inclusion criteria. Because of their frequently central location, both pulmonary CT and SCC commonly are sampled by simultaneous endobronchial biopsy, brushing, and washing, which, under the design of the current study, excluded a large number of cases. Moreover, SCC presenting as metastatic disease often is sampled by cytologic methods alone without histologic correlate. Despite this, our study of the recognition of NE neo-

**FIGURE 4.** (continued)
plasms in cytologic specimens does highlight the problems that may arise in this endeavor. Diagnostic yields may be low in exfoliative cytology specimens. Cytology specimens comprised of small cells may undergo further shrinkage and degeneration, precluding definitive interpretation. Separation of LCNEC from non-NEC is challenging.

The diagnostic difficulties within small cell categories arose predominantly in sparsely cellular or poorly preserved specimens, not infrequently bronchial brushing and washing specimens. It generally is unwise to render a diagnosis of malignancy on a hypocellular specimen. Moreover, poor cell preservation, suboptimal fixation, and staining may alter the morphologic appearance of relatively bland cells in CT so as to erroneously raise suspicion for a high grade lesion and possibly deny the patient curative surgical resection. In such cases, it may not be possible to

**FIGURE 5.** Case 15. Focal rosette formation in a large cell neuroendocrine carcinoma (Diff-Quik, ×400).
refine the diagnosis further than NE neoplasm, in which case further sampling is appropriate.

Features that facilitate the cytologic diagnosis of CT are a poorly cohesive population of small cells with uniformly bland morphology, with both clustering and single cell scatter being observed. Nuclei are central or slightly eccentric with smooth outlines and finely stippled chromatin. The finely granular cytoplasm has a tendency to strip off but molding is not noted. There is no necrosis and scant mitotic activity. Prominent vascularity has been described in pulmonary CT. Although a well differentiated adenocarcinoma should be considered in the differential diagnosis, appreciation of the above features should prompt consideration of NE differentiation and performance of immunocytochemical stains will expedite the diagnosis.

Features most helpful in recognizing SCC, even in hypocellular, degenerated, or necrotic material, are the recognition of a uniformly small tumor cell popu-
lation at low power. At higher power, significant pleomorphism is appreciated, even within the small cell range. Nuclei are hyperchromatic with coarsely speckled chromatin. Nucleoli are inconspicuous. Cytoplasm is extremely scant and nuclei mold. Crush artifact results in basophilic DNA streaming. There usually is abundant necrosis.\textsuperscript{34–38} Although prominent vascularity is described in CT, we also noted that perivascular tumor growth resulted in “feathery” patterns created by smeared tumor cells clinging to capillary walls in FNAs of SCC.

Most difficulty is encountered with tumors of larger cell size, including AC and LCNEC. One source of difficulty has been the inconstant nature of diagnostic criteria for AC. The misinterpretation of a spindle cell carcinoid as atypical carcinoid could have been avoided had current diagnostic criteria (i.e., the necessity of mitotic activity and necrosis) been adhered to. Previous authors have described greater nuclear pleomorphism and hyperchromatism in AC compared with typical CT and considered that separation of the two entities should not be problematic.\textsuperscript{25,26,31,34,39,40} However, in the most recently published World Health Organization histologic classification of lung tumors, necrosis and mitotic activity alone have been adopted as diagnostic criteria, whereas recognition of cytologic atypia is deemed more subjective.\textsuperscript{41} We consider that it may not be possible to subclassify a NEC as AC in cytologic material, unless one appreciates mitotic activity and necrosis in an otherwise typical CT. AC included in the current study more closely resembled CT in terms of cell size, uniformity of cell morphology, fine stippling of nuclear chromatin, mild pleomorphism, and sparsity of mitotic activity compared with high grade LCNEC. However, it should be possible to recognize that NE differentiation is present to differentiate from non-SCC.

Features commonly associated with adenocarcinoma, including rosette-like formations, ball-like cell clusters, columnar cell shapes, prominent nucleoli, and delicate cytoplasm, were associated with erroneous diagnoses in LCNEC. At present LCNEC is defined in terms of its histologic appearance and immunophenotype and to our knowledge there is scant description of distinguishing features in cytologic preparations.\textsuperscript{42} However there are some distinctive features identifiable in cytologic specimens of these large cell tumors that serve to distinguish them from non-NEC. Although vesicular nuclei are described in LCNEC, so also is the presence of coarsely or even finely granular nuclear chromatin.\textsuperscript{12} Moreover, although the more cohesive cell groups of LCNEC illustrate the misleadingly large cell size and ample cytoplasm, the smear background shows an abundance of dysplastic, singly dispersed cells with a tendency toward cytoplasmic stripping and nuclear molding. These features of chromatin stippling, poor cell cohesion, cytoplasmic stripping, and nuclear molding provide compelling evidence for the NE nature of these large cell carcinomas. Recognition of these features should prompt perfor-
mance of immunocytochemical studies to confirm the diagnosis.

Review of the mixed small and large cell NEC reveals difficulty in discerning and interpreting both small and large cell components in cytologic specimens. A population of small tumor cells was the sole element appreciated in the current study cases. The problem may reflect the degeneration and shrinkage of a polymorphous cell population to a uniformly small cell size, particularly in exfoliative cytology specimens. Alternatively, it may reflect sampling error. Furthermore, mixed small and large cell NEC may demonstrate both a range in cell size from small to large as well as a rather abrupt transition between the two. This has implications for diagnosis, the latter "two cell population" pattern being easier to identify whereas subtle gradation in size is difficult to appreciate in cytologic specimens. A potential diagnostic
pitfall is the misinterpretation of SCC as a more poorly differentiated component of non-SCC or spindled SCC cells as tumoral desmoplastic response. It behooves the cytopathologist to be mindful of the heterogeneity of lung tumors especially and to consider that two tumor populations may be present in one cytologic specimen while examining elements that do not fit the dominant pattern.

On retrospective review, it was believed that features of NE differentiation were present in 13 of 16 cases that were reported as atypical, suspicious, or positive for carcinoma, or as non-SCC. This in part reflects an unavoidable bias in a retrospective study in which certain features are being sought actively. The successful identification of NE features depends on examination of adequately sampled, prepared, and stained cytologic material. The cytologic features most persuasive when trying to establish the diagnosis of NE differentiation, in both small and large cell tumors, are fine stippling of nuclear chromatin, together with the dyshesive nature of the tumor cell population, the tendency toward cytoplasmic stripping, and nuclear molding. It also should be emphasized that not every “large cell” is a “non-small cell.” The patterns that we observed in LCNEC should serve not only as a diagnostic guide but also as a foundation for further study and validation. Application of these criteria to a mixture of NE and non-NE cases to determine their reproducibility should be the direction of future work. As the confusion regarding the nosology of NE neoplasia is addressed and resolved in the surgical pathology literature, clear diagnostic guidelines have been established. This also should inform the cytopathologist, who is increasingly likely to be the first person making the diagnosis of NE differentiation.

Although the diagnosis of CT and SCC in cytologic specimens often is straightforward, in the current study we tried to highlight some of problems and possible clues to appreciating the cytologic features of tumors that now extend across the spectrum of NE neoplasia.

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