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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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EDITORIAL

Critical considerations for the management of gastrointestinal mixed neuroendocrine non-neuroendocrine neoplasms and pure neuroendocrine carcinomas

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Abstract

Mixed neuroendocrine non-neuroendocrine neoplasms constitute rare tumors that are located mainly in the gastrointestinal (GI) tract and have high degrees of malignancy, and the frequency of these tumors has been increasing. They consist of a neuroendocrine neoplastic component with another component of adenocarcinoma usually and have a dismal prognosis. The rare GI pure neuroendocrine carcinoma is highly aggressive and requires complex and extensive management since a genetic distinction exists between it and GI non-neuroendocrine neoplasms, which are generally slow-growing lesions. The most common GI-mixed neuroendocrine non-neuroendocrine neoplasms are colorectal, followed by gastric, mainly in the gastroesophageal junction. Current imaging modalities of nuclear medicine and radiology play important roles in the accuracy of diagnosis. Liquid biopsy may contribute to early detection and timely diagnosis. Ultrasonography, either endoscopic or abdominal, is a technique that contributes to a diagnosis; additionally, contrast-enhanced ultrasonography is very helpful in follow-up appointments. Histopathology establishes a definite diagnosis and stage by evaluating the cell differentiation grade and the cell proliferation index Ki67. The genetic profile can be valuable in diagnosis and gene therapy. Surgical resection with wide lymphadenectomy, whenever possible, and adjuvant chemotherapy constitute the main therapeutic management strategies. Targeted therapy and immunotherapy achieve encouraging results.

Key Words: Neuroendocrine neoplasms; Gastrointestinal neuroendocrine neoplasms; Mixed gastrointestinal neuroendocrine neoplasms; Gastrointestinal neuroendocrine carcinomas; Neuroendocrine carcinoma; Neuroendocrine non-neuroendocrine neoplasms

Core Tip: The rare but steadily increasing number of gastrointestinal mixed neuroendocrine non-neuroendocrine neoplasms and pure neuroendocrine carcinomas require more radical treatment than slow-growing neuroendocrine neoplasms do and they are related to poor prognosis. They constitute a complicated diagnostic and therapeutic challenge. The current management strategy begins with surgery and is followed by chemotherapy. New chemotherapeutics and novel biological agents for targeted therapy, along with immunotherapy broaden the range of therapeutic options, providing promising outcomes. Effective management should be individualized and multidisciplinary.

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INTRODUCTION

Recently, in the *World Journal of Gastrointestinal Oncology*, the editorial by Cives *et al*[1] and previously the review by Díaz-López *et al*[2] presented the current aspects of the interesting issue of mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) of the gastroenteropancreatic tract in precise detail. These rare neoplasms consist of heterogeneous lesions of combined neuroendocrine neoplasms with epithelial carcinoma (at least 30% of each component) that exhibit high malignancy with rapid progression and a dismal prognosis[3]. The pathogenetic mechanism of MiNENs and neuroendocrine carcinoma (NEC) is still unclear. It seems that a possible association with Crohn's disease exists with more gene disorders and greater aggressiveness[4]. They are increasing in prevalence in the gastrointestinal (GI) tract, and their incidence is increasing every year[5]. A tenfold increase was reported between 2000 and 2017[6]. Although MiNENs were initially called mixed adenoneuroendocrine cancers, the recent World Health Organization (WHO) update established the current terminology[7].

Although MiNENs are rare entities, there is particular interest in their diagnosis and treatment. The usual aggressive behavior of these cells is influenced by poor cell differentiation and an increased Ki67 cell proliferation index according to histopathology assessment[8-11]. Pure NECs merit specific preoperative evaluation and wide operative management by radical surgery, including extended lymphadenectomy, followed by proper adjuvant therapy. This carcinoma is a subgroup that usually affects the GI tract in more than 35% of patients[12].

The most common GI-MiNENs are those of the colorectal region[13], followed by those of the gastroesophageal junction and stomach[14,15]. Colorectal MiNENs constitute the majority of poorly differentiated cells and should be managed as adenocarcinomas[13]. Gastric MiNENs differ biologically, histopathologically and clinically from stomach adenocarcinomas, represent the least common gastric neoplasms and are located more often in the gastroesophageal junction[16]. Ampullary MiNENs are extremely rare[17], and proper management constitutes a therapeutic extended operative excision and adjuvant chemotherapy[9]. Less common sites of GI-MiNENs include the appendix[18], which are associated with the best prognosis[6], small intestine, esophagus, liver, pancreas[19], biliary tree, and gallbladder (gallbladder NEC represents 0.5% of all NENs and 2.1% of gallbladder malignancies)[20]. GI-MiNENs may present apart from the neuroendocrine component, another epithelial neoplasm, instead of adenocarcinoma[3]. The histological types of MiNENs include collision, combined and amphicrine types[17].

When distant and high-grade metastases are present in GI-MiNENs, a treatment plan consisting of chemotherapy and targeted therapy, including novel biological agents and immunotherapy, can replace an otherwise ineffective and risky extended surgical resection[10]. Among various GI-MiNENs, different clinical and pathological manifestations may be found, but in any case, these manifestations do not substantially affect the prognosis[21]. The prognosis depends on histological grade, cell differentiation, mitotic rate and Ki67 proliferation index. The Ki67 proliferation index is the most reliable prognostic factor, with a crucial value of 55%[10,21].

DIAGNOSIS

Genetic profile analysis may be valuable in precise diagnosis and in novel targeted gene therapy. It has been postulated that, genetically, GI-NECs are different from GI-NETs. Mutations in the *TP53* gene and *RB1* gene are common in GI-NECs, as are mutations in the *CCNE1* gene and MYC proto-oncogene, BHLH transcription factor (*MYC*) gene. Nonpancreatic GI-NECs are the only ones characterized by mutations in the *Notch* gene family. Transcription factors, mainly the *SOX2* gene, are overexpressed in most GI-NECs[22]. In gastric and colorectal NECs, mutations in the *TP53*, *RB1*, and *KRAS* genes have been detected. However, *BRAF* gene mutations have been found only in colorectal NECs[23].

The identification of molecular biomarkers in circulation is a new diagnostic challenge. Recently, they have been used for precise assessment in ambiguous cases, including tumor cells, tumor DNA, microRNAs, and NETest. Another valuable current diagnostic test in serum is the so-called liquid biopsy, which depends on mRNA assessment, which

contributes to timely diagnosis and treatment monitoring[24-27]. The development and application of the above molecular biomarkers can accurately classify these neoplasms, ensuring their more effective management[28].

Current imaging modalities of nuclear medicine and radiology play important roles in accurate and timely diagnosis. These methods include fluorodeoxyglucose positron emission computed tomography (PET-CT) and, more precisely, gallium^{68} PET-CT or the novel most accurate 18F-fluoro-dihydroxyphenylalanine PET-CT, which is specific for distinguishing NENs, and single photon emission computed tomography[29-32]. The novel endoscopic and abdominal ultrasonography (US) technique contributes to diagnosis, and contrast-enhanced US is very helpful in follow-up appointments [26].

There are no specific reliable tumor markers, only the abovementioned biomarkers[26]. They are typically diagnosed by fine needle biopsy under imaging guidance or biopsy endoscopy (EUS-fine needle biopsy) for upper GI and colorectal neoplasms which are the gold standard for the preoperative diagnosis of MiNENs and NECs[26]. The staging in the definite histopathological assessment of the specimen must be accurate according to the WHO guidelines, which provide precise terminology, particularly the rate of mitoses and the necessary cell proliferation index Ki67[10,33]. In the majority (60%) of samples, the neuroendocrine component has a Ki67 proliferation index equal to or greater than 55%[21]. The WHO staging and recommendations must be followed precisely to reduce the risks of misdiagnosis.

MANAGEMENT

Compared with slow-growing NENs, mixed MiNENs and pure NECs require more radical treatment, ensuring necessary R0 resection without residual NENs. This means that in mixed neoplasms and pure carcinomas if a more advanced disease (mainly hepatic metastases) exists that cannot exclude any residual focal neoplastic lesion after attempting potentially curative operative excision, the disease should be characterized as inoperable. In contrast, for functional hypersecreting NENs, there is an indication for debulking surgery (90% resection of the tumor burden) for better control and alleviation of persistent symptoms; consequently, NENs with hepatic metastases are not characterized as inoperable a priori[34]. It is also well known for NENs that curative surgical management of the primary site is highly important, but the management of hepatic metastatic spread must be individualized, and meticulous long-term follow-up is imperative. The current management policy for NEN hepatic metastases includes systemic therapy as first-line therapy and hepatectomy only if systemic therapy fails[35].

In operable cases, whenever feasible, the ideal basic management for both MiNENs and NECs is a radically wide operation with extended lymphadenectomy followed by chemotherapy[36]. The physical status, age and comorbidities of a patient are the primary factors associated with extended surgical procedure outcomes. Therapeutic radical surgery includes complete excision (colectomy, gastrectomy, esophagectomy, proximal pancreatoduodenectomy, or enterectomy) with extended lymphadenectomy according to the location of the primary tumor. It is more risky and complicated but may offer a reasonable chance of cure. In inoperable advanced metastatic cases, any palliative treatment must be aimed at the predominant responsible metastatic component, either the neuroendocrine neoplasm or epithelial carcinoma[28]; this palliation may be achieved by debulking surgery; microwave or radiofrequency ablation; chemotherapy; drugs that suppress tumor growth, mainly in relapse after surgery; novel targeted therapy; and immunotherapy[24,25]. Although approximately 40% of patients have distant hepatic metastases at the time of diagnosis, 88% of all patients undergo some operative procedures[6].

For advanced MiNENs, first-line chemotherapy with 5-fluorouracil or capecitabine plus oxaliplatin has been used as treatment. However, it might differ according to the primary site or the proportion of tumor. The median overall survival was 14 months, depending on the Ki67 proliferation index. Survival was better (35.3 months *vs* 11.9 months) in patients whose Ki67 index was < 55%[37].

Novel targeted therapies include: (1) Toripalimab, a programmed cell death protein inhibitor, and surufatinib, a tyrosine kinase inhibitor that has been used with encouraging early results in advanced solid tumors, including MiNENs, NECs and NENs[38]; (2) Sunitinib, a tyrosine kinase inhibitor, and everolimus, an mechanistic target of rapamycin inhibitor[39]; and (3) Bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, and atezolizumab, a programmed cell death ligand 1 inhibitor, for advanced cases, also providing encouraging results[40].

The biological behavior of GI-MiNENs does not differ from that of pure GI-NECs, and the prognosis is similarly poor in both[41]. The median overall survival of all patients with colorectal MiNENs and NECs is 38 months and 42 months, respectively, whereas for those with stage III disease, it is 30 months and 25 months, respectively. Patients with stage III disease and less lymph node involvement have better survival after adjuvant chemotherapy, as determined by multivariate analysis[13].

The prognosis of GI-MiNENs is poorer than that of pure GI-NENs. The former is an independent risk factor for cancer-specific survival in terms of the size of the tumor, degree of lymph node involvement, degree of distant metastasis and applied surgical procedure[5]. The most commonly used chemotherapy for aggressive pure NECs is cisplatin plus etoposide, but the median overall survival time is one year[42]. Rectal NECs are rare and highly aggressive and have a poor prognosis, especially high-grade NECs with poor differentiation. Surgical resection and chemoradiotherapy may be helpful[43].

Apart from symptom palliation, treatment with somatostatin analogs may be beneficial in suppressing tumor growth. Thorough evaluation of somatostatin receptors, including the five subtypes identified by their immunohistochemical expression, is highly important for determining the effectiveness of applied therapy and predicting patient outcome. Somatostatin receptor antagonist targeted therapy has been used recently for its antineoplastic activity[44]. The newest such drug, pasireotide, which binds subtype 1 and 4 receptors, may be more effective[45].

Given that pure NECs constitute a subgroup of poorly differentiated NENs with a mitotic rate > 20%, a Ki67 proliferation index > 20%[34] and clear genetic distinction (gene alterations are prevalent in NECs and rare in NENs)[46], they are more aggressive and require wider radical excision than NENs, which are generally slow-growing lesions[34]. The evaluation of genetic profiles is important in determining the application of targeted therapy and immunotherapy in the usual advanced inoperable patients[46,47]. The characteristic endoscopic features (submucosal tumor elevation, such as white coating and ulceration) lead to accurate biopsies for histopathological and molecular analysis, contributing to proper management[48]. Cisplatin and etoposide or irinotecan have been used as first-line chemotherapies in advanced inoperable NECs and as second-line immunotherapies with nivolumab, a monoclonal antibody against programmed cell death protein 1 with satisfactory results[49,50]. Folinic acid, 5-fluorouracil, irinotecan and capecitabine, temozolomide were used as second-line chemotherapies for metastatic NECs in a multicenter study, with encouraging results (1-year overall survival of 28.4% for folinic acid, 5-fluorouracil, irinotecan and 32.4% for capecitabine, temozolomide)[51].

In any case, the effective treatment of GI-MiNENs and GI-pure NECs is difficult, since the prognosis is poor for these high malignancy neoplasms and different genetic factors are implicated. The novel treatment must be individualized, multidisciplinary and targeted. New chemotherapeutics and novel biological agents for targeted therapy, along with immunotherapy, broaden the range of therapeutic options mainly in inoperable cases, providing promising outcomes[10,21,34].

CONCLUSION

The current management of GI MiNENs and pure NECs constitutes a challenging multidisciplinary task that must be personalized for each patient. Early and accurate diagnosis has an important contribution to proper management. Apart from diagnostic and therapeutic modern endoscopic modalities, the role of gastroenterologists is also crucial, in diagnosis and scheduled follow-up appointments. Surgery is the cornerstone of any curative treatment accompanied by chemotherapy and novel drugs. Future perspectives should open new horizons in novel chemotherapies, targeted gene therapy and immunotherapy.

FOOTNOTES

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