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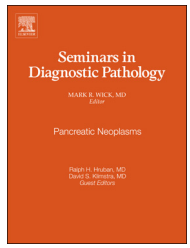

Problems with the diagnosis of metastatic neuroendocrine neoplasms. Which diagnostic criteria should we use to determine tumor origin and help guide therapy?

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ABSTRACT

Neuroendocrine neoplasms (NENs) can often present with metastatic disease before the primary tumor is discovered. Metastatic lesions are generally classified as well differentiated and poorly differentiated for prognostic and therapeutic purposes. In addition, for well-differentiated neuroendocrine tumors (WDNETs), pathologists are expected to determine the site of origin, if not already known, and grade the tumors. However, it is often difficult for pathologists to provide this information with certainty without knowing the site of tumor origin, as different criteria have been proposed by WHO for classification of gastrointestinal and pulmonary NENs. In this review, we will discuss the current classification and grading schema of NENs and their impact on clinical care, the differential diagnosis of NENs, the use of immunohistochemical stains that help identify tumor site of origin, and a proposed approach for the diagnosis and classification of metastatic NENs.

Introduction

Neuroendocrine neoplasms (NENs) are neoplasms derived from the diffuse neuroendocrine system and can arise from virtually any primary anatomic site, with the most common sites including the bronchopulmonary system, gastrointestinal tract, and pancreas. Not infrequently, NENs present as metastases to the liver before the primary tumor has been detected. In this review, we will discuss diagnostic criteria for metastatic NEN including grading, how to determine the site of origin of metastatic NEN, and recent developments and issues in this area.

Incidence of NEN

Based on Surveillance, Epidemiology, and End Results (SEER) data, the incidence of NENs has shown a nearly fivefold increase from 1973 to 2004, with the most frequent primary sites including lung (27%), rectum (17%), jejunum/ileum (13%), pancreas (6%), stomach (6%), and colon (4%).[1] This increase may be attributed to improved classification of these lesions, as well as increased detection secondary to improved imaging modalities and the increased frequency of endoscopic procedures. Primary pancreatic NENs had the highest rate of distant disease at diagnosis (64%), and showed the shortest

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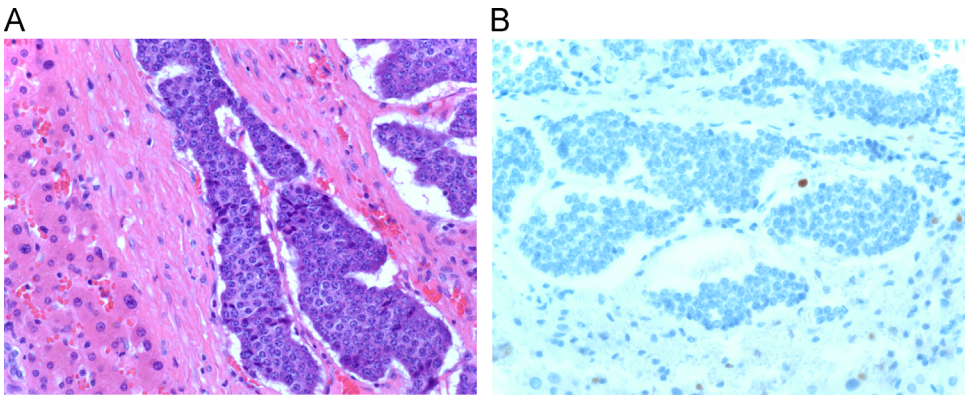

Fig. 1 – Metastatic low grade (G1) well-differentiated NET in the liver, of small bowel origin. Note the eosinophilic granularity of the cytoplasm (A). Ki-67 proliferative index is <1% (B), 20×.

mean survival (42 months), followed by cecum (44%, 83 months), colon (32%, 121 months), jejunum/ileum (30%, 88 months), and lung (28%, 193 months) primaries. A significant percentage (15%) of all NENs in this population were metastatic tumors of unknown primary origin. In a small single-institution-based study at UCSF of 123 patients presenting with metastatic NEN to the liver, the most common primary tumor locations were pancreas (35%), small intestine (27%), colon/rectum (12%), and pulmonary (4%).[2]

Terminology and classification varies by site of origin

Gastroenteropancreatic neuroendocrine neoplasms

The preferred terminology from the 2010 World Health Organization (WHO) classification of tumors of the digestive system is now well-differentiated neuroendocrine tumor (WDNET) or poorly differentiated neuroendocrine carcinoma (PDNEC), which includes both small cell carcinoma and large cell neuroendocrine carcinoma (LCNEC).[3] Historical terms such as "carcinoid" and "well-differentiated endocrine tumor/carcinoma" are no longer to be used for gastroenteropancreatic (GEP) tumors. WDNET are further graded based on proliferative activity into NET grade 1 (mitotic count <2 per 10 high power fields (HPF) and/or <3% Ki-67 proliferation index) (Fig. 1) and NET grade 2 (mitotic count 2–20 per 10 HPF and/or 3–20% Ki-67 proliferation index) (Fig. 2). Neuroendocrine carcinoma, grade 3 is defined in this classification as having a mitotic count >20 per 10 HPF and/or >20% Ki-67 proliferation index.

Of note, PDNEC including both small cell carcinoma (Fig. 3) and LCNEC (Fig. 4) are included in this grade 3 category. However, not all WDNETs belong to the grade 1 or 2 categories, as some can show >20% Ki-67 proliferation index, and whether these should be lumped together with PDNEC has been the source of some recent debate and discussion. Recently Basturk et al.,[4] in a multi-institutional study, demonstrated that grade 3 pancreatic NENs (tumors with Ki-67 > 20%) include both WDNET and PDNEC. Importantly, they found that patients with a grade 3 WDNETs (typically with Ki-67 proliferation index of 20–40%) have a longer median survival than those with PDNECs (typically with Ki-67 > 50%). The authors recommended that such tumors should be classified as "WDNET with an elevated proliferative rate" rather than G3 tumors (Fig. 5). This concept is further supported by the results of the "NORDIC NEC study" in which G3 tumors with a Ki-67 index of <55% were found to be less responsive than G3 tumors with a Ki-67 index of >55% to platinum-based chemotherapy; however, pathologic characteristics of the tumors were not evaluated in detail in this study.[5]

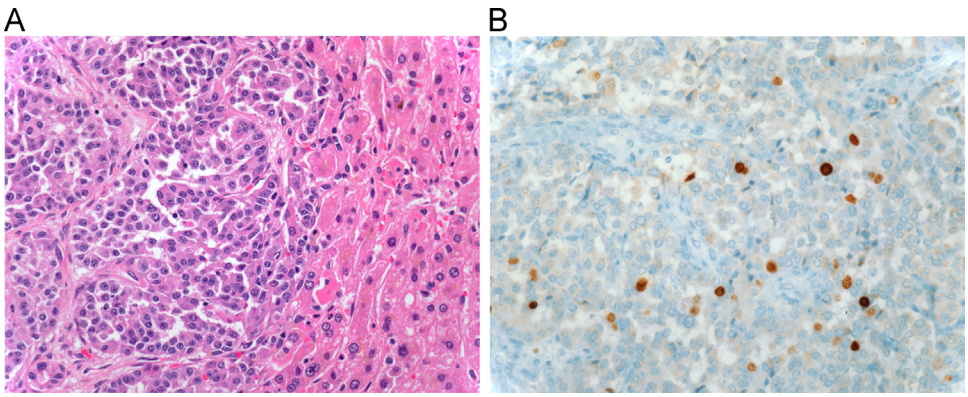

Fig. 2 – Metastatic intermediate grade (G2) well-differentiated NET in the liver, of pancreatic origin (A). Ki-67 proliferative index is approximately 10% (B), 20×.