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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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

Unveiling the clinicopathological enigma of crawling-type gastric adenocarcinoma

Grigorios Christodoulidis, Sara E Agko, Marina N Kouliou, Konstantinos E Koumarelas

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Abstract

In this editorial we comment on the article by Xu *et al*. Gastric adenocarcinoma (GA) is a malignancy which arises from the gastric mucosa and encompasses heterogenous tumors with varying characteristics. There are two main classifications: Lauren's and the World Health Organization distinguishing the diverse types of GA depending on clinical, genetic, morphological and epidemiological features. "Crawling-type" adenocarcinoma (CRA) is a subtype characterized by irregularly fused glands with low-grade cellular atypia. Moreover, CRA represents differentiated tumor cells resembling intestinal metaplasia which results in misdiagnosis. The diagnosis is of utmost importance, as well as the subclassification and thorough pathological assessment. With regard to the symptoms of GA, these depend on the stage of the disease. Diagnostic methods play a crucial role in assessing the extent of the tumor and the stage of the disease. Nevertheless, early detection of CRA remains challenging due to its histological features. In summary, CRA is a distinct type of GA with particular clinicopathological and histological characteristics. Despite its significance, it not distinguished as a subtype, resulting in diagnostic challenges. Diagnosis is based on careful observation and thorough biopsy analysis, indicating the importance of comprehensive pathological assessment.

Key Words: Crawling-type adenocarcinoma; Clinicopathological characteristics; Histological features; Gastric adenocarcinoma; Diagnosis; Treatment

Core Tip: Crawling-type adenocarcinoma has specific features, such as irregularly fused glands and low-grade cellular atypia, resembling intestinal metaplasia. Given this, precise attention to its histological characteristics is crucial when diagnosing "crawling-type" adenocarcinoma (CRA). Early detection of CRA is challenging which leads to the importance of the detection of molecular markers and thorough biopsy analysis for accurate classification and clinical management strategies.

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INTRODUCTION

In this editorial, we comment on the article published on the *World J Gastrointest Oncol*. Gastric adenocarcinoma (GA) is a malignant neoplasm located in the epithelium, which emerges from the gastric mucosa and is characterized by differences in the glands. It represents a biologically diverse group of malignant neoplasms in terms of morphology, histogenesis, molecular features and etiology[1]. Moreover, GA is defined by low-grade cellular atypia and irregular glandular anastomosis. It is important to note that GA is the third cause of cancer-related deaths and the fifth most common cancer[2]. While there has been a decline in its incidence and mortality, in some regions, gastric cancer (GC) prevalence remains high, particularly in Asia[3,4]. Intestinal histology is more common among Caucasians, whereas gastric tumors located in the cardia are less frequent in Africa and Latin America[4]. Risk factors for GC include both nonmodifiable factors such as sex, age, genetics and race as well as controllable factors like *Helicobacter pylori* infection, lifestyle, diet and exposure to certain chemicals or viruses[5]. Early detection and surveillance are crucial due to the challenging nature of diagnosing certain variants, particularly those presenting as superficial depressed or flat type tumors in the stomach. Treatment typically involves surgical interventions, including endoscopic mucosal resection or various forms of gastrectomy, depending on the location and stage of the tumor. Chemotherapy, either alone or in combination with surgery, is a common treatment approach, aimed at improving patient outcomes, particularly for those diagnosed at advanced stages[3].

There are two commonly used morphological classifications; the Lauren's and the World Health Organization (WHO). More specifically, the Lauren classification categorizes GA into diffuse type (33%), intestinal type (53%) and intermediate type (14%)[6,7]. This classification depends on the different clinical features, morphology, genetics, epidemiology, and expansion ability[8]. The diffuse type involves poorly cohesive single cells without gland formation, whereas the intestinal type has glandular and tubular components[8]. The WHO subdivides GAs into papillary, micropapillary, tubular, parietal cell, mucinous, mixed type, mucoepidermoid, hepatoid adenocarcinoma, poorly cohesive (including signet-ring cell carcinoma), Paneth cell and medullary carcinoma[2,7].

Gastric "crawling-type" adenocarcinoma (CRA) is a subtype of GA that constitutes a specific histological pattern and has specific clinicopathological features[9]. More specifically, it is characterized by irregularly fused glands with low-grade cellular atypia that spreads in the mucosa[10,11]. Furthermore, it is described by its growth in branching, tortuous, distending, spiky, abortive, and anastomosing patterns with glandular outgrowth. Additionally, the histological findings of CRA are well-differentiated tumor cells that mimic intestinal metaplasia, and it is cytologically low-grade. The lesions of this distinct type appear as ill-demarcated depressed lesions and the tumor glands are mainly in the middle third of the stomach with occasional signet-ring cells[10,12]. Another important histological diagnostic characteristic is that the shape of CRA glands recreate the letters W, H, Y and X[13]. Importantly, many cases of CRA are often misdiagnosed because the cells show minimal cellular atypia with extension into the epithelial proliferative zone but with sparing of the mucosal surface[10]. Given the subtle cytological abnormalities, tumor glands may resemble "intestinal metaplasia", a benign condition. Consequently, discriminating this form of GC from non-neoplastic lesions like intestinal metaplasia can be a huge challenge for both endoscopic and histological assessments. It is of outmost importance to remain vigilant for this variant, especially when encountering superficial depressed or flat type tumors in the midsection of the stomach[3]. In this Editorial we aimed to elucidate the clinicopathological features and histological characteristics of CRA. The uniqueness of the current investigation is based in its comprehensive exploration of CRA. What sets this investigation apart is its meticulous examination of the clinical and histological characteristics of CRA, emphasizing its subtle cytological abnormalities that contribute to frequent misdiagnosis. Moreover, the study emphasizes the necessity of utilizing various diagnostic modalities, contributes to our understanding of GC pathology and highlights the need for observation and biopsies for accurate diagnosis.

CLINICOPATHOLOGICAL AND HISTOLOGICAL CHARACTERISTICS OF CRAWLING-TYPE ADENOCARCINOMA

Diagnosis of GA is of foremost importance for staging and treatment determination. Initially, the subclassification of malignancies may indicate the treatment of the disease as cases with intestinal-type GA are prone to overexpression of human epidermal growth factor receptor-2 (HER2). Additionally, the pathologic report must involve the tumor grade and invasion as these are necessary for staging of the disease. Moreover, newly diagnosed patients should undergo universal testing for microsatellite instability by polymerase chain reaction/next-generation sequencing or mismatch repair (MMR) deficiency by immunohistochemistry. Finally, the tumor diameter and depth of invasion, the lymphovascular invasion and the mucosal and deep margin status should be included in the pathology report of endoscopic mucosal resection[14].

Studies have shown that crawling-type adenocarcinoma is distinguished by low-grade nuclear atypia and a morphology that mimics intestinal metaplasia with a laterally spreading pattern. The glands of this subtype are included in the characteristics of extremely well-differentiated adenocarcinomas of the stomach[15]. It is of utmost importance to note that not only the CRA tumor is superficial flat or a depressed type but also the margin is often indistinct[15,16]. On histological examination, the irregularly fused glands with architectural features similar to branching are the most important diagnostic key[15].

A study conducted by Okamoto *et al*[11] evaluated 25 crawling type GC (CTACs) consisting of 16 intramucosal and 9 submucosal invasive cancers. The results showed that CTACs were more often located in the middle third of the stomach. Histologically, all CTACs displayed cystic dilated glands and 16 lesions exhibited focal signet-ring cells. Invasive areas of the submucosal CTACs were characterized by poorly differentiated adenocarcinoma with an infiltrative growth pattern and abundant stroma[11].

Most importantly, the stage and the topography of GA are related to the clinical presentation of the disease[1]. The majority of people with early GC are asymptomatic but they are successfully diagnosed by screening programs, resulting in a better survival rate[1]. A study examined a total of 51 lesions classified as CRA and 126 categorized as conventional differentiated adenocarcinoma (CDA) were identified. There were notable disparities in tumor location frequency between CRA (62.8%) and CDA (36.5%). CRAs were situated in the middle third of the stomach compared to CDAs. Depressed type tumors were more prevalent in CRA (72.5%) than in CDA (36.5%)[1]. Immunohistochemistry findings such as β-catenin nuclear expression was notably less common in CRAs (2%) compared to CDAs (30.3%). Similarly, the occurrence of loss of MLH-1 expression was lower in CRAs (3.9%) compared to CDAs (15.1%). The frequency of TP53 mutations was notably higher in CRAs (37.3%) compared to CDAs (7.9%)[1]. On the contrary, physical examination may not be of such significance in the early stage of the disease[17]. Notably, symptoms such as abdominal mass, dyspepsia, epigastric pain, weight loss, emesis, nausea, dysphagia, and gastrointestinal hemorrhage are frequent at advanced disease stages[1,17,18].

CRA is frequently misdiagnosed as a benign non-neoplastic lesion, such as intestinal metaplasia, by pathologists. Furthermore, CRA is related to particular histological features and clinicopathological characteristics, but it is not included as a distinct histological subtype in the WHO classification[9].

Fujita *et al*[9] in their study compared the clinicopathologic and molecular characteristics of CRA and those of CDA by examining 51 lesions from patients with CRA and 126 lesions from patients with CDA[9]. It was observed that CRAs were located more in the middle third of the stomach than CDAs. Also, the CRA tumors were depressed type and larger than the CDA tumors. Additionally, the frequency of tumors with a mixed differentiated and poorly differentiated adenocarcinoma component was statistically higher for CRA than CDA[9]. Moreover, in this study it was observed that the loss of MLH-1, a MMR protein, and nuclear accumulation of β-catenin were not often found in CRA compared with CDA. Finally, it was shown that TP53 mutation was related to CRA pathogenesis, and that the presence of multiple allelic imbalances was linked to early carcinogenesis of CRA[9].

Another study conducted by Woo *et al*[10], involved 94 patients with CRA, 72 patients with CDA and 71 patients with poorly cohesive adenocarcinoma (PCA)[10]. It was observed that the rate of younger patients with CRA was greater compared with CDA. In addition, the size of the tumors was larger in CRA than in CDA. Furthermore, this study showed a nonsignificant difference in tumor location among CRA patients and CDA patients[10]. Also, CRAs and PCAs did not have loss of expression of the MMR proteins and showed negativity for HER2. In addition, MET overexpression was observed in CRA at a rate 4.4%, in PCA at a rate 2.8% and 19.4% in CDA. Also, EGFR overexpression in CRAs was 36.5%, in CDAs was 31.4% and in PCAs was 31%. Additionally, diffuse, and strong positive or complete loss of p53 expression was noted in 12.4% of CRA, 8.5% of PCA and 62.55% in CDA. Lastly, a minor component of poorly differentiated adenocarcinoma was observed in 25.5% of CRA cases[10]. The study by Joshi and Badgwell[18], compared the clinicopathological characteristics of CRA and CDA patients. CRAs tended to occur in younger patients compared to CDAs, the tumor sizes ranged from 0.1-8.4 cm, with CRAs generally larger than CDAs[14]. Among the 237 cases evaluated, all CRA cases displayed either negativity (89.8%) or weak positivity (10.2%)[18].

The gold standard method for GC diagnosis is endoscopic examinations of the gastric mucosa and biopsy of suspicious lesions[1,15,17]. In addition, endoscopic ultrasound (EUS) plays a significant role in the diagnosis and staging of the tumor as it can assess the depth of the tumor, and identify suspected metastasis[17,18]. Also, laparoscopy is particularly important in the peritoneal staging of GA as it allows for biopsy of the lesions and visualization of the peritoneal surface [17]. Another method of evaluating indeterminate lesions is fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography[18]. Diagnosis of CRA is difficult in the early stage due to low-grade nuclear atypia and the results of endoscopic resection can be incomplete with positive lateral margins[15].

CONCLUSION

In conclusion, CRA is a subtype of GA with specific clinicopathological and histological characteristics. Despite these features, it is not categorized in the WHO classification as a distinct histological subtype. Notably, it is difficult to diagnose at an early stage due to misinterpretation of the tumor with other types of GA. The complexities surrounding the diagnosis and management of CRA underscore the necessity for a thorough understanding of its clinicopathological and histological characteristics. Its subtle cytological abnormalities often lead to misdiagnosis, posing significant challenges for both endoscopic and histological assessments. Moreover, studies comparing CRA with CDA have shed light on key differences in tumor location, size and molecular characteristics, emphasizing the importance of accurate diagnosis and subclassification for tailored treatment strategies. Diagnostic modalities such as endoscopic examinations, EUS, laparoscopy, and FDG-PET/CT scans play vital roles in the evaluation and staging of GA, yet early detection of CRA remains challenging due to its low-grade nuclear atypia. Thorough observation and biopsies of all mucosal layers are of great importance as these are the key to accurate diagnosis of CRA. Continued research efforts aimed at elucidating the mechanisms and diagnostic approaches are essential for improving outcomes in patients with this subtype of GC.

FOOTNOTES

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