Management of Neuroendocrine Tumors of Unknown Origin

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Key Words
Neuroendocrine tumors, unknown primary, unknown origin

Abstract
Neuroendocrine tumors (NETs) of unknown origin account for more than 10% of all NETs. Most of these tumors are poorly differentiated and, thus, very aggressive. Establishing the location of the primary tumor can be challenging. Workup of these NETs of unknown origin includes a thorough family history, immunohistochemistry, imaging, and OctreoScan. If the location of the primary malignancy is not determined, treatment is often initiated based on the grade and level of differentiation of the tumor, with well- and moderately differentiated tumors treated as carcinoid tumors, whereas poorly differentiated tumors are treated similarly to small cell tumors. Therapy is chosen based on symptoms and with the goal of debulking tumor when feasible and safe. (JNCCN 2011;9:1397–1403)

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Learning Objectives
Upon completion of this activity, participants will be able to:

• Describe the clinical and epidemiologic features of NETs and NETs of unknown origin on the basis of a review
• Describe the diagnostic workup of NETs of unknown origin on the basis of a review
• Describe the treatment of NETs of unknown origin on the basis of a review

Neuroendocrine tumors (NETs) are formed from cells of the nervous and endocrine systems. They frequently arise from the pancreas, parathyroid,
NETs are diagnosed histologically using light microscopy. Diagnosis is based on morphology using hematoxylin and eosin stains or immunohistochemistry to identify cytosolic proteins. These immunohistochemistry stains often include chromogranin A, a component of the dense core granules that are seen in NETs, and synaptophysin, a membrane protein of presynaptic vesicles. Both of these markers have great specificity for neuroendocrine differentiation in tumors. In addition, aggressiveness of NETs is assessed pathologically through grading (well-differentiated, poorly differentiated, small cell features) and mitotic index, and through Ki-67 immunohistochemistry staining (> 20% considered as a more aggressive subtype regardless of histologic features). Because of the rarity of the diagnosis, an experienced pathologist is recommended to ensure appropriate diagnosis and grading.

Well-differentiated tumors progress slowly, and only 21% of patient cases in the SEER registry presented with distant metastases. This group includes typical carcinoid tumors, islet cell tumors, pheochromocytomas, paragangliomas, and medullary carcinomas. Poorly differentiated NETs comprise small cell carcinoma, large cell carcinoma, and occasionally carcinoids with poorly differentiated histology (atypical carcinoids). In marked contrast to well-differentiated NETs, patients with poorly differentiated tumors in the SEER registry had a poor prognosis, with a median survival of 10 months. Half of those patients had distant metastases at diagnosis.

Diagnosing NETs of Unknown Primary

Although most NETs come from a known primary site, a small minority have no known origin. NETs of unknown origin account for 13% of NETs according to the SEER database. In addition, they account for less than 5% of all unknown primary cancers. Well-differentiated, low-grade NETs constitute only 10% of NETs of unknown origin, whereas poorly differentiated tumors make up the vast majority. Identifying a NET of unknown primary is a diagnosis of exclusion after a comprehensive search for a primary lesion has been unsuccessful. With more sophisticated diagnostic testing, metastatic tumors that had previously been attributed to other sources have now been identified as NETs. Compared with other types of tumors of unknown origin, NETs...
have a more favorable outcome. Hence, there is an increasing need to investigate how these tumors should be evaluated and treated.

Evaluation of NETs of unknown origin begins with a thorough evaluation of the patient’s family history. This evaluation can help identify patients at particular risk for multiple endocrine neoplasia type 1 or 2. In addition, although most well-differentiated NETs of unknown origin are nonfunctional, tumor markers, although not diagnostic, can be suggestive of a primary tumor location. Thus, the workup for most of these tumors will require further diagnostic imaging or procedures to confirm a primary.

Just as immunohistochemistry can aid in identifying a tumor as having a neuroendocrine origin, it can also help localize the site of origin, especially for well-differentiated tumors. Oien points out that thyroid transcription factor 1 (TTF1) is present in 43% of pulmonary tumors and CDX2 is present in 86% of appendiceal and colonic tumors. Thus, a carcinoid tumor that is TTF1-negative but stains positive for CDX2 indicates that the likely site of origin is the appendix or colon. Unfortunately, these characteristics do not apply to poorly differentiated NETs.

As with other types of cancers with unknown origins, imaging studies are commonly used in the workup of NETs of unknown primary. CT of the chest, abdomen, and pelvis with triple phase of the liver and pancreas, or MRI should be performed to identify the primary tumor, especially when the primary tumors are suspected to arise from the lung, pancreas, or adrenals. However, the yield of CT scans in this situation varies based on the location of the primary tumor and its size. In patients with liver metastasis, for example, CT was much more effective in localizing a primary tumor of the pancreas than of the gastrointestinal tract (carcinoids), presumably because the average size of the pancreatic primaries (7.48 cm) were much larger than small (1.7 cm; $P < .01$) and large bowel (3.75 cm; $P < .01$) tumors. Avoid avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts, plantain, kiwi, dates, grapefruit, honeydew, walnuts, alcohol, coffee, tobacco, acetaminophen, ephedrine, diazepam, nicotine, glycercyl guaiacolate (in cough medicines), and phenobarbital 48 hours before urine collection, because these all affect results.

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### Table 1 Symptoms and Evaluation of Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Insulinoma</th>
<th>VIPoma</th>
<th>Gastrinoma</th>
<th>Glucagonoma</th>
<th>Carcinoid†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Hypoglycemia</td>
<td>Profuse, watery diarrhea</td>
<td>Ulceration of upper gastrointestinal tract</td>
<td>Rash</td>
</tr>
<tr>
<td><strong>Tumor markers</strong></td>
<td>C-peptide</td>
<td>Chromogranin A Electrolytes</td>
<td>Chromogranin A Gastrin (fasting &gt; 8 h and off proton pump inhibitor for 1 wk)</td>
<td>Chromogranin A Glucagon</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>CT or MRI (pancreatic triphasic) or Upper endoscopic ultrasound</td>
<td>CT or MRI (pancreatic triphasic) OctreoScan</td>
<td>CT or MRI (pancreatic triphasic) OctreoScan</td>
<td>CT or MRI OctreoScan</td>
</tr>
</tbody>
</table>

**Abbreviations:** 5-HIAA, 5-hydroxyindoleacetic acid; VIPoma, vasoactive intestinal polypeptidoma.

†Workup varies based on location.
‡For most blood studies, a 1-hour fast is recommended.
§Falsely elevated with proton pump inhibitor use.
Endoscopic ultrasound can help evaluate for tumors in the pancreas in patients with clinical signs or laboratory evidence indicating the presence of a neuroendocrine tumor. OctreoScan is also used in the workup of NETs and takes advantage of the presence of specific somatostatin receptors on these tumors. OctreoScans, however, like CT and MR imaging, are limited by the size of the primary tumor (minimal resolution is 5–10 mm). OctreoScan is also useful in determining potentially therapeutic interventions with octreotide analogs discussed later in this article. PET is another imaging modality that can be used to identify a primary tumor, especially in OctreoScan-negative tumors. Notably, OctreoScan is often negative in more aggressive NETs, such as NET of unknown primary, and this may be a setting in which to consider PET imaging.

Small cell tumors frequently originate in the lungs, and, thus evaluation of the lungs, whether with CT or bronchoscopy, is an important first step in identifying the primary tumor. Bronchoscopy can be helpful to further evaluate for endobronchial lung NETs. Still, small cell tumors can also arise in other parts of the body and the patient’s symptoms often help guide additional studies. As discussed in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Neuroendocrine Tumors, extrapulmonary small cell carcinomas can be found (in decreasing frequency) in the cervix, esophagus, pharynx, larynx, colon, rectum, and prostate (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Because of the aggressive nature of these tumors, imaging of the brain is often included in the workup of these tumors. Surgical exploration is another option to help determine the site of a primary tumor.

**Treatment of NETs of Unknown Primary**

If the primary NET site is identified through the above workup, the tumor is then treated based on the primary site. For example, a pancreatic islet cell NET could be managed with sunitinib as second-line therapy, whereas a carcinoid NET could be managed with the addition of interferon, underscoring the importance of identifying a primary if possible. In addition, finding a primary is essential to consider a potential complete surgical resection. If the primary tumor is not identified despite a comprehensive workup, the patient may need to be treated simply based on the grade and differentiation of the tumor. Given that most NETs of unknown primary are poorly differentiated histologies with aggressive clinical courses, the search for a primary must be weighed against the need to initiate prompt treatment. In addition, finding the primary tumor may not necessarily change a patient’s treatment plan. Thus, when a primary tumor cannot be found, well- and moderately differentiated tumors are treated similarly to carcinoid tumors given that this is statistically the most likely primary. Poorly differentiated tumors should be treated similarly to small cell tumors.

Locoregional or oligometastatic disease with potential for negative margins for moderately and well-differentiated NETs of unknown primary is generally treated with resection. No efficacious adjuvant therapy is currently known. The NCCN Guidelines for Neuroendocrine Tumors recommend that surveillance after resection include reevaluation 3 to 12 months after resection and every 6 to 12 months thereafter.

Evaluations should include a history and physical, and imaging studies and appropriate tumor markers depending on the level of concern for recurrence.

For metastatic well- to moderately differentiated NETs of unknown primary, standard first-line treatment modalities include octreotide therapy, observation, or resection if possible (see the NCCN Guidelines for Neuroendocrine Tumors, available at www.NCCN.org [CARC-5]). As discussed by Spigel et al., octreotide not only plays an important role in decreasing the symptoms of hormonal excess but is considered a first-line antineoplastic systemic therapy for patients with a positive OctreoScan. PROMID, a double-blind, randomized, controlled trial comparing octreotide with placebo showed significantly improved time to progression in the octreotide group (14.3 vs. 6 months in the placebo group; hazard ratio = 0.34; 95% CI; P = .000072) in both functionally active and inactive tumors, showing antineoplastic activity with this agent. Monthly depot injections are more convenient than daily injections, although an overlap of 2 weeks is needed because of the delayed onset with depot injections. A starting dose of octreotide...
150 to 250 mcg subcutaneously every 8 hours corresponds approximately to octreotide depot, 20 mg intramuscularly, given monthly. In general, given the more indolent course of these tumors, full resection or debulking could be considered for patients whose symptoms are not optimally controlled with octreotide alone. In addition, sunitinib, an oral multitargeted tyrosine kinase inhibitor, and everolimus, an mTOR inhibitor, have been shown to have antitumor activity in NETs. In a phase III trial comparing sunitinib with placebo in patients with well-differentiated pancreatic NETs, daily administration of sunitinib improved progression-free survival, overall survival, and objective response rate compared with placebo. A phase III trial compared everolimus with placebo in patients with advanced, low-grade, or intermediate-grade pancreatic NETs who showed radiologic progression within the previous 12 months. Everolimus significantly prolonged progression-free survival with minimal severe adverse events. Well-to moderately differentiated NETs with a Ki-67 greater than 20%, or which appear to have a more aggressive clinical course, should be considered for cytotoxic chemotherapy to achieve disease control. For patients with liver metastases as the only site of disease, whether it is well- to moderately differentiated or poorly differentiated, liver-directed options should be considered, including ablative techniques (radiofrequency ablation, cryotherapy, microwaves), chemoembolization, or radioembolization. These modalities have been found to improve tumor response and symptoms, although the effect on overall survival is unknown. The recent NET Clinical Trials Planning Meeting recommended that randomized phase II trials evaluate the relative efficacy and toxicity of embolization.

As with well-differentiated tumors, poorly differentiated tumors should be evaluated for resectability. For those deemed to be resectable, treatment entails resection and chemotherapy with or without radiotherapy, similar to guidelines for small cell carcinoma of the lung. For tumors that are unresectable but have not metastasized, treatment should include chemotherapy with radiation. Surveillance after resection for localized disease includes a history and physical along with imaging and potential tumor markers every 3 months for the first year and every 6 months thereafter. Metastatic poorly differentiated NETs of unknown primary are treated with regimens similar to those for small cell lung cancer, including a platinum-based chemotherapy with etoposide. In a phase II study, patients with untreated, metastatic, poorly differentiated neuroendocrine carcinoma, 62% of whom had an unknown primary, were given 4 courses of chemotherapy with paclitaxel, carboplatin, and etoposide. Major responses were seen in 53% of patients and the median survival was 14.5 months. The authors note, however, that this regimen was moderately toxic and did not have increased efficacy compared with platinum/etoposide regimens.

Conclusions
With advancements in diagnostic modalities, more tumors of unknown origin are being identified as NETs. Frequently, the primary tumor site cannot be found despite a comprehensive workup. In these cases, the NET is treated based on the grade, with well- and moderately differentiated tumors treated as carcinoid tumors, whereas poorly differentiated tumors are treated similarly to small cell tumors. Therapy is chosen based on symptoms and with the goal of debulking tumor when feasible and safe. Further information about NETs of unknown origin can be found in the NCCN Guidelines for Neuroendocrine Tumors (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

References
Polish et al.


CME Activity: Neuroendocrine Tumors of Unknown Origin Reviewed

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1. Which of the following statements about the clinical and epidemiologic features of neuroendocrine tumors (NETs) and NETs of unknown origin is most likely correct?
   A. Functionally active NETs include insulinomas, gastrinomas, vasoactive intestinal polypeptidoma, glucagonomas, and carcinoid tumors
   B. Functionally active NETs are always benign and do not metastasize
   C. NETs of unknown origin account for less than 5% of all NETs
   D. Most NETs of unknown origin are well differentiated and slow growing

2. A 54-year-old white woman presents with right upper quadrant pain and a large liver mass thought to be a metastasis from an NET of unknown origin. Which of the following statements about her diagnostic workup is most likely correct?
   A. Family history is not likely to be helpful
   B. Thyroid transcription factor 1 (TTF-1) is present in three quarters of pulmonary tumors
   C. CDX2 is present in one quarter of appendiceal and colonic tumors
   D. OctreoScan imaging takes advantage of the presence of specific somatostatin receptors on NETs

3. Diagnostic workup revealed no known primary tumor for the patient. Which of the following statements about her treatment is most likely correct?
   A. A well- or moderately differentiated tumor should be treated as a small cell tumor
   B. A poorly differentiated tumor should be treated as a carcinoid tumor
   C. Debulking the liver tumor is a consideration, provided that it is feasible and safe
   D. Octreotide therapy is not recommended for metastatic well- to moderately differentiated NETs of unknown primary