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EDITORIAL

Mixed neuroendocrine and adenocarcinoma of gastrointestinal tract: A complex diagnosis and therapeutic challenge

Santosh Shenoy

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Abstract

In this editorial we comment on the manuscript describing a case of adenocarcinoma mixed with a neuroendocrine carcinoma of the gastroesophageal junction. Mixed neuroendocrine and non-neuroendocrine neoplasms of the gastrointestinal system are rare heterogeneous group of tumors characterized by a high malignant potential, rapid growth, and poor prognosis. Due to the rarity of these cancers, the standard therapy is poorly defined. The diagnosis of these tumors is based on combination of morphological features, immunohistochemical and neuroendocrine and epithelial cell markers. Both endocrine and epithelial cell components can act independently of each other and thus, careful grading of each component separately is required. These cancers are aggressive in nature and the potential of each component has paramount importance in the choice of treatment and response. Regardless of the organ of origin, these tumors portend poor prognosis with increased proportion of neuroendocrine component. Multidisciplinary services and strategies are required for the management of these mixed malignancies to provide the best oncological outcomes. The etiopathogenesis of these mixed tumors remains obscure but poses interesting question. We briefly discuss a few salient points in this editorial.

Key Words: Mixed adenocarcinoma and neuroendocrine carcinoma; Mixed neuroendocrine and non-neuroendocrine neoplasm; Mixed adeno-neuroendocrine cancer; Cell reprograming; Tumor plasticity

Core Tip: Mixed neuroendocrine and non-neuroendocrine neoplasms and mixed adeno-neuroendocrine cancer of the gastrointestinal system are a rare heterogeneous group of tumors with high malignant potential, rapid growth, and poor prognosis. The occurrence of cells with both neuroendocrine and non-neuroendocrine morphological features co-exist in varying amounts, and these tumors occur in almost all organs. The origin of these mixed cancers is not clearly defined but may be the result of certain genetic alterations and growth stimulation by the neuroendocrine peptides produced by neuroendocrine component. Regardless of the organ of origin, these tumors portend poor prognosis with increased proportion of neuroendocrine component. Multidisciplinary services and strategies are required for the management of these mixed malignancies to provide the best oncological outcomes.

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INTRODUCTION

In this editorial we comment on the manuscript by Cheng *et al*[1], describing a case of early adenocarcinoma mixed with a neuroendocrine carcinoma (NEC) of the gastroesophageal junction in a young Chinese male patient. The authors also briefly describe the tumor genetic mutation analysis of 196 genes with next generation sequence analysis.

Mixed neuroendocrine and non-neuroendocrine neoplasms (MiNENs) and mixed adeno-neuroendocrine cancer (MANEC) of the gastrointestinal (GI) system are rare heterogeneous group of tumors. The occurrence of neuroendocrine together with non-neuroendocrine morphological features coexists in differing proportions, and these tumors have been diagnosed in various organs[2-5]. A recent review of GI tract MiNENs suggested an incidence of 15.9% for esophageal MiNENs when compared to all GI tract MiNENs. Commonest sites were in colon-rectum (43.5%)[6].

Although the incidence of adenocarcinoma of esophagus is rising in western population due to chronic inflammation from Barrett's esophagus, neuroendocrine tumors (NETs) also called carcinoid tumors and NEC of the esophagus are uncommon and account for less than 1% of GI tract malignancies. However, the incidence and prevalence of GI NETs are rising steadily, owing to increased detection of early-stage disease due to advances in imaging and endoscopic techniques. Overall, the prognosis and survival of benign well differentiated NETs has improved over time, but the prognosis and survival for NEC remains dismal[7,8].

Previously we have demonstrated a close association of GI tract NETs and risks for concurrent second primary malignancy[9]. A recent review of all organ NETs and second primary malignancy from SEER database demonstrated that amongst 58596 patients with NETs, 4612 patients (7.9%) presented with a secondary primary cancer, an increased absolute risk by a factor of 42.47 for all cancers per 10000 person years[10].

Approximately 20% of NETs present as a part of genetic syndrome. Classic genetic syndromes associated with NETs include: Multiple endocrine neoplasia's (MEN) types 1 and 2, neurofibromatosis type 1 and von Hippel-Lindau disease [11]. An increased risk of carcinoids and adenocarcinoma in the progeny has also been observed in parents diagnosed with carcinoid disease[12].

This case presented by Cheng *et al*[1], is unusual in the sense that most commonly the esophageal and GE junction MiNEN tumors are predominantly found in elderly males and the tumors generally consist of neuroendocrine and squamous cell carcinoma association with rare reports of adenocarcinoma in the background of Barrett's esophagus. This patient developed this tumor at a younger age and the non-neuroendocrine component was adenocarcinoma without Barrett's esophagus[5]. The etiopathogenesis of these mixed tumors remains obscure but poses interesting question. We briefly discuss these in this editorial.

Diagnosis of MiNEN and MANEC

Both the histopathological evaluation of hematoxylin and eosin-stained sections of the tumor specimen is essential for detecting the neuroendocrine and non-neuroendocrine components for the diagnosis of MiNEN and MANEC tumors. It also is confirmed by immunohistochemical neuroendocrine and epithelial cell markers. The most common neuroendocrine markers expressed by NETs are chromogranin A, synaptophysin, and CD56. Meanwhile carcinoembryonic antigen, carbohydrate antigen 19-9, cytokeratin's 7, 19, and AE 1/3 are commonly expressed by the epithelial cell components of the tumor[3,5,13].

In earlier World Health Organization classifications, it was suggested that each tumor component must constitute at least 30% of the tumor for the diagnosis of mixed MiNEN and MANEC tumors. This was based on the assumption that prognosis is influenced by the predominant histological component and to determine the correct treatment options. However, current evidence indicates that even a smaller proportion of neuroendocrine component may have a significant impact in the invasiveness, lymph node metastasis and overall survival and prognosis[5,14-16].

Although the current threshold for diagnosing a MiNEN remains that tumor consist of at least 30% of each component. In tumors with less than 30% neuroendocrine differentiation, it is important not to dismiss the lower proportion of the neuroendocrine differentiation as trivial[2-5,14-16]. Treatment plan discussed in the multidisciplinary meetings should include the neuroendocrine components as it has consistently shown to be associated with a poorer prognosis[2-5,14-16].

In addition, the diagnosis of MiNEN or MANEC applies only to treatment naïve tumors in patients that have not undergone neoadjuvant treatment. It is demonstrated that cancer cell reprogramming and phenotypic switch with endocrine differentiation may occur in cancers after chemotherapy[17]. Similarly, it is observed in a subset of GI tract cancer including esophageal adenocarcinoma wherein a proportion of neuroendocrine cells may actually increase after neoadjuvant treatment. Neuroendocrine cells, in general respond poorly to standard chemotherapy. Similar observations occur in non-small cell lung cancer patients treated with anti-epidermal growth factor receptor targeted therapy. These tumors commonly develop resistance and may recur, switching phenotype, most commonly to small cell lung cancer which is classified as a NEC. Similarly, the phenomenon of trans- differentiation occurs in castration resistant prostate adenocarcinoma where adenocarcinoma of the prostate treated with androgen receptor inhibitors switches to NEC of the prostate which carries a poorer prognosis. Cancer cells have the ability to switch phenotypes for survival and sustain its growth which contributes to metastasis and poor prognosis for patients[17-19].

Pathogenesis

MiNENs and MANEC of the GI system are a rare heterogeneous group of tumors and these tumors occur in almost all organs[2-5]. The origin of these mixed cancers is not clearly defined however; evidence suggests that these cancers may have a common monoclonal origin. This relation is demonstrated in the neuroendocrine mucinous tumors of the appendix and the adenocarcinoma colorectal cancers[20].

In addition, genetic alterations and growth stimulation by the peptides produced by neuroendocrine component may contribute to its pathogenesis. An initial oncogenic stimulus resulting in a driver mutation, confers the cells with a growth advantage. Subsequent rounds of growth and proliferation of this initial clone of cells, with newer somatic mutations and epigenetic rearrangements, along with possible contribution from peptides secreted by the tumor microenvironment gives rise to intra tumor-heterogeneity and complexity noted in the advanced tumors[3,5,17].

Molecular data of (MiNENs) and MANEC tumors indicate their monoclonal origin, as demonstrated by loss of heterozygosity, and mutation in *RB1*, *TP53*, *TP63*, *SOX2*, *DVL3*, *PTEN*, *PIK3A*, and *KRAS* genes. These genetic alterations have emerged as potential driver mutations of these mixed neoplasms[5,16,21]. An interesting question that may arise is, whether a paracrine effect or a field defect from biological peptides produced by the functional neuroendocrine component increases the risk for epithelial cell malignancy[9,17]?

Presence of excessive GI trophic hormones, under the optimal stressed conditions such as chronic mucosal inflammation, *Helicobacter pylori* infection, inflammatory bowel disease along with genetic mutations such as *TP53* and *Rb* mutations creates an ideal field condition that may indeed trigger a population of cells to acquire a malignant potential[9,17,22].

The regulatory peptides secreted by the neuroendocrine component function as GI hormones and neurotransmitters. They may act as growth factors, and non-neuroendocrine component of tumor cells can overexpress receptors for these regulatory peptides, thus promoting intratumor-heterogeneity as described earlier[22]. Response to the growth factors and resulting proliferation is a well-coordinated and tightly controlled process. Dysregulation of this process results in uncontrolled proliferation, leading to cancers[14,17,23]. In addition to presence of chronic inflammation, gut dysbiosis compromises and alters the local microenvironment and growth factors will have an exaggerated effect. Chronic gut dysbiosis is considered as a risk factor for GI tract malignancies[24].

GI tract neuroendocrine cells frequently are scattered and interspersed with normal epithelia, which may further support the hypothesis that growth factor stimulus can influence cancer stem cells at different locations. The receptors for these growth factors are expressed on tumor cells and stroma. The proposed mechanisms are both paracrine and autocrine stimulation of both tumor cells and stromal cells[9,23]. Some of peptides commonly produced by upper GI tract NETs such as gastrin, cholecystokinin and bombesin can stimulate gastric mucosa and pancreatic cell growth. Other growth factors including, platelet-derived growth factor, epidermal growth factor, fibroblast growth factors, and insulin-like growth factor play a key role in cell growth and differentiation, angiogenesis, vascular invasion with metastasis, leading to pathogenesis for these mixed MiNEN and MANEC tumors[9,23].

Briefly we would also like to include a brief mention on the role of glucagon-like peptide 1 (GLP-1) and 2 analogues produced by L-cells in the GI tract, which have recently become extremely popular as anti-obesity medicines. Semaglutide and liraglutide (GLP-1) receptor agonists are a class of antidiabetic medications that have shown encouraging results in glycemic control and weight loss in patients with obesity and type 2 diabetes and are approved for their use in the United States[25,26].

Teduglutide is (GLP-2), a potent intestinotrophic and antiapoptotic hormone, approved in the United States for short bowel syndrome. The trophic effects of GLP-2 result in stimulation of crypt stem cell proliferation leading to expansion of the normal intestinal mucosal epithelium which may cause hyperplasia of the villi. There also occurs an inhibition of crypt cell apoptosis and increased mitotic index[25,26].

Interestingly, GLP is also one of the peptides known to be produced by small bowel NETs. These medications are contraindicated in patients with medullary carcinoma of thyroid and familial multiple endocrine tumors (MEN type 2). Although preclinical studies have not described any increased risk for NETs in general population, whether its action, as described, translates into the growth of tumor cells in general population remains to be seen in the future post clinical follow up studies[25,26].

Management considerations

Mixed neuroendocrine and adenocarcinoma of the esophagus poses a management challenge. Due to the presence of different proportions of each component these cancers display a wide heterogeneity. Consequently, the prognosis and overall survival of these tumors are variable and depends on the tumor location within the GI tract[27-29].

From a Chinese registry for MiNEN tumors of GI tract compared the results of 55 randomly selected patients with gastroenteropancreatic (GEP NETs), 47 with NECs, and 58 with poorly differentiated adenocarcinoma followed up to a period of 72 months. The median overall survival was 30 months. Ki-67 index ≥ 50%, high proportion of NEC component, lymph node involvement, distant metastasis, and higher clinical stage were independent risk factors and predicted poor prognosis. The overall survival was shorter for patients with pure NEC tumors compared to those with MiNEN (14 months *vs* 30 months, $P = 0.001$), while the poorly differentiated tumors had a median survival of 18 months suggesting that that higher proportion of NEC component carries higher mortality, similar to poorly differentiated carcinoma when compared to mixed components (MiNEN)[29].

In another systemic review of 71 studies reporting on 752 patients with lower GI tract MANEC and MiNEN tumors reported that more than a quarter (29%) of patients presented with stage IV disease on diagnosis. More than 80% of these patients had a higher grade of neuroendocrine component (80%). The median overall survival was 12.3 months suggestive of poor overall prognosis of these tumors[28].

These conditions have created management dilemma for both surgical and medical oncologists in determining which of the component should be targeted primarily in treatment. For localized MiNENs, MANEC cancers, resection with curative intent remains the primary first treatment of choice[5]. For details on adjuvant chemotherapy, targeted therapies for metastatic or recurrent cancers, the management is beyond the scope for this editorial and we recommend following NCCN guidelines. Multidisciplinary services and strategies are required for the management of these mixed malignancies to provide the best oncological outcomes[3,5,27,28].

CONCLUSION

MiNENs and MANEC of the GI system are a rare heterogeneous group of tumors with high malignant potential, rapid growth, and poor prognosis. The occurrence of cells with both neuroendocrine and non-neuroendocrine morphological features co-exist in varying amounts, and these tumors occur in almost all organs. The origin of these mixed cancers is not clearly defined but may be the result of certain genetic alterations and growth stimulation by the neuroendocrine peptides produced by neuroendocrine component. Regardless of the organ of origin, these tumors portend poor prognosis with increased proportion of neuroendocrine component.

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