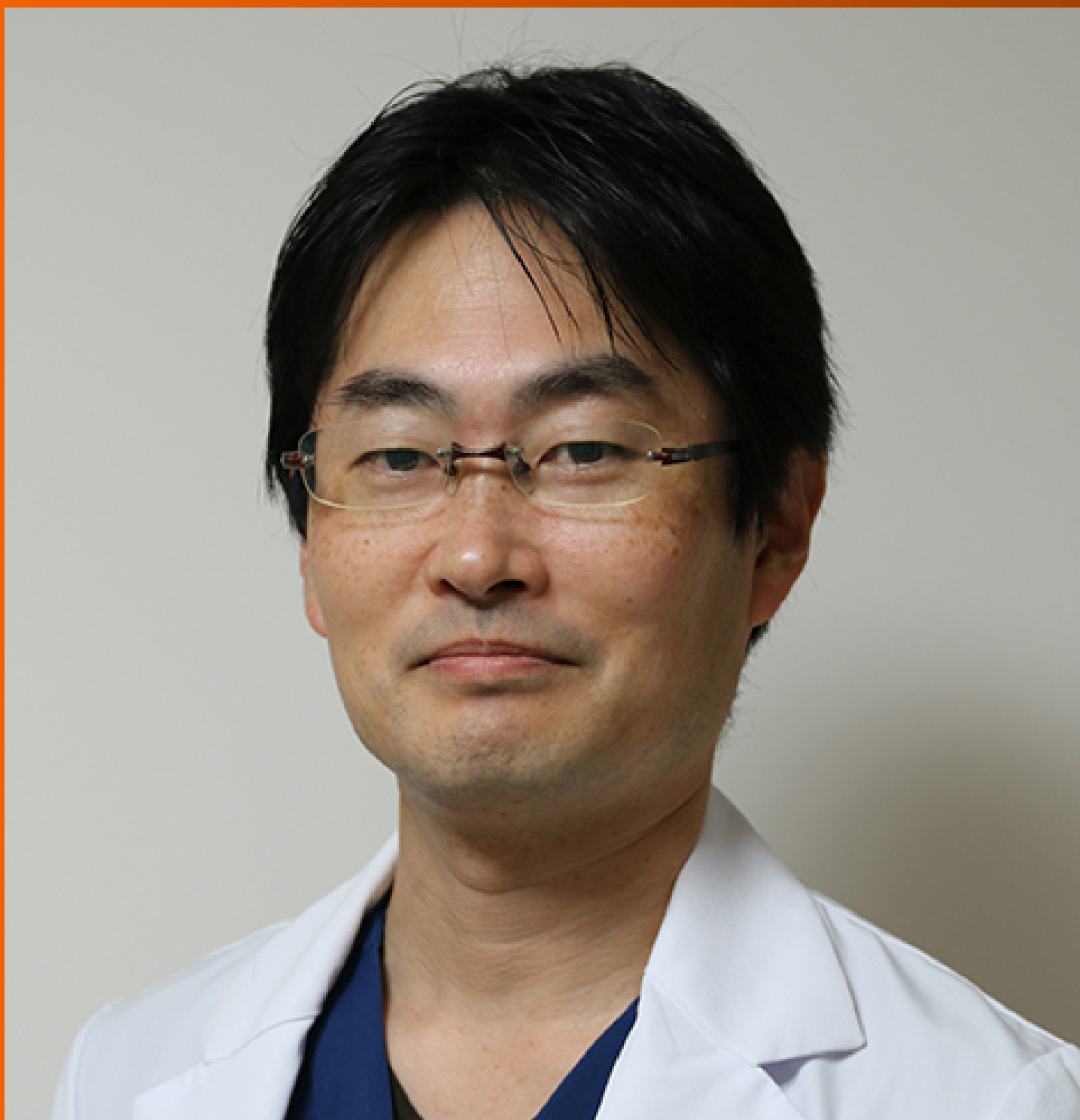


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The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research 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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Early adenocarcinoma mixed with a neuroendocrine carcinoma component arising in the gastroesophageal junction: A case report

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Abstract

BACKGROUND

Early adenocarcinoma mixed with a neuroendocrine carcinoma (NEC) component arising in the gastroesophageal junctional (GEJ) region is rare and even rarer in young patients. Here, we report such a case in a 29-year-old Chinese man.

CASE SUMMARY

This patient presented to our hospital with a 3-mo history of dysphagia and regurgitation. Upper endoscopy revealed an elevated nodule in the distal esophagus 1.6 cm above the GEJ line, without Barrett's esophagus or involvement of the gastric cardia. The nodule was completely resected by endoscopic submucosal dissection (ESD). Pathological examination confirmed diagnosis of intramucosal adenocarcinoma mixed with an NEC component, measuring 1.5 cm. Immunohistochemically, both adenocarcinoma and NEC components were positive for P53 with a Ki67 index of 90%; NEC was positive for synaptophysin and chromogranin. Next-generation sequencing of 196 genes demonstrated a novel germline mutation of the *ERCC3* gene in the DNA repair pathway and a germline mutation of the *RNF43* gene, a common gastric cancer driver gene, in addition to pathogenic somatic mutations in *P53* and *CHEK2* genes. The patient was alive without evidence of the disease 36 mo after ESD.

CONCLUSION

Early adenocarcinoma with an NEC component arising in the distal esophageal side of the GEJ region showed evidence of gastric origin.

Key Words: Adenocarcinoma; Neuroendocrine carcinoma; Gastroesophageal junction; Next generation sequencing; Case report

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Core Tip: We report a 29-year-old man with a 1.5-cm intramucosal adenocarcinoma with a neuroendocrine carcinoma component, which arose in the columnar-lined esophagus within 1.6 cm above the gastroesophageal junction (GEJ), without Barrett's esophagus. Next-generation sequencing revealed a novel germline mutation of the *ERCC3* gene in the DNA repair pathway of gastric cancer and a germline mutation of the *RNF43* gene as a tumor suppressor in gastric cancer. Our findings suggest this early-onset GEJ carcinoma originated from gastric cardiac mucosa with genetic abnormalities involved in the DNA repair pathway.

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INTRODUCTION

Esophageal carcinoma is the eighth most frequently occurring cancer and the sixth leading cause of cancer-related deaths worldwide[1]. In China, esophageal carcinoma remains a major health risk, ranking the fifth in cancer incidence and the fourth in cancer mortality[1]. However, the histological type of esophageal carcinoma varies geographically. For instance, esophageal adenocarcinoma (EAC) is predominant in North America and Europe, where the incidence increases steadily [2-4]. In China, however, esophageal squamous cell carcinoma remains the most prevalent[1], whereas EAC accounts for only 1%-4% of esophageal carcinomas[5-7], among which, < 1% occur in patients aged < 40 years[8]. In Chinese patients, most gastroesophageal junctional (GEJ) carcinomas represent the proximal extension of gastric cardiac cancers, unlike those in the patients from western countries[9], where GEJ adenocarcinoma is largely classified as part of EAC. In this case report, we analyzed the histopathological and genetic characteristics of an adenocarcinoma mixed with a neuroendocrine carcinoma (NEC) component arising on the distal esophageal side of the GEJ in a 29-year-old man.

CASE PRESENTATION

Chief complaints

A previously healthy 29-year-old man complained of dysphagia and gastroesophageal reflux symptoms for 3 mo.

History of present illness

A previously healthy 29-year-old man complained of dysphagia and gastroesophageal reflux symptoms for 3 mo.

History of past illness

The patient denied any specific personal past medical history. He denied alcohol or tobacco abuse. He had no history of Barrett's esophagus.

Personal and family history

The patient denied a family history of cancer.

Physical examination

All vital signs were stable and physical examination revealed no notable abnormalities. His body mass index was 20.22 kg/m².

Laboratory examinations

Preoperative serum tumor markers, such as α -fetoprotein, neuron-specific enolase, carcinoembryonic antigen, carbohydrate antigen (CA)19-9, CA724 and CA50, were all within normal limits. *Helicobacter pylori* (*H. pylori*) testing (¹³C urea breath test) was negative.

Imaging examinations

Endoscopic ultrasonography demonstrated a hypoechoic nodule without the sign of submucosal invasion. Neither distant metastasis nor lymph node involvement was seen on the thoracoabdominal enhanced computed tomography.

Endoscopic examinations

Esophagogastroduodenoscopy in our hospital revealed an elevated small nodular lesion on the esophageal side of the GEJ line without involvement of the proximal gastric cardia under white-light endoscopy (Figure 1). The lesion was surrounded by a short stretch of salmon-red columnar metaplastic esophageal mucosa at a maximum distance of 1.6 cm above the GEJ line. The rest of the esophageal mucosa was unremarkable. No evidence of Barrett's esophagus in the distal esophagus was noted. Preoperative narrow-band imaging endoscopy showed dilatation and irregular meandering of blood vessels in the lesion along with a demarcation line separating the neoplastic and non-neoplastic mucosae.

Histopathological examinations

A biopsy of the lesion was performed and diagnosed histopathologically as high-grade glandular dysplasia. After preoperative routine workups, this lesion was completely resected by endoscopic submucosal dissection (ESD). In the ESD resected specimen, a type 0-IIa + IIc lesion measured 11 mm × 6 mm grossly. Microscopically, the entire tumor arose in the columnar-lined esophagus (15 mm maximum length), which was confirmed by the presence of submucosal esophageal glands (Figure 2A). The tumor was poorly differentiated in most parts, with only a minor component of moderately differentiated adenocarcinoma (Figure 2B). A small portion of the tumor < 0.1 cm exhibited nuclear features of neuroendocrine differentiation (Figure 2C), including sheets and nests of smaller cells with hyperchromatic nuclei, powdery chromatin patterns, and scant cytoplasm (Figure 2D). No necrosis was noted. The mitotic rate was 4/high-power field. A few dysplastic glands with goblet cells were identified in the adjacent benign metaplastic mucosa (Figure 2E). In the distal part of the specimen, benign gastric cardiac mucosa with a maximum length of 4 mm showed mild chronic inflammation, but no evidence of atrophy or intestinal metaplasia. By routine immunohistochemistry, caudal type homeobox 2 was weakly positive for moderately differentiated adenocarcinoma, but negative for the poorly differentiated adenocarcinoma component (Figure 2F). In contrast, mucin 5AC was diffusely positive for poorly differentiated adenocarcinoma, but only focally positive for moderately differentiated adenocarcinoma (Figure 2G). Chromogranin and synaptophysin were diffusely positive for the cells with neuroendocrine features, but negative for adenocarcinoma (Figure 2H). The Ki-67 proliferative index was approximately 90% for both adenocarcinoma and NEC components (Figure 2I). p53 immunostaining was strongly positive in both components (Figure 2J). The tumor retained nuclear expression of MLH1, PMS2, MSH2, and MSH6. The carcinoma was HER2-negative with a score of 1⁺. The tumor invaded only muscularis mucosae without the evidence of submucosal, gastric cardiac, lymphovascular, and perineural invasion. Both the lateral and vertical margins of resection were free of dysplasia and carcinoma.

Molecular pathology examinations

Tumor genetic analysis by next-generation sequencing (NGS) was performed using a 196-gene panel (Genenseeq Technology, 196-cancer-relevant-gene, Nanjing, China) on the Illumina MiSeq platform. NGS data analysis identified 12 genetic mutations; two of which were germline mutations. The novel germline mutation at *ERCC3* c.2333A>G was identified, which is in the DNA repair pathway of gastric cancer. The scores of the SIFT and PolyPhen-2 analyses were 0.426 and 0.034, respectively, and predicted the impact of the amino acid substitution of lysine as tolerated and benign. Another germline mutation at *RNF43* c.434G>A was also identified. In somatic mutations, pathogenic mutations in *TP53* and *CHEK2* genes were discovered with allele frequencies of 10.43% and 1.38%, respectively. Other somatic mutations in *FANCD2*, *PALB2*, *ROS1*, *PIK3CA*, *RAD51B*, *PTEN* and *BRCA2* genes were found with allele frequencies < 3% (Table 1).

FINAL DIAGNOSIS

The patient was diagnosed with intramucosal poorly differentiated tubular adenocarcinoma mixed with a minor (< 1%) NEC component.

TREATMENT

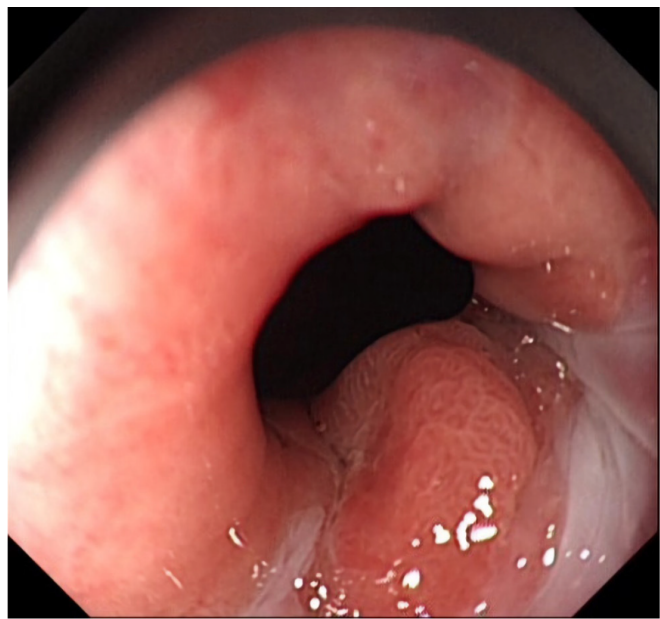
En bloc resection of the lesion along with the GEJ was achieved with ESD.

OUTCOME AND FOLLOW-UP

The postoperative course was uneventful. Follow-up esophagogastroduodenoscopy was conducted at 6, 12, 24 and 35 mo after ESD with negative results. A repeated ¹³C urea breath test at 33 mo after ESD remained negative. Routine computed topography was repeated at 6, 12 and 24 mo after ESD with unremarkable findings. The patient was alive without evidence of the disease 36 mo after ESD resection.

Table 1 Mutations found in early adenocarcinoma mixed with a neuroendocrine carcinoma component by next-generation sequencing analysis

Gene name	Mutation type	Reference allele	Observed allele	cDNA changed	Amino acid change	Variant type	Exon	Clinical significance	Allele frequency (%)
ERCC3	Germline	T	C	c.2333A>G	p.K778R	Missense	15	Uncertain significance	50.56
RNF43	Germline	C	T	c.434G>A	p.R145Q	Missense	4	Likely benign	44.79
TP53	Somatic	C	T	c.853G>A	p.E285K	Missense	8	Pathogenic/likely pathogenic	10.43
ERCC3	Somatic	G	A	c.377C>T	p.A126V	Missense	3	Uncertain significance	2.24
FANCD2	Somatic	G	A	c.4297G>A	p.E1433K	Missense	44	Uncertain significance	1.42
CHEK2	Somatic	G	A	c.538C>T	p.R180*	Stop gained	4	Pathogenic	1.38
PALB2	Somatic	C	T	c.2986G>A	p.E996K	Missense	9	Uncertain significance	1.33
ROS1	Somatic	C	T	c.4252G>A	p.V1418I	Missense	26	Uncertain significance	1.30
PIK3CA	Somatic	G	A	c.436G>A	p.V146I	Missense	2	Uncertain significance	1.24
RAD51B	Somatic	G	A	c.140G>A	p.R47Q	Missense	3	Uncertain significance	1.16
PTEN	Somatic	G	A	c.698G>A	p.R233Q	Missense	7	Uncertain significance	1.12
BRCA2	Somatic	C	A	c.2557C>A	p.Q853K	Missense	11	Likely benign	1.06

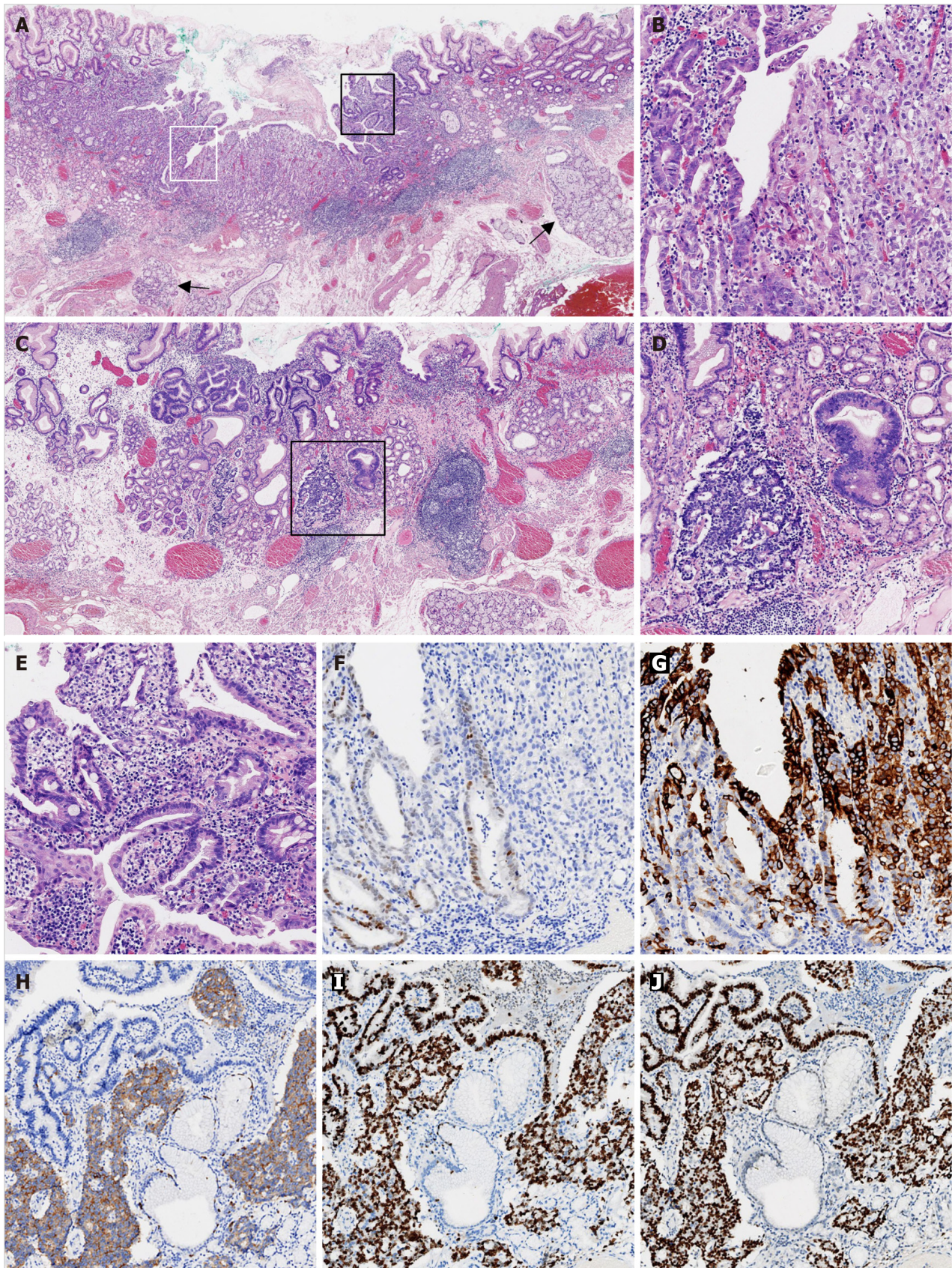


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Figure 1 A representative upper endoscopic image of a tumor in the gastroesophageal junction. An elevated mucosal lesion was found endoscopically in the distal esophageal side of the gastroesophageal junction. The metaplastic columnar epithelium extended focally in the distal esophagus above the gastroesophageal junction.

DISCUSSION

GEJ carcinoma in China is also known as gastric cardiac carcinoma, and not associated with EAC, which is rare in China [9]. A previous study of 5401 esophageal cancers in an endemic region of China identified only 217 (4%) cases of EAC, with the youngest patient aged 44 years[6]. Another study identified EAC in only 2% of 204 resection cases of distal esophageal carcinomas in China[5]. In general, EAC rarely occurs in patients < 40 years, even in western countries. According to two studies in American patients[10,11], young patients with EAC under the age of 40 years accounted for 5%, among which only two of 1146 patients were in their second decade of life. The pathogenesis mechanisms of this cancer in young patients remain unknown.



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Figure 2 Histological findings of poorly differentiated adenocarcinoma mixed with a neuroendocrine carcinoma component. A: Submucosal esophageal glands (arrow) were observed, indicating the distal esophageal location ($\times 20$); B: The area defined by the white rectangle in Figure 2A was enlarged and showed the mixture of moderately (left) and poorly (right) differentiated adenocarcinomas ($\times 100$); C: Adenocarcinoma with a neuroendocrine carcinoma (NEC) component arose in the cardiac mucosa ($\times 20$); D: The area in the black rectangle in Figure 2C exhibited a mixture of adenocarcinoma (right) with NEC (left; $\times 100$); E: The area defined by the black rectangle in Figure 2A was enlarged and demonstrated glandular dysplasia with goblet cells ($\times 100$); F: CDX2 was weakly

immunoreactive in moderately differentiated adenocarcinoma and immunonegative in poorly differentiated adenocarcinoma ($\times 100$); G: Mucin 5AC was diffusely immunopositive in poorly differentiated adenocarcinoma and focally immunopositive in moderately differentiated adenocarcinoma ($\times 100$); H: Synaptophysin was diffusely immunopositive in NEC, but immunonegative in adenocarcinoma ($\times 100$); I: The Ki-67 proliferative index was approximately 90% for both the adenocarcinoma and NEC components ($\times 100$); J: p53 was diffusely immunopositive for the adenocarcinoma and NEC components ($\times 100$). All controls stains were adequate.

In Chinese patients, the epicenters of carcinomas that involve the GEJ are most frequently located in the proximal stomach, rather than in the distal esophagus[9]. Moreover, long segment columnar-lined esophagus is rare in Chinese patients, unlike in western patients[6,9,12]. The vast majority of GEJ tumor resection cases with intestinal metaplasia in Chinese patients are the extension of intestinal metaplasia from the adjacent gastric cardia because of the continuity of cardiac mucosa from the gastric cardia to the distal esophagus up to 1.6 cm above the GEJ line[5,13]. In the present case, the tumor was entirely located on the distal esophageal side of the GEJ line without invading the gastric cardia. The adjacent benign mucosa was cardiac mucosa with intestinal metaplasia and focal dysplasia, suggesting the origin of this mixed carcinoma in cardiac mucosa, rather than a proximal extension of *H. pylori* gastric carditis, which are commonly seen in Chinese patients.

Similar to histological variants in proximal gastric carcinoma (gastric cardiac carcinoma), GEJ carcinomas in Chinese patients also vary widely in histology, including NEC[5,9]. The mixed NEC component in the present case was small in size, with a high Ki-67 index and strong p53 immunoreactivity, showing *TP53* gene missense mutation revealed by NGS analysis, which supports the diagnosis of NEC, but not grade 3 neuroendocrine tumor. In our young patient, the tumor arose in cardiac glands, as described previously[14-17], which is unusual, since esophageal NEC is more commonly mixed with squamous cell carcinoma in Chinese patients[18], rather than EAC in American patients[19]. Although there were reports of esophageal carcinoma with mixed adenocarcinoma and NEC components, without the evidence of background columnar-lined esophagus, it might be due to the possibility of destruction of columnar-lined esophagus by advanced large tumors[20,21].

To the best of our knowledge, the present case is the first report of an early-onset early GEJ adenocarcinoma mixed with a small NEC component, with NGS analysis in 196 genes. Somatic mutations of *RNF43*, which encodes an E3 ubiquitin ligase that negatively regulates *Wnt* signaling, are frequently revealed in gastric carcinomas, but not in esophageal carcinomas[22,23]. EAC also shows lower *APC* gene mutation rates than gastric carcinomas, suggesting a less prominent role of *Wnt*/ β -catenin in EAC tumorigenesis[24]. The germline mutation in the *RNF43* gene in our case supports the origin of gastric cardiac mucosa. The association between *ERCC3* gene, which encodes an ATP-dependent DNA helicase that functions in nucleotide excision repair, and drug resistance in human gastric cancer cells has been reported[25]. Similar *ERCC3* gene mutation has also been reported to be associated with ovarian cancer[26]. One of the two pathogenic somatic mutated genes in our case was *P53*, a well-known driver gene in gastric cancer and EAC[22]. It is of note that the other pathogenic somatic mutation was identified in the *CHEK2* gene; an important gene involved in the DNA homologous recombination repair pathway. *CHEK2* was reported as a driver mutation in both EAC and gastric cancer[27]. NGS analysis in our case also exhibited somatic mutations in *FANCD2*, *PALB2* and *RAD51B* genes, which are associated with the DNA homologous recombination repair pathway[28]. The molecular profile of the current case indicates that the genetic abnormalities involved in the DNA repair pathway may play a significant role in tumorigenesis of early-onset GEJ carcinoma of gastric origin.

The incidence of EAC and GEJ in young patients is increasing[29]. These young patients were reported to have a poor prognosis because of advanced stages at initial diagnosis and difficulty in early diagnosis[11,29]. The results from our case illustrate the importance of early diagnosis in young patients with clinical complaints of dysphagia and gastroesophageal reflux symptoms, which should be taken seriously for the possibility of malignancy, and upper endoscopy may help make an appropriate diagnosis. Once the biopsy diagnosis of early carcinoma without nodal and distant metastases is confirmed after routine work-up, ESD appears to be the subsequent step of choice for both diagnosis with staging and treatment with curative intent.

CONCLUSION

We reported a rare case of GEJ adenocarcinoma mixed with an NEC component with gastric origin in a young adult. Further studies in more cases are required to elucidate the underlying molecular tumorigenesis mechanisms in early-onset GEJ carcinoma.

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