Esophageal squamous cell carcinoma transformed into neuroendocrine carcinoma after neoadjuvant immunochemotherapy: A case report

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Abstract. Immunotherapy provides durable responses for locally advanced esophageal carcinoma clinical therapy in numerous patients. However, the mechanisms of resistance to immunotherapy have not been elucidated. The phenomenon of the histological transformation of non-small cell lung cancer to small cell lung cancer resulting in resistance to immune checkpoint inhibitors (ICIs) has been reported. It remains unclear whether ICIs or chemotherapy could cause a similar transformation from esophageal squamous cell carcinoma (ESCC) to esophageal neuroendocrine carcinoma (ENEC). The present study report the case of a patient initially diagnosed with stage II ESCC who underwent radical surgery after three cycles of neoadjuvant therapy with cisplatin, albumin bound paclitaxel and ICIs. Immunohistochemical staining confirmed the absence of the SCC component and the presence of the NEC component, with negativity for CK5/6 and tumor protein p40, but positive expression of tumor protein p53, pan-cytokeratin, synaptophysin and CD56. The patient was followed up for 5 months with no treatment or postoperative complications. In conclusion, histological transformation to ENEC is a potential mechanism of acquired resistance to ICIs in ESCC. Prospective larger studies are warranted to further characterize ESCC-to-NEC transformation on use of ICIs.

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Introduction

Esophageal cancer ranks as the ninth most common cancer (1), with 54% of the cases occurring in China in 2018 (2). Esophageal squamous cell carcinoma (ESCC) is the most common histological type, constituting 85.79% of all cases, followed by esophageal adenocarcinoma at 11.00% and others types as 3.21% (3). For locally advanced ESCC, important treatment options include neoadjuvant chemotherapy or chemoradiotherapy followed by surgery, as well as definitive chemoradiotherapy (4). However, the optimal approach for locally advanced ESCC remains unclear, necessitating further research. Several clinical trials have demonstrated the effectiveness of combining immune checkpoint inhibitors (ICIs) with chemotherapy for locally advanced ESCC (5-7). Yet, not all cases of ESCC respond to this combined therapy, with response rates ranging from 16.7 to 58.3%. The resistance mechanism to ICIs or chemotherapy in ESCC has not been comprehensively investigated. Reports have indicated that the transformation of non-small cell lung cancer (NSCLC) into small cell lung cancer (SCLC) can act as a resistance mechanism to ICIs (8,9). Treatments for advanced esophageal neuroendocrine carcinoma (ENEC) are similar to those used in SCLC (10). The similar transformation of ESCC to ENEC could serve as one possible resistance mechanism to ICIs. The present study report the case of a patient with a preoperative diagnosis of ESCC who underwent neoadjuvant treatment with ICIs in combination with chemotherapy, resulting in a pathological transformation into ENEC.

Case report

A 58-year-old man presented to Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China in April 2023 with epigastric pain that had persisted for 1 week. The patient had no significant medical or family history. Endoscopic ultrasonography revealed a 6-cm mass 25 cm into the esophagus when measured from the location of the incisors (Fig. 1A), invading the muscularis propria, with the thickest section measuring ~5.9 mm and the outer membrane remaining smooth, with two hypoechoic nodules in the mediastinum next to the lesioned esophagus

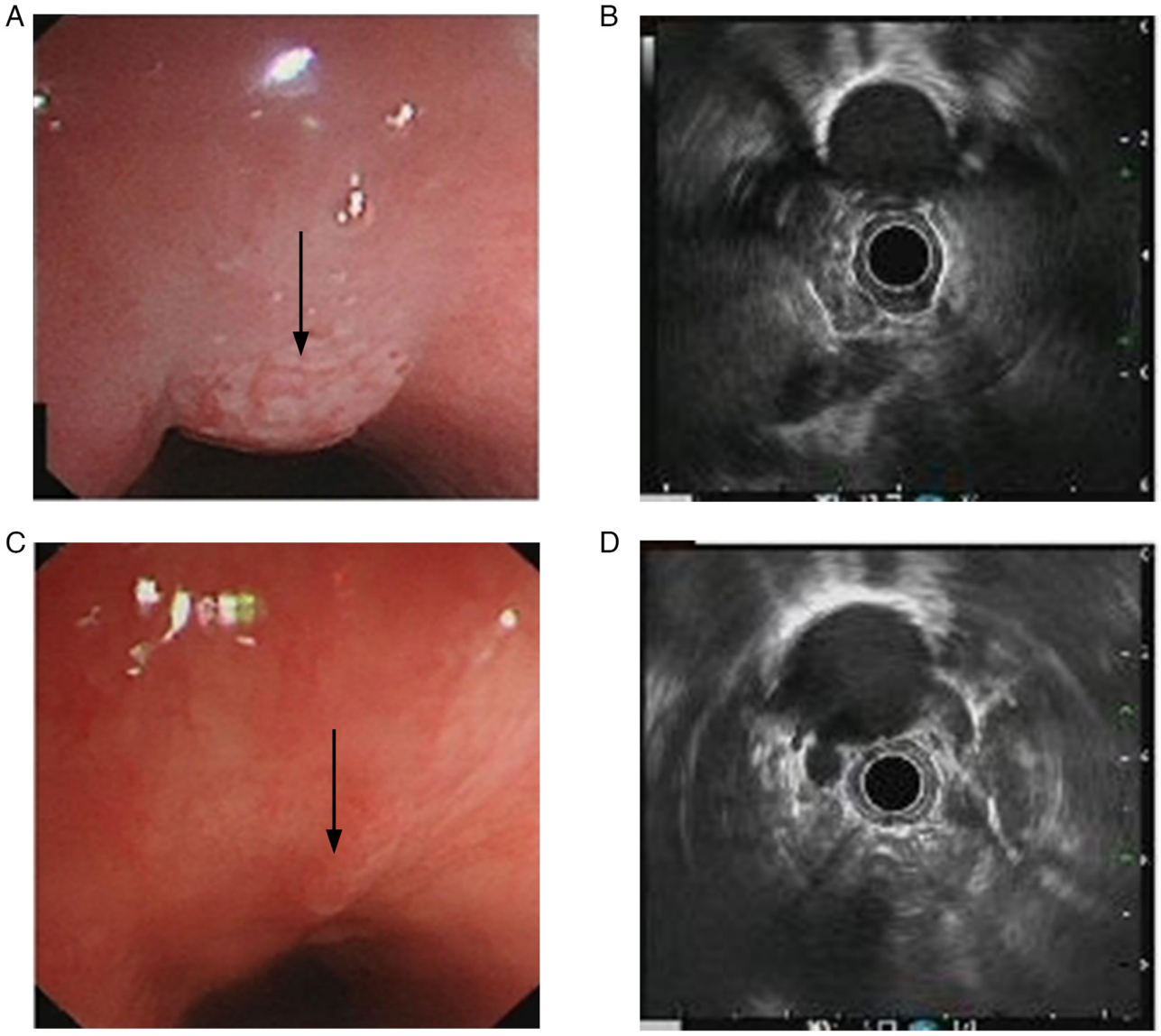

Figure 1. Upper gastrointestinal endoscopy results. (A) Pretreatment endoscopy revealed an elevated lesion with slight erosion on the surface (arrow). (B) Pretreatment ultrasonography suggested invasion into the muscularis propria, and two hypoechoic nodules were detectable in the mediastinum next to the lesioned esophagus. (C) Following three courses of neoadjuvant treatment, endoscopy revealed a reduction in the lesion size (arrow). (D) Post-treatment ultrasonography revealed a reduction in the lesion size.

(Fig. 1B). Hematoxylin and eosin (H&E) staining of a biopsy specimen showed heterogeneous hyperplasia of the squamous epithelium with keratinized pearl formation, leading to a diagnosis of SCC (Fig. 2). Pretreatment contrast-enhanced computed tomography (CT) revealed thickening of the middle esophagus wall with mild uneven enhancement (Fig. 3A), and a homogeneously enhanced nodular shadow ~3mm in diameter on the left side of the lesion, with no other metastatic foci observed in the abdominal CT and cranial magnetic resonance imaging. The levels of neuron-specific enolase, carbohydrate antigen 19-9, carbohydrate antigen 125 and carcinoembryonic antigen were normal in the blood before treatment. According to the 8th edition of American Joint Committee on Cancer staging, the patient's pretreatment clinical stage was cT2N1M0, stage II (11). The patient underwent standard neoadjuvant immunochemotherapy, receiving 200 mg tislelizumab, an anti-programmed cell death protein 1 (PD-1) drug, 50 mg/m^2 cisplatin and 150 mg/m^2 albumin-bound paclitaxel administered intravenously every 3 weeks from May 2023 until June 2023. The epigastric pain was elevated during the treatment and no adverse event was observed. Post-treatment endoscopic ultrasonography demonstrated a significant reduction of the lesion size, with the thickest section measuring ~2.9 mm (Fig. 1C and D). Enhanced CT scans showed that the thickening of the middle esophagus wall had not evidently changed since before treatment (Fig. 3B). The patient underwent a McKeown esophagectomy 3 weeks after the last treatment and an R0 resection was achieved. A total of 20 lymph nodes were biopsied for pathological examination. The postoperative pathology of the lesion showed a 1.0x0.6 cm grayish-white, hard-textured area on gross view. The resected specimen was fixed in 10% formalin and transferred to the Department of Pathology within 2 h. Histopathologically, the resected specimen displayed neuroendocrine cell tumors characterized by hyperchromatic nuclei and scant cytoplasm, with invasion depth restricted to the submucosa (Fig. 4A).

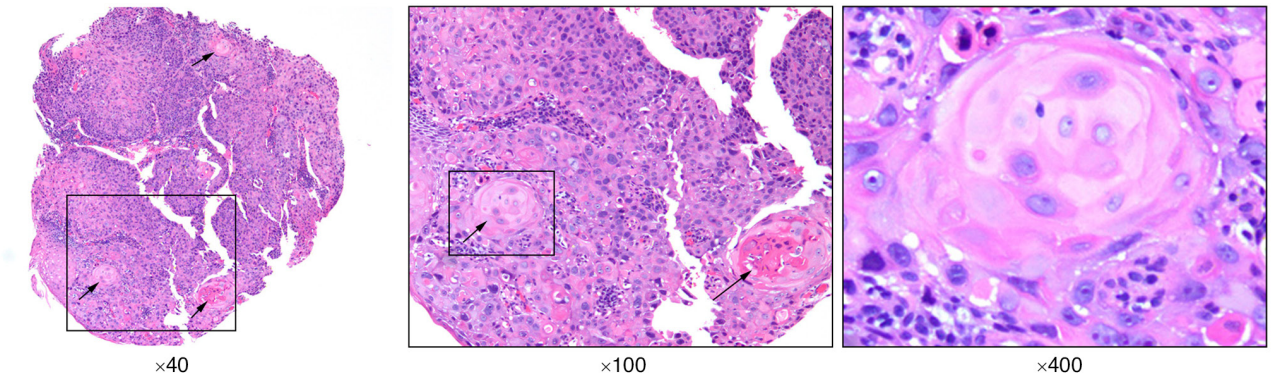

Figure 2. Pathological examination of the biopsy specimen (hematoxylin and eosin staining). The squamous cell carcinoma biopsy exhibited keratinization, and keratinized pearl formation (arrow) was observed.

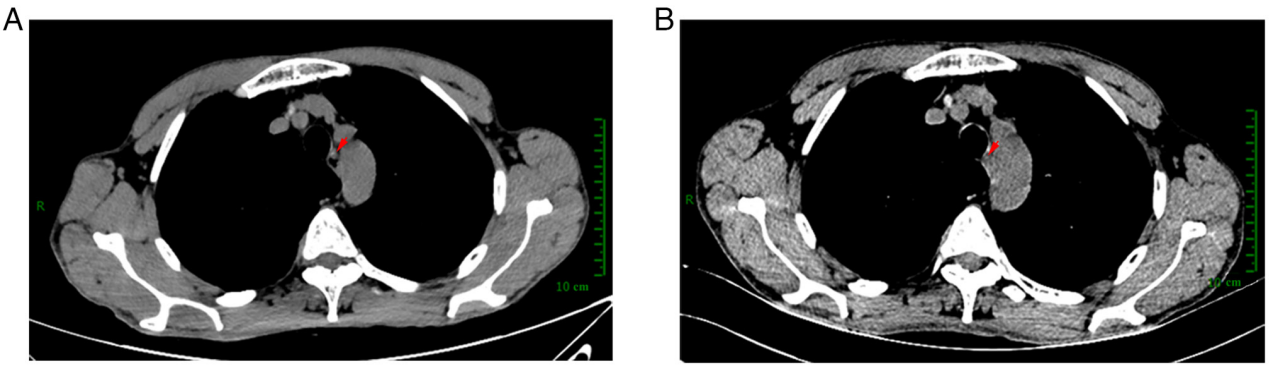

Figure 3. Contrast-enhanced CT results. (A) Pretreatment CT identified a mass within the esophagus (arrow) and suggested metastasis to the paraesophageal lymph nodes. (B) Post-treatment CT indicated a reduction in the lesion size (arrow). CT, computed tomography.

To accurately diagnose the carcinoma type, immunohistochemical staining was performed on the resected specimen. Immunohistochemistry results showed negativity for CK5/6 (Fig. 4B) and tumor protein p40 (Fig. S1), but positive expression of tumor protein p53 (p53), pan-cytokeratin and synaptophysin (Syn), patchy CD56-positive cells and Ki67 expression (Fig. 4B), indicating that the tumor was an ENEC with no remaining ESCC (12). The results of H&E staining and immunohistochemistry staining together indicated that p53 expression was localized mainly in the nucleus in nearly all the tumor cells, while Syn was expressed in the cytoplasm of the tumor cells. No metastatic lymph nodes were detected. The patient experienced no recurrence or adverse events during the 5-month follow-up period. The latest CT scan was performed in October 2023 and an endoscopy was performed in December 2023. The results revealed no recurrence or metastasis (Fig. 5). The patient did not receive further treatment after the surgery and follow-up will be performed every 3 months until recurrence or metastasis is detected.

Discussion

Esophageal cancer is among the most common malignancies worldwide and ranks within the top 10 cancers in terms of both morbidity and mortality (1). In China, ESCC is the predominant pathological type (13). Most patients are diagnosed with locally advanced ESCC at their first visit, and the 5-year survival rate for these patients is only 20% (3). Various strategies have been implemented to improve ESCC prognosis. The use of ICIs as neoadjuvant therapy for locally advanced ESCC has shown promising outcomes. According to the TD-NICE study, the pathological complete response (PCR) rate is as high as 50% (5). Additionally, a retrospective study of ICIs in neoadjuvant ESCC treatment reported a maximum PCR rate of 58.3% (6). However, not all ESCC cases respond to anti-PD-1 therapy, making it crucial to investigate drug resistance mechanisms. The present case provided a possible theory. To the best of our knowledge, this is the first report of ENEC transformation from ESCC through immunochemotherapy. This case may offer valuable insights into resistance to immunochemotherapy.

The resistance to ICIs in NSCLC has been explored (8,9), and a similar transformation may aid in understanding the resistance mechanism in ESCC. Imakita *et al* (14) first reported the NSCLC-to-SCLC transformation due to immunotherapy, with two transformation mechanisms proposed. The first hypothesis suggests that NSCLC cells histologically transform into SCLC cells. The second hypothesis is that the initial tumor contains both NSCLC and SCLC components, leading to small cell predominance with immunotherapy (15). Based on the present case, two transformation mechanisms for ESCC to ENEC are proposed. One hypothesis is that the initial tumors comprised both ESCC and ENEC, with the ESCC component diminishing due to treatment with

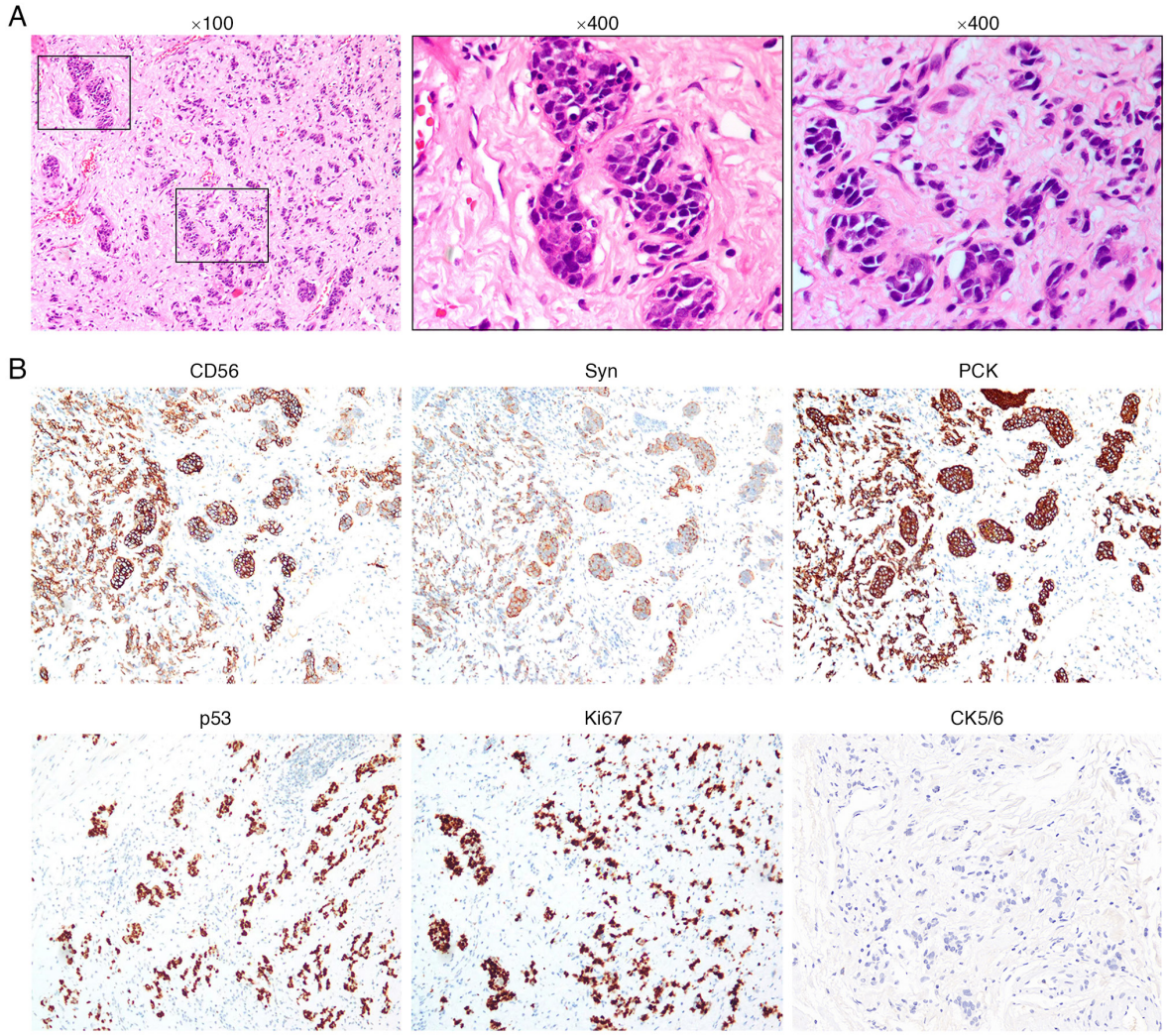

Figure 4. Histopathology and immunochemistry results. Neuroendocrine differentiation was evident in the postoperative specimen. (A) Hematoxylin and eosin staining revealed hyperchromatic nuclei and scant cytoplasm. (B) Immunohistochemistry staining showed negativity for CK5/6, but positive expression of p53, (PCK) and Syn, patchy CD56-positive cells and Ki67 staining (magnification, x100). p53, tumor protein p53; PCK, pan-cytokeratin; Syn, synaptophysin.

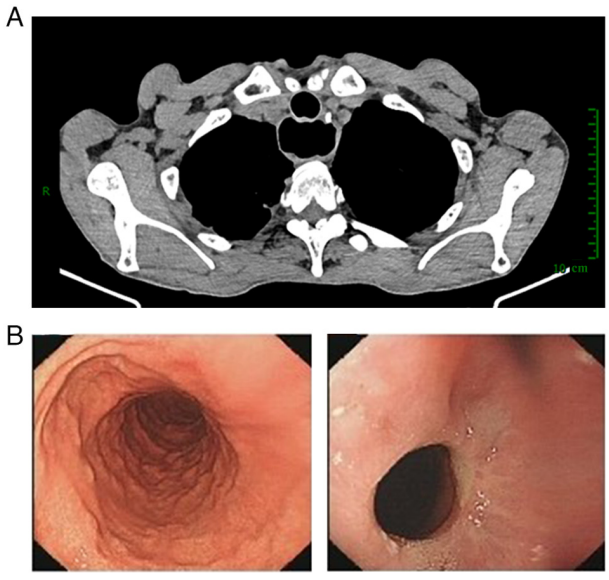

Figure 5. Follow-up results of CT scan and endoscopy. (A) A CT scan performed in October 2023 revealed no recurrence or metastasis. (B) Endoscopy performed in December 2023 revealed no recurrence. CT, computed tomography.

paclitaxel, cisplatin and tislelizumab, while the ENEC component was less sensitive to immunochemotherapy. The practice of using ICIs for ENEC is rare. There is limited evidence to guide the treatment of patients with advanced ENEC, as the incidence of ENEC is only 0.044 per 100,000 individuals (16). The National Comprehensive Cancer Network guidelines recommend a combination of chemotherapy and radiotherapy for locally advanced ENEC (10). Currently, only one phase II trial (NCT03901378) of pembrolizumab combined with etoposide plus carboplatin or etoposide plus cisplatin therapy in primary high-grade gastrointestinal NEC is underway, with efficacy and safety data yet to be reported. In the present study, insufficient pre-treatment biopsy samples were available for immunohistochemistry staining of CD56 and Syn to support this hypothesis. However, no abnormal neuron-specific enolase levels were detected in the blood before treatment, rendering the evidence for ENEC weak.

The alternate hypothesis suggests that ESCC cells underwent histological transformation to ENEC cells due to immunotherapy. Ho *et al* (17) proposed the hypothesis that ENEC with multiple components might develop from totipotent primitive cells. Reports of esophageal carcinomas

with different histological components support the notion that esophageal carcinomas possess multidirectional differentiation abilities (18,19). A report detailing the transformation of ENEC from ESCC through sequential endoscopy (20) also supports this hypothesis. Although the specific mechanism of this tumor transformation due to anti-PD-1 therapy remains unclear, its possibility cannot be dismissed. Moreover, the impact of chemotherapeutic agents on tumor transformation should be considered. The transformation was considered to be less influenced by paclitaxel and cisplatin than tislelizumab, as paclitaxel combined with cisplatin has been a standard therapy for ESCC for ~20 years, with no reports of these drugs causing ENEC transformation. The evolutionary genomic alterations underlying this resistance mechanism require further detailed exploration. In studies of NSCLC-to-SCLC transformation, researchers performed tissue transcriptome sequencing before and after immunotherapy, identifying similar TP53 mutations (9). Given that the TP53 mutation is one of the most common mutations in ESCC (21), it may play a crucial role in the transformation of ESCC into NEC and in resistance to immunotherapy. The lack of sufficient biopsy tissues for genomic testing presents a challenge in precision medicine, necessitating further research into the resistance mechanism of ESCC.

There are some limitations in the present case report. First, the biopsy specimen before treatment was not sufficiently large enough for immunohistochemistry staining to exclude the existence of NEC cells. The molecular alterations that may drive histological transformation were also unclear. Second, the images and data were obtained directly from the patient's medical records. The specific steps of H&E and immunohistochemical staining on resected specimen were not available, as the original medical record did not contain related information The information on the antibodies used in the immunohistochemistry staining was not included in the original medical records; thus, it is difficult to indicate the specific information on antibodies. Apart from that, the image of the resected specimen on gross view was not provided and this may cause difficulty in making a clear diagnosis regarding the depth of invasion or neural or vascular invasion. Third, tissue transcriptome sequencing before and after immunotherapy are clearly warranted for further investment on resistance mechanisms.

In summary, the present study reported a case of ESCC-to-ENEC transformation after neoadjuvant immunochemotherapy, suggesting that this pathological change may contribute to resistance to immunotherapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

GX and NS analyzed data, and wrote the paper as the co-first authors. KJ conceived the study and edited the manuscript. GX and NS confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Competing interests

The authors declare that they have no competing interests.

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